Send Orders for Reprints to reprints@benthamscience.net

Current Medicinal Chemistry, 2022, *29*, 2142-2166

REVIEW ARTICLE

The Roles of Signaling Pathways in Cardiac Regeneration

Amir Valizadeh[1,2], Samira Asghari[1], Parinaz Mansouri[2], Forough Alemi[3], Maryam Majidinia[4], Ata Mahmoodpoor[1] and Bahman Yousefi[3,*]

[1]*Stem Cell and Regenerative Medicine Institute, Tabriz University of Medical Sciences, Tabriz, Iran;* [2]*Students Research Center, Tabriz University of Medical Sciences, Tabriz, Iran;* [3]*Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran;* [4]*Solid Tumor Research Center, Urmia University of Medical Sciences, Urmia, Iran*

ARTICLE HISTORY

Received: March 03, 2021
Revised: July 05, 2021
Accepted: July 20, 2021

DOI:
10.2174/0929867328666210914115411

Abstract: In recent years, knowledge of cardiac regeneration mechanisms has dramatically expanded. Regeneration can replace lost parts of organs, common among animal species. The heart is commonly considered an organ with terminal development, which has no reparability potential during post-natal life. However, some intrinsic regeneration capacity has been reported for cardiac muscle, which opens novel avenues in cardiovascular disease treatment. Different endogenous mechanisms have been studied for cardiac repairing and regeneration in recent decades. Survival, proliferation, inflammation, angiogenesis, cell-cell communication, cardiomyogenesis, and anti-aging pathways are the most important mechanisms that have been studied in this regard. Several *in vitro* and animal model studies focused on proliferation induction for cardiac regeneration reported promising results. These studies have mainly focused on promoting proliferation signaling pathways and demonstrated various signaling pathways such as Wnt, PI3K/Akt, IGF-1, TGF-β, Hippo, and VEGF signaling cardiac regeneration. Therefore, in this review, we intend to discuss the connection between different critical signaling pathways in cardiac repair and regeneration.

Keywords: Signaling pathways, heart, regeneration, Wnt signaling, notch signaling, VEGF signaling, IGF-1 signaling.

1. INTRODUCTION

Recognizing organ regeneration mechanisms gives new insights into these biological processes, which provides valuable therapeutic targets for promoting regeneration [1]. Regenerative medicine follows the substitution of lost or harmed organs during chronic disorders. The reality of common mechanisms regulating organ repair and regeneration is an intriguing concept. In a sense, harm gives a facilitative milieu for regeneration. Cardiac repair and regeneration in humans were first described almost a century ago following the identification of split myocardial fibers in children infected with diphtheria affected by the toxin [2, 3]. This early study was initiated to the demonstrated concept of regenerative during human heart development [4]. Until previously, the proliferation and growth of mammalian cardiomyocytes (CMs) have been considered exclusively to embryonic stages, with little or no capacity to revive after these stages.

One of the reasons that suggested a rapid loss of regenerative capacity in adult cardiac mammals might be consequent DNA damage caused by ROS or postnatal enhancement in mechanical load, both of which occur after birth [5]. This discovery caused to open new avenues for this approach [6]. Physiological compensatory mechanisms promote and improve CMs loss and fibrosis in pathological remodeling [7]. Therefore, there is a need for policies to replace and regenerate CMs after cardiac injury [8].

To conserve the failing heart, investigators have recently focused on improving cardiac regeneration.

*Address correspondence to this author at the Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran; Tel: (+98) 09149117624; E-mail: yousefib@tbzmed.ac.ir

1875-533X/22 $65.00+.00

Herein, we focus on the perspectives and outcomes of approaches performed in association with signaling pathways involved in cardiac developing repair and renewal from researchers so far.

2. CARDIAC REGENERATION AND REPAIR OF VERTEBRATES

Some vertebrates, such as teleost zebrafish, newts, and neonatal mice [9], can restore damaged or lost heart tissue suffering from different injury types. Zebrafish serves as a proven model to review the heart repair process [10-12]. The first study of cardiac regeneration in zebrafish was done in 2002, revealed that zebrafish could restore their heart following amputation of nearly 20% of its ventricle. Indeed, the formation of fibrin clots after injury resulted in new CMs after 60 days post-injury (dpi), which resulted in getting back to normal [13]. Restoration of CMs in zebrafish is not based on the transdifferentiation of stem cells or other cells; in fact, based on the development of pre-existing CMs [14]. An in-depth understanding of the underlying mechanism of extra and intracellular signaling pathways involved in zebrafish cardiac regeneration might help find better alternatives to retrieve human cardiac function.

The renewal of human cardiac is limited compared with that of less complicated species; a stable developmental panorama expresses the initiating stage to investigate cardiac regeneration's principle steps and provide treatment procedures for regenerative medicine [15]. Bearing all these in mind, the human cardiac was not always regarded as a non–regenerative organ. Recently some of the investigations provided that the myocardium had some regenerative capacities. Physiological heart growth was enhanced by enhanced CM size instead of cell division [11].

Despite the disability of adult cardiac tissue in CM regeneration processes, the fetal and neonatal hearts preserve this prominence for a short time after birth. With this viewpoint, investigations in neonatal mice revealed that the retrieval reactions to heart damage after surgical resection at postnatal day 1 contributed to creating cardiac regeneration, while at day 7 resulted in fibrosis and scar disposition. In a sense, regeneration in neonatal mice looks to considerably depend on angiogenesis and the re-induction of perfusion after hurt damage. The short period in which the neonatal cardiac tissue can still retrieve from damage is called the "regenerative window", which in mice may be as short-lived as 3 days [16].

3. CHANGE FOR SIGNAL PATHWAYS ASSOCIATED WITH HEART DEVELOPMENT AS A STRATEGY FOR CARDIAC REGENERATION AND REPAIR

In a vital organ such as the heart, regeneration is charming and clinically relevant [17]. Indeed, one of the most significant challenges of regenerative medicine is extemporizing how to substitute the up to one billion CMs destroyed following myocardial infarction (MI) [18]. Several cardiac repair strategies are suggested, such as applying stem cell-derived CMs therapy, inducing the proliferation of existing CMs, directing non-muscle cells into CMs, utilizing hypoxic conditions to the heart, and employing pro-regenerative factors, which are seeded on engineered patches [19].

One of the main therapeutic challenges of modern cardiology is to design strategies to diminish myocardial death, optimize cardiac repair, and eventually diminish cardiac remodeling following injury [20]. The best strategy to improve HF's consequence is to regenerate damaged myocardium by making more functional CMs [21]. Previous studies have introduced response pathways such as retinoic acid (RA), JAK/Stat3, H_2O_2, and HIF1 signaling pathways involved in heart repair. Furthermore, several signaling pathways have been shown to regulate CMs proliferation, including Hippo, PI3K/Akt, IGF-1, periostin, and VEGF [22]. In this regard, known extracellular factors including IGF-1, FGF, periostin, and Nrg1 require PI3K to induce the proliferation of differentiated CMs (Fig. **1**). Moreover, it is worth mentioning that, unlike Nrg1, IGF-1, and FGFs increase cardiac hypertrophy [23].

4. CURRENT ADVANCES IN CARDIAC REGENERATION

Considerable advances have been made in recognizing cardiac repair and regeneration's cellular and molecular mechanisms, obtaining the ability to control cardiac regeneration [24]. A specific organ's structure and function in response to environmental stimulators are defined by a complex of evolutionarily protected roles encoded by a sequence preserved within core components and with the help of regulatory mechanisms [25, 26].

In the cellular-based approach, embryonic stem cells or induced pluripotent stem cells (iPSCs) [27] into CMs should be differentiated that could then be implanted into a damaged heart [28]. Adult myocardium has a low number of stem cells and low regeneration capacity after damage; however, in recent studies, some efforts have been made to stimulate the cardiac

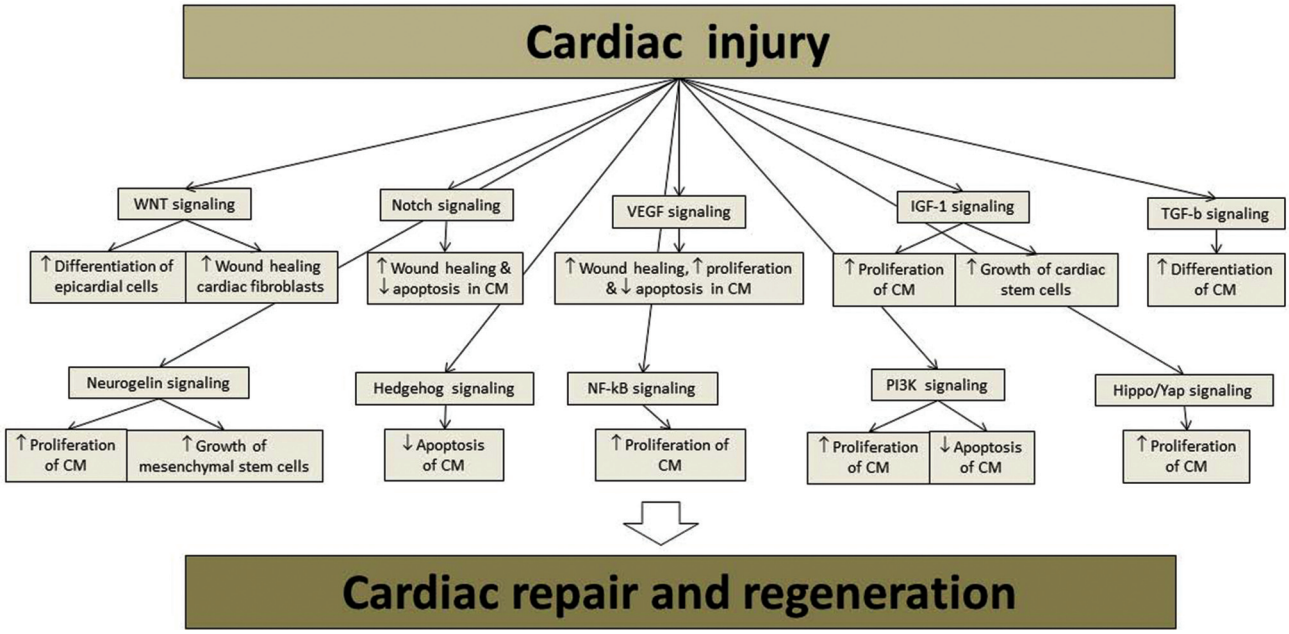

Fig. (1). Schematic overview of the various signaling pathway in cardiac regeneration. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

stem cells (CSCs) migration to the myocardium's infarcted era, to increase their proliferation and differentiation and protect them from apoptosis. These studies had promising results and created the hope that this approach would be able to realize the effective reconstruction of damaged heart tissue. For instance, one study on the animal model demonstrated that resveratrol, a natural component, can induce the CSCs proliferation, prevent apoptosis, increase VEGF expression, and reinforce myocardial regeneration after infarction [29].

It seems that some miRNAs are helpful in this regard. For example, one study has shown that miR 199a-5P reinforces CSCs proliferation and inhibits apoptosis by indirect p53 targeting [30]. Another study's stimulatory effect of miR-21 on CSCs migration is also demonstrated [31]. In addition to these, other approaches for cardiac regeneration have been studied in recent years. Overall, to date, medical efforts toward cardiac regeneration have concentrated on cell-based treatments, including bone marrow-derived cells (BMs), mesenchymal stem cells (MSCs), iPSCs, and presumed cardiac progenitor cells [19, 32]. MSCs produce an abundant variety of cytokines and growth factors (GFs), and many are involved in restoring or regenerating CMs. Factors including basic-fibroblast growth factor (b-FGF), insulin-like growth factor 1 (IGF-1), and hepatocyte growth factor (HGF) have been used to pre-condition MSCs and enhance their reparative effects.

Furthermore, paracrine factors that are secreted, including vascular endothelial growth factor (VEGF), transforming growth factor β (TGF-β), secreted frizzled-related protein 1 (sFRP-1) and sFRP-2 [33]. Genetic modification of MSCs to enhance cell viability, mobility, and angiogenesis has been explored in this connection. Besides, overexpression of the anti-apoptotic factor Bcl-2 in MSCs improves the survival capacity of the CMs and enhances cardiac function during post-MI transplantation [34]. With these perspectives, MSCs with IGF-1 overexpression improves stem cell mobilization and enhance angiogenesis, leading to myocardial reparation [35].

Also, researchers using a small molecule such as fluorine substituent (TT-10) derived from TAZ-12 vigorously stimulated CMs proliferation. Indeed, the TT-10-mediated enhancement in YAP-TEAD activities and the Wnt/β-catenin pathway can induce the proliferation of cultured CMs. Moreover, TT-10 plays an antioxidant role in protecting CMs from oxidative stress (OS), and thus, apoptosis is triggered by activating the Nrf-2 transcription factor. Interestingly, intraperitoneal injection of TT-10 enhances post-MI cardiac regeneration in mice [36].

From another view, exosomes are small nano-sized membrane-enclosed vesicles, which deliver RNA molecules and proteins to acceptor cells *via* binding, fusion, or endocytosis. Indeed, exosomes present a largely unknown ‘‘cell-to-cell’’ communication system that is now considered a potential diagnostic and therapeu-

tic agent used in cardiovascular disease (CVD) [37]. Exosomes secreted by CMs and progenitor cells affect cell viability and proliferation, thus regulating angiogenesis, cardiac preservation, and repair. These cardioprotective and regenerative behaviors can delay ischaemic heart failure (IHF) [38]. Besides, studies on cardiosphere-derived cells (CDCs) exosomes exert diverse but coordinated effects: inhibit apoptosis, promote the proliferation of CMs, and enhancing angiogenesis after MI [39]. In this regard, Namazi *et al.* suggested that exosomes released by CDCs under hypoxic circumstances enhanced tube formation in cardiac disorders under treatment by induction of angiogenesis *via* augmentation of pro-angiogenic exosomal miRNAs such as miR-210, miR-130a, and miR-126 [40].

5. EXTRACELLULAR SIGNALING PATHWAYS IN CARDIAC REGENERATION

5.1. Wnt Signaling

Wnt signaling possesses several potential pathways, but the most interesting is the Wnt/β-catenin signaling pathway [41]. β-catenin, as a bi-functional protein in normal cells, plays a vital role in composite junctions as a structural protein and works as a signaling molecule in the Wnt/β-catenin pathway [42]. The Wnt/β-catenin pathway has axial roles during embryonic development, adult homeostasis, and organ regeneration [43]. If β-catenin is decomposed, the Wnt/β-catenin pathway is inactivated [44].

Wnt pathway activation after heart disorders has been identified in CMs, endothelial cells, fibroblasts, and leukocytes. The two types of described Wnt pathways include β-catenin dependent (canonical) or β-catenin independent (noncanonical) pathways [45]. In the canonical Wnt pathway in the lack of ligand, β-catenin is phosphorylated by Glycogen synthase kinase 3 beta (GSK-3β) and casein kinase (CK)1a in complex with bemused, axin and adenomatous polyposis coli (APC), known as the degradation complex. Phosphorylated β-catenin is ubiquitinated by beta-transducing repeat-containing protein (BTrCP) and destructed by the proteasome, which leads to the prohibition of the signaling occurrence [43]. When the Wnt ligand binds to its co-receptors, LRP5/6, and frizzled (Fzd) isoform, BTrCP splits from the degradation complex, and the degradation complex is employed to the membrane and blocked from destructing β-catenin. The β-catenin is then capable of huddling and translocating into the nucleus, where it associates with T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) proteins to drive transcription. Also, signal transduction into the cytosol is prevented by the function of secreted antagonists of Wnt/co-receptor binding, including Dkk and sFRP, thus the inhibition of Wnt signaling [46]. The non-canonical Wnt pathways are subdivided into the Wnt/Ca^{2+} and the Wnt/planar cell polarity (PCP) pathway [45].

5.1.1. Crosstalk Wnt With Other Pathways

Crosstalk between signaling pathways has broader development and disease regeneration [47]. TGF-β signaling pathway family members, including activin A and BMP4, synergistically actuate the Wnt/β-catenin pathway during primitive streak (PS) formation and are pivotal for establishing downstream lineages [42]. Fibrosis is a usual procedure in restoring cardiac tissue after injury, formed by myofibroblast attack and collagen secretion. During the differentiation of myofibroblasts, the TGF-β pathway plays a critical role in interacting with the Wnt pathway. In this regard, Wnt-3a can elevate myofibroblast differentiation and TGF-β expression by starting the canonical Wnt pathway. A mouse model of autoimmune myocarditis demonstrated that Wnt signaling could increase the secretion of TGFβ in the β-catenin-dependent pathway, leading to the absence of β-catenin role in cardiac fibroblasts, which led to the improved cardiac operation and repressed interstitial fibroblasts in a mouse model of pressure excess [41]. Furthermore, the Hippo pathway can suppress the β-catenin/YAP interaction in differentiating CMs, contributing to the diminished proliferation of CMs [41]. Also, heart alpha kinase (HAK) or Alpha Protein Kinase 2 (ALPK2) is one of the six alpha kinases, a candidate negative regulator of WNT/β-catenin signaling cardiogenesis [48].

5.1.2. Role Of Wnt Pathway In Rodents And Mammals Cardiac Regeneration

The Wnt pathway is quiescent in the mammalian heart, whereas it is initiated in response to cardiac damage [49]; for example, it is activated in adult heart post-MI procedures [41]. Indeed, a wnt/β-catenin signaling pathway is active in various cardiac cells, following 72 h after damage [50]. In contrast, the Wnt pathway's repression using Wnt selective inhibitors such as pyvinium, WNT974 or ICG001, alleviates pathological remodeling and myocardial damage symptoms [51]. In this regard, Yang *et al.* demonstrated that CGX1321, as an inhibitory drug against the Wnt pathway, exerted a therapeutic effect on MI damage by reducing fibrosis and improving cardiac regeneration [49].

Wnt10b is temporarily induced in mice CMs in the post-MI peri-infarct region, which leads to attenuated fibrosis [47]. The mouse mutant for the Dvl1 model is more susceptible to infarct rupture after the induction of MI [52]. Furthermore, Wnt5a serum levels are enhanced in the failing myocardium [53]. Overexpression of canonical β-catenin in CMs led to pro-apoptotic effects, in which hypoxic CMs expression of Wnt3a serves as pro-apoptotic properties [54]. Meyer and colleagues elucidated that infarcts local areas activate noncanonical Wnt signaling, skews accumulating monocytes further into a pro-inflammatory state. Wnt Inhibitory Factor 1 (WIF1) is a pivotal roller in restricting this local inflammatory monocyte response, thereby exhibiting cardioprotective characterizes. This study revealed a strong up-regulation of WIF1 in CMs [55].

