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-Review manuscript –

The multiple functions of melatonin in regenerative medicine

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Highlights

- Melatonin research has been a hotspot in the last two decades.
- This popularity relates to the multifunctional potential of melatonin such as anti-inflammatory, anti-cancer, antioxidant activity, circadian and endocrine rhythm regulation.
- Recent studies have been focused on the regenerative potential of melatonin.
- This review discusses the the implication of melatonin in the regeneration of various tissues.

Abstract

Melatonin research has been experiencing hyper growth in the last two decades; this relates to its numerous physiological functions including anti-inflammation, oncostasis, circadian and endocrine rhythm regulation, and its potent antioxidant activity. Recently, a large number of studies have focused on the role of melatonin in the regeneration of cells or tissues after their partial loss. In this review, we discuss the recent findings on the molecular involvement of melatonin in the regeneration of various tissues including the nervous system, liver, bone, kidney, bladder, skin, and muscle, among others.

Abbreviations:

Neural stem/progenitor cells (eNSPCs); Umbilical cord blood (UCB)-MSCs(UCB-MSCs); Apoptotic adipose-derived MSCs (A-ADMSCs);Human adipose tissue-derived mesenchymal stromal cells (hASCs); Human dental pulp stem cells (hDPSCs); Mesenchymal stem cells (MSCs); Osteoblast precursor cells (MC3T3-E1 cells).

Keywords: Circadian rhythm, stem cell, tissue engineering, neuroregeneration, liver regeneration, kidney regeneration, bone regeneration, muscle regeneration.

1. Introduction

Melatonin is a molecule with an uncomplicated structure that is produced by the pineal gland and other organs (1). Although melatonin was initially evaluated for its ability to regulate seasonal reproduction (2), currently it is considered as a key molecule in cellular physiology due to its functional diversity (3). Circulating melatonin is primarily of pineal origin, although other organs may release a small amount of melatonin under some circumstances (4-6). L-tryptophan is the melatonin precursor and it is enzymatically converted to melatonin via a well-known pathway. Four enzymes are responsible for this reaction that include tryptophan hydroxylase, L-aromatic amino acid decarboxylase, N-acetyltransferase, and N-acetylserotonin methyltransferase (previously known as hydroxyindole-O-methyltransferase), although the sequence of two latter actions may be different than originally proposed (7). A broad range of biological functions has been identified for melatonin; for instance, antioxidant, anti-inflammation, oncostatic, and circadian and endocrine rhythm regulatory effects. Some of these processes are mediated through interactions with its specific G protein-coupled receptors (MT1 and MT2) (8-10) and also possibly via nuclear and cytoplasmic partners that include retinoid-related orphan nuclear hormone receptor family (11, 12). Other functions of melatonin are receptor-independent (13, 14). The nuclear binding sites are involved in the mediation of melatonin's immunomodulatory actions (15, 16).

An increasing number of studies have documented that melatonin is a multifunctional homeostatic factor and exerts protective effects in multiple cell and tissue types through its

potential in regulating various aspects of cell biology (17, 18). As a potent antioxidant, melatonin is involved in the detoxification of reactive oxygen species (ROS) and a variety of free radical intermediates including singlet oxygen, nitric oxide, peroxynitrite anion, and peroxyl and hydroxyl radicals (19-22). Melatonin also plays a role in the expression of antioxidant enzymes including catalase, glutathione reductase, superoxide dismutase, and glutathione peroxidase (23). In this context, the cell protective effects of melatonin also include the regulation of redox-sensitive transcription factors such as nuclear factor kappa-B (NF-κB) (24). As a key signaling pathway involved in the immune and inflammatory response, signal transduction through NF-κB mediates the promotion of the transcription of numerous enzymes and pro-inflammatory molecules, such as tumor necrosis factor-α (TNF- α), interleukin-2 and -6 (IL-2 and IL-6), adhesion and chemotaxis molecules and inducible nitric oxide synthase (iNOS) (25). Melatonin inhibits NF-κB transduction through preventing its translocation into the nucleus (26). Therefore, this inhibitory effect of melatonin represents an important cell protection mechanism against inflammation and inflammation-induced ROS production. Melatonin also controls other immune-inflammatory pathways including the cyclooxygenase-2-dependent prostaglandin E2-mediates, inhibition of IL-2 production and the control of IL-2 receptor function in human lymphocytes (27, 28).

Melatonin readily passes through biological membranes and accumulates unequally in subcellular organelles (29-32). In addition to its uptake into cells, mitochondria themselves may synthesize melatonin (33-35). It is suggested that melatonin has mitochondria protective effects, and along with the signaling modulatory actions, melatonin is involved in the regulation of apoptotic and inflammatory genes, which promote cell survival (36, 37). Either in normal cells or cells with an ageing accelerated phenotype, melatonin prevents the decay of the membrane

potential and energy-producing function of mitochondria (37, 38). Melatonin control the intrinsic pathway of apoptosis, which it does by its preventive effects on the mitochondrial damage induced by extra-mitochondrial sources of reactive oxygen species (ROS) (39, 40). Because of cell protective functions of melatonin, as well as the beneficial effects of its involvement as an antioxidant and anti-inflammatory agent in the suppression of the chronic wound severity and enhancement of the wound contraction, a large body of studies have investigated the possible roles of the melatonin in the regeneration of various damaged tissues (41). Herein, we discuss recent studies on the molecular mechanisms in which melatonin is involved, especially in the regeneration of various tissues from a variety of sites.

2. Regenerative medicine

Although humans have been concerned with the regeneration of the damaged tissues and organs since the earliest observations of accidents or trauma, only in the last few decades have such studies become commonplace. In this new "modern era of regenerative medicine", scientists are attempting to construct biological substitutes that mimic vital tissues with the ability to growth, function, repair, and remodel, for the purpose of inducing tissue regeneration with the intent of replacing of injured tissues. Additionally, due to the increasing number of patients suffering from damaged or diseased tissues and organs and the shortage of organ donors, the focus of regenerative studies has shifted to constructing human tissues outside the body; this requires the corporation of several areas of medical technology, including tissue engineering, stem cell manipulation, and therapeutic cloning.

2.1. Tissue engineering

The field of tissue engineering has been interchangeably used with regenerative medicine due to their overlapping definitions and goals to regenerate injured tissues. Thus, rather than repairing dysfunctional tissues, other options are considered. These approaches include cell preservation to provide adequate living cells, materials science for the supply of biocompatible materials, appropriate biochemical and growth factors, along with physical tools such as cyclic mechanical loading. The ultimate goal is the creation of tissue constructs using a combination of these above-mentioned factors which could replace the damaged tissues or organs (42, 43). Some important examples of organs targeted for tissue engineering include skin, cornea, liver, pancreas, cartilage, heart, kidney, neurons and spinal cord (44). Tissue engineered products are generally divided into two main categories: 1) a cellular matrices, which consist of a scaffold containing extracellular matrix (ECM)-proteins such as collagen, hyaluronic acid, and fibronectin, virus vectors or plasmids for the secretion of specific growth factors that depend on the organs natural ability to regenerate new tissue, 2) and cellular matrices (45, 46). Acellular products are usually provided by artificial scaffolds, or by eliminating some cellular components of tissues (45, 46). The cellular environment is an indispensable element for effective tissue engineering since it provides the cells with the more natural microenvironment. Various bioresorbable materials including synthetic biomaterials such as collagen, polyglycolic, polylactic, and the polycaprolactone family of polymers (47, 48), and natural scaffold-like protein-based products such as fibrin, collagen, and polysaccharide-based materials (e.g. alginate, chitosan, hyaluronic acid, glycosaminoglycans,) have been extensively used in tissue engineering(49).

An additional important consideration in tissue-engineering is to supply the exogenous chemical factors such as soluble growth and differentiation factors including bone morphogenetic proteins

(BMPs), vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), basic fibroblast growth factor (bFGF or FGF-2), and mechanical stimuli including cyclic mechanical loading, and fluid shear(50). Due to recent progress in the field of tissue engineering, there is hope for the possibility of reducing the need for organ replacement, with great acceleration in developing new therapeutic agents thereby eventually eliminating the need to wait for organs to become available from tissue donors.

2.2. Stem cells

A major focus of regenerative medicine is to use stem cells as a tool to generate a functional tissue or organ. In addition to the exclusive features of stem cells, e.g., the indefinite long-term self-renewal, their capacity to differentiate into different cell types, and their secretion of a wide range of bioactive macromolecules that play major roles in the structure of regenerative microenvironments, as well as their ability to provide immunoregulatory advantages, provide excellent regenerative potential for these cells (51, 52). Pluripotent stem cells including induced pluripotent stem cells (iPSCs), embryonic stem cells (ESCs) and multipotent stem cells such as adult stem cells are the most commonly used cells in regenerative medicine (53). Their ability to remain in an undifferentiated state *in vitro*, and their ability to differentiate into different cell linages, opens important avenues applicable to regenerative medicine. However, encountering issues such as the lack of histocompatibility, tumor formation or improper differentiation after transplantation, infection risks, and more importantly, ethical issues due to the source of ESCs (from a developing embryo), makes the use of these cells controversial(54).

Less controversial, but more promising, are adult stem cells derived from human tissues. These multipotent cells are capable of differencing into a limited number of cell types within a specific

lineage. Adult stem cells are obtained from different tissues including bone marrow, adipose tissue, peripheral blood, nervous tissue, skeletal muscle, and dermis (55). Various signals from the surrounding microenvironment composed of other cell types and multiple mechanical, chemical, and topographical factors, have a potent influence on the critical properties of these cells such as their self-renewal and differentiation ability(56). Micro- and nano-scale factors are present in the microenvironment and provide complicated signaling mechanisms to determine proliferation, differentiation, migration, and the generation of various protein molecules for tissue organization and repair(57).

