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The roles of Wnt/β-catenin pathway in tissue development and regenerative medicine

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Regenerative medicine is a translational field which combines tissue engineering and molecular biology to construct spare organs or help injured or defective tissues to regenerate or restore their normal functions. This is particularly important with specific organs such as heart, central nervous system, retina, or limbs which possess very limited regenerative capacity. As such, regenerative medicine has received peculiar attention in the last decade. In this regard, Wnt/β-catenin signaling pathway has been subject to intensive research, since it plays many essential roles in the regulation of the progenitor cell fate, developmental decisions, proliferation during embryonic development, and adult tissue homeostasis. In this paper, we will briefly introduce Wnt/β-catenin signaling pathway and discuss how it integrally contributes to both stem and cancer stem cell maintenance. Finally, we summarize the current understanding of the role of Wnt/β-catenin signaling in the development and regeneration of heart, lung, liver, bone, and cartilage.

KEYWORDS
regeneration, stem cell, tissue engineering, Wnt signaling pathway

1 | INTRODUCTION

Regenerative medicine, as a new broad scientific and medical field, is generally focused on utilization of the regenerative capabilities of the body along with the power of stem cells in order to restore the function of damaged cells, tissues, as well as organs (Fisher & Mauck, 2013). In other words, regenerative medicine combines tissue engineering, cell transplantation and gene therapies, stem cells, and therapeutic cloning to generate tissues and organs with better biological functions and structures (Fisher & Mauck, 2013; Jahanban-Esfahlan, Seidi et al., 2017). All organisms are continuously exposed to multiple injuries, ranging from physical to biochemical ones. However, the regenerative capacities to recover the normal function widely vary across different organs (Stoick-Cooper, Weidinger et al., 2007). In contrast to other vertebrates, human's regeneration ability is very limited. For instance, that they can just regenerate an injured liver and renew limited damages to muscle, bone, cornea, kidney, and digit tips, but they are not capable of the regeneration of the other tissues such as the heart, central nervous system, retina, or limbs (Majidinia, Sadeghpour, Mehrzadi et al., 2017; Poss, Wilson, & Keating, 2002; Stoick-Cooper, Moon, & Weidinger, 2007). Therefore, regenerative medicine has become the center of attention in recent decades and opens new avenues in the offering therapies for patients with end-stage organ failure. Since Wnt/β-catenin signaling pathway has essential roles in the regulation of the progenitor cell fate, developmental decisions, proliferation during embryonic development, and adult tissue homeostasis, it has been the subject of a huge number of researches for investigating its possible role in progenitor cell function during regeneration (Badalzadeh et al., 2015; Jahanban-Esfahlan, Mehrzadi

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et al., 2017). Multiple studies have reported the expression of Wnt ligands and components of the β-catenin signaling pathway in regenerating amphibian and fish appendages, and other studies have documented that Wnt/β-catenin signaling is functionally contributed in the proliferation of cells during regeneration of mammalian muscle, liver, and bone (Stoick-Cooper, Weidinger et al., 2007). Here, we will bring a brief introduction on the Wnt/β-catenin signaling and how the Wnt/β-catenin pathway is integrally contributed in both stem and cancer stem cell maintenance. Then, we summarize the current understanding of the roles of Wnt/β-catenin signaling in heart, lung, liver, bone, cartilage, development, and regeneration.

2 | SIGNALING THROUGH WNT/β-CATENIN PATHWAY

The Wnt/β-catenin signaling pathway is one of the early-activated pathways during regeneration, mostly through post-transcriptional modifications (Shiah, Shieh, & Chang, 2016). This signaling has a pivotal function in cell proliferation, differentiation, growth, survival, development, regeneration, self-renewal, and cell fate determination (Shi et al., 2016). This signaling pathway also plays important roles throughout development, for example, maintenance of intestinal homeostasis, regulation of hematopoietic stem/progenitors, lineage commitment of progenitors during hematopoiesis, etc. (Majidinia & Yousefi, 2017; Malhotra & Kincade, 2009). Other cell replacement activities that occur in the human body, for example, skin and liver turnover, hair growth, myogenesis, and neurogenesis, also involve Wnt signal transduction. Additionally, there is general agreement that Wnt signaling is important in stem cell biology. The Wnt/β-catenin signaling has been reported to maintain pluripotency in embryonic stem cells and is critical for the expansion of neural progenitors thereby increasing brain size (Miyabayashi et al., 2007; Mohammadian et al., 2013; Saleh, Shamsasanjan, Movassaghpourakbari, Akbarzadehlaleh, & Molaeipour, 2015; Sato, Meijer, Skaltsounis, Greengard, & Brivanlou, 2004; Zechner et al., 2003). The Wnt/beta-catenin signaling is also required for neural differentiation of ES cells, fate decision in neural crest stem cells and Wnt3a has been reported to promote differentiation into both the neural and astrocytic lineages by inhibiting neural stem cell maintenance (Otero, Fu, Kan, Cuadra, & Kessler, 2004; Zechner et al., 2003). Clearly, Wnt/beta-catenin signaling plays a critical role in lineage decision/commitment. Using a selective antagonist of the CBP/beta-catenin interaction ICG-001, the distinct roles of the coactivators CBP and p300 in the Wnt/beta-catenin signaling cascade was demonstrated. It was showed that CBP/beta-catenin-mediated transcription is critical for stem cell/progenitor cell maintenance and proliferation, whereas, a switch to p300/beta-catenin-mediated transcription is the initial critical step to initiate differentiation and a decrease in cellular potency (Emami et al., 2004).

The Wnt/β-catenin signaling pathway is initiated by the binding of the Wnt proteins to their seven-pass transmembrane Frizzled (Fz) receptors and results in the activation of the central player of the pathway, β-catenin at downstream (Badalzadeh et al., 2015). In the Wnt-off state, when an active Wnt ligand is absent, a cytoplasmic complex of glycogen synthase kinase 3β (Gsk3β) and casein kinase 1 (Ck1) phosphorylate the β-catenin at four N-terminal residues, as it is bound to the scaffolding protein axin, and the tumor suppressor adenomatous polyposis coli (Apc) (Badalzadeh et al., 2015). This Phosphorylated β-catenin is degraded by the proteasome after ubiquitination (Rao & Kühl, 2010). In the Wnt-on state, or when a Wnt ligand is available, Fz receptors and low-density lipoprotein receptor-related protein (LRP) 5/6, are activated upon ligand binding. Receptor occupancy leads to the phosphorylation of LRP5/6 by Gsk3β and Ck1 in its cytoplasmic region, and subsequently the recruitment of the dishevelled (DVL) 1–3 and axin (Rao & Kühl, 2010). The result is the inhibition of the destruction of complex and the stabilization of β-catenin in the cytoplasm. β-catenin then translocate into the nucleus, which is mediated by interaction with Fam53b/Smp (Yu & Virshup, 2014).