Interestingly, disruption of the Wnt/βcatenin signaling pathway in cardiac fibroblasts impairs wound healing and diminishes cardiac function [56]. Treatment of differentiating mouse or human embryonic stem cells (hESCs) in *in vitro* cell culture conditions with Wnt ligands increases CM development by improving mesoderm specialization. However, later addition of Wnts represses it, and the Wnt exerts anti-apoptotic effects [56] and promotes CM differentiation [57, 58]. Also, MSC-derived exosomes have been proved to increase myocardial survival and inhibit undesirable remodeling after myocardial ischemia/reperfusion (I/R) damage through the initiation of the Wnt/β-catenin pathway by exerting the anti-apoptotic and pro-survival effects on CMs [59].

5.1.3. Wnt In Zebrafish Cardiac Regeneration

Unlike the confined regenerative capacity of the adult mammalian cardiac, zebrafish preserve the cardiac's regenerative capacity all through life [13]. Aside from that Wnt/β-catenin pathway plays a critical role in mammalian heart regeneration procedure coming to pass in response to damage; its potential role in controlling zebrafish cardiac regeneration is under survey [43]. Furthermore, the Wnt/β-catenin signaling pathway regulates fibrosis, ECM deposition by fibroblasts, and hypertrophy following cardiac injury [60].

Indeed, robust heart repair and regeneration in neonatal mouse and adult zebrafish cardiac structure is mainly interceded by the proliferation of pre-existing CMs. Wnt pathway as a conserved obstacle to injury-induced CM dedifferentiation and proliferation.

5.2. Notch Signaling

Notch signaling plays a fundamental role in developmental gene expression and regenerative processes [61, 62]. This pathway is hugely preserved in invertebrates to mammals that control cell differentiation [63]. Shreds of evidence showed that the Notch pathway inhibits CMs' fate specification during early cardiogenesis. Indeed, activation or inhibition of this pathway in Xenopus provided evidence for a function of Notch in suppressing cardiomyogenesis [64]. Human genome compasses four (Notch1–4) genes [65], in which activation of the Notch pathway results in the interaction of Notch receptors with their ligands, including Delta-like (Dll) 1,3,4 and Jagged (Jag) 1,2 [65, 66]. Dominant mutations in Notch1 and Jag1 have been associated with early inborn cardiac diseases, including aortic valve disease 1 (AVD1) and Tetralogy of Fallot, respectively [65].

5.2.1. Crosstalk Notch With Other Pathways

In cardiac tissue, the Notch1 signaling pathway is implicated in the modulation of cellular viability, CSCs differentiation, and angiogenesis. These are the operators known to ascertain the expanse of pathological heart remodeling.

Notch1 protected against MIRI by reducing CM apoptosis [67]. Indeed, the Notch pathway could up-regulate anti-apoptotic factors, including Bcl-2 and Bcl-xl expression, and down-regulate pro-apoptotic factors, including Bax and Bim expression, thus preventing apoptosis [68]. With this perspective, PETN, a tumor suppressor factor, is the primary signaling component involved in crosstalking with significant progress regulators, including Wnt, Notch, and BMP [69].

Hes1 has been demonstrated as a negative regulator of PTEN, the PI3K/Akt pathway inhibitor, in thymocytes cells. In this regard, melatonin, the pineal gland's principal secretory substance, has a cardioprotective effect against MI by controlling Notch1/Hes1 signaling in a receptor-dependent manner, and PTEN/PI3K/Akt signaling pathways are a pivotal downstream mediator [67]. Notch signaling in the endocardium can also up-regulate Efnb2, promoting Nrg1 expression, a ligand for the ErbB2 receptor tyrosine kinases 2 and 4 (ErbB2 and ErbB4). Upon stimulates, ErbB2-ErbB4 can dimerize and activate ErbB2 tyrosine kinase activity to elevate the differentiation of trabecular myocytes [70]. It has also been shown that coordination of the activin/nodal, Wnt, FGF, and BMP signaling pathways act as a critical element in forming the early streak, mesoderm fate ascertainment, and differentiation lateral mesoderm cells into CMs [71]. Moreover, the inhibition of the Hippo pathway is a potent activator of Notch signaling, which has a well-defined role in sustaining immature CM proliferation and showing that

Wnt and Notch act downstream Hippo signaling pathway [72].

5.2.2. Role Of Notch In Rodents And Mammals Cardiac Regeneration

The proliferation capacity of immature CMs and delay their differentiation are strategies for treating heart regeneration. Regeneration of the myocardium in zebrafish and mice is correlated with the potential of CMs to increase instead of differentiation of residing CSCs. The potential of regeneration injury in neonatal mice is correlated with the constant proliferation of CMs up to 7 days after birth. Blocking the Notch pathway in immature neonatal CMs inhibits proliferation and causes apoptosis [73]. A study in mice has shown that inactivated Notch1 in the myocardium leads to enhanced apoptotic cell death and worsened function compared with wild-type mice [74]. From another view, mitochondrial permeability transition pore (mPTP) is a non-specialized channel in the mitochondrial inner membrane, opening during I/R injury [75]. In this regard, Zhou and colleagues demonstrated that in the rat model, activated Notch1 mitigated the loss of mitochondrial membrane potential ($\Delta\Psi m$) induced by hypoxia/reoxygenation (H/R). Simultaneously, knockdown of N1ICD during ischemic pre/post-conditioning aggravated the loss of $\Delta\Psi m$. These findings revealed that the mPTP opening stimulated by H/R is, to some extent, prevented by Notch1 signaling [76].

5.2.3. Notch In Zebrafish Cardiac Regeneration

The notch pathway is profoundly involved in various regenerative procedures of different zebrafish organs, such as the brain, caudal fin, and spinal cord [69]. A notch pathway is required for trans-differentiation of CMs from an atrial to ventricular following ventricular myocardial ablation in zebrafish larvae [77]. Moreover, in adult zebrafish, Notch pathway prevention contributed to enhanced expression of genes such as mylk3, acta1, and tcap, pointing to a decrease in CM dedifferentiation in the ventricle [61]. The requirement of the Notch pathway in cardiac regeneration appears to exist throughout the lifespan of zebrafish. Heart injury results in the induction of the expression of three Notch receptors (notch1a, notch1b, and notch2) tissue-specifically in the endocardium and epicardium, but not the myocardium. Conversely, hyperactivation of Notch pathway hinders zebrafish heart regeneration. Notch signaling is activated after cardiac damage in zebrafish, previously reported that the zebrafish ventricle's partial amputation stimulates expression of the Delta C and notch1 [78]. During regeneration, the expression of Notch pathway genes becomes confined to endocardial and epicardial cells to the damaged region's vicinity [69]. In adult zebrafish and neonatal mice models, Inhibition of the Notch pathway impedes CM proliferation and induces scarring [71]. Notch pathway inhibition diminishes the regeneration of the ventricular myocardium. It leads to a continuous fibrous and collagenous tissue generation, which shows the absolute urgency of Notch pathway activation for complete cardiac regeneration in zebrafish [69]. Indeed, these fibrotic tissues dissolve and are replaced by new CMs that have the potential to dedifferentiate and forcefully proliferate, allowing complete heart regeneration [69]. Transgenic repression of the Notch pathway impeded heart regeneration accompanied by reduced CM proliferation. Transgenic hyperactivation of the Notch pathway, through overexpression of NICD, blocked CM proliferation and cardiac regeneration in the zebrafish resection model; whereas, in zebrafish cryoinjury model, NICD overexpression increased CM proliferation [61]. Transgenic prevention of Notch signaling pathway defective cardiac regeneration, congruous with diminished CM proliferation.

In sum, the Notch pathway induces modulating regeneration processes during an injury in zebrafish. Unlike previous studies, ensuing evidence revealed that the Notch pathway's physiological relevance in adult mammals and rodents is not naturally active during heart injury.

5.3. VEGF Signaling

Vascular Endothelial Growth Factor, abbreviated as VEGF, is one of the most critical genes regulating multiple biological processes. VEGF enhances response to MI and promotes vascular regeneration [79]. VEGFs (particularly VEGF-A and VEGF-B) are endothelial cell-specific mitogen, which induces vascular progress during embryogenesis (vasculogenesis) as well as blood-vessel generation (angiogenesis) in the adult [80]. In mammals, five VEGF ligands, including VEGF-A, B, C, D, and placenta growth factor (PLGF), have been identified, which bind to three receptor tyrosine kinases (RTK), known as VEGFR-1 (also known as FLT1), VEGFR -2 (also known as KDR) and VEGFR -3, as well as to co-receptors such as heparan sulfate proteoglycans (HSPGs) and neuropilins in an overlapping pattern [80, 81].

5.3.1. Role Of VEGF In Rodents And Mammals Cardiac Regeneration

During heart progression and regeneration, angiogenesis shades tissue growth. VEGF enhances endoderm-derived tissues' progression, including the vascu-

lar endothelium and the endocardium, by stimulating different types of angiogenic cellular elements, including elevation of survival, migration, and differentiation, through the activation of Akt signaling in endothelial cells [79]. Kivelä *et al.* revealed that activation of the VEGFR2 pathway in mice heart endothelial cells induces angiogenesis and endocrine release of ErbB ligands. These ligands activate growth signaling in CMs; hence, the hypertrophy induced by angiogenic stimuli is reversible and does not progress to HF, thus resembling physiological cardiac growth [82]. It has been shown that VEGF can cause CM karyokinesis (enhanced number of CM nuclei). It means that post-intramyocardial injection of a plasmid encoding human recombinant VEGF (hrVEGF) in a pig model of chronic MI, in the lack of cytokinesis (enhanced amount of cell divisions, contributing to an enhanced number of CMs). These investigations reveal a role for VEGF in ascertaining the post-natal heart's physiological development, even in the absence of proper CM regeneration [83].

Moreover, the VEGF-A pathway has a crucial role in returning blood flow to ischemic tissue in different pathological states, including heart failure. VEGF-A is involved in up-regulated in the myocardium in chronic circulatory excess. Hypoxia also seems to increase VEGF-A expression, which seems to associate hypoxia-inducible factor-1α (HIF-1α) [84]. Also, VEGF-A is a crucial element in the steadiness of newly generated vessels and CMs. Indeed, VEGF-A's coupling to VEGFR-2 activates the PI3K signaling, subsequently enhanced the expression of Bcl-2 and diminished activation of caspase-3 and Bax. Intra-pericardial injection of recombinant VEGF-A (rVEGF-A) in a rabbit model of induced hypertrophy decreased CM apoptosis and revealed conserved contractility indices.

Similarly, in a rat model of AMI, intra-myocardial administration of VEGF-A cDNA considerably enhanced cardiac function and the suppression of apoptosis [84]. Likewise, PlGF has a task in angiogenesis under pathological disorders. Upon binding, PIGF to VEGF-1 activates endothelial cell migration and viability, enhancing angiogenesis and arteriogenesis. Intramyocardial administration and systemic distribution of PlGF through an adenoviral vector showed protection of cardiac performance in a rat model IR [85]. Cho *et al.* demonstrated that VEGF and HGF-secreting umbilical cord blood-derived MSCs enhanced angiogenesis in a rat MI model and mouse hindlimb ischemia model [86]. Also, VEGF-A promotes myocardial repair through, at least in part, enhancing the engraftment of CSCs mediated by the PKCα/VCAM-1 pathway [87]. Zangi *et al.* demonstrated a single intramyocardial injection of VEGF-A modification RNA ameliorated myocardial outcome and survival after MI [88].

During cardiac development, angiogenesis is a sign of tissue growth. The pivotal angiogenic factors as VEGF can affect cardiac regeneration in mammals singly, which is a query of therapeutic implication, which has been asked frequently, with various responses [89]. The investigation showed the cytoprotective results of exosomes on CMs, induced overexpression of VEGF pathway, and consequently enhanced vessel generation [38].

5.3.2. VEGF In Zebrafish Cardiac Regeneration

Studies on zebrafish demonstrated that VEGF signaling is essential for myocardium development [90]. Although VEGFB-D is mainly implicated in lymphangiogenesis, VEGFA is an endothelial cell mitogen with an essential function in vasculogenesis and angiogenesis [83]. Zebrafish harbor duplicate copies of VEGFA genes homologous to VEGFA in humans and mice, known as VEGFAA and VEGFAB [90]. VEGF-A showed a dual role during HF enabling ectopic cardiomyogenesis and restoration in the damaged region [91]. In zebrafish and mice hearts, VEGFAA overexpression is adequate to stimulate ectopic coronary vasculature. In mice and zebrafish hearts, the thickening of the ventricular wall by CM hyperplasia is firmly joined to coronary angiogenesis. In the meantime, during zebrafish cardiac restoration, defected angiogenesis imperils the regenerative process and leads to scarring [89].

Generally, cardiac damage leads to the extension of a progressive growth process and proliferation of spared CMs in zebrafish and neonatal mice. In the meantime, whether these effects can be attributed to adult rodents and humans or no, are currently under investigation.

5.4. IGF-1 Signaling

Insulin-Like Growth Factors1 (IGF-1) signaling has a key function in contractility, metabolism, hypertrophy, autophagy, senescence, and apoptosis of cardiac regeneration [92]. IGF-1 is mainly produced in the liver from growth hormone metabolism before its secretion into the bloodstream [93]. IGF-1 contains an insulin-like metabolic function (short-lived) and growth factor-like (long-lived) effects on cell proliferation, growth, and differentiation [94]. Studies have shown a reverse association between circulating IGF-1 levels and cardiovascular complications [95]. Low IGF-1 levels are thought to be associated with an elevated risk

for heart disorders, while cardiac activation of the IGF-1 receptor (IGF-1R) preserves it from MI's detrimental effects [93]. IGF-1 signaling activation of IGF-1R from Canonical and noncanonical pathways, in which IGF-1R activates two canonical pathways in CMs, the PI3K/Akt (PKB) the extracellular signal-regulated kinase pathway [96]. IGF-1R activates several pathways through its innate tyrosine kinase activity and *via* binding to G-protein [93]. Indeed, activation of the MAPK pathway is supposed to be indispensable for the mitogenic action of IGF-1 [94]. IGF-1 has also been shown to prevent necrosis of viable myocardium, ameliorate CM function, and diminish long-term left ventricular dilation and remodeling [97].

5.4.1. Regenerative Effects Of IGF-1 In Rodents and Mammals Cardiac

Despite these shed light, whether a damaged, mature mammalian CM can restore the function through the IGF-1 signaling pathway in humans is under investigation. IGF-1 overexpression enhances CSC number and growth, contributing to myocyte turnover and function in the aging heart. After MI, IGF-1 promotes engraftment, differentiation, and functional improvement of ESCs transplanted into the myocardium. In this regard, Davis and co-workers demonstrated cell therapy approaches using IGF-1 transfer by biotinylated nanofibers enhanced post-MI systolic function [98]. IGF-1 is a critical factor attracting stem cells to the MI zone and their differentiation through disseminating paracrine operatives and actuating molecular pathways of cell survival. Indeed, ex vivo overexpression of IGF-1 resulted in enhanced stromal cell-derived factor 1 alpha (SDF-1α) level, a potent chemoattractant of stem cells, which culminated in extensive angiomyogenesis in the MI [99]. IGF-1 and HGF are being assessed in diverse modalities of cardiac restoration. Mauricio *et al.* [100] showed that co-administration of IGF-1 and HGF-overexpressing MSC does not help a practical repair while improving neovascularization and fibrosis in the MSC-IGF-1/HGF-treated group, proposing that excess IGF-1 plus HGF levels enhance favorable effects which mildly ameliorates AMI recovery in a porcine model.

IGF-1 in CMs preserves the cardiac tissue from OS and enhances cardiac performance during post-MI recovery. Furthermore, CM overexpression of IGF-1R inhibits type 1 diabetes-induced cardiac fibrosis and diastolic malfunction [101, 102]. Also, the IGF pathway in CMs proliferation was also regulated by YAP, a co-activator downstream in the Hippo pathway in mice [92].

5.4.2. IGF-1 In Zebrafish Cardiac Regeneration

Repression of the IGF pathway in zebrafish leads to attenuated CM proliferation and defected cardiac regeneration, while IGF pathway agonists elevated proliferation [103]. In zebrafish, the IGF pathway is crucial for CM proliferation during cardiac regeneration. It offers that epicardium regulates the adult CMs' developmental gene expression profile through the heart's remodeling after the injury [11, 92]. Moreover, another study on zebrafish demonstrated that IGF-1 signaling has an essential role in cardiac development, and the absence of IGF-1R impair cardiac development and attenuates CM proliferation [92]. Also, IGF-1R is expressed in murine $Wt1^+$ epicardial cells and prohibits the IGF-1R in $Wt1^+$ lineages during post-MI decreased adipogenic differentiation [18].

5.5. Neuregulin1/ Erbb Signaling

The extracellular protein called Neuregulin1 (Nrg1) and its receptors (ErbB tyrosine kinases) have multiple roles in cardiovascular biology and regeneration and have been implicated as a CM mitogen [104]. Briefly, the Nrg family comprises four structurally related proteins (Nrg1-4) and is a member of the epidermal growth factor (EGF) family. Nrg family transducers are called tyrosine kinase receptors of the ErbB family, such as ErbB1 (Her1, EGFR), ErbB2 (Her2, Neu), ErbB3 (Her3), and ErbB4 (Her4). Nrg1, ErbB2, and ErbB4 express vastly during embryonic growth until the early neonatal stage, afterward meaningfully down-regulated in postnatal and adult cardiac tissue. This particular expression pattern is associated with the neonatal heart's great regenerative potential compared to the nominal regeneration capacity of adult cardiac [105]. Nrg1 can induce mononuclear mature CMs to re-enter the cell cycle and DNA synthesis status *via* the Nrg1/ErbB pathway. Manipulating the signaling proteins of Nrg1/ErbB2 and ErbB4 has reported positive results after HF in animal studies [35].