2.3. Nuclear cloning

Nuclear cloning, nuclear transplantation, and nuclear transfer are three similar terms that are commonly used in the process of transferring a nucleus from a somatic donor cell into an oocyte to produce an embryo genetically identical to the donor (58). This technique has been the subject of tremendous interest since 1997(59). Reproductive cloning and therapeutic cloning are the two types of nuclear cloning, which have created an ethical dilemma. An attempt to decipher the clear differences between these two might be beneficial in attenuating the ethical problems and controversies surrounding these technologies(59). Reproductive cloning employs somatic cell nuclear transfer for regeneration of an embryo with identical genetic material to a donor animal; thereafter it is into the uterus of a female for development(60). While therapeutic cloning is the same procedure for creating an embryo, the resulting cloned cells are grown in culture media to generate ESC lines with identical genetic material as the source(61). Thus, stem cells and in general regenerative medicine are highly applicable in the treatment of some almost incurable diseases, such as neurodegenerative diseases, end-stage kidney disease, and diabetes(62).

3. Melatonin in stem cell biology and regenerative medicine

Melatonin has been frequently reported to exert a potent regulatory effect on the viability, proliferation and differentiation of various types of stem cells including mesenchymal stem cells (MSCs), neural stem cells (NSCs), spermatogonial stem cells, endothelial progenitor cells (EPCs), periodontal ligament stem cells (PDLSCs), cardiac stem cells (CSCs), amniotic epithelial cells (AECs), induced pluripotent stem cells (iPSCs), etc. Proliferative and differentiative effects of melatonin on the embryonic stem cells (ESCs) is suspicious but recent studies is revealed that it could be as an anti-apoptotic, free radical scavenger and antioxidant in the ES cells (63). This aspect of melatonin function opens up new avenues for its applications in regenerative medicine and treatment of ageing- related diseases. Melatonin regulates the differentiation of MSCs into chondrogenic, osteogenic, and myogenic lineages, through controlling the survival, proliferation, differentiation and apoptosis of these cells (64). Various signaling pathways, such as Wnt and MAPK signaling, contribute to melatonin function in the MSCs biology (65). The Wnt/β-catenin signaling pathway is a central controller of MSC differentiation to the chondrogenic and the osteogenic lineage through the low or high activity of the Wnt signaling pathway, respectively. In addition, when Wnt signaling pathway is not active, the MSCs differentiated into adipogenic lineage. On the other hand, the Runx2 gene expression is down-regulated by activation of PPARγ, whereas a decrease in Runx2 has the positive effect in differentiation to adipogenesis. Recent findings have demonstrated melatonin enhances osteogenesis and chondrogenesis and inhibits adipogenesis through enhancing Wnt/β-catenin signaling pathway and Runx-2 expression and suppressing PPARγ expression (66). Melatonin protects against oxidative stress-induced apoptosis in MSCs (67). Melatonin attenuates

intracellular ROS generation to improve cell viability and enhances MSCs differentiation into other linages. Melatonin causes a significant alternation in SOX2 (SRY-box 2/sex determining region Y-box 2), FGFR-2 (fibroblast growth factor receptor-2), Nrf2 (nuclear factor-erythroid 2-related factor 2) and TLX (NR2E1/Nuclear receptor subfamily 2 group E member 1) expression to improve NSCs survival and proliferation (68, 69). Melatonin also plays important roles in the regulation of the ESCs proliferation and differentiation (70). Supplementation of culture medium with melatonin has positive effects on the ESCs during primary colony formation and expression of pluripotent genes. Moreover, melatonin has anti-apoptotic effects to agitate extracellular signal regulated kinase (ERK) and increases phosphorylation of protein kinase B (PKB/Akt), as a free radical scavenger and a broad-spectrum antioxidant in ESCs (71). In the case of iPSCs, melatonin was reported to enhance the efficacy of the generation of these cells through suppression of the p53-dependent apoptotic pathways, as well as increases in histone H3 hyperacetylation. Another potential mechanism is the direct free radical scavenging function and activation of the ERK/MAPK pathway, which inhibits cell apoptosis in a melatonin receptor-independent manner (72).

4. Melatonin in ageing biology

Biological ageing, a highly sophisticated process comprised of progressive events, is generally defined as alternation in the functional programs of living cells, time-dependent loss of physiological integrity, consequent enhancement in vulnerability to senescence and finally death (73). All levels of organismal function are subjected to these alternations, which range from minor change such as disruption in cellular protein production and alternations in the configuration of cellular macrofeatures, to larger modifications including numerous changes in

the physiochemical environments of cells and total decline in the efficiency of organ or system function, all of these increase the occurrence of various diseases (13). In fact, the maintenance of tissue hemostasis and regeneration is strongly dependent on the appropriate function of stem cells and ageing-related any dysfunctional alternations have deleterious effects on the regenerative capacity of tissues (74). Hence, elucidating the basic molecular pathways involved in the functional changes such as impaired self-renewal and aberrant differentiation potential, in stem cells with age, is of the utmost importance for regenerative medicine (74). In general, aging of somatic tissues and organs is accompanied by a significant decrease in regenerative capacity.

A reduction in the nocturnal melatonin peak in elderly persons is a critical observation suggesting the relationship between melatonin and aging (75). It has been hypothesized that melatonin can prolong life span (13). The importance of melatonin in the ageing is discussed in five categories, which was comprehensively explained by earlier studies. First, melatonin is a key molecule involved in the maintenance of circadian amplitudes, entrainment and the synchrony of oscillators and consequently sleeps initiation. Age-dependent disruption in circadian rhythms, which are closely associated with melatonin, is most apparent in sleep disturbances (76, 77). The maintenance of circadian rhythmicity by melatonin has been proposed to have anti-aging actions (77). The second category is comprised of metabolic sensing action of melatonin, which mediated by the modulation of important signaling pathways such as sirtuin 1, AMP-dependent protein kinase (AMPK), phosphatidylinositol 3-kinase (PI3K) and Akt. Sirtuin 1 is an ageing suppressor and its upregulation has been demonstrated in conditions related to ageing (73, 78).

Melatonin also has a significant impact on mitochondrial proliferation. It was suggested that this effect may be related to metabolic sensors and some other factors including peroxisome

proliferator-activated receptor (PPAR)-γ and PPAR-coactivator-1α (79). In addition to beneficial effects of melatonin on mitochondrial proliferation, in the third category, melatonin is also involved in the regulation of synthesis of respirasomal proteins, improvements in respiratory efficiency, reduction of electron leakage, prevention of cardiolipin peroxidation and induction of anti-apoptotic effects. In the fourth category; melatonin can upregulate antioxidant enzymes, improve formation and availability of reduced glutathione and NO metabolism (80, 81). Finally, melatonin secreted by pineal gland and leukocytes can exert a potent immune-modulatory function in multiple ways(82). This function is relevant to immune remodeling during aging and is a particularly important aspect of inflammation(82).

5. *Melatonin in regenerative medicine*

3.1. Peripheral nervous system (PNS)

- Current strategies in PNS regeneration:

Considering the severity of peripheral nerve injuries, there have been disappointing treatment outcomes with serious effects on life quality (83). Following any transection injury to a peripheral nerve, the metabolic demands of regeneration increase leading to swelling of the perikaryon, which is followed by Wallerian degeneration of the distal stump during where Schwann cells (SCs) are recruited; also macrophages clear the debris from the distal stump of myelin and axon for regenerating growth cone (83). Although the PNS has greater regenerative potential than the central nervous system (CNS), spontaneous regeneration is rarely incomplete without successful functional recovery(84). A major reason for incomplete regeneration is the lack of surgical approximation of the nerve stumps such that a substantial gap exists between nerve stumps(85). Thus, the main goal of PNS regenerative medicine is to design grafts to bridge

the gap between nerve stumps to support axonal regrowth(85). The gold standard for the suturing nerve stumps is implantation of an autologous graft. This technique includes the application of functionally less important nerves such as superficial cutaneous or sural nerve segments self-donated from other sites(86, 87). In addition to the applicability of this technique, multiple restrictions have been defined that include: i), limited supply of donor nerves, ii), requirement of a second surgical procedure, iii), donor nerve defects, iv), neuroma formation in recipients, v), and a mismatch between the donor nerve and the recipient site(88, 89). The introduction of allografts is a promising alternative approach for nerve transplantation, but researchers soon designed an alternative strategy due to problems that are encountered with this technique, and the need for systemic immunosuppression (90-92). Recent advances in regenerative medicine and particularly in tissue engineering have provided cutting-edge strategies that apply to numerous biological and artificial nerve grafts for the supplementation or even replacement of the autografts. Tissue engineering constructs, which are made from either natural materials (such as fibrin, collagen, gelatin, keratin, silk or chitosan) or synthetic ones (including polyglycolic acid, polycaprolactone, polyhydroxybutyrate, polyhedral oligomeric silsesquioxane) have been largely investigated and have yielded bearing encouraging results (89, 93-105). Finally, synthetic materials may be the forthcoming of the next generation of nerve grafts by virtue to their accessibility, tunable mechanical properties, simplicity and low-cost manufacturing procedure.

- The potential role of melatonin in PNS regeneration

Recently, remarkable progress in the peripheral nerve repair and regeneration have occurred due to the numerous investigations in the design of microsurgical instruments, as well as novel and effective strategies in nerve repair(106). However, despite intensive efforts, the clinical outcomes

of nerve regeneration following injuries are usually discouraging, and functional recovery is often not as expected(107). More importantly, collagen scar formation and consequent neuroma formation are among the most problematic challenges for neurosurgeons. Excessive amounts of collagen result in the creation of a mechanical burden to nerve regeneration and prevention of axonal regrowth. The development of effective technologies to reduce scar and neuroma formation is among the primary goals of researchers (108, 109). It has been now suggested that the balance between collagen scar formation and Schwann cell regeneration is the determining factor for the recovery of a peripheral nerve. Studies have reported that exogenous melatonin treatment significantly reduces scar formation in nerve stump and collagen synthesis in the granulation tissue in the peripheral nerve of pinealectomized animals (107, 110, 111). In a study in rats by Weichselbaum et al(112), the authors demonstrated that pinealectomy led to slower wound healing while exogenous administration of melatonin proved an effective treatment to reverse the effects of pinealectomy. Other studies have reported elevated amounts of tissue collagen content in pinealectomized rats as a result of low levels of melatonin (110-113). The number of studies that have evaluated the therapeutic role of melatonin in peripheral nerve regeneration has gradually increased. Some of these studies are highlighted in Table 1.