β-catenin initiates the transcription of its target gene with a nuclear binding partner, transcription factors of the T cell factor (Tcf)/lymphoid enhancer factor (Lef) family. In addition to mentioned pathway, which is known as canonical Wnt/β-catenin pathway, two other forms of signaling pathway also exist. The signals of Wnt/Ca^{2+} pathway are transmitted via calmodulin kinase II and protein kinase C (Bengoa-Vergniory & Kypta, 2015). The Wnt/JNK or planar cell polarity pathway signals via small GTPases, and plays important roles in the cytoskeletal organization and epithelial cell polarity. Some members of the family of Wnt ligands, from which 19 members have been identified so far, activate both canonical and the non-canonical pathways, whereas some others, such as WNT5a, known to be specific for the non-canonical pathway (Majidinia, Alizadeh, Yousefi, Akbarzadeh, & Zarghami, 2016).

Deregulation of Wnt signaling contributes to the disease sates such as cancer, metabolic and also degenerative diseases. Thus, inhibitors of this pathway could be used to reverse the pathological state (Logan & Nusse, 2004). As such, deregulation of Wnt/β-catenin pathway implicates in the promotion of fibrosis, cardiomyocyte hypertrophy, and heart injury. Transient modulation of Wnt/β-catenin signaling via shRNA knockdown or small molecule inhibitors such as Cardiogenol C affect the differentiation of human pluripotent stem cells (hPSC) to cardiomyocytes. While Wnt inhibition at an earlier phase of cardiac differentiation hinders hPSC differentiation, a late phase inhibition promotes differentiation into cardiac cells (Ozhan & Weidinger, 2015).

Many small molecules have been recognized as potential inhibitors of Wnt/Catenin signaling (Voronkov & Krauss, 2013). While many clinically used anti-metabolites and alkylating agents fail to inhibit WNT signaling, the small molecule Ethacrynic Acid (EA) used as diuretic agent acts as a potent blocker of Wnt/β-Catenin signaling. EA is shown to induce apoptosis in different cancer cells such as Chronic Lymphocytic Leukemia Cells through blocking the trans-activation function of β-catenin by interaction with LEF-1 and also inhibiting Glutathione S-transferase (GST) activity (Lu et al., 2009). Ciclopirox olamin which is shown to induce apoptosis by affecting the cell cycle proteins (CDKs, Bcl-xL, survivin), is also shown as Wnt/catenin

signaling inhibitor by reducing the levels of LEF-1 in the murine myeloma cell line MPC1 (Wall & Schmidt-Wolf, 2014). Given to the pivotal role of WNT pathway in cell fate, potent inhibitors of Wnt signaling such as Ethacrynic Acid could be integrated into the contemporary regenerative medicine advocating this novel field of study to accomplish its full potential in the clinic.

3 | REGENERATIVE MEDICINE

From the first introduction of the term "regenerative medicine" in 1992, the popularity of this field has increased because of many reasons (Kaiser, 1991). One of the most important reasons is the designing of novel biological substitutes with the ability of the restoration and maintenance of normal function, which is the main scope of tissue engineering, as a major component of regenerative medicine (Fisher & Mauck, 2013). In fact, tissue engineers combine cell transplantation, biomaterials science, life science principles, and mechanical engineering principles to construct new tissues for implantations (Fisher & Mauck, 2013). This purpose is achieved by using two tissue engineering strategies; acellular and cellular matrices (Domenech, Polo-Corrales, Ramirez-Vick, & Freytes, 2016;Montazami, Kheir Andish, Majidi, Yousefi, & Yousefi, 2015). As it is inferred from its name, acellular matrices consist of a matrix with virus vectors or plasmids, to secretion of specific growth factors or hormones, extracellular matrix (ECM)-proteins including collagen, hyaluronic acid, and fibronectin, to insure biocompatibility, and without any cells and act by binding to the host and matrix–cell interactions (Bonadio, Smiley, Patil, & Goldstein, 1999; Jimenez & Jimenez, 2004).

Contrary to acellular matrices, cellular products consist of a collagen or polyglactin scaffold containing living cells, keratinocytes, and fibroblasts (Montazami et al., 2015). For using these cells for tissue engineering purposes, individual cells are separated from a piece of the target tissue and then implanted directly into the host. In some cases, the dissociated cells are cultured, attached to support matrix, and reimplanted into the host (Jimenez & Jimenez, 2004). From among three different sources of donor tissues, including heterologous (different species such as bovine), allogeneic (same species, different individual), and autologous (derived from the biopsy of tissue obtained from the host), autologous cells are most preferred due to minimized risk of rejection (Atala, 2007). However, in some situations such as end-stage organ failure, where a tissue biopsy may not produce enough cells for expansion, or when there is no possibility of expanding cells from a distinct organ, such as the pancreas, stem cells are being alternative sources (Majidinia, Sadeghpour, & Yousefi, 2017). In addition, the proliferation capacity of many adult organ-specific cells is low and long-term in vitro cultivation, in particular, reduces their functional quality. Their differentiation potential and their capacity to undergo extensive replication have been drawn so much attention to pluripotent or multipotent stem cells (Ringe, Kaps, Burmester, & Sittinger, 2002).

Stem cells including embryonic stem cells (ESCs), bone marrow mesenchymal stem cells (BM-MSCs), umbilical cord-derived mesenchymal stem cells (UC-MSCs), induced pluripotent stem cells (iPSCs), and other cells derived from fetal tissue, or adult sources (bone marrow, fat, skin), have the future potential to be used therapeutically (Majidinia, Sadeghpour, & Yousefi, 2017). Therapeutic cloning, as another component of regenerative medicine, has also been known as nuclear transplantation, nuclear transfer, and nuclear cloning and plays an undeniable pivotal role in the development of this field (Hall & Stojkovic, 2006). Therapeutic cloning involves the introduction of a nucleus from a donor cell into an enucleated oocyte to produce an embryo with a genetic makeup identical to its cell source. As a result, therapeutic cloning provides an alternative limitless source of cells used in tissue engineering and tissue replacement applications (Hall & Stojkovic, 2006). Because of an incredible progress in tissue engineering and regenerative medicine during the last 2 decades, some of the biological products and therapies are commercially available with Food and Drug Administration (FDA) approval. Autologous or allogeneic differentiated cells, which still maintain proliferative capacity, are among these FDA approved products (Mao & Mooney, 2015). The first biological product consisted of autologous chondrocytes, which has received the FDA-approval, is Carticel. It is applied in the treatment of focal articular cartilage defects. laViv, which is consisted of autologous fibroblasts is applied for the improvement of the appearance of nasolabial fold wrinkles; Epicel, which is consisted of autologous keratinocytes, is applied to the severe burn wounds, and Celution, which is a medical device for the extraction of cells from adipose tissue-derived from liposuction are other common therapies generated by regenerative medicine (Mao & Mooney, 2015). Generally, the efficacies of these products are better or comparable to pre-existing products.