5.5.1. Regenerative Effects Of Nrg1 In Rodents And Mammals Cardiac

The first evidence about ErgB1/ErbB4 signaling in heart development is a study that demonstrated that the absence of ErbB4 in mice causes death during embryogenesis due to cardiac development impairment [106]. Later, the importance of Nrg1 in cardiac development and embryonic CM differentiation was demonstrated by another study [107]. In the adult heart, the Nrg1 downstream signaling pathway has been shown to modulate cell growth, survival, sarcomere structure, myocardial performance, and CM re-entry into the cell

cycle [108]. Only differentiated and mononucleated CMs but not binucleated CMs exhibit proliferative capacity in the presence of Nrg1 [109]. Begeman *et al.* demonstrated that ErbB2 expression is robustly down-regulated in neonatal mice after a week. Also, transient induction of active ErbB2 in injured adult mice hearts can retrieve the capability to regenerate CMs, supporting the positive effect of ErbB2 levels on Nrg1/ErbB2 pathway-mediated cardiac repair [110]. Nrg1 can induce mononuclear mature CM to re-enter the cell cycle and DNA replication status *via* the Nrg1/ErbB pathway [35]. Nrg1/ErbB signaling pathway activation is up-regulated in response to pathophysiological stress and ischemia-induced HF [104]. Upon, binding of Nrg1 to ErbB4 receptor enhances its kinase activity and contributes to heterodimerization with ErbB2 or homodimerization by ErbB4 and activates PI3K/Akt signaling facilitates cell survival [35] and induction of intracellular signal transduction pathways [23]. Mice mutant in Nrg1, or its receptors ErbB2/4, die at mid-gestation or later with cardiac-restricted mutations from thin ventricular walls and aberrant trabeculation [26]. Indeed, Nrg1/ErbB2/ErbB4 complex regulates CM survival and myofibril disorderliness. Furthermore, ErbB4 overexpression augmented MSC survival in the MI and increased Nrg1 generation to renovate the diminishing Nrg1 in the infarcted area and induce CM regeneration by attenuating apoptosis *via* PI3K/Akt pathway [35]. In this regard, MX *et al.* [111] demonstrated that four weeks of exercise training up-regulated Nrg1 protein expression and activated ErbB/PI3K/Akt pathway, which beneficial effect in promoting cardiac regeneration by inducing CM, DNA synthesis, recruiting c-kit^{+} cells, ameliorating angiogenesis, and suppressing apoptosis.

Recombinant Nrg1 (rNrg1) preparation is helpful for acquiring heart disease in most animal models. Indeed, rNRG1 is pursued as an investigational new drug to improve HF and effective adult patients with a left ventricular ejection fraction (LVEF). Thus, rNrg1 is available and suitable for administration in humans [112]. The recombinant human Nrg1 has been applied in clinical trials to reduce chronic HF damage in China and Australia, which improved heart function and repair [35].

5.5.2. Nrg1 In Zebrafish Cardiac Regeneration

Nrg1 expression in adult zebrafish is up-regulated following cardiac injury in regulatory T cells (Treg) and the ventricular wall's perivascular cells to induce CM proliferation. Aside from the overexpression of Nrg1 in undamaged cardiac initiates CM proliferation, leading to cardiomegaly *via* continuous accumulation in the cardiac muscle wall [110]. Adult zebrafish, compared to adult mammals, sustain ErbB2 expression in the cardiac, which leads to restoring cardiac regenerative potential in damaged cardiac tissues and inducing CM proliferation in response to ectopic Nrg1 expression in damaged hearts [110]. Nrg1 pathway is pivotal for cardiac myofiber trabeculation [23]. Nrg1-treated cardiac tissues after MI had minor hypertrophy at the C level, as distinguished by cross-sectional zone. Indeed, it is observable enhanced cardiac performance after injection of NRG1 in many different animal models of HF [23]. Moreover, the Inhibition of Nrg1/ErbB in zebrafish leads to diminishing CM proliferation, while overexpressing Nrg1 in CMs enhanced CM proliferation and caused cardiomegaly when the injury was absent [26].

Nrg1/ErbB2/4 pathway plays an essential role in cardiac progress and homeostasis and is a major pathway involved in the molecular dialogue supporting CMs proliferation and replacement after MI. Overall, the Nrg1/ErbB pathway promotion is a profitable way to stimulate the CMs to proliferate, dedifferentiate, and regenerate after cardiac injury.

5.6. TGF-B Signaling

The transforming growth factor-beta (TGF-β) pathway has been involved in different developmental and disorder conditions; however, the crucial role of its numerous elements in cardiac regeneration is under survey. TGF-β is synthesized and secreted by leukocytes, platelets, and fibroblasts in the injured myocardium and also induces myofibroblast transdifferentiation and increases ECM protein synthesis [113]. TGF-β is a latent complex that cannot bind to and activate its receptors but can be promptly released and activated in response to ROS production [114], activations of proteases, and mechanical strain [115-117]. Canonically, the TGF-β signaling pathway *via* the fundamentally active type II receptor (TβRII) at the outer side of the cell membrane subsequently recruits transphosphorylation of the type I receptor (TβRI) known as ALK5. TβRI activation increases downstream intracellular signals *via* the Smad proteins; Smad2 and Smad3 are activated *via* phosphorylation by ALK5 [118]. In noncanonical pathways, TGF-β activates many signaling pathways such as PI3K/Akt, Erk, JNK, p38 MAPK, and small GTPase pathways [117, 119]. Three TGF-β isoforms (1, 2, and 3) exist in mammals, which are markedly up-regulated in the MI, information on isoform-specific function is restricted [120].

5.6.1. Regenerative Effects Of TGF-β In Rodents And Mammals Cardiac

TGF-β plays a pivotal role in controlling cardiac repair's cellular functions by regulating inflammatory, compensator activities, angiogenic, and fibrogenic responses [20]. *In vitro* studies show that TGF-β stimulation enhanced cardiac transcription factors in ESCs, to CMs differentiation. Conversely, another *in vitro* experiment revealed that the used selective TGF-β inhibitor elevates proteasomal degradation of TβRII and enhances differentiation of unspecified mesoderm to cardiomyocytes [121]. Also, in zebrafish, repression of TβRI abrogated cardiac regeneration following cryoinjury. Oppositely, inhibition of TβRI increases proliferation of $Nkx2.5^{+}$ cardiomyoblasts and results in enhanced endogenous cardiomyoblast mediated repair in mice [121]. *In vivo* investigations indicated the TGF-β pre-programmed $CD117^{+}$ stem cells into the MI-induced angiogenesis resulted in an elevated regenerative response [118, 122]. MSCs could ameliorate myocardial function and enhance myofibroblasts to gather in the infarcted zone by activating the TGF-β1/Smad2 signaling pathway after MI [123]. Besides, in a study on MI in rats, shreds of evidence have been shown intra-myocardial implantation of the TGF-β1-treated rat bone marrow MSCs to the MI diminished scar area, enhanced muscle cells, and ameliorated cardiac function [120]. TGF-β is maybe a well known pro-fibrotic growth factor, which it seems the TGF-β family has a vital role in cardiac development, and it is shown that TGF-β2 null mice have impairments in the formation of different parts of the cardiovascular system, such as the outflow tract and atrioventricular (AV) canal [124].

Studies on porcine and mouse models suggested that after MI, the TGF-β levels are increased, localized in infarct macrophages. In this regard, in mice, TGF-β1 and β2 mRNA levels presented a primitive peak after 6–72 h of reperfusion; however, TGF-β3 up-regulation showed an extended time with steadily enhanced expression after 7 days of reperfusion [125]. Fibrosis and hypertrophy of CMs in the mouse cardiac tissue can be related to the TGF-β overexpression [117]. Systemic prevention of TGF-β in the first 24 h after MI enhanced death and defected cardiac function in mice; while, TGF-β suppression at a later phase attenuated cardiac remodeling. Indeed, the initial fibrotic response is necessary for treatment after myocardial damage [24]. After MI, one of the probable mechanisms involved in fibrosis in CMs during TGF-β signaling may be suppressing the synthesis of cardioprotective genes, including GDF-15, IL-33, and TSP-4 [121]. Recently, Ferreira *et al.* revealed that in mice model of chronic Chagas' heart disease 30 days after treatment interruption with GW788388 as a selective inhibitor of TβR1/ALK5 reversed the loss of connexin-43 enriched intercellular plaques and attenuated fibrosis. Indeed, inhibiting the TGF-β pathway attenuated TGF-β/pSmad2/3 enhanced MMP-9 and Sca-1 and partially restored GATA-6 and Tbox-5 transcription, supporting cardiac recovery [126]. Hodges and colleagues demonstrated that TGF-β1 is differentially expressed in adult and fetal sheep after MI. They revealed that fetal myocardial regeneration after MI might in part be the result of reduced TGF-b1 expression, whereas inhibition of TGF-b1 "fetalizes" the gene expression profile of adult cardiac fibroblasts [127].

5.6.2. TGF-B In Zebrafish Cardiac Regeneration

In zebrafish, the TGF-β pathway is crucial for heart regeneration; in disease conditions, enhanced this pathway by up-regulation of two activin type 2 receptor ligands of the TGF-β family Inhibin beta Aa (inhba), Myostatin b (mstnb), and TGF-β stimulates hypertrophy, fibrosis, and apoptosis [10]. Inhba is overexpressed after cardiac damage, either mammals or zebrafish, but conceivably prevent it from inducing regeneration to mammalian cardiac; it means that it enhanced the rate of CM proliferation zebrafish. Furthermore, up-regulation of mstnb suppressed CM proliferation and impaired heart regeneration. Indeed, prolonged up-regulation of Inhba is correlated with the stimulation of fibrosis post-MI in mammalian, resulting in cardiac remodeling and failure [128]. On the other hand, TGF-β pathway implication is an essential factor contributing to the pathogenesis of heart tissue remodeling and fibrosis induced by pressure overload in mammals. At the same time, Dogra and colleagues reported that adult zebrafish therapy with a TGF-β receptor inhibitor stopped cardiac regeneration [10].

In sum, inconsistent results from different studies may reflect various experimental models' characteristics. Whether it is a friend or a foe and precise mechanism involved in cardiac regeneration through the TGF-β pathway has required more investigation.

5.7. Hedgehog Signaling

The Hedgehog (Hh) signaling pathway, first identified in Drosophila [129], controls cell fate specification, proliferation, and differentiation, and it is implicated in cell cycle regulation. This pathway is also involved in regulating embryonic cardiac tissue and coronary vascular system progression. It conserves its activity in the adult mammalian cardiac tissue at a basic

level. However, it gets higher during ischemic cardiac damage [130]. Hh proteins are recognized in different organisms, from insects to humans. The Hh genes in other organisms vary from only one gene in Drosophila to the 3 to 5 genes in vertebrates. All Hh proteins are constituted of an N-terminal 'Hedge' domain and a C-terminal 'Hog' domain [131]. The attachment of Hh proteins, including Patched1 (Ptc1) or Patched2 (Ptc2) receptors, initiates the Hh signaling pathway [132]. The lack of Hh proteins, Ptc1 prevents smoothened (Smo) activity, which controls the activation of the Glioma-associated oncogene homolog [18]: includes Gli1, Gli2, and Gli3, but in the presence of Hh proteins, with attaching Smo is released from repression. This event resulting in translocation into the nucleus and starting transduce Hh signaling pathway [133, 134].

5.7.1. Role And Crosstalk Of Hedgehog Pathways In Cardiac Regeneration

One study previously demonstrated that endogenous Shh seems to exacerbate ischemic disease, but remains studies suggested that the Hh pathway plays a pivotal role in cardiac restoration and regeneration so far [129]. In this regard, elimination of either Smo ($Smo^{-/-}$) or Ptc1 ($Ptc1^{-/-}$), or double knockouts of Shh; Ihh ($Shh^{-/-}$; $Ihh^{-/-}$) leads to embryonic lethality due to cardiovascular impairments [12]. The regeneration process includes cellular proliferation, differentiation, and dedifferentiation. Smo can function as a GPCR with a strong affinity to all the Gi protein families [135]. Activation of Gi by Smo is essential for Gli to actuation in some of the cell types, which leads to different basic levels of PKA activity which negatively regulates Hh signaling pathway through phosphorylation of Gli2 and Gli3 in the regulatory site, which prepares them for further modification by glycogen synthase-3β (GS-3β) and casein kinase-1 (CK-1) and following incomplete proteasomal degradation [136]. With this perspective, the elimination of Smo with a wrong allele leads to vasculature collapse and heart failure [136]. One study on rats demonstrated that after the ischemia-reperfusion injury leads to the Shh pathway's stimulation, this pathway has a cardioprotective effect [137]. Indeed, this pathway in adult rats after MI ameliorated cardiac regeneration by enhancing angiogenic cytokines that mediate neovascularization, reducing fibrosis and cardiac apoptosis.

One contributor display for cardioprotective effects of Shh is IGF-1 that has been shown to be up-regulated in Shh-induced cardiac fibroblasts and bone marrow-derived cells. Indeed, IGF-1 participates in the transcription of angiotensin II, thus inhibiting ROS protection during OS [130]. Also, the sonic hedgehog (Shh) signaling pathway improves myocardial recovery after injury through VEGF induction and enhancing the incorporation of bone marrow-derived progenitor cells [134]. Shh signaling has been involved in the metabolic reprogramming of adipocytes and Mouse embryonic fibroblasts (MEFs) in a transcription-independent model. Activation of Smo in these cells leads to a rapid increase in glucose uptake, which is mediated by the activation of AMP-activated protein kinase (AMPK) [131]. Besides these results, in embryonic growth and adult tissue homeostasis, Hh signaling is active in progenitor cell populations in regenerative and developing organs. In this viewpoint, the inactivation of Hh signaling in cardiac progenitor cells *in vivo* leads to increased CM differentiation gene expression, premature differentiation, and Congenital Heart Disease. Indeed, expression of the Hh transcription factor, Gli1, in cardiac progenitors supports preserving a progenitor-specific regulatory network and hinders the beginning of the CM differentiation [138]. Besides this finding, some scientists believe that $CD34^{+}$ stem cells promote angiogenesis or stimulate vasculogenesis in ischemic regions of the cardiac muscle. $CD34^{+}$ Shh has capable of improving functional protection of heart tissue as compared with control cells in MI patients [139].

5.7.2. Hedgehog In Zebrafish Cardiac Regeneration

This pathway regulates cardiac development and is mainly reactivated through cardiac regeneration to damage [134]. This pathway involved cardiac regeneration in the production of potential CM mitogens in zebrafish embryos applying a transgenic reporter system, enabling live visual monitoring of proliferating CMs. Indeed, activation of a transgenic reporter system that mirrors the expression of the Hh target gene ptch2 exists in CMs within the regeneration region [18]. Investigations on zebrafish embryos demonstrate that Hh signaling is vital for CM remodeling and proliferation in the zebrafish; for example, treating embryos with Hh signaling Smo agonist increased antagonists such as cyclopamine reduced the number of proliferating CM [132].

Bearing all this in mind, further investigation is required to exhibit the therapeutic perspective and risks of activating the Hh pathway during cardiac diseases in humans CMs.

6. INTRACELLULAR SIGNALING PATHWAYS IN CARDIAC REGENERATION

6.1. NF-κB Signaling

Nuclear factor-kappa B (NF-κB) has vast regenerative process functions, with a central portion to CM

dedifferentiation, proliferation, and epicardial damage responses. However, NF-κB is not essential for cardiac development but has essential cardiovascular health and disease [27]. NF-κB factors were primarily recognized approximately 30 years ago as a family of transcription factors that bind to κ light chain enhancers in lymphocytes [140]. Although many dimeric forms of NF-**κ**B have been identified, NF-κB1 (p50 and its precursor p105), NF-κB2 (p52 and its precursor p100), RelA (p65), RelB, and Rel (c-Rel) [141], the main form of NF-κB is a heterodimer of the p50 and p65/RelA subunits [142]. IkBa is the predominant inhibitory protein that binds to the p50/p65 heterodimer in the cytoplasm and prevents NF-kB's nuclear translocation [143]. NF-κB is activated through two pathways, the canonical and noncanonical pathways. Canonical signaling uses the RelA, p50, and c-Rel subunits, while RelB and p100/p52 perform activation of the noncanonical pathway [144]. NF-κB signaling has been reported to have a broad spectrum of different functions, influencing cell survival, tissue growth and proliferation, and chromatin structure. NF-κB activation is an essential step in TGFβ2/PDGFBB-induced cardiac EMT. Also, be required for IL-1b/TGFβ2-induced endothelial-to-mesenchymal transition (EndoMT) in human umbilical vein endothelial cells [29].

NF-κB activity is enhanced during cardiac disorders, and its signaling is mainly involved in the development of cardiac remodeling (fibrosis), hypertrophy, and heart failure [142]. In cardiac tissue, NF-κB signaling is attributed as a hypertrophic effect and is correlated with the expression of cardiac response genes like ANF and β-MHC [140]. The mammalian heart augments the expression of a fetal gene related to stress. In this regard, long-term NF-κB activity may be harmful to the mammalian heart by enhancing CM atrophy and fetal reprogramming CMs [27]. The NF-κB pathway is induced in CMs following damage. Myocardial prevention of NF-κB activity stops heart repair with pleiotropic effects, diminishing both CM proliferation and epicardial responses [21]. Pereira *et al.* demonstrated that c-Rel-defective mice have a smaller heart during their infancy and adulthood, and cardiac hypertrophy and fibrosis after chronic angiotensin infusion will not occur in their heart [142]. Peterson *et al.* demonstrated that NF-κB ablation in murine dystrophic CMs leads to chromatin remodeling on enhancers of calcium genes, which in turn permits enhanced gene expression and an overall improvement in cardiac function [145].

Exosomes induced pro-inflammatory cytokines by the TLR9-NF-κB pathway, relevant to exosomal mtDNA. Therefore, this pathway may reveal a new molecular mechanism for developing chronic inflammatory disorders, including chronic heart failure (CHD), which is significant for preventing and treating these disorders [146].

6.2. PI3K/AKT Signaling

The Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway has been well characterized as the critical signaling pathway that preserves the cardiac tissue against reperfusion damage. Activation of PI3K/Akt signaling shows a strong anti-apoptotic effect against myocardial I/R injury [67]. PI3K has three classes: Class 1A PI3K is a heterodimeric complex consisting of a p110 catalytic subunit and a p85 regulatory subunit positioned on the cell membrane [147]. Akt, also called protein kinase B (PKB), is a serine/threonine PK. At least three Akt family members include Akt1/PKBα, Akt2/PKBβ, and Akt3/PKBγ [148]. Upon activation of PI3K, PI3K phosphorylates, the inositol ring leads to the anchoring of AKT to the plasma membrane, phosphorylated and entirely activated 3-phosphoinositide-dependent kinases 1 (PDK1). Phosphatases, including PETN and SHIP, diminish the source of available phospholipids and resulting Akt inactivation [147].