3.2. Central nervous system (CNS)

- Current strategies in CNS regeneration

The spontaneous regenerative potential of mature CNS neurons is minimal. Full recovery of CNS after trauma or neurodegenerative injuries is rare; this suggests the importance of the development of novel regenerative strategies for patients suffering from CNS injuries or diseases(131). The known mechanisms of CNS injuries that result in the loss of motor, sensory, and cognitive functions depend on the injury site and severity. These include the necrotic and

apoptotic demise of astrocytes, neurons, and oligodendrocytes, axonal demyelination, axonal injury excitotoxicity, ischemic injuries, oxidative stress, and inflammation(132). Extensive research has been devoted to developing effective strategies for the promotion of injured CNS tissue regeneration. One of these approaches is cell-based therapies that are defined as the transplantation of the MSCs(133, 134), ESCs(135), neural stem/progenitor cells (NSPCs)(136), or iPSCs(137) into the injured tissues. This procedure has the potential of repairing the damaged cells, when the cells integrate into the tissue directly, or by altering the local milieu by liberating factors that participate in the promotion of neuroprotection or neurogenesis. This eventually increases the likelihood of regeneration(138).

Another important strategy in CNS tissue regeneration is the delivery of bioactive molecules with defined effects on tissue repair. These bioactive substances include growth factors, and small molecules and antibodies derived from cells that are identified as producers of these factors(139, 140). Among the most applicable small molecules in CNS regeneration are: a) neurotrophic factors (ciliary neurotrophic factor (CNTF), neurotrophin-3 (NT-3) such as nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF); b) leukemia inhibitory factor (LIF), and glial cell-derived neurotrophic factor (GDNF); and c) ECM proteins (fibronectin, laminin, collagen I/III and IV)(139-143). While intravenous injections that are not directly applied into or not adjacent to the damaged site have systemic side effects, as other therapeutic strategies, these factors must be taken into consideration(144). A combination of cell transplantation and bioactive molecule delivery, along with biomaterials technology has been introduced as a promising approach to increase survival and integration of cells following transplantation. More importantly, this approach would circumvent the blood-brain barrier and systemic side effects(139, 145). Biomaterials can be used to distribute therapeutic molecules to

supply sustained and controlled drug release and afford physical support for cells to warrant their accumulation and dissemination at a transplantation site (146).

- The potential role of melatonin in CNS regeneration

During the last three decades, an increasing number of studies have investigated the potential correlation between melatonin and CNS injuries, as well as the circadian profiles of melatonin in these type of injuries. It is generally suggested that brain stem and high spinal cord injuries lead to a compromised level of endogenous melatonin, with a loss of the circadian melatonin rhythm(147). Additionally, however, due to lack of effective neuroprotective drugs for the treatment of CNS injuries, researchers suggest that melatonin might be an ideal choice as a neuroprotection for devastating injuries. Numerous studies have reported the potential therapeutic benefits of melatonin in CNS injuries (148-154). Furthermore, the combination of melatonin with corticosteroid drugs such as methylprednisolone(155, 156) or dexamethasone(157), has a greater efficacy as anti-inflammatory agents in preserving the ultrastructural integrity of neural lesions, reduction of the lipid peroxidation, and suppression of the progression of the secondary injuries. The anti-inflammatory and anti-oxidative effects of melatonin were reported to be more potent than oxytetracycline or prostaglandin E1, and even significantly more than octreotide(158, 159).

Melatonin-mediated reduction of matrix metalloproteinase (MMP-2 and -9) and TNF-α was also demonstrated as a possible mechanism for the protective role of melatonin(160). Moreover, the MAPK signaling pathway and high-mobility group box 1 protein (HMGB1) contribute in melatonin-dependent protection against secondary brain injuries(161). In a study by Samantaray et al(162), melatonin's inhibitory action on the inflammatory response is mediated by a reduction

in the activation of astrocytes, microglia, and macrophages, which results in the reduction of axonal degeneration following SCI injury. Additionally, the authors showed that melatonin treatment led to attenuation of neuronal cell death through considerable downregulation of calpain and caspase-3 activity in rat model of acute spinal cord injury. Similar findings were also reported by Genovese et al(163) when they documented that melatonin treatment caused a significant improvement in the limb function recovery. Melatonin also and it exhibited strong anti-inflammatory performance in a model of spinal cord injury in animals.

Wu et al(164), investigated the mechanisms by which melatonin influences blood-spinal cord barrier (BSCB) integrity and microcirculation in SCI. They reported that melatonin (50 mg/kg) treatment significantly decreased BSCB permeability. Furthermore, melatonin attenuates edema, limits microvessel loss, protects pericytes, the tight junction proteins, and endothelial cells. Melatonin also reduced the number of cells lost to apoptosis; and lowered the expression levels of MMP3/AQP4/HIF-1/VEGF/VEGFR2. The authors concluded that melatonin is involved in the stabilization of microvascular barrier function and microcirculation in the CNS.

As in PNS regeneration, scar formation is also an important challenge for surgeons in the CNS. The effect of melatonin on scar formation in a model of severe crush injury in mice was evaluated by Krityakiarana et al(165). The intraperitoneal administration of melatonin (10mg/kg) after injury resulted in higher expression of the neuronal marker, βIII-tubulin, and drops in the IL-1β, NG2 and glial fibrillary acidic protein (GFAP) expression levels, as indicators of the significant decrease in the inflammatory response. Melatonin-treated mice also displayed less scar formation. Indeed, the authors suggested that melatonin inhibits scar formation by acting on inflammatory cytokines after spinal cord injury.

Melatonin also alleviates acute spinal cord injury in rats by promoting endogenous neural stem/progenitor cells (eNSPCs) proliferation and differentiation into neurons and glial cells, and hence, effectively promotes locomotor function recovery after injury(166). The beneficial effects of melatonin on the inhibition of neural cell death and promotion of the locomotor recovery after spinal cord injury is mediated by activations of the Wnt/β-catenin signaling pathway (167). Additionally, Gao et al(168) showed that in bovine amniotic epithelial cells, melatonin plus Wnt-4 induced neural differentiation and protected from spinal cord trauma.

The neuroprotective potential of melatonin at the level of the cerebral cortex has also been recently investigated. Multifactorial complex etiologies including oxidative and nitrosative stresses lead to an interruption of the macro- and micro-circulation in the area of the injury, causing opportunistic infections, lymphocytopenia, perturbations in the sleep-wake cycles, suppression of nonspecific resistance, as well as damage caused by toxins(152, 169). These factors accelerate the development of heterogeneous clinical symptoms during the second phase of injury. The protective effects of the melatonin against damage following cerebrocortical injuries have been reported in multiple *in vitro* and *in vivo* studies(169). Due to its free radical scavenging functions and its influence on oxygen and nitrogen-based substances, melatonin is involved in the attenuation of neural injury due to craniocerebral damage. Melatonin is useful in reducing infections and lymphocytopenia as opportunistic factors through activation of adhesion molecules and inhibition of pro-inflammatory cytokines (170). Melatonin also decreases the toxicity while increasing the efficacy of therapeutic agents utilized in the management of brain tissue in the clinic including antidepressants, anti-epileptics, anti-psychotics, anti-ulcer agents, anti-anemics, and also steroidal/nonsteroidal anti-inflammatory agents (169, 171). In the study of Kelestemur et al(172), it was documented that the combination of melatonin with memantine, an

N-methyl-d-aspartate-type glutamate receptor (NMDAR) antagonist, reduced p38 and ERK-1/2 phosphorylation, which significantly decreased DNA fragmentation and brain injury in comparison to single therapy alone. As compared with single therapy treatments, SAPK/JNK-1/2 phosphorylation and iNOS activity were also reduced in animals with combined melatonin/memantine treatments. Qiu et al(173) studied the neuroprotective effect of melatonin against hypoxic-ischemic brain injury in neonatal rats and the mechanisms involved. Melatonin at 0.01 mg/g body weight limited the size of the damaged area and volume of the injury. TUNEL assay showed that the proportion of apoptotic neurons in the hypoxia-ischemic rats was significantly greater than that in melatonin-treated animals. These workers showed that melatonin not only reduces hypoxia-ischemia-induced brain injury but also promotes nerve regeneration in neonatal rats.

3.3. Liver

-Current strategies in liver regeneration

Liver, a vital organ with a broad range of metabolic and detoxifying functions, has a unique and undeniable regenerative ability(174). Hepatocytes comprise 80% of hepatic parenchyma, along with other hepatic cells including Kupffer, endothelial, stellate cells, and lymphocytes, which are activated by any hepatic injuries. In spite of their long survival and minimal cell division, hepatocytes have the potential of proliferation in response to various hepatic injuries induced by toxins and infections. Using a partial hepatectomy model, in which two-thirds of the liver is removed, and with the use of genetically engineered rodents, there have been significant advances in the elucidation of the molecules and signaling pathways involved in liver regeneration(175). Liver regeneration is a hyperplastic response involved in the replication of all

mature functioning intrahepatic cells. The newly generated liver tissues are anatomically different from the original liver, since the lost liver lobes do not regrow, or increase in size(176). Hepatocytes generally initiate replication within the first day after liver resection, while mitotic activity of other cell types is delayed. The sophisticated process of liver regeneration includes two critical phases: a) transition to the quiescent G0 phase into the cell cycle (priming), which need Kupffer cell-derived cytokines such as IL-6 and TNF-α, and b) progression into S phase and beyond the checkpoint in the G1 phase which requires mitogenic or growth factors including epidermal growth factor (EGF), transforming growth factor α (TGF-α) and hepatocyte growth factor (HGF),. After the termination of replication phases, growth, i.e., an increase in cell size occurs within several days, and the removed tissues are completely restored within 3 months(177, 178).