Cell transplantation/cell therapy is another promising dimension of regenerative medicine to restore the lost function of injured or damaged tissue rather than producing a new organ. Application of cell therapy varies from a simple blood transfusion for cell replacement therapy to implementation of pluripotent stem cells to treat disease conditions including cardiovascular implications, such as myocardial infarction; neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's, Hormonal dysfunction, such as diabetes; or damages in the other organs such as cornea, joints, bones, skin, and skeletal muscle (Sanchez, Schimmang, & Garcia-Sancho, 2012). The cell resources for cell therapy include primary cells or embryonic stem cells/multipotent adult progenitor cells. Some cell therapies have been established and accepted for clinical application, including pancreatic islet transplantation, or artificial skin derived from keratinocytes (O'Brien & Barry, 2009). Though stem cell based therapies represent encouraging results, the insufficiency of the initial material may be a serious constraint and one switch to xenotransplants rather than allotransplants derived from domestic animals, as suitable and abundant donors for tissue/cell transplantation. Animals such as pigs could be used as a source of a variety of primary cells in sufficient quantities to progress cell therapy to the clinic (Edge, Gosse, & Dinsmore, 1998).

The purpose of regenerative medicine could also be pursued by gene therapy techniques. By transferring genetic material, gene

therapy introduces a new function to cells. For a therapeutic effect, gene vectors should be safe and ensure maintained expression of the desired gene in enough number of the cell population (Seo et al., 2013). Ex vivo lenti-or retroviral vectors, along with viral and nonviral vectors, in vivo, ex vivo, and in situ strategies are examples of gene transfer agents at present. Induced progenitor stem cells (iPS), as well as stem cells with a natural source such as adult tissues, hematopoietic, embryonic, or mesenchymal cells can be adapted by gene therapy for practice in regenerative medicine. Though an obvious clinical benefit is shown for hematopoietic stem cells, iPS cells hold enormous prospective with no ethical issues (Munoz Ruiz & Regueiro, 2012).

4 | WNT/β-CATENIN PATHWAY AND STEM CELLS CONTROL

As being one of the most important components of regenerative medicine, special attention has been given to the use and collection of stem cells. ESCs could allow the production of type-matched tissues for each patient, either by the use of nuclear cloning or via stem cell banking (Hewitt, Priddle, Thomson, Wojtacha, & McWhir, 2007). These cells have two significant properties: the capability of differentiation into various specialized cell types, and capability of proliferation in an undifferentiated, but pluripotent (self-renew) state (Kühl & Kühl, 2013). The isolation of these cells is achieved by immunosurgery from the inner cell mass of the embryo during the blastocyst stage (after about six cleavage divisions of the fertilized egg) and are usually grown on feeder layers consisting of mouse embryonic fibroblasts or human feeder cells (Kühl & Kühl, 2013). Various studies have recently reported the involvement of Wnt/β-catenin signaling pathways in murine and human ESCs. One of the most interesting facts about the impact of Wnt/β-catenin signaling on the ECSs has been achieved from the observation that Wnt proteins are contributed in the maintenance of the pluripotency in murine and human ES cells (Sato et al., 2004; Singla, Schneider, LeWinter, & Sobel, 2006). The treatment period is an important factor in the effects of the Wnt proteins in ESCs pluripotency, such that some studies showed that long-term treatment of ESCs with Wnt3a caused differentiation toward a mesendodermal lineage (Bakre et al., 2007; Lindsley, Gill, Kyba, Murphy, & Murphy, 2006). In addition, previous documents indicated that the key components of Wnt/β-catenin signaling including Wnt3, 5a, 5b, 7a, 7b, 8a, 8b, 9a, and 11, all Frizzled receptors and Ror2, are expressed in ESCs (Figure 1). They also indicated that ESCs responded to activation of the Wnt/β-catenin signaling pathway (Katoh, 2008; Sato et al., 2004). Mouse ESCs are maintained by LIF-Stat3 signaling through transcriptional activation of Myc gene. Myc is the common transcriptional target of LIF-Stat3 and canonical Wnt signaling cascades. Because Myc protein is further stabilized by canonical Wnt signaling cascade, activation of canonical Wnt signaling cascade is necessary for the maintenance of undifferentiated mouse ESCs (Cartwright et al., 2005; Hao, Li, Qi, Zhao, & Zhao, 2006; Sato et al., 2004). Mesenchymal stem cells (MSCs) such as BM-MSCs and UC-MSCs are somatic stem cells are other most practical cell sources in regenerative medicine. These cells are found in numerous tissues including bone marrow, umbilical cord blood, and adipose tissues.