6.2.1. Role And Crosstalk Of PI3K/AKT Pathways In Cardiac Regeneration

PI3K/Akt pathway modulates cell proliferation, differentiation, apoptosis, and autophagy under physiological and pathological conditions. Akt serves a crucial role in repressing cellular apoptosis. It can diminish pro-apoptotic Bad and Bax levels but elevates anti-apoptotic Bcl-2 [149]. This pathway is also essential for cardiac development, and Akt1-deficient mice have a high mortality rate after birth [150]. The activation of the PI3K/Akt pathway in MSCs leads to overexpression of some main components of the pathway that have been used to induce the repair of infarcted cardiovascular cells and were demonstrated to enhance the efficacy of MSCs [151]. C3 or f58 is a novel paracrine factor secreted from MSCs, known as hypoxia and Akt induced stem cell factors (HASF). HASF gene overexpression protected CMs from apoptosis and cell death *via* PKC's selective activation *in vitro* and *in vivo*. This approach treated rat neonatal CMs with HASF recombinant protein-enhanced DNA synthesis *via* the cell-cycle regulator cycle-dependent kinase 7 (CDK7) complex and promoted mitosis and cell division. These effects were shown through PI3K and PKB pathways [135]. Also, Akt can regulate NF-κB by IκB kinase (IKK), and therefore, the transcription activating genes involved in survival [147]. Indeed, the Akt activated

pathway results in an initiate cascade of downstream targets that regulate cellular functions. For instance, Akt regulates cell migration through Rac1 and RhoA, ameliorates cell viability through the increased bcl-2 level and decreased Bax, enhances angiogenesis *via* VEGF, and enhances cell proliferation activation mammalian target of rapamycin (mTOR) [151]. Also, the pivotal role of Akt has been demonstrated in physiological cardiac hypertrophy *via* attenuating pathological hypertrophy. This process depends on the IGF/PI3K/AKT/mTOR signaling pathway [60].

Interestingly, overexpression of HASF as a novel inducer of both cell-cycle re-entry and proliferation of neonatal and adult mammalian beneficial is for cardiac repair and regeneration [152, 153]. The correlation between Notch1 and Akt/PI3K signaling pathway leads to regulation of regeneration in the heart. Notch1 knockdown noticeably enhanced PETN expression and diminished Akt/PI3K activity in MI/RI. Indeed, in T-cell acute lymphoblastic leukemia (T-ALL), the Notch1/Hes1 pathway induces the PI3K/Akt pathway's excessive expression by down-regulating PETN [67]. Besides, Yang *et al.* demonstrated that tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK), a member of the TNF superfamily, which protected the cardiac apoptosis by activation of cardioprotective pathway PI3K/AKT during IR and resulting in Inhibition the myocyte death of myocardial IR injury [154]. In connection with exosomes derived from CXCR4-overexpressing MSCs actuated the Akt pathway *in vitro* and a murine MI model.

6.3. Hippo/Yap Signaling

The Hippo signaling pathway is an evolutionarily preserved pathway demonstrated to control cell proliferation and organ size in developing hearts, which was first described in the fruit fly, Drosophila melanogaster. This pathway is a kinase cascade that prevents developing CM proliferation and regeneration, upregulated in human heart failure [155]. Post-MI prevention of the Hippo pathway in the cardiac tissue increases CM proliferation and enhances cardiac performance in mice [156].

Hippo pathway is activated *via* phosphorylation of a series of proteins, such as mammalian STE20-like protein kinase 1 (Mst1; also identified as Stk4) and Mst2 (also identified as Stk3), protein Salvador homolog 1 (Sav1)/WW45, Transcriptional enhancer factor A (TEA) domain family member 1 (Tead1-4) [157], and large tumor suppressor homolog 1 (Lats1) and Lats2, which coincidently phosphorylate and deactivate the transcriptional co-activator Yes-associated protein 1 (Yap1) and Taz that cooperatively bind DNA with Tead factors [155]. Yap contains two consecutive WW domains; meanwhile, Taz is a Yap paralog in mammals and displays a similar domain organization but has only one WW domain [158]. Yap and Taz have been shown to control cell-autonomous manner, myocardial proliferation, myocardial hypertrophy, regenerative capacity, and the heart's total size [25]. Phosphorylation of Yap1 at Ser127 sequesters [25] blocks nuclear transposition and leads to Yap1 being preserved in the cytoplasm, thereby resulting in cell apoptosis [159].

6.3.1. Crosstalk Hippo/YAP With Other Pathways

Nppa (natriuretic peptide A) marker is markedly down-regulated in Yap transgenic myocardium that elevated CM proliferation is associated with impaired differentiation [160]. Also, in endocardial cells, Yap/Taz regulates Nrg1 expression, which actuates ErbB2/4 receptors. In mammary cells, Nrg1 binding to ErbB receptors stimulates the cleavage of ErbB4 and follows an intracellular domain (ICD) release that connects to Yap *via* the WW domain. The Yap/ErbB4/ICD complex enters the nucleus [161], binds TEAD factors, and stimulates the expression of Yap-dependent proliferation-related genes. With this perspective, Hippo signaling may indirectly be linked *via* Nrg1/ErbB signaling to control cardiogenesis [25, 26],

Also, from another way, Hippo inhibits a gene program that controls multiple aspects of ECM composition, affecting vessel development, including endothelial cell proliferation, migration, and vessel branching, which is used to benefit the development of heart regeneration. In this regard, Dpp4 controls ECM characteristics and vascular remodeling [162].

Consequently, cell cycle-associated genes were upregulated in the cardiac tissue after Hippo signaling prohibition. Still, stress response genes, including those related to an antioxidant response and mitochondrial quality control genes include Park2, were also upregulated. Since inhibition of the Hippo pathway is correlated with the risk of off-target cell proliferation, antioxidant elements have been analyzed and administered into the damaged adult mouse cardiac tissue as an alternative method [24, 156]. Also, during ischemia/reperfusion [7] activates Mst1 through a K-Ras Rassf1A dependent mechanism in mitochondria, where Mst1 stimulates the mitochondrial mechanism of apoptosis by phosphorylating Bcl-xL, and subsequently the Beclin 1, thereby inhibiting autophagy [159]. Yap activated the insulin-like growth factor-1 receptor (IGF-1R) signaling pathway in CMs, contributing to the inactivation of glycogen synthase kinase 3 beta (GSK-3β), which increased b-catenin as a positive regulator

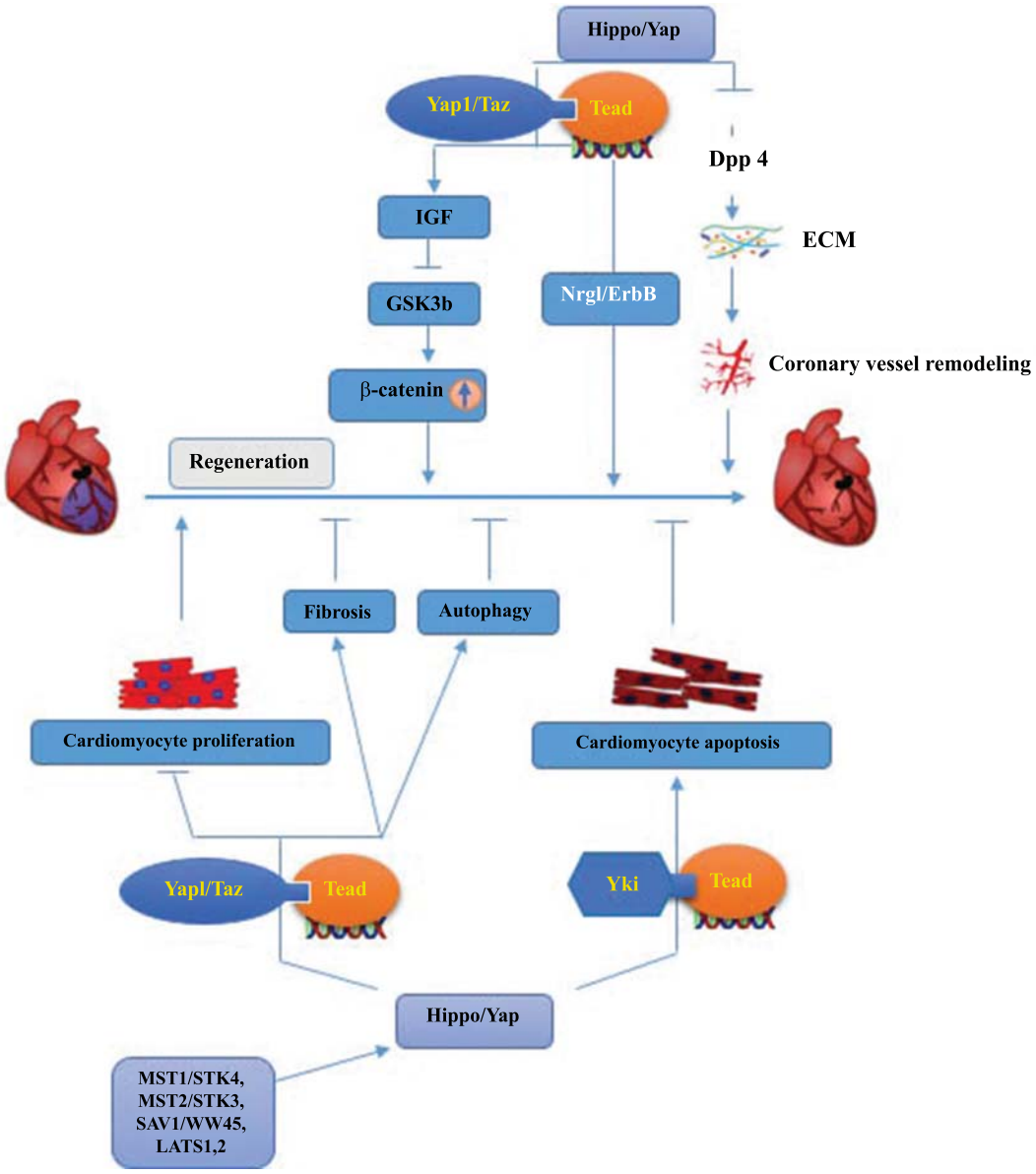

Fig. (2). Schematic overview of the complex Hippo/Yap signaling pathway in human heart failure regeneration. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

of cardiac growth [163]. Indeed, Yap a nexus for coupling the IGF, Wnt/β-Catenin, and Hippo signaling pathways, which results in a developmental program for heart growth [163]. The hippo signaling pathway has been involved in therapeutic approaches to control the cardiac tissue's regenerative response to damage and is a fundamental regulator of heart size (Fig. **2**).

6.3.2. Role of Hippo/YAP in rodents and mammals cardiac regeneration

Initially, points are this question: Can the activation of YAP stimulate cardiac regeneration and repair in adults? Yap is necessary for heart development and heart regeneration during the neonatal period. During the fetal stage, cardiac growth is originally is mediated by the proliferation of pre-existing CMs. In contrast, postnatal cardiac growth is mainly directed by physiological hypertrophy of CMs rather than by proliferation [164]. Yap/Taz activity is suppressed a few days (day seven) after birth with enhancement in Hippo pathway kinases' activity [165]. Besides, in mice heart samples with pathological conditions such as MI, I/R, which lead to hypertrophic cardiomyopathy, Yap levels are increased, and the prohibitory phosphorylation at Ser127 of Yap is alleviated, proposing a role for nuclear YAP in hypertrophic cardiac muscle disease [166]. In this regard, genetic manipulation of the Hippo pathway elements in adult CMs provokes CM development *via* the S phase and mitosis. However, the overexpression of activated YAP is adequate to enhance the pro-

liferation of postmitotic CMs [164]. To confirm whether Yap activation is adequate for postnatal heart regeneration, created αMHC-YapS112A transgenic mice overexpressing stimulated Yap in the cardiac under the αMHC promoter's control. Both wild and αMHC-Yap^{S112A} transgenic mice were exposed to MI at day seven postnatally and assessed at P21.

Wild-type mice exhibited wide scar formation, loss of myocardial tissue, and ventricular dilatation in their cardiac tissue after damage. In opposite, αMHC-Yap^{S112A} hearts were fully regenerated with minimal or no fibrosis [167]. Other studies in the mice model revealed that with doxycycline-inducible Yap^{S127A} expression, Yap activation elevated CM proliferation and division. When Yap^{S127A} expression was stimulated in adult mice with MI, YAP activation was adequate to increase heart performance and alleviate infarct size [168]. Besides, to identify whether Yap/Taz stimulates heart regeneration after MI in adult mice, activation of Yap/Taz applying an adeno-associated virus subtype 9 (AAV9) with deleting Sav1or Lats1/Lats2 triggered heart repair, which finally resulted in enhanced cardiac function and elevated mouse survival [168]. Overexpression of Mst1 caused dilated cardiomyopathy due to excessive apoptosis. Triastuti and colleagues demonstrated that treatment with XMU-MP-1 as an Mst1/2 selective inhibitor improved heart function and decreased apoptosis and fibrosis of heart hypertrophy due to the pressure overload mouse model [169].

Furthermore, intraperitoneal administration of TT-10 in mice after MI can induce Yap activity by directly improving the Yap–Tead complex's transcriptional activity. This compound can enhance CM proliferation and alleviated infarct size and fibrosis, leading to cardiac performance improvement [36]. In general, in adult mice, Yap deletion by using αMHCCre significantly enhanced the apoptosis of CMs. Also, apoptosis of CMs was enhanced in mice with the coincided deletion of Yap and Taz [170].

As mentioned above, the Hippo pathway is active in adults, and consequently, Yap1 expression is minimal. Impressive Results of a study recently published by Camberos and *et al.* revealed that microgravity hinders the Hippo pathway, driving adult CMs to express higher levels of active Yap1. Indeed, this study provides new insight into the changes that occur in space and how the effects of these changes correlate to cardiac regeneration [171].

6.3.3. Hippo/YAP In Zebrafish Cardiac Regeneration

Unlike adult mammals and mice hearts, zebrafish hearts did not reduce cardiomyocyte proliferation and could regenerate throughout life. Yap null ($Yap^{-/-}$) zebrafish are viable to adulthood; Flinn and colleagues showed that CM proliferation was not impaired regeneration in zebrafish hearts. Their findings also reported that Yap plays in scar formation by regulating factors that mediate ECM deposition and macrophage activity following ventricle cryoinjury in the zebrafish [172].

The hippo pathway is a potent inhibitor of CM proliferation, which applied strategies to inhibit this pathway could ameliorate cardiac regeneration. Bearing all this in mind, Yap/Taz activation in adult CMs not only initiates proliferation but also causes CMs reprogramming and regeneration. Notwithstanding whether these properties can be attributed to humans or no, it is currently under investigation. Further investigation is also essential for exhibiting the therapeutic potential and risks of activating Yap/Taz during MI in humans.

7. OTHER SIGNALING PATHWAYS

7.1. Periostin

Shreds of evidence show stimulating proliferation of CMs with extracellular regeneration factors like periostin enhances cardiac regeneration and repair in rodents [173, 174]. Periostin has a critical function in cardiac regeneration and the EMT [175]. In neonatal heart incision model in mice showed that signal transducer and activators of transcription 3 (STAT3)/periostin signaling are crucial mediators of interleukin 13 (IL13) signaling in the regenerating mouse cardiac tissue [175]. With these approaches, periostin's role in myocardial regeneration and restoration has been controversial in adult rodents. Besides, the injection of MSCs overexpressing periostin into the infarcted rat cardiac tissue area diminished post-MI remodeling [176]. Only a handful of adult myocardial cells in a million have a detectable nuclear-DNA synthesis. Since adult CMs typically have two nuclei, the extent to which these rare nuclear divisions produce new cells is unknown. The fundamental cellular events leading to metaplasia are increased proliferation of cells and tissues, concomitant by angiogenesis, exactly the pivotal proceedings needed for myocardial regeneration if they can be targeted to the heart. Periostin is a protein that participated in cell survival and angiogenesis secreted by many human tumors on cardiac repair. The recombinant form of periostin elevated the DNA synthesis rate in adult CMs in tissue culture by stimulating integrins to actuate the PI3K in the PKB pathway [177].

7.2. Fibroblast Growth Factor-1

Both repair and regeneration are controlled by various agents, including cytokines, growth, and differenti-

ation factors. Among them are the fibroblast growth factors (FGFs) that master the regeneration of target organs and tissue [178]. FGF signaling pathway is required for heart regeneration. FGFs actuate various signaling cascades upon binding to receptors that the Ras/Erk1/2 signaling pathway is most prominent [178]. During zebrafish heart regeneration, FGFs induce epicardial cell activation and EMT as well as neovascularization [179]. In another position, FGF signaling is obligatory for the stimulation of shh and Wnt5b, which construct the different segments of the wound epithelium. In rats, post-MI levels of FGF1 are up-regulated in inflammatory cells and fibroblast-like cells in the boundary zone of infarcted myocardium, whereas FGF2 is stimulated in both the boundary zone (first in endothelial cells) and the infarct region (in CMs) [18]. Follistatin-like 1 signaling pathway is a key epicardial cardiomyogenic factor that ameliorates regenerative repair and function following MI [17].

Also, besides these signaling pathways, other pathways, including EGF [180], HGF [181], pro-fibrotic signalings such as PDGF [182-184], BMPs [185], *etc*., play a crucial role in heart regeneration.

CONCLUSION

Despite substantial heart disease therapy progress, it requires new clinical approaches for alternative treatment options. Besides understanding the molecular mechanisms by which many factors affect the signaling pathways and their role in physiological and disease conditions, the fundamental question remains unanswered: why cardiac regeneration defects in adult humans, yet. Targeting the signaling pathway has enormous potential for improving cardiac remodeling and regeneration therapeutic strategies. To date, efforts devoted to understanding the heart's regenerative potential have shown the minimal regenerative capacity of adult human cardiac tissue. New research in heart regeneration in different experimental models reveals that many ways, including signaling pathways, stem cells, exosome-derived stem cells, *etc.*, may involve heart regeneration. Overall, given the tremendous potential of the signaling pathway for regeneration that appears from the recent study, we can now wait for an exciting substantial and translational study on signaling to pave the way for new clinical methods in regenerative medicine.