The ultimate goal of the recent liver regenerative research is the introduction of safe and well-established treatments for end-stage liver failure; this is considered as an alternative to organ transplantation. Although there are important advantages to liver transplantation including a split-liver, complete liver, and related donor liver transplantation, there are also some major limitations. These obstacles which include life-long immunosuppressive treatment and a donor organ shortage; these shortcomings promoted researchers to develop cell-based therapeutic strategies(179). In 1994, a three-dimensional (3D) matrix was used for isolated hepatocyte culture and transplantation. The 3D construction of neo-tissue and the induction of the cell growth by various applied changes of the matrix surface, as an important regulatory factor for the appropriate cell differentiation, are assisted with polymeric matrices(180). Thus, the addition of ECM-molecules and growth factors to the matrices result in the improvement and differentiation of hepatocytes. In 2012, Uygun et al(181) showed the architecture of a 3D liver from which

parenchymal cells were removed, and its original matrix composition and functional vasculature. Moreover, they were successful in re-cellularization of the graft *in vitro* and this artificial 3D liver was viable. In 2013 a functional human organ was generated by Takebe et al (182) from pluripotent stem cells. They applied iPSC to construct a functional human liver with vasculature. It is suggested that the generation of bio-printed livers will be feasible using 3D printing technology; the aim of this technology is to reproduce 3D objects from the 3D models through a procedure controlled by computer to lay down consecutive layers of material (183).

- The potential role of melatonin in liver regeneration

Because of its protective role against oxidative stress, particularly, its ability to remove free oxygen radicals and its regulation of antioxidant enzymes, melatonin has been of great investigative interest in a large number of studies related to oxidative stress, inflammation, lipid oxidation, and its potential therapeutic functions in controlling relaed disorders (184). Liver damage is a common consequence of the exposure to chemical pollutants, drugs, and alcohol. Accumulated finding have revealed the protective and attenuating role of melatonin against liver damage induced by carbon tetrachloride (CCl_4)(185-190), benzene(191), toluene(192), cadmium(193-196), lead(197), mycotoxins such as aflatoxins(198, 199), ochratoxin A(200-202), α-naphthylisothiocyanate(203-205), methanol(206), fluoride(207), aluminum chloride(208), dimethyl-nitrosamine(209), thioacetamide(210), nicotine(211), and paraquat(212).

Multiple mechanisms have been documented for the protective effects of melatonin in the liver including, a) an increase in the hepatic content of antioxidants (ascorbic acid and glutathione (GSH); an augmented activity of the antioxidant enzymes such as catalase (CAT), glutathione reductase (GSSG-R), superoxide dismutase (SOD), and, glutathione-S-transferase (GST) and

other enzymes including nicotinamide adenine dinucleotide phosphate (NADPH) NADPH): quinone oxidoreductase-1, cytochrome P_{450}2E1, b) a reduction in the accumulation of the liver lipid peroxides (LPO), lipid hydroperoxides (LOOH), and depressed activities of xanthine oxidase (XO), GSH peroxidase (GSH-Px), aspartate transaminase (AST) and alanine transaminase (ALT), c) decrease in the malondialdehyde (MDA) levels, prevention of protein oxidation, inhibition of the production of pro-inflammatory cytokines, and attenuation of hepatocyte death.

Melatonin also exerts protective effects against hepatotoxicity induced by multiple prescription medications, such as anti-tumor therapeutics, immunosuppressive drugs, psychiatric and neurological agents, and acetaminophen. An important finding is that a transient enhancement of mitochondrial peroxidation occurs in the early phase of liver regeneration after partial hepatectomy. A decline in the mitochondrial GSH has been demonstrated, suggesting the possibility of a robust generation of ROS in liver mitochondria following partial hepatectomy. On the other hand, a rise in lipid peroxidation results in the modulation of cell division, due to the mitotic arrest of cells in the regenerating liver(213). These observations support the idea for investigating melatonin functions as an antioxidant during liver regeneration. In a study by Abbasoglu et al(214), it was observed that pinealectomy significantly limited regeneration of rat liver after partial hepatectomy. They reported that the hepatic regenerative capacity, which was assessed by the mitotic index of hepatocytes and bromodeoxyuridine incorporation into DNA, was considerably lower in the pinealectomized rats compared to sham operated animals. Gonzales et al(215), reported that treatment with melatonin modulated the degree of oxidative stress and prevented alterations in liver function, both before and during liver regeneration. In addition, it was demonstrated that after warm ischemia melatonin increased survival, reperfusion,

and liver regeneration by inhibiting IKK and JNK pathways and modifying cell proliferation. Thus melatonin therapy increased hepatic recovery(216).

The joint effect of melatonin and trimetazidine (TMZ) as superior to Institute Georges Lopez solution (IGL-1) solution in the modulating autophagy and endoplasmic reticulum (ER) stress in steatotic liver grafts was investigated by Zaouali et al(217). They reported that AMP-activated protein kinase (AMPK) activation triggered by the combination of TMZ/ melatonin resulted in the rise in endothelial NOS (eNOS); thereafter, hypoxia-inducible factor-1 (HIF-1a) stabilization and more importantly, a reduction in ER stress and increase in autophagy in fatty liver implants due to modulation of AMPK activity was absorbed. The combination of these agents induced protective genes activation including VEGF, bcl-2, heat shock protein 70 (HSP70), HO-1, and erythropoietin. In addition to the antioxidant capacity of the melatonin, Laliena et al(218), demonstrated that melatonin mitigates inflammation and stimulates regeneration in a model of fulminant hepatitis of viral origin in rabbits. In this study, rabbit hemorrhagic disease virus (RHDV) infection suppressed the hepatic regenerative/proliferative response, with a decline in the transcription of EGF, HGF, PDGF-B and VEGF and their receptors; melatonin administration prevented these responses. Melatonin treatment significantly reduced transcription levels of phosphorylated Janus kinase and increased expression levels of extracellular mitogen-activated protein kinase (ERK) and signal transducer and activator of transcription (STAT) 3. Human dental pulp stem cells (hDPSCs), readily available in adults have the potential of differentiation into hepatocyte-like cells and their transplantation, may inhibit development of liver fibrosis in CCl_4- induced injury. Additionally, the positive role of melatonin on the hepatogenic differentiation of these cells was reported by Cho et al(219), They demonstrated that the transcription of hepatic markers including cytokeratin-18, albumin, hepatic

nuclear factor-1a (HNF1a), and CCAAT box enhancer-binding protein a (C/EBPa) were significantly enhanced, as were hDPSCs when treated with melatonin in liver fibrosis.

3.4. Bone

-Current strategies for bone regeneration

Even though inherent bone tissue regeneration and repair of induced damage occur in large and massive bone defects or some pathological fractures, these processes often fail. Therefore, bone regeneration with clinical interventions is required(220). In addition, bone repair can be negatively affected by numerous conditions including infection of the bone or adjacent tissues, insufficient blood supply, and systemic diseases(220). A bone graft, which is an implanted material, induces bone repair through osteogenesis, osteoinduction, and osteoconduction. Bone grafting is also done in combination with other material(s)(221); these include autografts, allografts, xenografts, and bone graft substitute(222). More importantly, the grafted material has four major characteristics including induction of osteogenesis (generating new bone tissues by osteoblast differentiated from osteoprogenitor cells), osteoinductivity [the ability of the bone graft materials to promote the production of the bone-forming cells(223, 224)], osteoconductivity [occurring when graft material serves as resorbable and permanent scaffold for new bone growth(224-226)], and osseointegration(binding to the peripheral bone tissues with no interfering layer of fibrous tissue) which is vital for an ideal bone graft material in successful bone regeneration(227).

The gold standard for bone-grafting material, autografts, autologous, or autogenous bone grafts is defined as transplantation of a cancellous or cortical bone tissue from one part of the body to another within the same individual(228, 229). A fresh autograft consists of surviving cells and

osteoinductive factors including FGF, PDGF, IGF, BMP-2, and BMP-7. Due to the lack of immunogenicity, viral transmission deficiencies, as well as immediate retaining of viability after transplantation, autografts are the best bone grafting material that exists(230). In addition, an autograft is the only grafting material that possesses all the main features of an ideal graft with respect to the presence of growth factors, MSCs, osteogenic cells, and osteoprogenitor cells(224-231). However, since an additional surgery is required for harvesting of autografts from another body site, this procedure increases donor site pain, morbidity, complications, as well as pathologic fractures and massive bone defects, leading to autograft limitations; other graft materials are introduced to overcome these shortcomings(230).

From the clinical and experimental point of view, an allograft, which is a bone tissue obtained from one donor and transplanted into a recipient of the same species, is considered a common substitute for autografts(232). These are prepared as cortical, cancellous, or a combination of them, and can be utilized in both morselized and structural forms(226). Allografts are harvested either from living donors or cadavers when the latter are available as a commercial product and when they have retained their cellular and organic content(228, 233). The disadvantages of autografts do not apply to allografts. Thus, this type of graft material is preferred due to their availability in a broad range of shapes and sizes(223, 234). However, the lack of viable cells, and hence, lower osteogenic potential, the risk of transmitting bacterial and viral infections, including HIV, hepatitis B and hepatitis C, lower rate of healing, and also induction of immunological reactions, are among the most important limitations of using allografts for enhancing bone healing efficacy(226, 234-236).