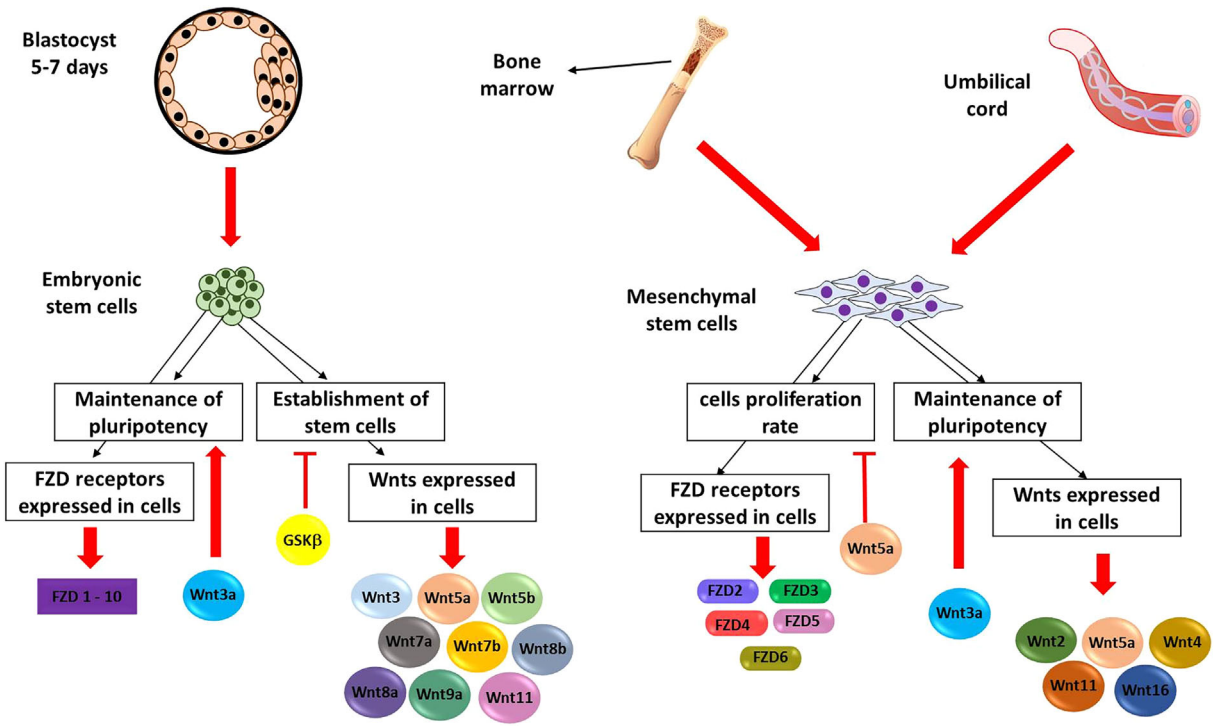

FIGURE 1 Wnt/β-catenin pathway and stem cells control

The MSCs can differentiate into a wide range of cells such as osteocytes, fibroblasts, mesoderm-derived chondrocytes, myocytes, adipocytes, nonmesoderm-derived hepatocytes, and neurons (Ling, Nurcombe, & Cool, 2009). These cells can be isolated as a fraction of the adherent bone marrow colony forming units-fibroblastic (CFU-F) (Majidinia, Sadeghpour, & Yousefi, 2017). UC-MSCs are also similar to BM-MSCs in the case of gene expression profile, however, they are able to differentiate into adipocytes, osteoblasts, hepatocytes, and neuronal-like cells (Majidinia, Sadeghpour, & Yousefi, 2017). Similar to ESCs, the regulation of proliferation and differentiation of MSCs is also affected by Wnt/β-catenin signaling. A huge number of conducted studies have reported the expression of Wnt ligands including; Wnt2, Wnt4, Wnt5a, Wnt11, and Wnt16; numerous Wnt receptors, including FZD2, 3, 4, 5, and 6; and various coreceptors and Wnt inhibitors in MSCs as well as (Etheridge, Spencer, Heath, & Genever, 2004; Ling et al., 2009; Ross et al., 2000; Wagner et al., 2005). Furthermore, canonical Wnt/β-catenin signaling plays a substantial role in the maintenance of self-renewing and undifferentiated state in MSCs (Boland, Perkins, Hall, & Tuan, 2004; Cho et al., 2006). Due to increase in self-renewal potential and a decrease in apoptosis, cell cultures treatment with Wnt3a enhance the multipotential population of MSCs as well as human adipose-derived stem cells (Baek et al., 2003). Additionally, the overexpression of LRP5 has been shown to increase the proliferation rate of MSCs (Baksh, Boland, & Tuan, 2007). In contrast to Wnt3a, Wnt5a inhibited the proliferation of MSCs by activating the non-canonical pathway (Baksh et al., 2007; Baksh & Tuan, 2007). The dual effects of Wnt/β-catenin signaling, in which Wnts increase MSC proliferation rate at low dose while suppressing it at high dose, reveal that the intensity of Wnt signals can result in various or even opposite biological functions.

5 | WNT/β-CATENIN SIGNALING IN REGENERATIVE MEDICINE

The amazing continuous self-regeneration of multiple mammalian tissues continues to be an enigmatic mystery in biology over years and decades. For example, by using intravital microscopy, visualization of stem cells has demonstrated the replacement of the ablated stem cells by more differentiated cells, recalled to the stem cell niche, whereupon they regain stem cell identity to affect tissue repair (Furlani et al., 2009). Therefore, lineage barriers between stem cell and differentiated fates are not always stringent and can be traversed during times of tissue damage. Reactivated Wnt signals may be instrumental in this process, and perhaps such signals could be exploited in order to enkindle tissue regeneration after injury or disease. From a pragmatic perspective, Wnt signals have already found practical use in manipulating stem cells, enabling propagation of stem cells in vitro as self-renewing cell populations and as organoids. Therefore, in the next section, we discuss the roles of Wnt/β-catenin signaling in heart, lung, liver, bone, cartilage, development, and regeneration.

5.1 | Wnt/β-CATENIN PATHWAY IN HEART

5.1.1 | Role in the heart development

Vertebrate heart developed from the lateral plate mesoderm, which fuses together to form cardiac crescent after migration and subsequently organized to the myocardium and endocardium of the heart. As the heart tube forms, the cells of primary mesoderm populations or first heart field (FHF) differentiate to cardiomyocytes and contribute to the left ventricle and atria, while the cells within the second heart field (SHF) contribute most of the cells from cardiac outflow tract, right ventricle, some cells of left ventricle and atria (Kelly, Brown, & Buckingham, 2001; Kelly & Buckingham, 2002). Wnt/β-catenin signaling pathway has a complex array of functions in during vertebrate heart development (Tzahor, 2007). Although, accumulating recent studies have demonstrated that inhibition of Wnt/β-catenin signaling is necessary for heart specification, which is most substantially observed from the organization of ectopic hearts as a result of inactivation of β-catenin in the definitive endoderm of the mouse embryo, other results, mostly in cultured mouse and human ESCs, uncovered that the opposite is true (Eisenberg & Eisenberg, 2006). Since this signaling pathway exerts different functions at different developmental stages mediated by distinguished downstream effectors, the acceptance of the contradictory impacts of the Wnt/β-catenin pathway on cardiogenesis and heart development is rational. We discussed the key roles of Wnt/β-catenin signaling pathway in the regulation of heart development in four distinct categories. First of all, some studies reported that Wnt/β-catenin signaling pathway suppresses cardiac cell fate specification at distinct stages of embryogenesis. Signals through Wnt/β-catenin pathway during early embryonic development activate the formation of the lateral mesoderm, whereas its inhibitory activity contributes to the definition of the proper size of the heart-forming field. Marvin, Di Rocco, Gardiner, Bush, and Lassar (2001). showed that Wnt pathway in the primitive streak inhibits cardiogenesis in the posterior lateral plate mesoderm. However, Tzahor and Lassar (2001) supposed Wnt signal resulted from the neural tube prevent cardiogenesis in the cranial paraxial mesoderm. Second, a recent broad of studies in zebrafish and mouse embryos, as well as ESCs showed that Wnt/b-catenin signaling induces cardiogenesis prior to gastrulation and suppress heart specification at a later developmental stage, as investigated by heat-shocked (hs) Wnt8 and Dkk1 transgenic zebrafish embryos (Ueno et al., 2007). Third, studies using cardiac-specific mouse Cre lines revealed that that the Wnt/β-catenin signaling modulates SHF derivatives such as the right ventricle, cardiac outflow tract, pharyngeal mesoderm, and the branchial arches. This fact has been obtained from studies, in which genetic loss- and gain-of-function alleles of b-catenin destroy Wnt/β-catenin signaling in the heart. Ablation of β-catenin is not compatible with life. More importantly, perturbation in signaling through Wnt/β-catenin pathway has a strong correlation with the onset of a common form of human congenital heart disease cardiac, outflow tract defects (Ai et al., 2007; Cohen et al., 2007; Kwon et al., 2007; Qyang et al., 2007). Finally, based on the proposed model developed by Qyang et al. (2007) and

finding from studies in zebrafish and mouse embryos and ESCs, it was cleared that Wnt/β-catenin signaling has played temporally distinct roles during pre-specification, differentiation, and renewal of cardiomyocytes. A possible mechanistic explanation for this fact revealed when treatment of early ECSs with Wnt-3A can promote cardiac cardiomyocyte differentiation via repression of the Wnt pathway, while later treatment with Wnt inhibits and the Wnt inhibitor Dickkopf1 (Dkk1) induce cardiomyocyte differentiation.