LIST OF ABBREVIATIONS

AMPK = AMP-activated Protein Kinase

ALPK2 = Alpha Protein Kinase 2

AV = Atrioventricular

AVD1 = Aortic Valve Disease 1

b-FGF = Basic-fibroblast Growth Factor

BMs = Bone Marrow-derived Cells

BTrC = Beta-transducing Repeat-containing Protein

CDCs = Cardiosphere-derived Cells

CDK7 = Cycle-dependent Kinase 7

CHD = Chronic Heart Failure

CK = Casein Kinase

CMs = Cardiomyocytes

CSCs = Cardiac Stem Cells

CVD = Cardiovascular Disease

Dll = Delta-like

dpi = Days Post-injury

EndoMT = Endothelial-to-mesenchymal Transition

EGF = Epidermal Growth Factor

FGFs = Fibroblast Growth Factors

Fzd = Frizzled

GFs = Growth Factors

GSK-3β = Glycogen Synthase Kinase 3 Beta

HAK = Heart Alpha Kinase

HASF = Hypoxia and Akt Induced Stem Cell Factors

hESCs = Human Embryonic Stem Cells

HGF = Hepatocyte Growth Factor

Hh = Hedgehog

HIF-1α = Hypoxia-inducible Factor-1α

H/R = Hypoxia/Reoxygenation

HSPGs = Heparan Sulfate Proteoglycans

ICD = Intracellular Domain

IGF-1 = Insulin-like Growth Factor 1

IHF = Ischaemic Heart Failure

iPSCs = Induced Pluripotent Stem Cells

inhba = Inhibin Beta Aa

I/R = Ischemia/Reperfusion

LVEF = Left Ventricular Ejection Fraction

MEFs = Mouse Embryonic Fibroblasts

MI = Myocardial Infarction

mPTP = Mitochondrial Permeability Transition Pore

MSCs = Mesenchymal Stem Cells

Mst1 = Mammalian STE20-like Protein Kinase 1

mstnb = Myostatin b

mTOR = Mammalian Target of Rapamycin

NF-κB = Nuclear Factor-kappa B

Nppa = Natriuretic Peptide A

OS = Oxidative Stress

PDK1 = 3-phosphoinositide-dependent Kinases 1

PI3K = Phosphatidylinositol 3-kinase

PKB = Protein Kinase B

PLGF = Placenta Growth Factor

Ptc = Patched1

PCP = Planar Cell Polarity

PS = Primitive Streak

TCF/LEF = T-Cell Factor/Lymphoid Enhancer-Binding Factor

Tead = Transcriptional Enhancer Factor A Domain Family Member

RA = Retinoic Acid

RTK = Receptor Tyrosine Kinases

Sav1 = Salvador Homolog 1

SDF-1α = Stromal Cell-derived Factor 1 Alpha

sFRP-1 = Secreted Frizzled-related Protein 1

Shh = Sonic hedgehog

Smo = Smoothened

STAT3 = Signal Transducer and Activators of Transcription 3

T-ALL = T-cell Acute Lymphoblastic Leukemia

TEA = Transcriptional Enhancer Factor A

TGF-β = Transforming Growth Factor-beta

TWEAK = Tumor Necrosis Factor Like Weak Inducer of Apoptosis

VEGF = Vascular Endothelial Growth Factor

WIF1 = Wnt Inhibitory Factor 1

Yap1 = Yes-Associated Protein 1

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors would like to thank Shohada Clinical Research Development Unit, Shohada Hospital, Tabriz University of Medical Science, Tabriz, Iran.

REFERENCES

[1] Kawakami, Y.; Rodriguez Esteban, C.; Raya, M.; Kawakami, H.; Martí, M.; Dubova, I.; Izpisúa Belmonte, J.C. Wnt/beta-catenin signaling regulates vertebrate limb regeneration. *Genes Dev.,* **2006**, *20*(23), 3232-3237. http://dx.doi.org/10.1101/gad.1475106 PMID: 17114576

[2] Polezhaev, L.V.; Kolchin, S.P.; Solntseva, G.N. Stimulation of regeneration of the heart muscle in the course of diphtherial myocarditis. *Dokl. Akad. Nauk SSSR,* **1965**, *164*(4), 949-952. PMID: 5877446

[3] He, L.; Nguyen, N.B.; Ardehali, R.; Zhou, B. Heart Regeneration by Endogenous Stem Cells and Cardiomyocyte Proliferation: Controversy, Fallacy, and Progress. *Circulation,* **2020**, *142*(3), 275-291. http://dx.doi.org/10.1161/CIRCULATIONAHA.119.045566 PMID: 32687441

[4] Voges, H.K.; Mills, R.J.; Elliott, D.A.; Parton, R.G.; Porrello, E.R.; Hudson, J.E.J.D. Development of a human cardiac organoid injury model reveals innate regenerative potential. *Development,* **2017**, *144*(6), 1118-1127. http://dx.doi.org/10.1242/dev.143966 PMID: 28174241

[5] Torrini, C.; Cubero, R.J.; Dirkx, E.; Braga, L.; Ali, H.; Prosdocimo, G.; Gutierrez, M.I.; Collesi, C.; Licastro, D.; Zentilin, L.; Mano, M.; Zacchigna, S.; Vendruscolo, M.; Marsili, M.; Samal, A.; Giacca, M. Common Regulatory Pathways Mediate Activity of MicroRNAs Inducing Cardiomyocyte Proliferation. *Cell Rep.,* **2019**, *27*(9), 2759-2771. http://dx.doi.org/10.1016/j.celrep.2019.05.005 PMID: 31141697

[6] Porrello, E.R.; Mahmoud, A.I.; Simpson, E.; Hill, J.A.; Richardson, J.A.; Olson, E.N.; Sadek, H.A. Transient regenerative potential of the neonatal mouse heart. *Science,* **2011**, *331*(6020), 1078-1080. http://dx.doi.org/10.1126/science.1200708 PMID: 21350179

[7] Lenneman, A.J.; Birks, E.J. Treatment strategies for myocardial recovery in heart failure. *Curr. Treat. Options Cardiovasc. Med.,* **2014**, *16*(3), 287. http://dx.doi.org/10.1007/s11936-013-0287-9 PMID: 24492922

[8] Xin, M.; Kim, Y.; Sutherland, L.B.; Murakami, M.; Qi, X.; McAnally, J.; Porrello, E.R.; Mahmoud, A.I.; Tan, W.; Shelton, J.M.; Richardson, J.A.; Sadek, H.A.; Bassel-Duby,

[9] Flinn, M.A.; Link, B.A.; O'Meara, C.C. Upstream regulation of the Hippo-Yap pathway in cardiomyocyte regeneration. *Semin. Cell Dev. Biol.,* **2020**, *100*, 11-19. http://dx.doi.org/10.1016/j.semcdb.2019.09.004 PMID: 31606277

[10] Dogra, D.; Ahuja, S.; Kim, H-T.; Rasouli, S.J.; Stainier, D.Y.R.; Reischauer, S. Opposite effects of Activin type 2 receptor ligands on cardiomyocyte proliferation during development and repair. *Nat. Commun.,* **2017**, *8*(1), 1902. http://dx.doi.org/10.1038/s41467-017-01950-1 PMID: 29196619

[11] Beffagna, G. Zebrafish as a Smart Model to Understand Regeneration After Heart Injury: How Fish Could Help Humans. *Front. Cardiovasc. Med.,* **2019**, *6*(107), 107. http://dx.doi.org/10.3389/fcvm.2019.00107 PMID: 31448289

[12] Gomes, R.S.; Skroblin, P.; Munster, A.B.; Tomlins, H.; Langley, S.R.; Zampetaki, A.; Yin, X.; Wardle, F.C.; Mayr, M. "Young at heart": Regenerative potential linked to immature cardiac phenotypes. *J. Mol. Cell. Cardiol.,* **2016**, *92*, 105-108. http://dx.doi.org/10.1016/j.yjmcc.2016.01.026 PMID: 26827899

[13] Poss, K.D.; Wilson, L.G.; Keating, M.T. Heart regeneration in zebrafish. *Science,* **2002**, *298*(5601), 2188-2190. http://dx.doi.org/10.1126/science.1077857 PMID: 12481136

[14] Chablais, F.; Veit, J.; Rainer, G.; Jaźwińska, A. The zebrafish heart regenerates after cryoinjury-induced myocardial infarction. *BMC Dev. Biol.,* **2011**, *11*(1), 21. http://dx.doi.org/10.1186/1471-213X-11-21 PMID: 21473762

[15] Leung, C.S.; Yang, K.Y.; Li, X.; Chan, V.W.; Ku, M.; Waldmann, H.; Hori, S.; Tsang, J.C.H.; Lo, Y.M.D.; Lui, K.O. Single-cell transcriptomics reveal that PD-1 mediates immune tolerance by regulating proliferation of regulatory T cells. *Genome Med.,* **2018**, *10*(1), 71. http://dx.doi.org/10.1186/s13073-018-0581-y PMID: 30236153

[16] Günthel, M.; Barnett, P.; Christoffels, V.M. Development, proliferation, and growth of the mammalian heart. *Mol. Ther.,* **2018**, *26*(7), 1599-1609. http://dx.doi.org/10.1016/j.ymthe.2018.05.022 PMID: 29929790

[17] Uygur, A.; Lee, R.T. Mechanisms of Cardiac Regeneration. *Dev. Cell,* **2016**, *36*(4), 362-374. http://dx.doi.org/10.1016/j.devcel.2016.01.018 PMID: 26906733

[18] Cao, J.; Poss, K.D.J.N.R.C. The epicardium as a hub for heart regeneration. *Nat. Rev. Cardiol.,* **2018**, *15*(10), 631-647. http://dx.doi.org/10.1038/s41569-018-0046-4 PMID: 29950578

[19] Cahill, T.J.; Choudhury, R.P.; Riley, P.R. Heart regeneration and repair after myocardial infarction: translational opportunities for novel therapeutics. *Nat. Rev. Drug Discov.,* **2017**, *16*(10), 699-717. http://dx.doi.org/10.1038/nrd.2017.106 PMID: 28729726

[20] Vilahur, G.; Juan-Babot, O.; Peña, E.; Oñate, B.; Casaní, L.; Badimon, L. Molecular and cellular mechanisms involved in cardiac remodeling after acute myocardial infarction. *J. Mol. Cell. Cardiol.,* **2011**, *50*(3), 522-533. http://dx.doi.org/10.1016/j.yjmcc.2010.12.021 PMID: 21219908

[21] Karra, R.; Knecht, A.K.; Kikuchi, K.; Poss, K.D. Myocardial NF-κB activation is essential for zebrafish heart regeneration. *Proc. Natl. Acad. Sci. USA,* **2015**, *112*(43), 13255-13260. http://dx.doi.org/10.1073/pnas.1511209112 PMID: 26472034

[22] Lin, Z.; Pu, W.T. Harnessing Hippo in the heart: Hippo/Yap signaling and applications to heart regeneration and rejuvenation. *Stem Cell Res. (Amst.),* **2014**, *13*(3 Pt B), 571-581. http://dx.doi.org/10.1016/j.scr.2014.04.010 PMID: 24881775

[23] Bersell, K.; Arab, S.; Haring, B.; Kühn, B. Neuregulin1/ErbB4 signaling induces cardiomyocyte proliferation and repair of heart injury. *Cell,* **2009**, *138*(2), 257-270. http://dx.doi.org/10.1016/j.cell.2009.04.060 PMID: 19632177

[24] Hashimoto, H.; Olson, E.N.; Bassel-Duby, R. Therapeutic approaches for cardiac regeneration and repair. *Nat. Rev. Cardiol.,* **2018**, *15*(10), 585-600. http://dx.doi.org/10.1038/s41569-018-0036-6 PMID: 29872165

[25] Artap, S.; Manderfield, L.J.; Smith, C.L.; Poleshko, A.; Aghajanian, H.; See, K.; Li, L.; Jain, R.; Epstein, J.A. Endocardial Hippo signaling regulates myocardial growth and cardiogenesis. *Dev. Biol.,* **2018**, *440*(1), 22-30. http://dx.doi.org/10.1016/j.ydbio.2018.04.026 PMID: 29727635

[26] Gemberling, M.; Karra, R.; Dickson, A.L.; Poss, K.D. Nrg1 is an injury-induced cardiomyocyte mitogen for the endogenous heart regeneration program in zebrafish. *eLife,* **2015**, *4*, e05871. http://dx.doi.org/10.7554/eLife.05871 PMID: 25830562

[27] Maier, H.J.; Schips, T.G.; Wietelmann, A.; Krüger, M.; Brunner, C.; Sauter, M.; Klingel, K.; Böttger, T.; Braun, T.; Wirth, T. Cardiomyocyte-specific IκB kinase (IKK)/NF-κB activation induces reversible inflammatory cardiomyopathy and heart failure. *Proc. Natl. Acad. Sci. USA,* **2012**, *109*(29), 11794-11799. http://dx.doi.org/10.1073/pnas.1116584109 PMID: 22753500

[28] Bruneau, B.G. Signaling and transcriptional networks in heart development and regeneration. *Cold Spring Harb. Perspect. Biol.,* **2013**, *5*(3), a008292. http://dx.doi.org/10.1101/cshperspect.a008292 PMID: 23457256

[29] Ling, L.; Gu, S.; Cheng, Y. Resveratrol activates endogenous cardiac stem cells and improves myocardial regeneration following acute myocardial infarction. *Mol. Med. Rep.,* **2017**, *15*(3), 1188-1194. http://dx.doi.org/10.3892/mmr.2017.6143 PMID: 28138705

[30] Liu, J.; Wang, Y.; Cui, J.; Sun, M.; Pu, Z.; Wang, C.; Du, W.; Liu, X.; Wu, J.; Hou, J.; Zhang, S.; Yu, B. miR199a-3p regulates P53 by targeting CABLES1 in mouse cardiac c-kit^{+} cells to promote proliferation and inhibit apoptosis through a negative feedback loop. *Stem Cell Res. Ther.,* **2017**, *8*(1), 127. http://dx.doi.org/10.1186/s13287-017-0515-4 PMID: 28583208

[31] Zhou, Q.; Sun, Q.; Zhang, Y.; Teng, F.; Sun, J. Up-regulation of miRNA-21 expression promotes migration and proliferation of Sca-1+ cardiac stem cells in mice. *Med. Sci. Monit.,* **2016**, *22*, 1724-1732. http://dx.doi.org/10.12659/MSM.895753 PMID: 27210794

[32] Sayed, A.; Valente, M.; Sassoon, D. Does cardiac development provide heart research with novel therapeutic approaches? *F1000 Res.,* **1756**, *2018*, 7.

[33] Kim, J.; Shapiro, L.; Flynn, A. The clinical application of mesenchymal stem cells and cardiac stem cells as a therapy for cardiovascular disease. *Pharmacol. Ther.,* **2015**, *151*, 8-15. http://dx.doi.org/10.1016/j.pharmthera.2015.02.003 PMID: 25709098

[34] Li, W.; Ma, N.; Ong, L.L.; Nesselmann, C.; Klopsch, C.; Ladilov, Y.; Furlani, D.; Piechaczek, C.; Moebius, J.M.; Lützow, K.; Lendlein, A.; Stamm, C.; Li, R.K.; Steinhoff, G. Bcl-2 engineered MSCs inhibited apoptosis and improved heart function. *Stem Cells,* **2007**, *25*(8), 2118-2127. http://dx.doi.org/10.1634/stemcells.2006-0771 PMID: 17478584

[35] Liang, X.; Ding, Y.; Zhang, Y.; Chai, Y.H.; He, J.; Chiu, S.M.; Gao, F.; Tse, H.F.; Lian, Q. Activation of NRG1-ERBB4 signaling potentiates mesenchymal stem cell-mediated myocardial repairs following myocardial infarction. *Cell Death Dis.,* **2015**, *6*, e1765. http://dx.doi.org/10.1038/cddis.2015.91 PMID: 25996292

[36] Hara, H.; Takeda, N.; Kondo, M.; Kubota, M.; Saito, T.; Maruyama, J.; Fujiwara, T.; Maemura, S.; Ito, M.; Naito, A.T.; Harada, M.; Toko, H.; Nomura, S.; Kumagai, H.; Ikeda, Y.; Ueno, H.; Takimoto, E.; Akazawa, H.; Morita, H.; Aburatani, H.; Hata, Y.; Uchiyama, M.; Komuro, I. Discovery of a small molecule to increase cardiomyocytes and protect the heart after ischemic injury. *JACC Basic Transl. Sci.,* **2018**, *3*(5), 639-653. http://dx.doi.org/10.1016/j.jacbts.2018.07.005 PMID: 30456335

[37] Zhang, Y.; Hu, Y.W.; Zheng, L.; Wang, Q. Characteristics and roles of exosomes in cardiovascular disease. *DNA Cell Biol.,* **2017**, *36*(3), 202-211. http://dx.doi.org/10.1089/dna.2016.3496 PMID: 28112546

[38] Shanmuganathan, M.; Vughs, J.; Noseda, M.; Emanueli, C. Exosomes: basic biology and technological advancements suggesting their potential as ischemic heart disease therapeutics. *Front. Physiol.,* **2018**, *9*, 1159. http://dx.doi.org/10.3389/fphys.2018.01159 PMID: 30524292

[39] Ibrahim, A.G-E.; Cheng, K.; Marbán, E. Exosomes as critical agents of cardiac regeneration triggered by cell therapy. *Stem Cell Reports,* **2014**, *2*(5), 606-619. http://dx.doi.org/10.1016/j.stemcr.2014.04.006 PMID: 24936449

[40] Namazi, H.; Mohit, E.; Namazi, I.; Rajabi, S.; Samadian, A.; Hajizadeh-Saffar, E.; Aghdami, N.; Baharvand, H. Exosomes secreted by hypoxic cardiosphere-derived cells enhance tube formation and increase pro-angiogenic miRNA. *J. Cell. Biochem.,* **2018**, *119*(5), 4150-4160. http://dx.doi.org/10.1002/jcb.26621 PMID: 29243842

[41] Fu, W.B.; Wang, W.E.; Zeng, C.Y. Wnt signaling pathways in myocardial infarction and the therapeutic effects of Wnt pathway inhibitors. *Acta Pharmacol. Sin.,* **2019**, *40*(1), 9-12. http://dx.doi.org/10.1038/s41401-018-0060-4 PMID: 30002488

[42] Palpant, N.J.; Pabon, L.; Roberts, M.; Hadland, B.; Jones, D.; Jones, C.; Moon, R.T.; Ruzzo, W.L.; Bernstein, I.; Zheng, Y.; Murry, C.E. Inhibition of β-catenin signaling respecifies anterior-like endothelium into beating human cardiomyocytes. *Development,* **2015**, *142*(18), 3198-3209. PMID: 26153229

[43] Ozhan, G.; Weidinger, G. Wnt/β-catenin signaling in heart regeneration. *Cell Regen. (Lond.),* **2015**, *4*(1), 3. http://dx.doi.org/10.1186/s13619-015-0017-8 PMID: 26157574

[44] Bergmann, M.W. WNT signaling in adult cardiac hypertrophy and remodeling: lessons learned from cardiac development. *Circ. Res.,* **2010**, *107*(10), 1198-1208. http://dx.doi.org/10.1161/CIRCRESAHA.110.223768 PMID: 21071717

[45] Meyer, I.S.; Leuschner, F. The role of Wnt signaling in the healing myocardium: a focus on cell specificity. *Basic Res. Cardiol.,* **2018**, *113*(6), 44. http://dx.doi.org/10.1007/s00395-018-0705-y PMID: 30327885