In addition to allografts, xenografts, which are also known as xenogenic or heterologous grafts, are an alternative to autografts(237). Heterologous grafts originate from a species other than

human, commonly from coral, porcine, and bovine sources(237, 238). In terms of their processing into safe transplantation materials in human, they can be considered as an unlimited supply of available bone graft materials(237). However, the risk of transmission of zoonotic diseases and prion infections, and lack of osteogenic characteristics result in poor clinical outcomes for xenografts(235, 238). Bone graft substitutes are final options in managing bone defects. These substitutes include tissue scaffolds generated from natural-based material including cellulose, collagen, chitosan, elastin and alginate, and synthetic materials such as different types of mono-, bi-, and tricalcium phosphate including b-tricalcium phosphate (b-TCP), glass-ceramics, hydroxyapatite (HA), and calcium-phosphate cement (239, 240). These materials induce the proliferation, migration, and differentiation of bone cells for bone regeneration (195, 196). Regarding the pros and cons of all bone graft material used for bone regeneration, the research in this field is still ongoing.

- The potential role of melatonin in bone regeneration

Stimulatory actions of melatonin on bone formation and its inhibitory effects on bone restoration have been reported in a number of studies(241). It has been suggested that the osteoblast-enhancing function of melatonin is mediated by its direct action on the differentiation and proliferation of the bone-forming cells. Moreover, enhancement in the bone alkaline phosphatase levels and mineralization(242-245), promotion of the synthesis of collagen type I(246), increase in the bone mass(247), and facilitation of new bone growth and osteointegration(248), are among the positive functions of melatonin on bone. These make melatonin an appealing molecule in bone regeneration. Both *in vitro* and *in vivo* studies have examined melatonin's potential to influence bone repair.

Son et al(249). evaluated the effects of melatonin on osteoblastic mineralization and differentiation of MC3T3-E1 cells in hypoxic settings. They reported that treatment of cells with 50μM melatonin resulted in a significant promotion of the osteoblastic mineralization and differentiation of preosteoblastic cells through the p38 MAPK and PRKD1 signaling pathways. They showed that these effects of melatonin are mediated by increasing ALP activity and transcription levels of Alp, osterix, Ocn and Col1. The same researchers found that when melatonin-treated cells were laser-irradiated, there was a substantial rise in the osterix transcription levels, ALP activity, and mineralized nodules as compared with only melatonin-treated or laser-irradiated cells. Moreover, melatonin in combination with photobiomodulation increased the mineralization and differentiation of MC3T3-E1 cells by p38 MAPK and PRKD1 signaling mechanisms. Luzindole, a selective antagonist of the melatonin receptors strikingly repressed these effects (250).

Park et al(251). reported that BMP/ERK/Wnt signaling pathways is involved in melatonin induced osteoblastic differentiation in MC3T3-E1 cells. Interestingly, they demonstrated that melatonin improved wound closure and triggered osteogenesis markers such as BMP-2 and -4, osteocalcin and runt-related transcription factor 2 (Runx2) in a dose-dependent fashion. The protective effects of melatonin on the potential of mesenchymal stem cells (BMSCs) for osteogenic differentiation against iron overload-induced dysfunction were also examined. Yang et al(252). showed that osteogenic differentiation of BMSCs was significantly reduced by iron overload, but melatonin treatment restored the osteogenic differentiation of BMSCs. Melatonin counteracted the reduction of cell proliferation by iron overload in BMSCs *via* reversing the upregulation of p53, ERK, and p38 protein expression in cells. Hence, the authors concluded that melatonin plays a protective role in iron overload-induced osteogenic differentiation dysfunction

and senescence through blockage of ROS accumulation and p53/ERK/p38 activation. In addition to *in vitro* studies, *in vivo* studies have also established the benficial actions of melatonin on bone. In a study by Satomura et al(253), it was reported that i.p injection of melatonin in mice enlarged the size of the newly-made cortical bone of the femur, in addition to its stimulatory effects on the proliferation, ALP activity, and mRNA transcripts of osteopontin, type I collagen, osteocalcin, and bone sialoprotein of human osteoblasts *in vitro*. Combining melatonin with various scaffolds and its potential application for bone regeneration have investigated in different studies as summarized in Table 2.

3.5. Kidney

-Current strategies for kidney regeneration

The repair of functional nephrons, which can be achieved after various levels of tubular damage, is mediated by cellular regeneration in all organisms including the human(263). However, nephron neogenesis, defined as the capacity to regenerate entire renal tissue is a characteristic feature restricted to the limited number of animals such as fish, reptiles, amphibians, but not birds or mammals(263, 264). Also, renal regeneration through tissue engineering technologies such as scaffold designing, electrospinning, 3D printing would be theoretically and technically difficult, since the heterogeneity of kidney is very high as a result of the presence of 14 different cell types, and the necessity of a special 3D structure organized into functional segments and the necessary interactions between the tubular epithelial cells, peri-tubular vessels, luminal ultra-

filtrate, and the interstitial space (265). Thus, decellularization of xenogeneic or allogeneic donor kidneys using detergents such as anionic sodium dodecyl sulfate (SDS) and non-ionic Triton X-100 (266-270), or enzymes to remove the antigenic parenchyma completely may be a favorable alternative strategy to design effective scaffolds for regenerating the complete kidney(269). However, there are few reports of the successful transplantation of scaffolds produced from rodent(266, 267, 269, 270), pig(267, 269, 271, 272), or human kidney(267, 269), mostly due to the inherent thrombogenicity of the non-endothelialized vasculature(273). It is also established that renal ECM has vital functions in the regulation of multiple cellular processes. As a result, a cooperative scaffold that controls stem cell differentiation and kidney development was suggested, since previous studies reported more metabolically active stem cells on ECM of decellularized kidney (265). The native vasculature of decellularized complete kidney scaffold enables uniform dissemination of nutrient-enriched culture media to cells in entire scaffold, and custom bioreactor systems have been developed(268, 274). The final step is evaluating the efficacy of the transplantable kidney grafts prior to implantation, in order to identify the appropriate function of various immature stem or progenitor cells present in scaffolds. This requires a comprehensive functional test. Furthermore, the discovery of renal progenitors by using an assessment of CD133 and CD24 provide a remarkably promising application in renal regeneration(275). This small population of stem cells with a limited capacity of self-repairing has the potential of differentiation into multiple renal cells, especially glomerular and tubular epithelial cells(276). However, two challenges are encountered and include generation of a pure and large amount of a single differentiated cell type and generation of self-organizing nephron-like structures; this research is just emerging.

- The potential role of melatonin in kidney regeneration

Accumulating studies document that melatonin confers renal protective effects against pathological damage induced by ischemia-reperfusion(277-280), severe burns(281), unilateral ureteral obstruction(282), lead(283), aluminum(284), mercury(285), cadmium(286), paraquart(287), S-methylisothiourea(288), doxorubicin(289), fumonisin(290), ochratoxin A(202), etc. The beneficial effects are mainly related to the antioxidative, anti-apoptotic, and anti-inflammatory potential of this ubiquitously-acting molecule. In addition, it was reported that melatonin pretreatment of stem cells improved their renoprotective and prosurvival actions. For example, Zhao et al(291) explored the effects of melatonin on human adipose tissue-derived mesenchymal stromal cells (hASCs), and the influence of the resultant hASCs-conditioned media (CM) on cisplatin-exposed human kidney cells. They observed that pretreatment of these cells with melatonin significantly boosted their proliferation and expression of antioxidative enzymes, heme oxygenase and (HO)-1 and catalase, as well as prosurvival P-Akt and P-Erk1/2. Moreover, pretreatment of HK-2 human kidney epithelial cells with the CM from hASCs resulted in a significantly higher proliferation and migration. Melatonin pretreatment of hASCs markedly improved their viability and beneficial regenerative potential on damaged tissue *in vitro*. Similarly, Chen et al(292) showed that a combination therapy of melatonin with apoptotic adipose-derived MSCs (A-ADMSCs) offered superior benefits in protecting against sepsis-induced acute kidney injury. In addition to their protective functions, it has been shown that MSCs injection resulted in a significant improvement in the structural and functional repair and regeneration of injured organs; this was presumed to be related to their transdifferentiation ability into the cell phenotype of the host organs. Additionally, secretion of the various important

mitogenic and vasculotropic factors may also have been involved in the improvement of the tissue regeneration mediated by MSCs.

Mias et al(293). demonstrated that melatonin pre-administration potently enhanced the survival of MSCs in a rat model of acute renal failure. This action was accompained by an increase in the proliferation of renal cells, higher expression of bFGF and HGF, angiogenesis and enhanced recovery of renal function. The underlying mechanisms includes the diverse antioxidant roles of melatonin. Also, conditioned media (CM) from melatonin-treated MSCs in culture promoted proliferation of proximal tubule cells and tube formation by endothelial progenitor cells.

The enhanced renoprotective effects of early outgrowth endothelial progenitor cells by melatonin was also reported in acute ischemic kidney injury(294). Hence, pretreatment of stem cells with melatonin potentially offers a novel and safe strategy for improving the beneficial effects of regenerative medicine in kidney diseases. Recent studies have reported that one of the main consequences of the acute renal injury is the necrosis and apoptosis of renal tubular epithelial cells (TECs). In this situation, inhibition of repair and regeneration of injured kidneys occurred, which later was demonstrated to be mediated by TECs arrest in the G2/M phase(295-297). Stimulatory agents, such as melatonin, that can trigger TECs proliferation and overcome cell cycle arrest may contribute to the regeneration and repair of damaged kidneys. In this regard, Zhu et al(298). showed that melatonin pretreatment expedited the regeneration and repair of TECs by accelerating proliferation and decreasing the percentage of cells in the abnormal cell cycle stage.

3.6. Muscle

-Current strategies for muscle regeneration

The regenerative capacity of the skeletal muscle can lead to complete recovery of the original structure of damaged muscle; however, commonly the repair process is accompanied by remodeled and distorted structures such as forked or branched fibers, tissue scar and new myotendinous junctions at the site of the rupture(299). Muscle regeneration, which is a complex process requires synchronized regulation of the inflammatory response, energy metabolism, and myofiber growth. These commonly occur in two overlapping phases: a) myolysis, which includes active muscle degeneration and inflammatory responses, and b) reconstruction, which is performed by tissue undifferentiated myogenic precursor cells and satellite cells(300-302). Considering the limited capability of the regenerative potential of muscles in advanced age, and a massive volumetric skeletal-muscle loss, other alternative strategies would be helpful. Autografts of healthy donor muscle tissue are the clinical gold standard treatment for these situations. However, this strategy has some limitations such as shortage of donor tissue, the risk of dysfunction at the donor site, and an increase in the donor-site morbidity(303-305).