5.1.2 | Role in the cardiac regeneration

Cardiovascular disorders still are one of the leading causes of morbidity and mortality worldwide with an increase rate over the last decade (Nichols, Townsend, Scarborough, & Rayner, 2014). Therefore, regenerative medicine becomes a beacon of hope for millions of patients suffering from heart disorders, because of the capability of regenerating an injured heart (Duelen & Sampaolesi, 2017). The heart, historically considered as non-regenerative and terminally differentiated organ, without any functional stem cell population (Carvajal-Vergara & Prósper, 2016). Therefore, in contrast to lower vertebrates, it exhibits a limited regeneration capacity (Duelen & Sampaolesi, 2017). Heart transplantation is the standard therapeutic strategy for patients with heart injuries because heart regeneration capacity is unable to compensate the severe loss of cardiomyocytes during myocardial disorders (Carvajal-Vergara & Prósper, 2016). However, two finding has been challenged previous views about heart regeneration; reports of cardiomyocyte replenishment during the adult lifetime, and discovery of various cardiac resident stem cell populations such as pluripotent stem cells (PSCs) and cardiac stem cells (Duelen & Sampaolesi, 2017). PSCs including ESCs and iPSCs are the most important stem cells population with the greatest capacity for cardiac regeneration, mostly because of the distinguished potential to proliferative unlimitedly and differentiate into the main cardiovascular lineages (cardiomyocytes, smooth muscle, and endothelial cells) (Ozhan & Weidinger, 2015). As with its involvement in cardiac specification and development, the Wnt/β-catenin pathway has been demonstrated by accumulating research groups to be contributed in proreparative and profibrotic response to cardiac ischemic injury (Bastakoty et al., 2016; Le Dour et al., 2017; Palevski et al., 2017). Seventy-two hours after cardiac injury, the activation of Wnt/β-catenin signaling pathway is observed in multiple cells of the heart (Aisagbonhi et al., 2011; Oerlemans et al., 2010). Reactivation of the Wnt/β-catenin signaling following cardiac injury is showed to have pivotal impacts on cardiac progenitors in several ways, as was documented by Zelarayán et al. (2008). The authors have reported that β-catenin depletion induced recovery in a resident cardiac progenitor cell population exhibiting αMHC-promoter activity and expression of cardiac transcription factors GATA4 and Tbx5 after infarction. This effect was mediated by enhancing cardiomyogenic differentiation of αMHC + SCA1+ cardiac progenitors. Stabilization of β-catenin using the same promoter decreased cardiomyogenic differentiation of these cardiac progenitors. In another study by Noack et al. (2012) showed that knockdown of KLF15 (Kruppel-like-15 transcription factor), which is a negative regulator of β-catenin/TCF transcriptional activity resulted in cardiac β-catenin transcriptional activation along with functional cardiac deterioration in normal homeostasis and upon hypertrophy. On the other hand, KLF15 deletion induced endothelial lineage differentiation of cardiac progenitor cells. They concluded that KLF15 controls cardiac progenitor cells homeostasis in the adult heart similar to embryonic cardiogenesis via inhibition of β-catenin transcription. Treatment of SCA1+ progenitor cells with a Wnt inhibitor, secreted a Frizzled-related protein (sFRP)-2, promote differentiation of these cells after ischemia-reperfusion injury. In other words, treatment of progenitor cells with sFRP-2 suppressed their proliferation and primed them for cardiac differentiation. The underlying mechanism is binding of sFRP-2 to Wnt6, thus, inhibition of Wnt6 canonical pathway, and current activation of non-canonical Wnt signals (Schmeckpeper et al., 2015). Majidinia and Yousefi (2016a) showed that sFRP-2 is the key stem cell paracrine factor that mediates myocardial survival and repair after ischemic injury. They demonstrate that cardiomyocytes treated with sFRP-2 increase cellular β-catenin and up-regulate expression of antiapoptotic genes. Therefore, Wnt inhibition by sFRP-2, is credited with promoting survival of cardiomyocytes. Bastakoty et al. (2016) showed that Wnt inhibition augmented roliferation of interstitial cells in the distal myocardium, inhibited apoptosis of cardiomyocytes, and educed myofibroblast proliferation in the peri-infarct region. Injection of recombinant Wnt3a protein (r-Wnt3a) in the left ventricular free wall, was found to decrease the proliferation of adult cardiac side population cells, depleted the endogenous pool of cardiac progenitors and worsened cardiac remodeling after infarction, through suppression of cell cycle progression. (Oikonomopoulos et al., 2011). An opposite prosurvival role of Wnt/β-catenin pathway in cardiomyocytes was reported by other studies, in which nonphosphorylatable, active β-catenin transfer to the infarct zone by adenovirus-mediated gene transfer. They showed that β-catenin overexpression, and consequently activation of Wnt/β-catenin pathway, decreased myocardial infarct size through differentiation of fibroblasts into myofibroblasts and resulted in slight improvement in cardiac function and a decrease in infarct size (Hahn et al., 2006). In a study by Duan et al. (2012) it was reported that Wnt1/β-catenin signaling pathway is induced in the epicardium after cardiac infraction to promote cardiac repair. They reported that Wnt1 signaling leads to differentiation of epicardial cells into fibroblasts via the process of epithelial to mesenchymal transition (EMT). Some studies investigated the effects of Wnt/β-catenin signaling on neovascularization after cardiac injuries. Some of them showed the positive effects of this signaling, such as Paik et al. (2015). the study, in which Wnt10b Gain-of-function improves cardiac repair by arteriole formation and attenuation of fibrosis through VEGF and ANG1 signals. In another study by Laeremans et al. (2011). it was reported that inhibition of Wnt/ Frizzled signaling with a peptide mimic of WNT3A/5A improves neovascularization. Furthermore, crosstalk between Wnt/β-catenin signaling and other important signaling pathways cause further complication in healing outcomes. One of these signaling pathways is CK-Iα, which phosphorylate β-catenin to inhibit canonical Wnt pathway. On the other hand, CK-Iα

also potentiates the Hedgehog signaling pathway, one of the important networks for maintenance of coronary vasculature during injury repair (Lavine, Kovacs, & Ornitz, 2008). Interaction of two non-canonical branch of Wnt pathway, Ca/Cam kinase and JNK also affects healing (Schmeckpeper et al., 2015). Taking together, the role of the Wnt/β-catenin signaling pathway in cardiovascular diseases, repair and regeneration are very sophisticated and multifaceted, need more investigation to understand impacts of Wnt modulation using genetic models and other researching methods.