[46] Li, V.S.; Ng, S.S.; Boersema, P.J.; Low, T.Y.; Karthaus, W.R.; Gerlach, J.P.; Mohammed, S.; Heck, A.J.; Maurice, M.M.; Mahmoudi, T.; Clevers, H. Wnt signaling through inhibition of β-catenin degradation in an intact Axin1 complex. *Cell,* **2012**, *149*(6), 1245-1256. http://dx.doi.org/10.1016/j.cell.2012.05.002 PMID: 22682247

[47] Paik, D.T.; Rai, M.; Ryzhov, S.; Sanders, L.N.; Aisagbonhi, O.; Funke, M.J.; Feoktistov, I.; Hatzopoulos, A.K. Wnt10b gain-of-function improves cardiac repair by arteriole formation and attenuation of fibrosis. *Circ. Res.,* **2015**, *117*(9), 804-816. http://dx.doi.org/10.1161/CIRCRESAHA.115.306886 PMID: 26338900

[48] Hofsteen, P.; Robitaille, A.M.; Strash, N.; Palpant, N.; Moon, R.T.; Pabon, L.; Murry, C.E. ALPK2 promotes cardiogenesis in zebrafish and human pluripotent stem cells. *iScience,* **2018**, *2*, 88-100. http://dx.doi.org/10.1016/j.isci.2018.03.010 PMID: 29888752

[49] Yang, D.; Fu, W.; Li, L.; Xia, X.; Liao, Q.; Yue, R.; Chen, H.; Chen, X.; An, S.; Zeng, C.; Wang, W.E. Therapeutic effect of a novel Wnt pathway inhibitor on cardiac regeneration after myocardial infarction. *Clin. Sci. (Lond.),* **2017**, *131*(24), 2919-2932. http://dx.doi.org/10.1042/CS20171256 PMID: 29162747

[50] Bastakoty, D.; Young, P.P. Wnt/β-catenin pathway in tissue injury: roles in pathology and therapeutic opportunities for regeneration. *FASEB J.,* **2016**, *30*(10), 3271-3284. http://dx.doi.org/10.1096/fj.201600502R PMID: 27335371

[51] Xie, S.; Fu, W.; Yu, G.; Hu, X.; Lai, K.S.; Peng, X.; Zhou, Y.; Zhu, X.; Christov, P.; Sawyer, L. Discovering small molecules as Wnt inhibitors that promote heart regeneration and injury repair. *J. Mol. Cell Biol.,* **2020**, *12*(1), 42-54. PMID: 30925593

[52] Ng, L.F.; Kaur, P.; Bunnag, N.; Suresh, J.; Sung, I.C.H.; Tan, Q.H.; Gruber, J.; Tolwinski, N.S. WNT Signaling in Disease. *Cells,* **2019**, *8*(8), E826. http://dx.doi.org/10.3390/cells8080826 PMID: 31382613

[53] Abraityte, A.; Vinge, L.E.; Askevold, E.T.; Lekva, T.; Michelsen, A.E.; Ranheim, T.; Alfsnes, K.; Fiane, A.; Aakhus, S.; Lunde, I.G.; Dahl, C.P.; Aukrust, P.; Christensen, G.; Gullestad, L.; Yndestad, A.; Ueland, T. Wnt5a is elevated in heart failure and affects cardiac fibroblast function. *J. Mol. Med. (Berl.),* **2017**, *95*(7), 767-777. http://dx.doi.org/10.1007/s00109-017-1529-1 PMID: 28357477

[54] Tao, S.; Tang, D.; Morita, Y.; Sperka, T.; Omrani, O.; Lechel, A.; Sakk, V.; Kraus, J.; Kestler, H.A.; Kühl, M.; Rudolph, K.L. Wnt activity and basal niche position sensitize intestinal stem and progenitor cells to DNA damage. *EMBO J.,* **2015**, *34*(5), 624-640. http://dx.doi.org/10.15252/embj.201490700 PMID: 25609789

[55] Meyer, I.S.; Jungmann, A.; Dieterich, C.; Zhang, M.; Lasitschka, F.; Werkmeister, S.; Haas, J.; Müller, O.J.; Boutros, M.; Nahrendorf, M.; Katus, H.A.; Hardt, S.E.; Leuschner, F. The cardiac microenvironment uses non-canonical WNT signaling to activate monocytes after myocardial infarction. *EMBO Mol. Med.,* **2017**, *9*(9), 1279-1293. http://dx.doi.org/10.15252/emmm.201707565 PMID: 28774883

[56] Duan, J.; Gherghe, C.; Liu, D.; Hamlett, E.; Srikantha, L.; Rodgers, L.; Regan, J.N.; Rojas, M.; Willis, M.; Leask, A.; Majesky, M.; Deb, A. Wnt1/βcatenin injury response acti-

vates the epicardium and cardiac fibroblasts to promote cardiac repair. *EMBO J.,* **2012**, *31*(2), 429-442. http://dx.doi.org/10.1038/emboj.2011.418 PMID: 22085926

[57] Ueno, S.; Weidinger, G.; Osugi, T.; Kohn, A.D.; Golob, J.L.; Pabon, L.; Reinecke, H.; Moon, R.T.; Murry, C.E.J.P.N.A.S. Biphasic role for Wnt/β-catenin signaling in cardiac specification in zebrafish and embryonic stem cells. *Proc. Natl. Acad. Sci. USA,* **2007**, *104*(23), 9685-9690. http://dx.doi.org/10.1073/pnas.0702859104 PMID: 17522258

[58] Paige, S.L.; Osugi, T.; Afanasiev, O.K.; Pabon, L.; Reinecke, H.; Murry, C.E. Endogenous Wnt/β-catenin signaling is required for cardiac differentiation in human embryonic stem cells. *PLoS One,* **2010**, *5*(6), e11134. http://dx.doi.org/10.1371/journal.pone.0011134 PMID: 20559569

[59] Cui, X.; He, Z.; Liang, Z.; Chen, Z.; Wang, H.; Zhang, J. Exosomes from adipose-derived mesenchymal stem cells protect the myocardium against ischemia/reperfusion injury through Wnt/β-Catenin signaling pathway. *J. Cardiovasc. Pharmacol.,* **2017**, *70*(4), 225-231. http://dx.doi.org/10.1097/FJC.0000000000000507 PMID: 28582278

[60] Werner, J.H.; Rosenberg, J.H.; Um, J.Y.; Moulton, M.J.; Agrawal, D.K. Molecular discoveries and treatment strategies by direct reprogramming in cardiac regeneration. *Transl. Res.,* **2019**, *203*, 73-87. http://dx.doi.org/10.1016/j.trsl.2018.07.012 PMID: 30142308

[61] Münch, J.; Grivas, D.; González-Rajal, Á.; Torregrosa-Carrión, R.; de la Pompa, J.L. Notch signalling restricts inflammation and *serpine1* expression in the dynamic endocardium of the regenerating zebrafish heart. *Development,* **2017**, *144*(8), 1425-1440. PMID: 28242613

[62] Balistreri, C.R.; Madonna, R.; Melino, G.; Caruso, C. The emerging role of Notch pathway in ageing: Focus on the related mechanisms in age-related diseases. *Ageing Res. Rev.,* **2016**, *29*, 50-65. http://dx.doi.org/10.1016/j.arr.2016.06.004 PMID: 27328278

[63] Liu, Z.; Brunskill, E.; Varnum-Finney, B.; Zhang, C.; Zhang, A.; Jay, P.Y.; Bernstein, I.; Morimoto, M.; Kopan, R. The intracellular domains of Notch1 and Notch2 are functionally equivalent during development and carcinogenesis. *Development,* **2015**, *142*(14), 2452-2463. http://dx.doi.org/10.1242/dev.125492 PMID: 26062937

[64] MacGrogan, D.; Nus, M.; de la Pompa, J.L. Notch signaling in cardiac development and disease. *Curr. Top. Dev. Biol.,* **2010**, *92*, 333-365. http://dx.doi.org/10.1016/S0070-2153(10)92011-5 PMID: 20816401

[65] Salazar, J.L.; Yamamoto, S. Integration of drosophila and human genetics to understand notch signaling related diseases. *Adv. Exp. Med. Biol.,* **2018**, *1066*, 141-185. http://dx.doi.org/10.1007/978-3-319-89512-3_8 PMID: 30030826

[66] Lee, A.; Wei, S.; Schwertani, A. A Notch more: Molecular players in bicuspid aortic valve disease. *J. Mol. Cell. Cardiol.,* **2019**, *134*, 62-68. http://dx.doi.org/10.1016/j.yjmcc.2019.05.018 PMID: 31150732

[67] Yu, L.; Liang, H.; Lu, Z.; Zhao, G.; Zhai, M.; Yang, Y.; Yang, J.; Yi, D.; Chen, W.; Wang, X.; Duan, W.; Jin, Z.; Yu, S. Membrane receptor-dependent Notch1/Hes1 activation by melatonin protects against myocardial ischemia-reperfusion injury: *In vivo* and *in vitro* studies. *J. Pineal Res.,* **2015**, *59*(4), 420-433. http://dx.doi.org/10.1111/jpi.12272 PMID: 26308963

[68] Yu, B.; Song, B. Notch 1 signalling inhibits cardiomyocyte apoptosis in ischaemic postconditioning. *Heart Lung Circ.,* **2014**, *23*(2), 152-158. http://dx.doi.org/10.1016/j.hlc.2013.07.004 PMID: 23948289

[69] MacGrogan, D.; Münch, J.; de la Pompa, J.L. Notch and interacting signalling pathways in cardiac development, disease, and regeneration. *Nat. Rev. Cardiol.,* **2018**, *15*(11), 685-704. http://dx.doi.org/10.1038/s41569-018-0100-2 PMID: 30287945

[70] Grego-Bessa, J.; Luna-Zurita, L.; del Monte, G.; Bolós, V.; Melgar, P.; Arandilla, A.; Garratt, A.N.; Zang, H.; Mukouyama, Y.S.; Chen, H.; Shou, W.; Ballestar, E.; Esteller, M.; Rojas, A.; Pérez-Pomares, J.M.; de la Pompa, J.L. Notch signaling is essential for ventricular chamber development. *Dev. Cell,* **2007**, *12*(3), 415-429. http://dx.doi.org/10.1016/j.devcel.2006.12.011 PMID: 17336907

[71] Fang, X.; Miao, S.; Yu, Y.; Ding, F.; Han, X.; Wu, H.; Zhao, Z-A.; Wang, Y.; Hu, S.; Lei, W. MIR148A family regulates cardiomyocyte differentiation of human embryonic stem cells by inhibiting the DLL1-mediated NOTCH signaling pathway. *J. Mol. Cell. Cardiol.,* **2019**, *134*, 1-12. http://dx.doi.org/10.1016/j.yjmcc.2019.06.014 PMID: 31233755

[72] Diez-Cuñado, M.; Wei, K.; Bushway, P.J.; Maurya, M.R.; Perera, R.; Subramaniam, S.; Ruiz-Lozano, P.; Mercola, M. miRNAs that induce human cardiomyocyte proliferation converge on the hippo pathway. *Cell Rep.,* **2018**, *23*(7), 2168-2174. http://dx.doi.org/10.1016/j.celrep.2018.04.049 PMID: 29768213

[73] Collesi, C.; Zentilin, L.; Sinagra, G.; Giacca, M. Notch1 signaling stimulates proliferation of immature cardiomyocytes. *J. Cell Biol.,* **2008**, *183*(1), 117-128. http://dx.doi.org/10.1083/jcb.200806091 PMID: 18824567

[74] Croquelois, A.; Domenighetti, A.A.; Nemir, M.; Lepore, M.; Rosenblatt-Velin, N.; Radtke, F.; Pedrazzini, T. Control of the adaptive response of the heart to stress via the Notch1 receptor pathway. *J. Exp. Med.,* **2008**, *205*(13), 3173-3185. http://dx.doi.org/10.1084/jem.20081427 PMID: 19064701

[75] Badalzadeh, R.; Azimi, A.; Alihemmati, A.; Yousefi, B. Chronic type-I diabetes could not impede the anti-inflammatory and anti-apoptotic effects of combined post-conditioning with ischemia and cyclosporine A in myocardial reperfusion injury. *J. Physiol. Biochem.,* **2017**, *73*(1), 111-120. http://dx.doi.org/10.1007/s13105-016-0530-4 PMID: 27771871

[76] Zhou, X.L.; Wan, L.; Xu, Q.R.; Zhao, Y.; Liu, J.C. Notch signaling activation contributes to cardioprotection provided by ischemic preconditioning and postconditioning. *J. Transl. Med.,* **2013**, *11*, 251. http://dx.doi.org/10.1186/1479-5876-11-251 PMID: 24098939

[77] Zhao, L.; Ben-Yair, R.; Burns, C.E.; Burns, C.G. Endocardial notch signaling promotes cardiomyocyte proliferation in the regenerating zebrafish heart through wnt pathway antagonism. *Cell Rep.,* **2019**, *26*(3), 546-554. http://dx.doi.org/10.1016/j.celrep.2018.12.048 PMID: 30650349

[78] Zhao, L.; Borikova, A.L.; Ben-Yair, R.; Guner-Ataman, B.; MacRae, C.A.; Lee, R.T.; Burns, C.G.; Burns, C.E. Notch signaling regulates cardiomyocyte proliferation during zebrafish heart regeneration. *Proc. Natl. Acad. Sci. USA,* **2014**, *111*(4), 1403-1408.

http://dx.doi.org/10.1073/pnas.1311705111 PMID: 24474765

[79] Xiao, N.; Qi, X.Y.; Tang, L.N.; Tan, L.L.; Chen, Y.Q.; Zhao, H.M. VEGF promotes cardiac stem cells differentiation into vascular endothelial cells via the PI3K/Akt signaling pathway. *Artif. Cells Nanomed. Biotechnol.,* **2014**, *42*(6), 400-405. http://dx.doi.org/10.3109/21691401.2013.837473 PMID: 24059532

[80] Olsson, A-K.; Dimberg, A.; Kreuger, J.; Claesson-Welsh, L. VEGF receptor signalling - in control of vascular function. *Nat. Rev. Mol. Cell Biol.,* **2006**, *7*(5), 359-371. http://dx.doi.org/10.1038/nrm1911 PMID: 16633338

[81] Eichmann, A.; Simons, M. VEGF signaling inside vascular endothelial cells and beyond. *Curr. Opin. Cell Biol.,* **2012**, *24*(2), 188-193. http://dx.doi.org/10.1016/j.ceb.2012.02.002 PMID: 22366328

[82] Kivelä, R.; Hemanthakumar, K.A.; Vaparanta, K.; Robciuc, M.; Izumiya, Y.; Kidoya, H.; Takakura, N.; Peng, X.; Sawyer, D.B.; Elenius, K.; Walsh, K.; Alitalo, K. Endothelial cells regulate physiological cardiomyocyte growth *via* VEGFR2-mediated paracrine signaling. *Circulation,* **2019**, *139*(22), 2570-2584. http://dx.doi.org/10.1161/CIRCULATIONAHA.118.036099 PMID: 30922063

[83] Madonna, R.; De Caterina, R. VEGF receptor switching in heart development and disease. *Cardiovasc. Res.,* **2009**, *84*(1), 4-6. http://dx.doi.org/10.1093/cvr/cvp270 PMID: 19654124

[84] Taimeh, Z.; Loughran, J.; Birks, E.J.; Bolli, R. Vascular endothelial growth factor in heart failure. *Nat. Rev. Cardiol.,* **2013**, *10*(9), 519-530. http://dx.doi.org/10.1038/nrcardio.2013.94 PMID: 23856679

[85] Binsalamah, Z.M.; Paul, A.; Khan, A.A.; Prakash, S.; Shum-Tim, D. Intramyocardial sustained delivery of placental growth factor using nanoparticles as a vehicle for delivery in the rat infarct model. *Int. J. Nanomed.,* **2011**, *6*, 2667-2678. PMID: 22114497

[86] Cho, H.M.; Kim, P.H.; Chang, H.K.; Shen, Y.M.; Bonsra, K.; Kang, B.J.; Yum, S.Y.; Kim, J.H.; Lee, S.Y.; Choi, M.C.; Kim, H.H.; Jang, G.; Cho, J.Y. Targeted genome engineering to control VEGF expression in human umbilical cord blood‐derived mesenchymal stem cells: Potential implications for the treatment of myocardial infarction. *Stem Cells Transl. Med.,* **2017**, *6*(3), 1040-1051. http://dx.doi.org/10.1002/sctm.16-0114 PMID: 28186692

[87] Tang, J.M.; Luo, B.; Xiao, J.H.; Lv, Y.X.; Li, X.L.; Zhao, J.H.; Zheng, F.; Zhang, L.; Chen, L.; Yang, J.Y.; Guo, L.Y.; Wang, L.; Yan, Y.W.; Pan, Y.M.; Wang, J.N.; Li, D.S.; Wan, Y.; Chen, S.Y. VEGF-A promotes cardiac stem cell engraftment and myocardial repair in the infarcted heart. *Int. J. Cardiol.,* **2015**, *183*, 221-231. http://dx.doi.org/10.1016/j.ijcard.2015.01.050 PMID: 25679991

[88] Zangi, L.; Lui, K.O.; von Gise, A.; Ma, Q.; Ebina, W.; Ptaszek, L.M.; Später, D.; Xu, H.; Tabebordbar, M.; Gorbatov, R.; Sena, B.; Nahrendorf, M.; Briscoe, D.M.; Li, R.A.; Wagers, A.J.; Rossi, D.J.; Pu, W.T.; Chien, K.R. Modified mRNA directs the fate of heart progenitor cells and induces vascular regeneration after myocardial infarction. *Nat. Biotechnol.,* **2013**, *31*(10), 898-907. http://dx.doi.org/10.1038/nbt.2682 PMID: 24013197

[89] Karra, R.; Foglia, M.J.; Choi, W-Y.; Belliveau, C.; DeBenedittis, P.; Poss, K.D. Vegfaa instructs cardiac muscle hyperplasia in adult zebrafish. *Proc. Natl. Acad. Sci. USA,* **2018**, *115*(35), 8805-8810. http://dx.doi.org/10.1073/pnas.1722594115 PMID: 30104362

[90] Zhu, D.; Fang, Y.; Gao, K.; Shen, J.; Zhong, T.P.; Li, F. Vegfa impacts early myocardium development in zebrafish. *Int. J. Mol. Sci.,* **2017**, *18*(2), 444. http://dx.doi.org/10.3390/ijms18020444 PMID: 28230770

[91] Psarras, S.; Beis, D.; Nikouli, S.; Tsikitis, M.; Capetanaki, Y. Three in a box: understanding cardiomyocyte, fibroblast, and innate immune cell interactions to orchestrate cardiac repair processes. *Front. Cardiovasc. Med.,* **2019**, *6*(32), 32. http://dx.doi.org/10.3389/fcvm.2019.00032 PMID: 31001541

[92] Huang, Y.; Harrison, M.R.; Osorio, A.; Kim, J.; Baugh, A.; Duan, C.; Sucov, H.M.; Lien, C-L. Igf signaling is required for cardiomyocyte proliferation during zebrafish heart development and regeneration. *PLoS One,* **2013**, *8*(6), e67266. http://dx.doi.org/10.1371/journal.pone.0067266 PMID: 23840646

[93] Troncoso, R.; Ibarra, C.; Vicencio, J.M.; Jaimovich, E.; Lavandero, S. New insights into IGF-1 signaling in the heart. *Trends Endocrinol. Metab.,* **2014**, *25*(3), 128-137. http://dx.doi.org/10.1016/j.tem.2013.12.002 PMID: 24380833

[94] Ren, J.; Anversa, P. The insulin-like growth factor I system: physiological and pathophysiological implication in cardiovascular diseases associated with metabolic syndrome. *Biochem. Pharmacol.,* **2015**, *93*(4), 409-417. http://dx.doi.org/10.1016/j.bcp.2014.12.006 PMID: 25541285

[95] Kennedy-Lydon, T.; Rosenthal, N. Cardiac regeneration: epicardial mediated repair. *Proc. Biol. Sci.,* **2015**, *282*(1821), 20152147. http://dx.doi.org/10.1098/rspb.2015.2147 PMID: 26702046

[96] Durham, W.J.; Li, Y.-P.; Gerken, E.; Farid, M.; Arbogast, S.; Wolfe, R.R.; Reid, M.B. Fatiguing exercise reduces DNA-binding activity of NF-κB in skeletal muscle nuclei. *J Appl Physiol (1985),* **2004**, *97*(5), 1740-1745.