Tissue-engineering products are one of the best options to provide the functional and structural requirements of damaged muscle regeneration. Hence, IT offers a promising novel strategy for patients suffering from musculoskeletal trauma and other muscular disorders(306). Generally, three main strategies are included for muscle regeneration during the use of tissue-engineering constructs: a) the isolation of muscle progenitor cells from an autologous source, in vitro culture and expansion of the progenitor cells seeding into a 3D scaffold and the implantation of the cell-seeded scaffold into the defect site, b) the delivery of autologous progenitor cells, without in vitro expansion, directly to the defective site via a scaffold, and c) the implantation of a cell-free,

3D scaffold designed to release cytokines and/or growth factors to stimulate the endogenous healing cascade leading to tissue regeneration. The main goal of ongoing research is the identification and design of the novel alternative, gene- and cell-therapy strategies to promote muscle tissue regeneration(307, 308).

- The potential role of melatonin in muscle regeneration

As discussed above, because of its anti-oxidative, anti-inflammatory effects, and its ability to improved microcirculation, the action of melatonin on the skeletal muscle after injury is being heavily investigated. It has been reported that melatonin provides a significant microvascular boost during reperfusion injury in skeletal muscle. In a study by Wang et al(309), administration of melatonin (10 mg/kg) substantially increased arteriole diameter, ameliorated capillary perfusion, and improved endothelial dysfunction of skeletal muscle capillaries after four hours warm ischemia.

Oner et al(310) documented that melatonin is an effective agent for the prevention of skeletal muscle atrophy induced by castration in rats. They also reported that the protective effects of melatonin were arbitrated *via* the IGF-I axis since strong immunostaining of IGF-I was observed in the animals treated with melatonin. The favorable effects of melatonin against muscle atrophy were also investigated by Lee et al(311) in a rat model of stork-induced muscular atrophy. They showed that long-term exogenous melatonin administration may have a prophylactic impact on muscle atrophy through the muscle ring finger 1 (MuRF1) and muscle atrophy F-box (MAFbx) signaling pathways, as well as a potential therapeutic effect via the IGF-1-mediated hypertrophic signaling pathway.

The possible protective effect of melatonin on tissue homeostasis and cellular functions in muscular repair of injured skeletal muscle has also been evaluated in recent years. Mehanna et

al(312) noted that an intra-peritoneal injection of 10 mg/kg body weight/ day of melatonin resulted in the significant rise in the twitch force of injured muscle. The MT1a membrane receptor was also overexpressed as a result of melatonin administration. The anti-apoptotic action of this indole was validated by the significant drop in Bax levels in the injured soleus muscle. The existence of the melatonin receptor in the muscle suggested that melatonin may exert its restorative effects through both direct and indirect mechanisms. A similar finding was also reported by Statros et al(313); they claimed a significant rise in transcription of MT1a receptor in the blunt-induced injured muscle. The results of both studies predicted the involvement of the MT1a in the protective effect of melatonin during recovery of the contractile function and regenerative capacity of damaged muscle; this possibly involved the tuning of signaling pathways linked with apoptosis. The authors also demonstrated that melatonin reduced infiltration of leukocyte and elevated the quantity of satellite cells. Likewise, ERK phosphorylation reached highest levels in the melatonin-treated animals after injury.

In addition to animal models, melatonin function has been investigated in undifferentiated C2C12 skeletal muscle cells, after their contact to numerous apoptotic chemical triggers, including staurosporine, etoposide, and hydrogen peroxide. Morphofunctional and molecular analyses illustrated that in myoblasts melatonin prevented chemical-induced apoptosis and oxidative stress which at least partially involved a mitochondrial pathway(314). Finally, Hong et al(315) noted melatonin-prompted accelerated muscle tissue remodeling on gastrocnemius of rats with collagenase-induced knee laxity.

3.7. The potential role of melatonin in the regeneration of other tissues

The regenerative capacity of melatonin has been investigated in other tissues including bladder, pancreas, and skin. Melatonin was also shown to possess protective effects against deleterious

changes induced by antineoplastic agents including cyclophosphamide(316, 317), physiological conditions such as aging(318), and pathological threats such as ischemia-reperfusion(319, 320) and water avoidance stress(321). Interestingly, Gomez-Pinilla et al(322), reported that melatonin restored impaired contractility of aged guinea pig urinary bladder, which may have been a consequence of increased [Ca^{2+}]. They showed that melatonin treatment restored deficient contractility via control of Ca^{2+} usage and Ca^{2+} sensitization pathways including Rho kinase and protein kinase C (PKC). They suggested that melatonin may have therapeutic potential for palliating aging-related urinary bladder contractile impairment.

Hemorrhagic cystitis induced by cyclophosphamide, which is associated with apoptosis, breakdown of the bladder urothelium, and rapid regeneration via proliferation and differentiation of urothelial cells, was completely restored to normal in three weeks, as shown by Zupancic et al(323). This group reported that co-administration of melatonin (10mg/kg) and cyclophosphamide (100mg/kg) significantly reduced apoptosis and enhanced proliferation of urothelial cells. Hence, it prevented the extensive loss of urothelial cells, and with a drop at days 4 and 7 after co-treatment; this resulted in the prevention of a hyperplastic response. The results demonstrated the positive effects of melatonin on the regeneration and restoration of normal urothelium. In another study, it was shown that a combination treatment of melatonin (20 mg/kg) and adipose-derived mesenchymal stem cell resulted in an improved protection against cyclophosphamide (150 mg/kg)-induced acute interstitial cystitis in rats(324).

The modulatory effects of melatonin have been evaluated on pancreatic self-regeneration in experimentally induced acute pancreatitis. Melatonin administration limited the severity of acute pancreatic inflammation. The rate of DNA synthesis, nucleic acid content, pancreatic amylase and pancreatic proteins levels were significantly elevated, as a consequence of melatonin

administration. Additionally, the histopathological analysis indicated significantly lower total tissue injury in melatonin-treated animals(325). The positive effects of melatonin on the pancreatic tissue were also evaluated in the diabetic rat. Kenter et al(326), observed that melatonin administration (10mg/ml) caused a marked drop in the increased serum glucose, a minor reduction in concentrations of serum insulin and slight partial regeneration/proliferation of β-cells of islets.

The effects of melatonin on the skin regeneration during wound repair in skin excision wound model in mice were investigated by Lee et al(327). They stated that melatonin pretreatment of 'implanting umbilical cord blood (UCB)-MSCs' boosted re-epithelialization, granulation, and wound closure where significantly more grafts of UCB-MSCs in the skin wound sites were noticed. Treatment with melatonin (1 μM) significantly enhanced the motility of UCB-MSCs, which had been suppressed through knockdown of MT2 receptors. Additionally, Gαq coupling with MT2 and the binding of Gαq to the MT2 receptor uniquely activated an atypical isoform of PKC, PKCζ. Melatonin stimulated the proteins related to cytoskeletal reorganization such as F-actin, cofilin-1, profilin-1, increased active Arp2/3 and Cdc42 level, and induced the phosphorylation of paxillin and FAK in UCB-MSCs. Finally, inhibition of the signaling through the MT2 receptor in UCB-MSCs throughout a skin implantation study in mice compromised wound healing and fewer engrafted stem cells were engaged at the wound area.

Conclusion

Melatonin is a hormone with myriad biological functions in the human body, including but not limited to anti-inflammation, oncostatis, circadian and endocrine rhythm regulation and tumor inhibition. Owing to its vast biological activities, it is not surprising if now the potential of regeneration of different organs are also added to the collection of melatonin-related functions.

In addition, melatonin is used in various areas including stem cell biology, tissue engineering and aging biology. In this context, melatonin is becoming progressively attractive as tools for the development and regeneration of several tissues, such as liver, muscle, bone and neural system. Current strategies of melatonin in defferent tissues is discussed, and it is concluded that in both preclinical and clinical studies. It is clear that the protective/regenerative effects of melatonin can be applied in treatment of a vast spectrum of human degenerative/destructives diseases, in particular tissues as discussed in-depth earlier. For instance, osteogenesis is enhanced and adipogenesis is inhibited by melatonin; as a result, bone marrow precursor cells can be shifted from an adipocytic to osteoblastic differentiation that be of importance in bone repair technologies. Our current knowledge on the implication of melatonin in tissue regeneration ,and considering the potential of this hormone in regenerative medicin that was discussed, is just the tip of iceberg, but there is no doubt that melatonin plays a big role in regenerative medicine in the future.

Conflict of interest

The authors declare no conflict of interest.

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Figure legends:

Fig 1. Implication of melatonin in regenerative medicine. The beneficial effects of melatonin therapy and the underlying molecular cues involved in regeneration process of various human organs including nerve system, muscle, bone, skin, bladder, kidney and hepatocyte are illustrated.