5.2 | Wnt/β-catenin pathway in lung

5.2.1 | Role in the lung development

Lung development during embryogenesis can be defined in four distinct periods based on the morphological changes of epithelial cells and alternation in the structure of the airway tubes (Herriges & Morrisey, 2014). These stages include: i) the pseudoglandular stage, characterized with establishment of primordial airway tubules, and distinct bronchial and respiratory systems, and columnar morphology endoderm-derived epithelium, cuboidal morphology of bronchial epithelial cells, and columnar to cuboidal shape of epithelium lining the acinar tubules; ii) the canalicular period, which is marked by the downregulation of the surfactant proteins and exhibiting differentiated features by the airway epithelium, appearance of the cuboidal type 2 cells, and squamous type 1 cells in pulmonary acinus; iii) the saccular period, which is characterized by the formation of alveolar ducts and alveolar sacs, a flattened epithelium; iv) the alveolar stage, is defined by the initiation of alveolar septation increase in the surface area of the lung (Smith, McKay, van Asperen, Selvadurai, & Fitzgerald, 2010). Wnt/β-catenin signaling is among other important and cell fate determinant signaling pathways that it modulation was demonstrated in the embryonic and adult lung. Since from the first report of the expression of Wnt in 1990 (Gavin, McMahon, & McMahon, 1990), several studies have been exerted huge efforts to prove the involvement of this signaling pathway in lung development. Okubo and Hogan (2004) showed that canonical branch of Wnt/β-catenin signaling is hyperactive throughout lung development in mouse embryos. In another word, it was reported that numerous Wnt ligands, receptors, and components of this pathway are expressed in a highly cell-dependent pattern in the developing lung. For example, WNT2 is expressed predominantly in the distal mesenchyme (Levay-Young & Navre, 1992), whereas, WNT7b is highly expressed in the epithelium (Shu, Jiang, Lu, & Morrisey, 2002). Additionally, the expression of WNT5a and Wnt11 is observed in both cell types (Li, Xiao, Hormi, Borok, & Minoo, 2002). The localization of β-catenin in the cytoplasm and often the nucleus of the differentiating alveolar epithelium, undifferentiated primordial epithelium, and adjacent mesenchyme was also demonstrated (Tebar, Destrée, de Vree, & Ten Have-Opbroek, 2001). In addition to Wnts and β-catenin, Fz-1, -2, and -7 and several intracellular components of pathway including Tcf-1, -3, -4, Lef1, sFRP-1, -2, and -4 have been reported to be found in spatio-temporal- dependent patterns in the developing lung (Tebar et al., 2001). The vital function of Wnt/β-catenin signaling in lung development such important that mice embryos carrying knockout of WNT2/2B or b-catenin fail to form lungs (Goss et al., 2009). Additionally, mice with a genetic knockout of the non-canonical ligand WNT5A could not survive because of respiratory failure (Li et al., 2005). This study is one of the few studies, which investigated the importance of non-canonical Wnt signaling in lung development. In mice with a WNT5A knockout, the lung is smaller than in the wild-type, from the morphological point of view, alveolar development is delayed.

5.2.2 | Role in the lung regeneration

Wnt/β-catenin signaling controls stem and progenitor cell function, which is responsible for the slow homeostatic turnover of the lung epithelium and replacing most of the cells in both the developing and the adult lung (Pongracz & Stockley, 2006). Therefore, the lung is quiescent but can be activated by injury. The differentiated epithelial cells have the capacity to dedifferentiate, proliferate, and trans-differentiate into multiple cell lineages (Giangreco, Reynolds, & Stripp, 2002). In a study by Chilosi et al. (2003) the expression patterns of β-catenin and two downstream target genes of Wnt signaling pathway, cyclin-D1, and matrilysin was investigated on lung samples from patients with idiopathic pulmonary fibrosis (IPF). They reported a considerable increase in the number of the epithelial cells expressing β-catenin nuclear accumulation, as well as aberrant cyclin D1 and matrilysin in bronchiolar lesions, damaged alveoli, and fibrotic foci. Königshoff et al. (2008) showed that Wnt1, 7b and 10b, Fzd2 and 3, β-catenin, and Lef1 expression was significantly increased in IPF. In addition, they reported localized Wnt1, Wnt3a, β-catenin, and Gsk-3β expression largely to the alveolar and bronchial epithelium. They concluded that increased Wnt/β-catenin signaling may be contributed to epithelial cell injury and hyperplasia, as well as impaired epithelial-mesenchymal cross-talk in IPF. In addition, some studies demonstrated the involvement of the Wnt/β-catenin signaling in the survival of alveoepithelial cells in bleomycin-induced lung injury models. Depletion of the β-catenin caused an increase in the AEC death. Opposite resulted was also demonstrated in another study, in which inhibition of the Wnt pathway via administration of Wnt inhibitors attenuated bleomycin-induced pulmonary fibrosis (Henderson et al., 2010; Sun et al., 2014). Andersson-Sjöland, Karlsson, and Rydell-Törmänen (2016) also showed that bleomycin administration resulted in the activation of the endothelial cells, increase in the number of β-catenin-positive nuclei and the expression levels of Wnt3a and Wnt5a. They suggested that bleomycin-induced reactive oxygen species causes DNA stress affecting the endothelial niche, initiating repair processes including Wnt signaling. Canonical Wnt/β-catenin signaling is activated during lung epithelial regeneration and regulates bronchioalveolar stem cells (BASCs) proliferation in response to naphthalene-based acute lung injury. Moreover, suppression of the Wnt pathway by GATA6, zinc finger transcription factor was seemed to be necessary for differentiation and proper regeneration of the damaged epithelium (Zhang et al., 2008). One of the important problems related to increasing in the prevalence of fibrotic lung diseases is that the efficacy

of the regeneration after injury is very low in the lung (Ley & Collard, 2013). In summary, although the Wnt pathway is involved in the promotion of the proliferation and expansion of at least a population of regenerative cell lineages, and is extensively indicated to be activated in response to injury, however, the regeneration of the injured lung seems to be insufficient to repulse fibrotic diseases. Furthermore, the accumulating studies reporting the contribution of the Wnt pathway in promoting profibrotic signals by mesenchymal cells (Kim et al., 2009) reveal a controversial effect of Wnt activation resulting in regenerative epithelial signals.