[97] Rabbani, S.; Soleimani, M.; Sahebjam, M.; Imani, M.; Haeri, A.; Ghiaseddin, A.; Nassiri, S.M.; Majd Ardakani, J.; Tajik Rostami, M.; Jalali, A.; Ahmadi Tafti, S.H. Simultaneous delivery of Wharton's jelly mesenchymal stem cells and insulin-like growth factor-1 in acute myocardial infarction. *Iran. J. Pharm. Res.,* **2018**, *17*(2), 426-441. PMID: 29881402

[98] Davis, M.E.; Hsieh, P.C.H.; Takahashi, T.; Song, Q.; Zhang, S.; Kamm, R.D.; Grodzinsky, A.J.; Anversa, P.; Lee, R.T. Local myocardial insulin-like growth factor 1 (IGF-1) delivery with biotinylated peptide nanofibers improves cell therapy for myocardial infarction. *Proc. Natl. Acad. Sci. USA,* **2006**, *103*(21), 8155-8160. http://dx.doi.org/10.1073/pnas.0602877103 PMID: 16698918

[99] Haider, H.Kh.; Jiang, S.; Idris, N.M.; Ashraf, M. IGF-1-overexpressing mesenchymal stem cells accelerate bone marrow stem cell mobilization via paracrine activation of SDF-1α/CXCR4 signaling to promote myocardial repair. *Circ. Res.,* **2008**, *103*(11), 1300-1308. http://dx.doi.org/10.1161/CIRCRESAHA.108.186742 PMID: 18948617

[100] Gómez-Mauricio, G.; Moscoso, I.; Martín-Cancho, M-F.; Crisóstomo, V.; Prat-Vidal, C.; Báez-Díaz, C.; Sánchez-Margallo, F.M.; Bernad, A. Combined administration of mesenchymal stem cells overexpressing IGF-1 and HGF enhances neovascularization but moderately improves cardiac regeneration in a porcine model. *Stem Cell Res. Ther.,* **2016**, *7*(1), 94.

http://dx.doi.org/10.1186/s13287-016-0350-z PMID: 27423905

[101] Vinciguerra, M.; Santini, M.P.; Claycomb, W.C.; Ladurner, A.G.; Rosenthal, N. Local IGF-1 isoform protects cardiomyocytes from hypertrophic and oxidative stresses via SirT1 activity. *Aging (Albany NY),* **2009**, *2*(1), 43-62. http://dx.doi.org/10.18632/aging.100107 PMID: 20228935

[102] Vinciguerra, M.; Santini, M.P.; Martinez, C.; Pazienza, V.; Claycomb, W.C.; Giuliani, A.; Rosenthal, N. mIGF-1/JNK1/SirT1 signaling confers protection against oxidative stress in the heart. *Aging Cell,* **2012**, *11*(1), 139-149. http://dx.doi.org/10.1111/j.1474-9726.2011.00766.x PMID: 22051242

[103] Choi, W.Y.; Gemberling, M.; Wang, J.; Holdway, J.E.; Shen, M.C.; Karlstrom, R.O.; Poss, K.D. *In vivo* monitoring of cardiomyocyte proliferation to identify chemical modifiers of heart regeneration. *Development,* **2013**, *140*(3), 660-666. http://dx.doi.org/10.1242/dev.088526 PMID: 23293297

[104] Hedhli, N.; Huang, Q.; Kalinowski, A.; Palmeri, M.; Hu, X.; Russell, R.R.; Russell, K.S. Endothelium-derived neuregulin protects the heart against ischemic injury. *Circulation,* **2011**, *123*(20), 2254-2262. http://dx.doi.org/10.1161/CIRCULATIONAHA.110.991125 PMID: 21555713

[105] Singh, A.P.; Umbarkar, P.; Guo, Y.; Force, T.; Gupte, M.; Lal, H. Inhibition of GSK-3 to induce cardiomyocyte proliferation: a recipe for *in situ* cardiac regeneration. *Cardiovasc. Res.,* **2019**, *115*(1), 20-30. http://dx.doi.org/10.1093/cvr/cvy255 PMID: 30321309

[106] Gassmann, M.; Casagranda, F.; Orioli, D.; Simon, H.; Lai, C.; Klein, R.; Lemke, G. Aberrant neural and cardiac development in mice lacking the ErbB4 neuregulin receptor. *Nature,* **1995**, *378*(6555), 390-394. http://dx.doi.org/10.1038/378390a0 PMID: 7477376

[107] Rentschler, S.; Zander, J.; Meyers, K.; France, D.; Levine, R.; Porter, G.; Rivkees, S.A.; Morley, G.E.; Fishman, G.I. Neuregulin-1 promotes formation of the murine cardiac conduction system. *Proc. Natl. Acad. Sci. USA,* **2002**, *99*(16), 10464-10469. http://dx.doi.org/10.1073/pnas.162301699 PMID: 12149465

[108] Rochais, F.; Fischmeister, R. Acute cardiac effects of neuregulin-1/ErbB signalling. *Cardiovasc. Res.,* **2010**, *88*(3), 393-394. http://dx.doi.org/10.1093/cvr/cvq316 PMID: 20926427

[109] Xin, M.; Olson, E.N.; Bassel-Duby, R. Mending broken hearts: cardiac development as a basis for adult heart regeneration and repair. *Nat. Rev. Mol. Cell Biol.,* **2013**, *14*(8), 529-541. http://dx.doi.org/10.1038/nrm3619 PMID: 23839576

[110] Begeman, I.J.; Kang, J. Transcriptional programs and regeneration enhancers underlying heart regeneration. *J. Cardiovasc. Dev. Dis.,* **2018**, *6*(1), 2. http://dx.doi.org/10.3390/jcdd6010002 PMID: 30583498

[111] Cai, M.X.; Shi, X.C.; Chen, T.; Tan, Z.N.; Lin, Q.Q.; Du, S.J.; Tian, Z.J. Exercise training activates neuregulin 1/ErbB signaling and promotes cardiac repair in a rat myocardial infarction model. *Life Sci.,* **2016**, *149*, 1-9. http://dx.doi.org/10.1016/j.lfs.2016.02.055 PMID: 26892146

[112] Polizzotti, B.D.; Ganapathy, B.; Walsh, S.; Choudhury, S.; Ammanamanchi, N.; Bennett, D.G.; dos Remedios, C.G.; Haubner, B.J.; Penninger, J.M.; Kühn, B. Neuregulin stimulation of cardiomyocyte regeneration in mice and human myocardium reveals a therapeutic window. *Sci. Transl. Med.,* **2015**, *7*(281), 281ra45. http://dx.doi.org/10.1126/scitranslmed.aaa5171 PMID: 25834111

[113] Rockey, D.C.; Bell, P.D.; Hill, J.A. Fibrosis--a common pathway to organ injury and failure. *N. Engl. J. Med.,* **2015**, *372*(12), 1138-1149. http://dx.doi.org/10.1056/NEJMra1300575 PMID: 25785971

[114] Gilbert, R.W.D.; Vickaryous, M.K.; Viloria-Petit, A.M. Signalling by transforming growth factor beta isoforms in wound healing and tissue regeneration. *J. Dev. Biol.,* **2016**, *4*(2), E21. http://dx.doi.org/10.3390/jdb4020021 PMID: 29615587

[115] Talman, V.; Ruskoaho, H. Cardiac fibrosis in myocardial infarction-from repair and remodeling to regeneration. *Cell Tissue Res.,* **2016**, *365*(3), 563-581. http://dx.doi.org/10.1007/s00441-016-2431-9 PMID: 27324127

[116] Frangogiannis, N.G. The inflammatory response in myocardial injury, repair, and remodelling. *Nat. Rev. Cardiol.,* **2014**, *11*(5), 255-265. http://dx.doi.org/10.1038/nrcardio.2014.28 PMID: 24663091

[117] Dobaczewski, M.; Chen, W.; Frangogiannis, N.G. Transforming growth factor (TGF)-β signaling in cardiac remodeling. *J. Mol. Cell. Cardiol.,* **2011**, *51*(4), 600-606. http://dx.doi.org/10.1016/j.yjmcc.2010.10.033 PMID: 21059352

[118] Frangogiannis, N.G. The role of transforming growth factor (TGF)-β in the infarcted myocardium. *J. Thorac. Dis.,* **2017**, *9*(Suppl. 1), S52-S63. http://dx.doi.org/10.21037/jtd.2016.11.19 PMID: 28446968

[119] Derynck, R.; Zhang, Y.E. Smad-dependent and Smad-independent pathways in TGF-beta family signalling. *Nature,* **2003**, *425*(6958), 577-584. http://dx.doi.org/10.1038/nature02006 PMID: 14534577

[120] Lv, Y.; Liu, B.; Wang, H.P.; Zhang, L. Intramyocardial implantation of differentiated rat bone marrow mesenchymal stem cells enhanced by TGF-β1 improves cardiac function in heart failure rats. *Braz. J. Med. Biol. Res.,* **2016**, *49*(6), e5273. http://dx.doi.org/10.1590/1414-431x20165273 PMID: 27254663

[121] Hanna, A.; Frangogiannis, N.G. The role of the TGF-β superfamily in myocardial infarction. *Front. Cardiovasc. Med.,* **2019**, *6*, 140. http://dx.doi.org/10.3389/fcvm.2019.00140 PMID: 31620450

[122] Behfar, A.; Zingman, L.V.; Hodgson, D.M.; Rauzier, J.M.; Kane, G.C.; Terzic, A.; Pucéat, M. Stem cell differentiation requires a paracrine pathway in the heart. *FASEB J.,* **2002**, *16*(12), 1558-1566. http://dx.doi.org/10.1096/fj.02-0072com PMID: 12374778

[123] Singh, A.; Singh, A.; Sen, D. Mesenchymal stem cells in cardiac regeneration: a detailed progress report of the last 6 years (2010-2015). *Stem Cell Res. Ther.,* **2016**, *7*(1), 82-82. http://dx.doi.org/10.1186/s13287-016-0341-0 PMID: 27259550

[124] Bartram, U.; Molin, D.G.; Wisse, L.J.; Mohamad, A.; Sanford, L.P.; Doetschman, T.; Speer, C.P.; Poelmann, R.E.; Gittenberger-de Groot, A.C. Double-outlet right ventricle and overriding tricuspid valve reflect disturbances of looping, myocardialization, endocardial cushion differentiation, and apoptosis in TGF-β(2)-knockout mice. *Circulation,* **2001**, *103*(22), 2745-2752. http://dx.doi.org/10.1161/01.CIR.103.22.2745 PMID: 11390347

[125] Dewald, O.; Ren, G.; Duerr, G.D.; Zoerlein, M.; Klemm, C.; Gersch, C.; Tincey, S.; Michael, L.H.; Entman, M.L.;

Frangogiannis, N.G. Of mice and dogs: species-specific differences in the inflammatory response following myocardial infarction. *Am. J. Pathol.,* **2004**, *164*(2), 665-677. http://dx.doi.org/10.1016/S0002-9440(10)63154-9 PMID: 14742270

[126] Ferreira, R.R.; Abreu, R.D.S.; Vilar-Pereira, G.; Degrave, W.; Meuser-Batista, M.; Ferreira, N.V.C.; da Cruz Moreira, O.; da Silva Gomes, N.L.; Mello de Souza, E.; Ramos, I.P.; Bailly, S.; Feige, J-J.; Lannes-Vieira, J.; de Araújo-Jorge, T.C.; Waghabi, M.C. TGF-β inhibitor therapy decreases fibrosis and stimulates cardiac improvement in a pre-clinical study of chronic Chagas' heart disease. *PLoS Negl. Trop. Dis.,* **2019**, *13*(7), e0007602. http://dx.doi.org/10.1371/journal.pntd.0007602 PMID: 31365537

[127] Hodges, M.M.; Zgheib, C.; Xu, J.; Hu, J.; Dewberry, L.C.; Hilton, S.A.; Allukian, M.W.; Gorman, J.H., III; Gorman, R.C.; Liechty, K.W. Differential expression of transforming growth factor-β1 is associated with fetal regeneration after myocardial infarction. *Ann. Thorac. Surg.,* **2019**, *108*(1), 59-66. http://dx.doi.org/10.1016/j.athoracsur.2018.12.042 PMID: 30690019

[128] Yndestad, A.; Ueland, T.; Øie, E.; Florholmen, G.; Halvorsen, B.; Attramadal, H.; Simonsen, S.; Frøland, S.S.; Gullestad, L.; Christensen, G.; Damås, J.K.; Aukrust, P. Elevated levels of activin A in heart failure: potential role in myocardial remodeling. *Circulation,* **2004**, *109*(11), 1379-1385. http://dx.doi.org/10.1161/01.CIR.0000120704.97934.41 PMID: 14993131

[129] Wang, Y.; Lu, P.; Zhao, D.; Sheng, J. Targeting the hedgehog signaling pathway for cardiac repair and regeneration. *Herz,* **2017**, *42*(7), 662-668. http://dx.doi.org/10.1007/s00059-016-4500-y PMID: 27878328

[130] Johnson, N.R.; Wang, Y. Controlled delivery of sonic hedgehog morphogen and its potential for cardiac repair. *PLoS One,* **2013**, *8*(5), e63075. http://dx.doi.org/10.1371/journal.pone.0063075 PMID: 23690982

[131] Lee, R.T.H.; Zhao, Z.; Ingham, P.W. Hedgehog signalling. *Development,* **2016**, *143*(3), 367-372. http://dx.doi.org/10.1242/dev.120154 PMID: 26839340

[132] Dunaeva, M.; Waltenberger, J. Hh signaling in regeneration of the ischemic heart. *Cell. Mol. Life Sci.,* **2017**, *74*(19), 3481-3490. http://dx.doi.org/10.1007/s00018-017-2534-9 PMID: 28523343

[133] Brennan, D.; Chen, X.; Cheng, L.; Mahoney, M.; Riobo, N.A. Noncanonical Hedgehog signaling. *Vitam. Horm.,* **2012**, *88*, 55-72. http://dx.doi.org/10.1016/B978-0-12-394622-5.00003-1 PMID: 22391299

[134] Kawagishi, H.; Xiong, J.; Rovira, I.I.; Pan, H.; Yan, Y.; Fleischmann, B.K.; Yamada, M.; Finkel, T. Sonic hedgehog signaling regulates the mammalian cardiac regenerative response. *J. Mol. Cell. Cardiol.,* **2018**, *123*, 180-184. http://dx.doi.org/10.1016/j.yjmcc.2018.09.005 PMID: 30236923

[135] Praktiknjo, S.D.; Saad, F.; Maier, D.; Ip, P.; Hipfner, D.R.J.J.B.C. Activation of Smoothened in the Hedgehog pathway unexpectedly increases $G\alpha_s$-dependent cAMP levels in *Drosophila. J. Biol. Chem.,* **2018**, *293*(35), 13496-13508. http://dx.doi.org/10.1074/jbc.RA118.001953 PMID: 30018136

[136] Carbe, C.J.; Cheng, L.; Addya, S.; Gold, J.I.; Gao, E.; Koch, W.J.; Riobo, N.A.J.A.J.P-H. Gi proteins mediate activation of the canonical hedgehog pathway in the myocardium. *Am. J. Physiol. Heart Circ. Physiol.,* **2014**, *307*(1), H66-H72. http://dx.doi.org/10.1152/ajpheart.00166.2014 PMID: 24816261

[137] Paulis, L.; Fauconnier, J.; Cazorla, O.; Thireau, J.; Soleti, R.; Vidal, B.; Ouillé, A.; Bartholome, M.; Bideaux, P.; Roubille, F.; Le Guennec, J.Y.; Andriantsitohaina, R.; Martínez, M.C.; Lacampagne, A. Activation of Sonic hedgehog signaling in ventricular cardiomyocytes exerts cardioprotection against ischemia reperfusion injuries. *Sci. Rep.,* **2015**, *5*, 7983. http://dx.doi.org/10.1038/srep07983 PMID: 25613906

[138] Rowton, M.; Hoffmann, A.D.; Steimle, J.D.; Yang, X.H.; Guzzetta, A.; Lazarevic, S.; Kim, C.; Deng, N.; Lu, E.; Jacobs-Li, J.; Yu, S.; Hanson, E.; Perez-Cervantes, C.; Chan, S.S-K.; Ikegami, K.; Garry, D.J.; Kyba, M.; Moskowitz, I.P. Hedgehog signaling controls progenitor differentiation timing during heart development. *Semin. Cell Dev. Biol.,* **2021**. http://dx.doi.org/10.1016/j.semcdb.2021.06.002 PMID: 34144893

[139] Mackie, A.R.; Klyachko, E.; Thorne, T.; Schultz, K.M.; Millay, M.; Ito, A.; Kamide, C.E.; Liu, T.; Gupta, R.; Sahoo, S.; Misener, S.; Kishore, R.; Losordo, D.W. Sonic hedgehog-modified human CD34+ cells preserve cardiac function after acute myocardial infarction. *Circ. Res.,* **2012**, *111*(3), 312-321. http://dx.doi.org/10.1161/CIRCRESAHA.112.266015 PMID: 22581926