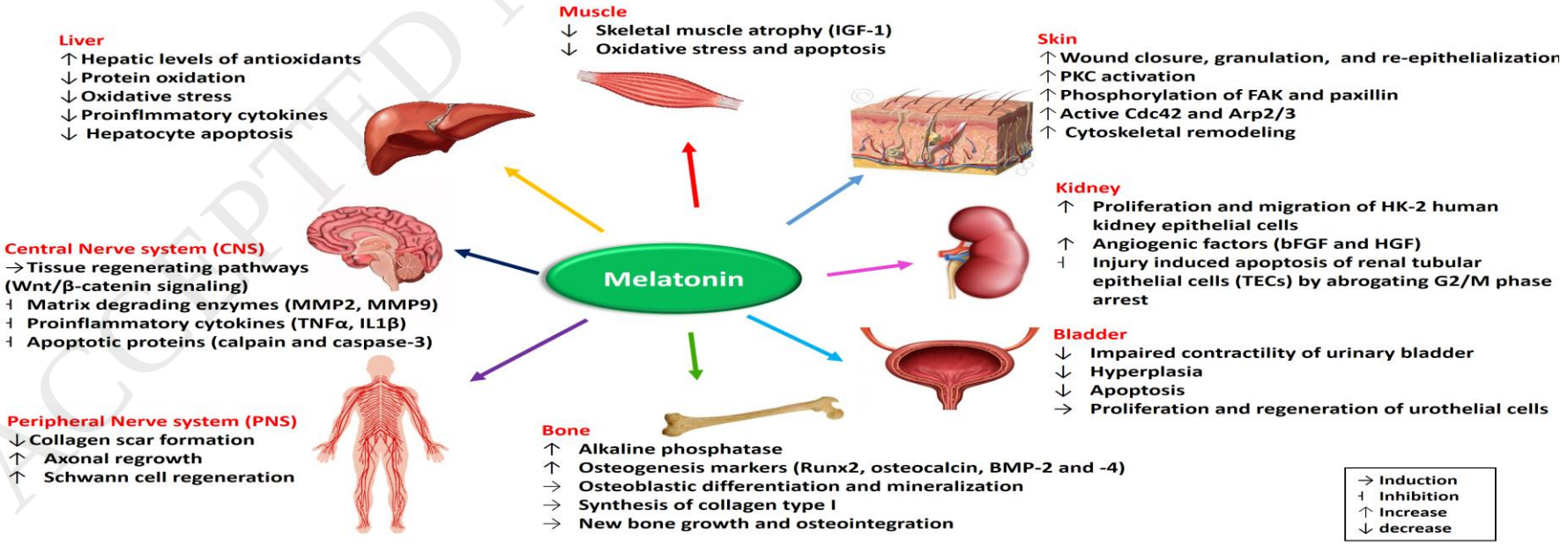

Fig 2. Components of regenerative medicine. This figure shows the main components of regenerative medicine consisting of tissue engineering, cell therapy, gene therapy and nuclear cloning, all perusing the final goal of either restoring the lost function or introducing a new function to the damaged tissues/organs.

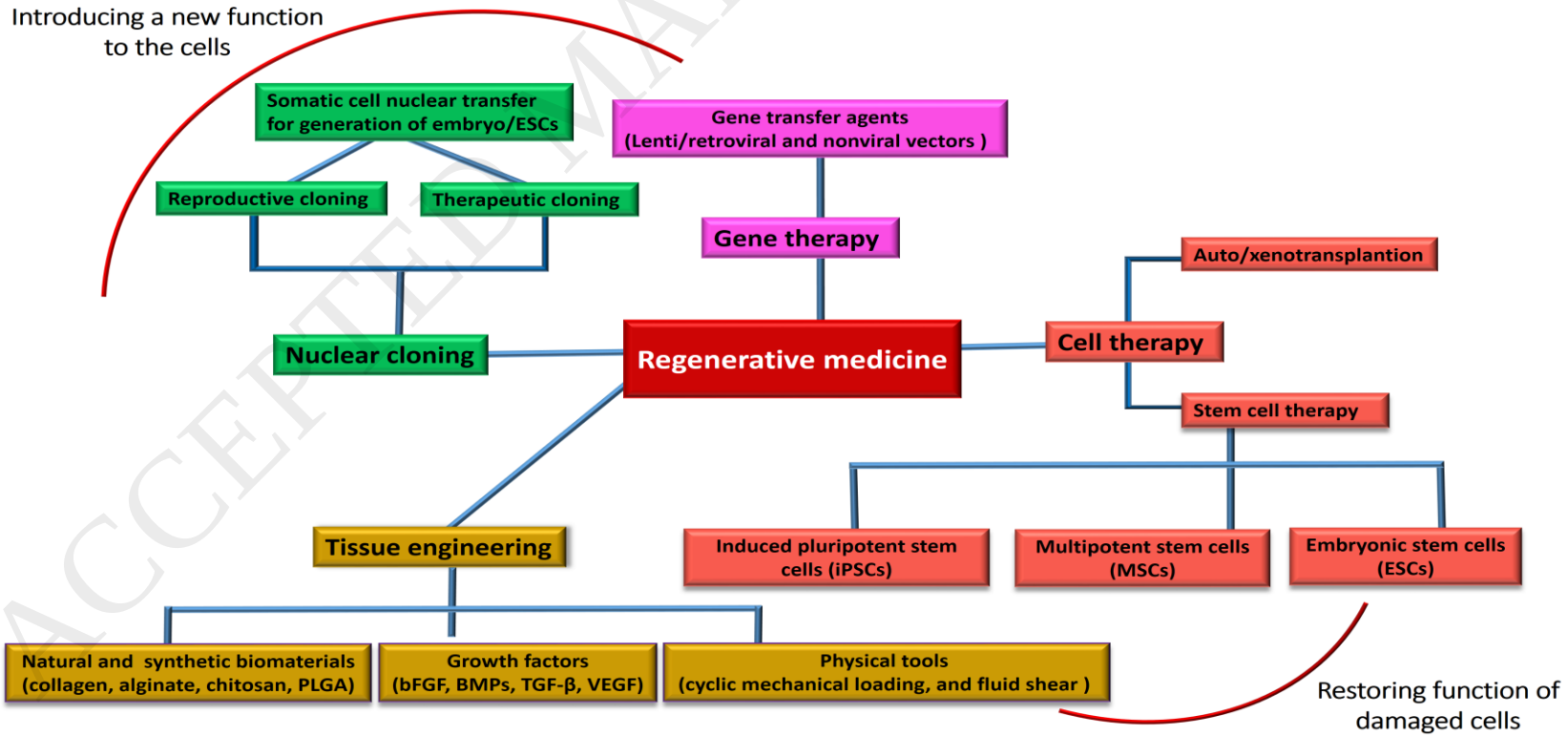

Fig 3. The effects of melatonin on stem cell fate. The favorable effects of melatonin treatment on enhancing survival, migration and differentiation potential of different stem cells into the various cell types is shown.

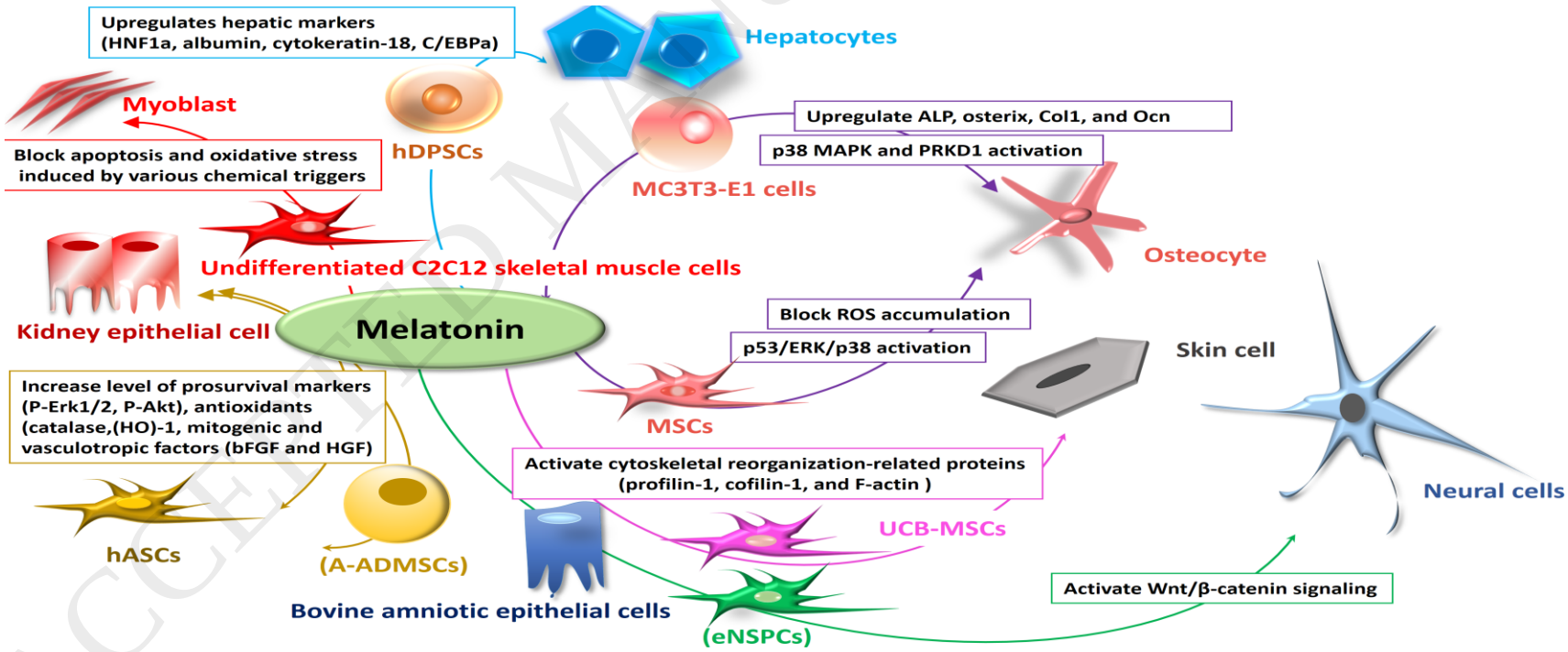

Table 1. The effect of melatonin treatment on the peripheral nerve injuries.