5.3 | Wnt/β-catenin pathway in kidney

5.3.1 | Role in the kidney development

A huge number of studies have been revealed the expression of the key component of the Wnt/β-catenin signaling pathway during development of various stages of the embryonic kidney (Halt & Vainio, 2014). During embryogenesis, function units of kidney, metanephros, which is consisted of epithelial ureteric and the metanephric mesenchyme, appears in midgestation (Mugford, Sipilä, McMahon, & McMahon, 2008). Various gene knockout models and ex vivo studies have reported substantial evidence that Wnt-mediated signals are necessary for renal ontogeny (Halt & Vainio, 2014). Several Wnts including Wnt4, Wnt2b, and Wnt7b are transiently expressed in specific cell lineages and these are able to activate the canonical signaling pathway, however, other Wnts such as Wnt6, Wnt9, and Wnt11, which are expressed in the fetal kidney cannot activate the canonical signaling pathway (Iglesias et al., 2007). Wnt1 is not present in the developing kidney (Vainio, 2003). The embryonic spinal cord is one of the potent embryonic tissues to promote nephron differentiation in cap mesenchyme (Halt & Vainio, 2014). This capacity in the induction of the nephrogenesis is mediated by the expression of the Wnts, such as Wnt4, Wnt1, Wnt3a, Wnt4, Wnt7a, and Wnt7b (Halt & Vainio, 2014; Roker, Nemri, & Yu, 2017). The considerable investigation was made to discover the ureteric bud-derived signal after the identification of Wnt4 as the key metanephric mesenchyme-derived nephrogenesis regulation signal (Stark, Vainio, Vassileva, & McMahon, 1994). Eventually, it was reported that Wnt9b was the primary ureteric bud-derived factor that has the capacity to induce the cap mesenchyme to differentiate from the stem cell stage to the nephron cell lineages (Carroll, Park, Hayashi, Majumdar, & McMahon, 2005). The Wnt9b expression was observed in the epithelial Wolffian duct prior to induction of metanephros development. Its expression continues in the ureteric bud and maintained in the collecting ducts until adulthood (Karner et al., 2009). Wnt9b-mediated provocation in the cap mesenchyme initiates expression of Wnt4, and other factors including fibroblast growth factor 8 (Fgf8), LIM homeobox protein 1 (Lhx1), and paired box 8 (Pax8). Knockout of Wnt9 gene in mice resulted in early death after birth, because of the failure in the expression of these genes (Carroll et al., 2005; Grieshammer et al., 2005; Perantoni et al., 2005; Stark et al., 1994). Just like Wnt9b, the Wnt4 knockout resulted in in nephron differentiation, therefore, signaling prevents nephrogenesis and consequence formation of a vestigial kidney (Stark et al., 1994). Totally, Wnt4 acts in cap mesenchyme downstream of ureteric bud derived Wnt9b and are essential for the organization of the pretubular aggregate and then epithelial derivatives. Frizzled receptors including Fz2, Fz4, Fz6, Fz7, Fz8, and Fz10, are also expressed in mouse embryonic kidney. Knockout of Fz4 and Fz8 allows the segmentation of the nephron but the kidney size is decreased because of reduced proliferation (Ye, Wang, Rattner, & Nathans, 2011).

5.3.2 | Role in the kidney regeneration

The recovery capacity of the kidney in acute injuries, which are resulted from the nephrotoxic agents or ischemia, is in an acceptable range. The fact that which type renal cells are involved in the repair of injuries is still not well understood. However, an increasing body of the recent investigations suggests that proliferative and de-differentiated tubular epithelial cells play a pivotal role in the kidney repair (Kamo, Akazawa, Suzuki, & Komuro, 2016). On the other hand, in spite of this repair capacity against acute injuries or intrinsic healing potential, morbidity and mortality due to acute damages to kidney increase every year, which is an indicative of the limitations in kidney regeneration capacity. The activation of the canonical Wnt/β-catenin signaling pathway during acute kidney injuries was indicated in a study by Lin et al. (2010). The authors reported that kidney macrophages secrete Wnt proteins in response to kidney injury in an ischemia-reperfusion-induced kidney injury model. When macrophages are depleted from the injured kidney, the canonical Wnt pathway response in kidney epithelial cells is decreased. In addition, administration of the Wnt pathway regulator Dkk2 increased the repair process. They also showed that Frizzled receptor-4-(FZD4) expressing tubular epithelial cells are Wnt responsive. On the other hand, the suppression of canonical Wnt signaling due to mutation of FZD4 receptor decreased reduced regeneration of tubular epithelium by enhancing the apoptosis of tubular epithelial cells. Another study demonstrated that the ablation of tubular β-catenin substantially aggravated renal lesions, in acute kidney injuries induced by ischemia reperfusion or folic acid. Additionally, apoptosis was increased in kidneys of the knockout mice. Activation of β-catenin by Wnt1 or stabilization of β-catenin protected tubular epithelial cells from apoptosis. Hence, endogenous β-catenin is substantial for renal tubular protection after acute kidney injury by provoking cell survival through multiple mechanisms (Zhou et al., 2012). Acute kidney injury is increasingly identified as a major risk factor for progression to chronic kidney diseases (CKD). Xiao et al. (2015) showed that sustained activation of Wnt/β-catenin signaling pathway trigger acute kidney injury to CKD Progression. The authors also indicated that blockade of Wnt/b-catenin pathway activity by a small molecule inhibitor could suppress progression to CKD. In another study by Beaton et al. (2016), it was suggested that Wnt6 and signaling through a FzD7 receptor in epithelialization in animal models of acute tubular injury and renal fibrosis. In addition, Wnt6 expression leads to de novo tubulogenesis in renal epithelial cells grown, rescued epithelial cell dedifferentiation,

and reversed TGF-β-mediated increases in vimentin and loss of epithelial phenotype. The activation of the Wnt/β-catenin signaling pathway has also been observed to involve to CKD progression by promoting podocyte dysfunction (Dai et al., 2009). In summary, these studies propose that transient activation of Wnt/β-catenin signaling may promote regeneration in the kidney, as similar to the lung. However, over sustained injury, a hyperactivation of the Wnt pathway seems to promote signals in various cell types and consequently resulted in progressive fibrosis.

5.4 | Wnt/β-catenin pathway in bone

5.4.1 | Role in the bone development

During embryonic development, bone is formed by two distinct processes including intramembranous ossification or endochondral ossification (Zhong, Ethen, & Williams, 2014). In intramembranous ossification, which is involved in the formation of the flat bones including cranial bones, mandible, and the clavicle, osteoblasts are directly differentiated from mesenchymal progenitors. As intramembranous ossification, endochondral ossification starts with mesenchymal cells. However, the important difference between these two processes is that cartilage is present during endochondral ossification (Zhong et al., 2014). The contribution of the Wnt/β-catenin pathway in the regulation of skeletal development and homeostasis, as well as controlling bone mass has been established by accumulating bodies of studies, in which the number of human bone diseases associated with mutations in this pathway (Kim et al., 2013; Kobayashi, Maeda, & Takahashi, 2008; Regard, Zhong, Williams, & Yang, 2012). In other words, during early skeletal development, Wnt signaling regulates pattern formation before the establishment of the skeletal elements, and disruption in the Wnt signaling has a strong association with defects of the human skeleton. The first report of this is when a study in 1994 was shown that Wnt3a-deficient embryos exhibited axial defects (Takada et al., 1994). Loss-of-function mutations in LRP5 was also found to be associated with osteoporosis pseudoglioma, in which bone mass reduces dramatically (Yousefi, Samadi, Baradaran, Shafiei-Irannejad, & Zarghami, 2016). Other studies also demonstrated that mutations in LRP5 blocked sclerostin- and DKK1-mediated binding and inhibition and consequently resulted in an increased bone (Boyden et al., 2002; Little et al., 2002). Loss- of- function mutations LRP5 and LRP6 were strongly related to alterations in human bone mass and osteoporosis (Johnson & Summerfield, 2005; Mani et al., 2007; Van Wesenbeeck et al., 2003). Nonetheless, the Wnt signaling pathway has important functions in promoting the osteogenic differentiation of MSCs (Cawthorn et al., 2012). It has been reported that the canonical Wnt pathway provoke the progression of MSCs from osteoblastic precursor cells into more mature osteoblasts, by upregulating the osteogenic regulators Runx2, Dlx5, and osterix, while inhibiting the differentiation into adipogenic and chondrogenic lineages, through suppression of the major adipogenic inducers PPARγ and CCAAT/enhancer binding protein α (Bennett et al., 2005; Case and Rubin, 2010; Glass et al., 2005; Kang et al., 2007).