[140] Hayden, M.S.; Ghosh, S. NF-κB, the first quarter-century: remarkable progress and outstanding questions. *Genes Dev.,* **2012**, *26*(3), 203-234. http://dx.doi.org/10.1101/gad.183434.111 PMID: 22302935

[141] Park, S.R.; Kim, K.H.; Kwun, M.J.; Lee, J.Y.; Won, R.; Han, C.W.; Choi, J.Y.; Joo, M. Differential Regulation of NF-κB and Nrf2 by Bojungikki-Tang Is Associated with Suppressing Lung Inflammation. *Evid. Based Complement. Alternat. Med.,* **2018**, *2018* http://dx.doi.org/10.1155/2018/5059469

[142] Gaspar-Pereira, S.; Fullard, N.; Townsend, P.A.; Banks, P.S.; Ellis, E.L.; Fox, C.; Maxwell, A.G.; Murphy, L.B.; Kirk, A.; Bauer, R.; Caamaño, J.H.; Figg, N.; Foo, R.S.; Mann, J.; Mann, D.A.; Oakley, F. The NF-κB subunit c-Rel stimulates cardiac hypertrophy and fibrosis. *Am. J. Pathol.,* **2012**, *180*(3), 929-939. http://dx.doi.org/10.1016/j.ajpath.2011.11.007 PMID: 22210479

[143] Tsoulfas, G.; Geller, D.A. NF-kappaB in transplantation: friend or foe? *Transpl. Infect. Dis.,* **2001**, *3*(4), 212-219. http://dx.doi.org/10.1034/j.1399-3062.2001.30405.x PMID: 11844153

[144] Frantz, S.; Fraccarollo, D.; Wagner, H.; Behr, T.M.; Jung, P.; Angermann, C.E.; Ertl, G.; Bauersachs, J. Sustained activation of nuclear factor kappa B and activator protein 1 in chronic heart failure. *Cardiovasc. Res.,* **2003**, *57*(3), 749-756. http://dx.doi.org/10.1016/S0008-6363(02)00723-X PMID: 12618236

[145] Peterson, J.M.; Wang, D.J.; Shettigar, V.; Roof, S.R.; Canan, B.D.; Bakkar, N.; Shintaku, J.; Gu, J-M.; Little, S.C.; Ratnam, N.M.; Londhe, P.; Lu, L.; Gaw, C.E.; Petrosino, J.M.; Liyanarachchi, S.; Wang, H.; Janssen, P.M.L.; Davis, J.P.; Ziolo, M.T.; Sharma, S.M.; Guttridge, D.C. NF-κB inhibition rescues cardiac function by remodeling calcium

genes in a Duchenne muscular dystrophy model. *Nat. Commun.,* **2018**, *9*(1), 3431. http://dx.doi.org/10.1038/s41467-018-05910-1 PMID: 30143619

[146] Ye, W.; Tang, X.; Yang, Z.; Liu, C.; Zhang, X.; Jin, J.; Lyu, J. Plasma-derived exosomes contribute to inflammation via the TLR9-NF-κB pathway in chronic heart failure patients. *Mol. Immunol.,* **2017**, *87*, 114-121. http://dx.doi.org/10.1016/j.molimm.2017.03.011 PMID: 28433888

[147] Okkenhaug, K. Signaling by the phosphoinositide 3-kinase family in immune cells. *Annu. Rev. Immunol.,* **2013**, *31*, 675-704. http://dx.doi.org/10.1146/annurev-immunol-032712-095946 PMID: 23330955

[148] Tian, H.; Guo, M.; Zhuang, Y.; Chu, J.; Zhang, S. Enhanced proliferation of bone marrow mesenchymal stem cells by co-culture with TM4 mouse Sertoli cells: involvement of the EGF/PI3K/AKT pathway. *Mol. Cell. Biochem.,* **2014**, *393*(1-2), 155-164. http://dx.doi.org/10.1007/s11010-014-2055-x PMID: 24748323

[149] Li, J.W.; Wang, X.Y.; Zhang, X.; Gao, L.; Wang, L.F.; Yin, X.H. (-)-Epicatechin protects against myocardial ischemia-induced cardiac injury via activation of the PTEN/PI3K/AKT pathway. *Mol. Med. Rep.,* **2018**, *17*(6), 8300-8308. http://dx.doi.org/10.3892/mmr.2018.8870 PMID: 29658565

[150] Chang, Z.; Zhang, Q.; Feng, Q.; Xu, J.; Teng, T.; Luan, Q.; Shan, C.; Hu, Y.; Hemmings, B.A.; Gao, X.; Yang, Z. Deletion of Akt1 causes heart defects and abnormal cardiomyocyte proliferation. *Dev. Biol.,* **2010**, *347*(2), 384-391. http://dx.doi.org/10.1016/j.ydbio.2010.08.033 PMID: 20816796

[151] Chen, J.; Crawford, R.; Chen, C.; Xiao, Y. The key regulatory roles of the PI3K/Akt signaling pathway in the functionalities of mesenchymal stem cells and applications in tissue regeneration. *Tissue Eng. Part B Rev.,* **2013**, *19*(6), 516-528. http://dx.doi.org/10.1089/ten.teb.2012.0672 PMID: 23651329

[152] Leach, J.P.; Martin, J.F. Cardiomyocyte proliferation for therapeutic regeneration. *Curr. Cardiol. Rep.,* **2018**, *20*(8), 63. http://dx.doi.org/10.1007/s11886-018-1011-x PMID: 29904823

[153] Bareja, A.; Hodgkinson, C.P.; Payne, A.J.; Pratt, R.E.; Dzau, V.J. HASF (C3orf58) is a novel ligand of the insulin-like growth factor 1 receptor. *Biochem. J.,* **2017**, *474*(5), 771-780. http://dx.doi.org/10.1042/BCJ20160976 PMID: 28096202

[154] Yang, B.; Yan, P.; Gong, H.; Zuo, L.; Shi, Y.; Guo, J.; Guo, R.; Xie, J.; Li, B. TWEAK protects cardiomyocyte against apoptosis in a PI3K/AKT pathway dependent manner. *Am. J. Transl. Res.,* **2016**, *8*(9), 3848-3860. PMID: 27725864

[155] Leach, J.P.; Heallen, T.; Zhang, M.; Rahmani, M.; Morikawa, Y.; Hill, M.C.; Segura, A.; Willerson, J.T.; Martin, J.F. Hippo pathway deficiency reverses systolic heart failure after infarction. *Nature,* **2017**, *550*(7675), 260-264. http://dx.doi.org/10.1038/nature24045 PMID: 28976966

[156] Heallen, T.; Morikawa, Y.; Leach, J.; Tao, G.; Willerson, J.T.; Johnson, R.L.; Martin, J.F. Hippo signaling impedes adult heart regeneration. *Development,* **2013**, *140*(23), 4683-4690. http://dx.doi.org/10.1242/dev.102798 PMID: 24255096

[157] von Gise, A.; Lin, Z.; Schlegelmilch, K.; Honor, L.B.; Pan, G.M.; Buck, J.N.; Ma, Q.; Ishiwata, T.; Zhou, B.; Camargo, F.D.; Pu, W.T. YAP1, the nuclear target of Hippo signaling, stimulates heart growth through cardiomyocyte proliferation but not hypertrophy. *Proc. Natl. Acad. Sci. USA,* **2012**, *109*(7), 2394-2399. http://dx.doi.org/10.1073/pnas.1116136109 PMID: 22308401

[158] Jang, J.W.; Kim, M.K.; Bae, S.C. Reciprocal regulation of YAP/TAZ by the Hippo pathway and the Small GTPase pathway. *Small GTPases,* **2020**, *11*(14), 280-288. http://dx.doi.org/10.1080/21541248.2018.1435986 PMID: 29457552

[159] Ikeda, S.; Sadoshima, J. Regulation of myocardial cell growth and death by the hippo pathway. *Circ. J.,* **2016**, *80*(7), 1511-1519. http://dx.doi.org/10.1253/circj.CJ-16-0476 PMID: 27302848

[160] Zhou, Q.; Li, L.; Zhao, B.; Guan, K.L. The hippo pathway in heart development, regeneration, and diseases. *Circ. Res.,* **2015**, *116*(8), 1431-1447. http://dx.doi.org/10.1161/CIRCRESAHA.116.303311 PMID: 25858067

[161] Haskins, J.W.; Nguyen, D.X.; Stern, D.F. Neuregulin 1-activated ERBB4 interacts with YAP to induce Hippo pathway target genes and promote cell migration. *Sci. Signal.,* **2014**, *7*(355), ra116. http://dx.doi.org/10.1126/scisignal.2005770 PMID: 25492965

[162] Xiao, Y.; Hill, M.C.; Zhang, M.; Martin, T.J.; Morikawa, Y.; Wang, S.; Moise, A.R.; Wythe, J.D.; Martin, J.F. Hippo signaling plays an essential role in cell state transitions during cardiac fibroblast development. *Dev. Cell,* **2018**, *45*(2), 153-169. http://dx.doi.org/10.1016/j.devcel.2018.03.019 PMID: 29689192

[163] Xin, M.; Kim, Y.; Sutherland, L.B.; Qi, X.; McAnally, J.; Schwartz, R.J.; Richardson, J.A.; Bassel-Duby, R.; Olson, E.N. Regulation of insulin-like growth factor signaling by Yap governs cardiomyocyte proliferation and embryonic heart size. *Sci. Signal.,* **2011**, *4*(196), ra70. http://dx.doi.org/10.1126/scisignal.2002278 PMID: 22028467

[164] Wang, J.; Liu, S.; Heallen, T.; Martin, J.F. The Hippo pathway in the heart: pivotal roles in development, disease, and regeneration. *Nat. Rev. Cardiol.,* **2018**, *15*(11), 672-684. http://dx.doi.org/10.1038/s41569-018-0063-3 PMID: 30111784

[165] Moya, I.M.; Halder, G. Hippo-YAP/TAZ signalling in organ regeneration and regenerative medicine. *Nat. Rev. Mol. Cell Biol.,* **2019**, *20*(4), 211-226. http://dx.doi.org/10.1038/s41580-018-0086-y PMID: 30546055

[166] Wang, P.; Mao, B.; Luo, W.; Wei, B.; Jiang, W.; Liu, D.; Song, L.; Ji, G.; Yang, Z.; Lai, Y-Q.; Yuan, Z. The alteration of Hippo/YAP signaling in the development of hypertrophic cardiomyopathy. *Basic Res. Cardiol.,* **2014**, *109*(5), 435. http://dx.doi.org/10.1007/s00395-014-0435-8 PMID: 25168380

[167] Mia, M.M.; Singh, M.K. The hippo signaling pathway in cardiac development and diseases. *Front. Cell Dev. Biol.,* **2019**, *7*, 211. http://dx.doi.org/10.3389/fcell.2019.00211 PMID: 31632964

[168] Lin, Z.; von Gise, A.; Zhou, P.; Gu, F.; Ma, Q.; Jiang, J.; Yau, A.L.; Buck, J.N.; Gouin, K.A.; van Gorp, P.R.; Zhou, B.; Chen, J.; Seidman, J.G.; Wang, D.Z.; Pu, W.T. Cardiac-specific YAP activation improves cardiac function and sur-

vival in an experimental murine MI model. *Circ. Res.,* **2014**, *115*(3), 354-363. http://dx.doi.org/10.1161/CIRCRESAHA.115.303632 PMID: 24833660

[169] Triastuti, E.; Nugroho, A.B.; Zi, M.; Prehar, S.; Kohar, Y.S.; Bui, T.A.; Stafford, N.; Cartwright, E.J.; Abraham, S.; Oceandy, D. Pharmacological inhibition of Hippo pathway, with the novel kinase inhibitor XMU-MP-1, protects the heart against adverse effects during pressure overload. *Br. J. Pharmacol.,* **2019**, *176*(20), 3956-3971. http://dx.doi.org/10.1111/bph.14795 PMID: 31328787

[170] Liu, S.; Martin, J.F. The regulation and function of the Hippo pathway in heart regeneration. *Wiley Interdiscip. Rev. Dev. Biol.,* **2019**, *8*(1), e335. http://dx.doi.org/10.1002/wdev.335 PMID: 30169913

[171] Camberos, V.; Baio, J.; Bailey, L.; Hasaniya, N.; Lopez, L.V.; Kearns-Jonker, M. Effects of spaceflight and simulated microgravity on YAP1 expression in cardiovascular progenitors: implications for cell-based repair. *Int. J. Mol. Sci.,* **2019**, *20*(11), E2742. http://dx.doi.org/10.3390/ijms20112742 PMID: 31167392

[172] Flinn, M.A.; Jeffery, B.E.; O'Meara, C.C.; Link, B.A. Yap is required for scar formation but not myocyte proliferation during heart regeneration in zebrafish. *Cardiovasc. Res.,* **2019**, *115*(3), 570-577. http://dx.doi.org/10.1093/cvr/cvy243 PMID: 30295714

[173] Ladage, D.; Yaniz-Galende, E.; Rapti, K.; Ishikawa, K.; Tilemann, L.; Shapiro, S.; Takewa, Y.; Muller-Ehmsen, J.; Schwarz, M.; Garcia, M.J.; Sanz, J.; Hajjar, R.J.; Kawase, Y. Stimulating myocardial regeneration with periostin Peptide in large mammals improves function post-myocardial infarction but increases myocardial fibrosis. *PLoS One,* **2013**, *8*(5), e59656. http://dx.doi.org/10.1371/journal.pone.0059656 PMID: 23700403

[174] Shimazaki, M.; Nakamura, K.; Kii, I.; Kashima, T.; Amizuka, N.; Li, M.; Saito, M.; Fukuda, K.; Nishiyama, T.; Kitajima, S.; Saga, Y.; Fukayama, M.; Sata, M.; Kudo, A. Periostin is essential for cardiac healing after acute myocardial infarction. *J. Exp. Med.,* **2008**, *205*(2), 295-303. http://dx.doi.org/10.1084/jem.20071297 PMID: 18208976

[175] Chen, Z.; Xie, J.; Hao, H.; Lin, H.; Wang, L.; Zhang, Y.; Chen, L.; Cao, S.; Huang, X.; Liao, W.; Bin, J.; Liao, Y. Ablation of periostin inhibits post-infarction myocardial regeneration in neonatal mice mediated by the phosphatidylinositol 3 kinase/glycogen synthase kinase 3β/cyclin D1 signalling pathway. *Cardiovasc. Res.,* **2017**, *113*(6), 620-632. http://dx.doi.org/10.1093/cvr/cvx001 PMID: 28453729

[176] Cho, Y.H.; Cha, M.J.; Song, B.W.; Kim, I.K.; Song, H.; Chang, W.; Lim, S.; Ham, O.; Lee, S.Y.; Choi, E.; Kwon, H.M.; Hwang, K.C. Enhancement of MSC adhesion and therapeutic efficiency in ischemic heart using lentivirus delivery with periostin. *Biomaterials,* **2012**, *33*(5), 1376-1385. http://dx.doi.org/10.1016/j.biomaterials.2011.10.078 PMID: 22112759

[177] Dorn, G.W. II. Periostin and myocardial repair, regeneration, and recovery. *N. Engl. J. Med.,* **2007**, *357*(15), 1552-1554. http://dx.doi.org/10.1056/NEJMcibr074816 PMID: 17928607

[178] Maddaluno, L.; Urwyler, C.; Werner, S. Fibroblast growth factors: key players in regeneration and tissue repair. *Development,* **2017**, *144*(22), 4047-4060. http://dx.doi.org/10.1242/dev.152587 PMID: 29138288

[179] Missinato, M.A.; Saydmohammed, M.; Zuppo, D.A.; Rao, K.S.; Opie, G.W.; Kühn, B.; Tsang, M. Dusp6 attenuates Ras/MAPK signaling to limit zebrafish heart regeneration. *Development,* **2018**, *145*(5), dev157206. http://dx.doi.org/10.1242/dev.157206 PMID: 29444893

[180] Lian, H.; Ma, Y.; Feng, J.; Dong, W.; Yang, Q.; Lu, D.; Zhang, L. Heparin-binding EGF-like growth factor induces heart interstitial fibrosis via an Akt/mTor/p70s6k pathway. *PLoS One,* **2012**, *7*(9), e44946. http://dx.doi.org/10.1371/journal.pone.0044946 PMID: 22984591

[181] Wang, Y.; Ahmad, N.; Wani, M.A.; Ashraf, M. Hepatocyte growth factor prevents ventricular remodeling and dysfunction in mice *via* Akt pathway and angiogenesis. *J. Mol. Cell. Cardiol.,* **2004**, *37*(5), 1041-1052. http://dx.doi.org/10.1016/j.yjmcc.2004.09.004 PMID: 15522281

[182] Kim, J.; Wu, Q.; Zhang, Y.; Wiens, K.M.; Huang, Y.; Rubin, N.; Shimada, H.; Handin, R.I.; Chao, M.Y.; Tuan, T-L.; Starnes, V.A.; Lien, C.L. PDGF signaling is required for epicardial function and blood vessel formation in regenerating zebrafish hearts. *Proc. Natl. Acad. Sci. USA,* **2010**, *107*(40), 17206-17210. http://dx.doi.org/10.1073/pnas.0915016107 PMID: 20858732

[183] Chong, J.J.; Reinecke, H.; Iwata, M.; Torok-Storb, B.; Stempien-Otero, A.; Murry, C.E. Progenitor cells identified by PDGFR-alpha expression in the developing and diseased human heart. *Stem Cells Dev.,* **2013**, *22*(13), 1932-1943. http://dx.doi.org/10.1089/scd.2012.0542 PMID: 23391309

[184] Yue, Z.; Chen, J.; Lian, H.; Pei, J.; Li, Y.; Chen, X.; Song, S.; Xia, J.; Zhou, B.; Feng, J.; Zhang, X.; Hu, S.; Nie, Y. PDGFR-β Signaling Regulates Cardiomyocyte Proliferation and Myocardial Regeneration. *Cell Rep.,* **2019**, *28*(4), 966-978. http://dx.doi.org/10.1016/j.celrep.2019.06.065 PMID: 31340157

[185] Beets, K.; Staring, M.W.; Criem, N.; Maas, E.; Schellinx, N.; de Sousa Lopes, S.M.C.; Umans, L.; Zwijsen, A. BMP-SMAD signalling output is highly regionalized in cardiovascular and lymphatic endothelial networks. *BMC Dev. Biol.,* **2016**, *16*(1), 34. http://dx.doi.org/10.1186/s12861-016-0133-x PMID: 27724845