Target tissue	Target injury	Melatonin concentration	Major comments	Ref.
Rats hypoglossal nucleus	Transection of right hypoglossal nerve	100 mg/ kg	Melatonin treatment resulted in the marked depression of neuronal NADPH-d/NOS expression. In the hypoglossal nucleus, melatonin treatment increased the number of living motoneurons. Melatonin reduces the oxidative stress of peripheral nerve damage.	(114)
Neonatal rat motoneurons	Sciatic nerve transection	1–50 mg/kg	Melatonin decreased neuronal death. Melatonin reduced the intensity of astrocytic hypertrophy.	(115)
Rat sciatic nerve	Reperfusion injury	10 mg/kg	Melatonin treatment reversed the ischemia-reperfusion (I/R)-induced SOD increase and MDA decrease. Melatonin rescued nerve fibers from ischemic degeneration. Melatonin-treated animals showed less injury and less edema to the axons and myelin sheaths.	(116)
Rat sciatic nerve	Sciatic nerve transection	50 mg/kg	Melatonin administration significantly benefited cut sciatic nerve repair in dark period. The cut sciatic nerve recovery was not affected by melatonin therapy in dark period. The melatonin effects on the repair of the cut injured sciatic nerve are time-dependent and follow a circadian rhythm.	(117)
Rat sciatic nerve	Sciatic nerve transection and crushing	50 mg/kg	Melatonin treatment preserved structure of myelin sheaths. Melatonin resulted in lower lipid peroxidation and higher levels of glutathione peroxidase, catalase, and SOD in sciatic nerve.	(118)
Rat sciatic nerve	Sciatic nerve transection	30 µg/100 g	Three different strategies were used to evaluate nerve regeneration: autologous nerve graft repair, collagen conduit repair, and platelet gel-enriched collagen conduit repair. Platelet gel positively affected nerve regeneration, while local platelet gel combined with	(108)

			melatonin did not benefit the nerve repair.	
Rat Schwann cell line (RSC 96 cells), musculocutaneous nerve	End-to-side neurorrhaphy	1 nM	In Schwann cells, MT1 is the main receptor. Melatonin administration increased the number of RSC 96 cells and enhanced phosphorylation of ERK1/2. Melatonin efficiently amplified the Schwann cell proliferation. Melatonin re-innervated motor end plates in target muscles. Melatonin enhanced proliferation of Schwann cell and nerve regeneration.	(119)
Rat sciatic nerve	Sciatic nerve transection, craniotomy, pinealectomy	10 mg/kg	Pinealectomy resulted in the poor organization of the repair area, increased the diameter of the extrafascicular connective tissue and markedly elevated the amount of endoneural collagen. Melatonin treatment resulted in thinner epineurium, less endoneural collagen, and a better collagen organization. Nerve recovery was effectively enhanced by melatonin.	(120)
Rat sciatic nerve suture	Sciatic nerve transection	30 mg/100 g	Pinealectomy increased formation of macroscopic neuroma and collagen content of the sciatic nerve. The same region showed a significant drop in collagen content in melatonin-treated pinealectomized animals. As a consequence of pinealectomy, a strong immunoreactivity for collagen Type I and Type III was especially demonstarted in the epineurium. The immunoreactivity of the repair area significantly reduced by melatonin treatment in animals. In the suture repair site, melatonin enhanced nerve recovery by reducing collagen accumulation and neuroma formation.	(111)
Rats hypoglossal hypoglossal	Hypoglossal nerve transection	100 mg/kg	Following melatonin administration, the nNOS elevation was effectively repressed and Cu/Zn-SOD, Mn-SOD, and choline acetyltransferase activities were successfully conserved.	(121)

motoneurons			Melatonin lessened fibrillation to potentiate functional recovery.	
Rat sciatic nerve suture	Sciatic nerve transection	30 µg/100 g	Epineurium of the pinealectomized animals showed high expression of bFGF and/or TGF-b1. Melatonin treatment caused negative or weak staining in animals. Both TGF-b1 and bFGF actively regulated collagen formation and accumulation of neuroma at the anastomotic site. Melatonin advanced nerve recovery.	(122)
Rat sciatic nerve	Left sciatic nerve crush	5 and 20 mg/kg	Electrophysiological and theoretical analysis revealed the effective role of melatonin in nerve recovery.	(123)
Rat sciatic nerve	Sciatic nerve transection	30 mg/kg	The administration of exogenous melatonin was effective in suppressing trauma-caused extrafascicular connective tissue proliferation in neuroma of the proximal nerve stump as well as fibroma formation in the distal nerve stump.	(124)
Rabbit peripheral facial nerve	Peripheral facial nerve neurorrhaphy	30 mg/kg	Melatonin prevented myelin degeneration and reduced the accumulation of myelin debris. Melatonin increased regeneration after peripheral facial nerve neurorrhaphy.	(125)
Rat sciatic nerve	Sciatic nerve transection	30 µg/100 g	Pinealectomized animals displayed a high proliferation of connective tissue and formation of large neuroma at the proximal ends of transected nerves. Melatonin positively declined content of connective tissue of the same region in pinealectomized animals. Axonal regeneration was promoted by melatonin through blocking neuroma formation.	(126)
Rat sciatic nerve	Blunt sciatic nerve injury	10 mg/kg vs 50 mg/kg	Though low-dose melatonin lowered trauma-induced axonal alterations and myelin collapse, the ultrastructural changes were almost entirely prevented by a high-dose melatonin in the sciatic nerve. A potent neuroprotective effect was demonstrated with 50 mg/kg dose of melatonin, which rescued peripheral neural fibers from blunt trauma induced lipid peroxidative damage.	(127)
Ovariectomized-	Sciatic nerve	5 or 20 mg/kg	Melatonin alleviated the electrophysiological properties of the sciatic nerve in ovariectomized-	(128)

aged rats	transection		aged rats. Melatonin supplementation may have clinical application in treatment of postmenopausal peripheral nerve degeneration.	
Rat sciatic nerve	Sciatic nerve crushing	100μM	Exposure to melatonin cause a higher repair percentage of severed rat sciatic axons induced by polyethylene glycol. Melatonin enhanced regeneration of severed sciatic axons of rat in vitro and in vivo.	(129)
Rat sciatic nerve	Sciatic nerve transection	50 mg/kg	Melatonin improved nerve conduction velocity (NCV), sciatic functional index (SFI) and the force of gastrocnemius muscle contraction as compared to untreated rats. Melatonin treatment markedly increased SOD, bcl-2, and Nerve growth factor (NGF) while IL-1β was significantly reduced. SFI reached the control level; melatonin therapy in the dark considerably improved IL-1β and muscle contraction. Melatonin highly accelerated neural regeneration, especially when the rats were treated during the dark period. Melatonin may employ for treatment of nerve injury.	(130)

Table 2. The effects of the addition of the melatonin to the various scaffolds and its potential application for bone regeneration.

Target tissue	Target animal	Scaffold	Melatonin concentration	Major finding	Ref.
Calvaria	Rat	Calcium aluminate (CA)	1 mg/mL	Compared to CA scaffolds, CA-Mel scaffolds boosted the proliferation, survival, and adhesion of normal human osteoblasts cells. Melatonin increases the osteoinductive and osteoconductive properties of CA scaffolds. Bone regeneration was highest in CA-Mel scaffold implanted animals as verified by fluorochrome imaging at three and six months.	(254)
Proximal metaphyseal part of tibia	Rabbit	Bone implants	5 mg/mL	The cortical bone length was increased by melatonin therapy. In tibiae of rabbits, the length and width of cortical bone nearby implants was more swiftly regenerated by melatonin than the nearby control implants without melatonin supplementation.	(255)
Proximal metaphyseal part of tibia	Rabbit	Bone implants	1.2 mg/ml	There were no residual or healed bone changes related to the melatonin graft. Melatonin promoted formation of a thicker new bone. In melatonin group, the cortical formation length significantly differed from the control group. After melatonin treatment, the number of vessels was meaningfully changed.	(256)
Mandible	Dogs	Rough discrete calcium deposit (DCD) surface implants	5 mg/mL	Melatonin combined with porcine bone considerably amplified the edge of bone that was in direct interaction with the treated grafts, new bone, and bone density compared with porcine bone alone. On DCD surface, the melatonin-collagenized porcine bone may enhance osteointegration by acting as a biomimetic molecule to home endo-osseous dental	(257)

				transplants.	
Proximal metaphyseal part of tibia	Rabbit	Collagenized porcine bone (MP3) grafts	1.2 mg/ml	The length of the cortical bone formation was augmented by melatonin. In tibiae rabbits, melatonin accelerated the regeneration of length and the width of cortical bone compared with collagenized porcine bone. Melatonin elicit bone stimulating effects in comparison with control sites and porcine bone.	(258)
Proximal Metaphyseal part of tibia	Rabbit	Zirconia implants with micro-grooved surfaces versus titanium implants	N/A	Melatonin supplemented implants displayed greater bone/implant contact (BIC)%. Micro-grooved zirconia garfts supplemented with melatonin presented the maximum BIC among all the groups. Connective tissue was higher in titanium and zirconia melatonin untreated bone.	(259)
Mandibular premolars (P2, P3, and P4) and first molar (M1)	Fox	Collagen sponges	N/A	New bone formation was higher in melatonin group than apigenin and control group. Topical use of melatonin or apigenin hastens early healing stages in bone tissue. Melatonin greatly stimulated bone maturation at two months of follow-up.	(260)
Calvarial defects	Mice	Titanium particle	5 mg/kg or 50 mg/kg	Melatonin inhibited titanium particle-induced osteolysis and increased bone formation at osteolytic sites. Osteoclast numbers decreased dramatically in the low- and high-melatonin administration mice. Melatonin alleviated titanium particle-induced depression of osteoblastic differentiation and mineralization in mMSCs. Melatonin reduced the degradation of β-catenin, levels of which were decreased in presence of titanium particles both *in vivo* and *in vitro*.	(261)

				Melatonin modulated the balance between osteoprotegerin and receptor activator of NF-κB ligand via activation of Wnt/β-catenin signaling pathway.	
Calvaria	Rat	Plastic cap	10mg/ml	In the melatonin group, formation of new bone inside the plastic cap was significantly increased compared to the control group. Melatonin enhances vertical bone augmentation.	(262)