5.4.2 | Role in the bone regeneration

The capacity of adult bone in regeneration and healing after injury or fracture is very high (Chen & Alman, 2009). This process is similar in more aspect to the embryonic bone development; however, exerting an inflammatory response is the most important difference of the fracture healing and embryonic bone development (Chen & Alman, 2009). Because of the regulation of a broad range of the cell-fate decisions related to osteogenesis, Wnt signaling has been suggested to be contributed throughout the healing process. More importantly, canonical Wnt signaling through the β-catenin is substantially induced in the fracture callus (Minear et al., 2010). As mentioned before, gain-of-function in Wnt/β-catenin signaling pathway resulted in the high bone mass in mouse models, therefore, not surprisingly the mice models with an activated form of β-catenin in osteoblasts and the knockout of Axin2 have a considerable increase in bone healing (Yan et al., 2009). On the other hand, Wnt/β-catenin signaling plays controversial roles in diverse phases of fracture repair in a fracture-healing model contributing of both endochondral and intramembranous ossification. For instance, either inhibition or activation of Wnt pathway during early stages of bone healing suppress the differentiation of MSCs into osteoblasts. At later stages, Wnt pathway positively controls osteoblasts after the commitment of the undifferentiated cells to the osteoblast lineage (Krishnan, Bryant, & MacDougald, 2006). Administration of recombinant Wnt3a and lithium chloride can increase healing potential following the start of treatment after the bone fracture (Komatsu et al., 2010). Vice versa, inhibition of Wnt signaling in the injury site by adenoviral expression of DKK1 can suppress the differentiation of osteoblastic cells (Kim et al., 2007). This finding is proved by the observation of the increased levels of DKK1 in pathologic bone samples (Ray et al., 2017). Ransom et al. (2016) Wnt-responding cells, which are undergoing a transient step of cell differentiation induced by local Wnt stimuli, can increase or restore the regenerative capacity of bone. They reported that ablation of these WRCs disrupts healing after injury, and three-dimensional finite element modeling of the regenerate delineates their essential role in functional bone regeneration.

5.5 | Wnt/β-catenin in regeneration of other tissues

Other tissues demonstrate the sophisticated and either positive or negative function of the Wnt pathway in the regeneration after injury. Skeletal muscle, a tissue with a partial regenerative capacity, facilitate regeneration of injured muscle fibers by satellite cells (von Maltzahn, Chang, Bentzinger, & Rudnicki, 2012). The involvement of the Wnt signaling pathway in myogenic differentiation was established by previous studies. An early suppression of the Wnt signaling pathway and then a brief activation is essential for complete regeneration of skeletal muscle (Brack, Conboy, Conboy, Shen, & Rando, 2008). Upon injury, Wnt/β-catenin signaling was detected in muscle fibers with centrally located nuclei. As considering the Wnt as a profibrotic factor, Majidinia and Yousefi (2016b) reported that a continued increase in activity of the canonical Wnt signaling pathway in myogenic

progenitors is related to enhance in the differentiation of myogenic satellite cells to fibrogenic lineages in aging mice. Huraskin et al. (2016) also reported the same resulted and showed that upon injury, Wnt/β-catenin signaling was detected in muscle fibers with centrally located nuclei. Another tissue with successful regulation after injuries induced by drug or alcohol toxicity and persistent viral infection is liver. The regenerative capacity of the liver is due to the proliferation of resident mature epithelial cells (Okabe et al., 2016). Canonical Wnt/β-catenin signaling pathway becomes a highly promising pathway for liver regeneration because of numerous finding. Among the several investigated hepatic mitogenic pathways, only Wnt/β-catenin pathway was directly associated with liver regeneration after the APAP treatment (Yousefi, Darabi, Baradaran, Shekari Khaniani, & Rahbani, 2012). In addition, activation of Wnt/β-catenin pathway stimulated proliferation of hepatocytes (Gougelet & Colnot, 2012; Wang, Zhao, Fish, Logan, & Nusse, 2015), and the more quiescent liver progenitors (Yang et al., 2008), which often contributes toward liver regeneration (Saliani et al., 2013). Pre-treatment with a Wnt/β-catenin agonist activates the inhibited hepatocyte proliferation in the small-for-size rat liver graft model (Ma et al., 2015). It was also observed that Wnt/β-catenin pathway can mediate the protection of the liver against oxidative injury by preserving mitochondrial functions (Karimaian, Majidinia, Bannazadeh Baghi, & Yousefi, 2017). A recent study reported that Wnt/β-catenin signaling drives thioacetamide-mediated heteroprotection against acetaminophen-induced lethal liver injury. They showed that that rapid activation and appropriate termination of Wnt/β-catenin signaling underlie in this heteroprotection (Dadhania, Bhushan, Apte, & Mehendale, 2017). The hair follicle is another most- investigated organ, which its morphogenesis and regeneration would be influenced intensely in the inhibition or disruption of the canonical Wnt/β-catenin signaling pathway (Andl, Reddy, Gaddapara, & Millar, 2002). A huge number of studies have been reported that some Wnt ligands such as Wnt3a, Wnt7a, and Wnt7b regulate the hair cycle (Kandyba & Kobielak, 2014; Kandyba et al., 2013). In two separated studies by Li, Zhang, Ye, Lian and Yang (2011) and Li et al. (2013), it was demonstrated that Wnt10b activate hair follicle proliferation through the canonical Wnt signaling pathway and that the upregulation of Wnt10b promotes hair follicle regeneration in vivo. In another study, the authors reported that the upregulation of Wnt5a inhibits the transition of hair follicles from telogen to anagen (Xing et al., 2013). The involvement of Wnt5a was also evaluated in the hair follicle regeneration by Xing et al. (2016) and it was found that overexpression of Wnt5a suppressed the expression and translocation of β-catenin during hair follicle regeneration. The phenotype and expression patterns were similar with the results of the β-catenin knockdown. In another word, Wnt5a suppresses hair follicle regeneration by suppressing the activation of the canonical Wnt signaling pathway. Taking together, in various mammalian tissues, the contribution of the Wnt/β-catenin signaling pathway in stem cell homeostasis, proliferation, and differentiation, as well as tissue regeneration, regardless of their intrinsic regenerative and self-renewal potential, is very noticeable and need more investigation. Given that, therapeutic agents that allow targeting of a key component of the overall Wnt/β-catenin signaling pathway and fine-tuning of the level of Wnt inhibition in a spatiotemporally restricted manner may be essential to achieving a therapeutically related regenerative outcome.

6 | CONCLUSIONS

In this paper, we reviewed the various components of the Wnt/β-catenin signaling pathway. We then focused on the mechanisms by which this pathway contributes to stem and cancer stem cell maintenance. Finally, we summarized in detail, the current understanding of the role of Wnt/β-catenin signaling in both development and regeneration of heart, lung, liver, bone, and cartilage. We believe that a deeper understanding of the molecular phenomena underlying development and regeneration of different organs and appreciating the core and organ-specific processes involved can help fabricate new organs through tissue engineering or enable defective organs to regain their regenerative potential and finally bring novel therapies from bench to the bedside.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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