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Factors Involved in Tissue Regeneration

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Abstract

In the event of injury, tissues have limited potential for self – repair. Tissues can be regenerated *in vitro*. There are a lot of factors involved in this process such as signaling pathway, regulators molecular, materials for tissue engineering including pluripotent stem cells, scaffolds, bioreactors. Selecting factors and material with high efficiency can improve tissue regeneration process and treatment of damaged tissues by repairing or replacing with normal tissues. This review article encompass summary of factors and materials involved in tissue regeneration.

Keywords: Regenerative medicine; Tissue engineering; Biomaterials; Review

Introduction

Tissue and organs may lose their function and structure due to age, disease tissue, trauma and congenital defects. Regenerative technique can help to repair damaged tissues or organs or replace them with normal structure and functional. Regeneration can be affected by two different paths: external condition including temperature, gravity, light, chemical changes, pressure and internal factors such as structure, material constitution, polarity and orientation. Regenerative researches are focused on different clinical and biological context such as cytology, chromosome, epigenetic and transplantation [1].

Regenerative medicine term first appeared in the 1990, tissue engineering and regenerative medicine therapies encompass several strategies base including a cell base, molecular base and material base [2].

Myo clinical center sponsored some clinical trials for regenerative medicine. These clinical trials categories are included neurological, cardiac, lung, cancer, musculoskeletal, liver and gastrointestinal, kidney disease, wound healing (pressure ulcers), urology, surgery (pop soft tissue repair) and ophthalmology [3].

Subsections of different strategies of regenerative technique have been classified in three broad:

- Reconstructing tissue and organ structure via scaffold fabrication, bioprinting and self -assembly.
- Combining grafts with the host environment via innovation and vascularization
- Changing the host environment to induce therapeutic responses.

Three important issues for advancement of regenerative can be considered:

- Isolating and inducing stem cells from adult tissue and safety control after transplantation.
- Technologies for anastomosing tissue with host vessels and permitting for graft survival
- Creating a pro-regeneration environment within the patient [4].

Numerous studies have been performed in tissue regeneration field. Progressive in this field can help to improve many of issues such as transplantation and cancer. In this review we intend to asses recent and critical studies that are accomplished in tissue engineering and regenerative medicine context.

Bone Regeneration

Bone tissue is capable of regeneration. Following the large defects (trauma, tumor resection), autologous bone grafting (ABG) is the gold standard for bone repair however there are some limitations such as cost of this approach and risk of infection. Bone tissue engineering (BTE) is an alternative strategy, that can fill the clinical needs for ABG in this strategy it utilizes different cell sources including bone fragment, bone marrow stem cells (BMSCs), fat and multipotent mesenchymal stem cells [5]. The aim of most recent studies were to increase and assess quality of bone regeneration through selecting the best source of cells, scaffolds, growth factor and molecular regulators.

Allograft, xenograft or synthetic scaffolds integrated with stem cells and growth factor are new strategies for bone repair. Mesenchymal stem cells (MSCs) located in bone marrow have ability grow in media containing fetal calf or fetal bovine serum. New media containing are offered for expanding MSCs and using as scaffold coating is human platelet lysate (PL). PLs contain a several of bioactive factors that facilitate MSCs attachment, proliferation and differentiation so is thrilling opportunity for bone defect repair as cell culture supplement, osteo-conductive scaffolds and guided bone regeneration (GBR) implements [6].

Collagen membranes have demonstrated biocompatibility and capability of increasing injury healing. Use of collagen membrane for guided tissue regeneration (GTR) procedures is more efficiency than other membrane [7].

Studies showed Resorbable Collagen Membranes (RCM) are more efficacy than porcine- derived collagen matrix at enhancing new bon formation in facilitating GBR (around standardized rat calvarial defects) [8].

Efficacy of Bone marrow derived mesenchymal stem cells (BMSCs) are assessed for promoting GBR. In this experiment, there are four groups including control, bone graft, bone graft covered with a collagen membrane (CM) and bone graft soaked in BMSCs and covered with CM. Results showed highest quality for adjunct BMSCs with bone graft and CM in bone volume of newly formed bone (NFB) than other groups for GBR. Results analysis did by *in vivo* micro-computed tomographic (μCT) and histological analysis [9].

The *in vivo* μCT results for using of recombinant human platelet – derived growth factor (rhPDGF) with and without restorable collagen membrane (RCM) manifested greatest decrease in remnant bone particle volume (RBPV) and mineral density (RBPMD) belong to bone graft (BG) + rhPDGF + RCM group [10].

Another experiment assessed efficacy of a combination of recombinant human bone morphogenetic pro 2 (rhBMP-2) and bio phasic calcium phosphate (BCP) with and without RCM in regeneration of standardized calvarial defects (SCD) in rat. Results of this experiment showed BMP+ BCP with and without RCM were effective in developing bone regeneration [11]. But where in the presence of CM leads to a greater percentage of new bone formation within SCD [12].

Using particulate graft material (Bio-oss) with and without CM and analysis of bone volume and bone mineral density (BMD) of newly formed bone (NFB) and remnant bone particle determined that NFA starts as early as 4 week in SCD undergoing GBR with Bio-osscompared with NFB at 6 week in defects undergoing GRB with Bio-oss alone [13]. Real time, *in vivo* (μCT) and histological results showed NFB in the Bio-oss and β tricalcium phosphate (βTCP) with adjunct rhPDGF at 10 weeks and BMD significantly increased in rhPDGF + βTCP compared with other group [14].

Biophosic calcium phosphate (BCP) (a bone substitute biomaterial) is used as scaffold, drug delivery system and carrier of growth factor [15]. BCP with high ratio of hydroxyapatite/TCP determined good osteoconductive Properties and would be useful for stable graft volume in calvarial defect [16].

The scaffold was fabricated by combining the layer solvent casting with the freeze-dying and lamination technique. The Scaffolds are eliminated by a repeated freeze-thawing process after locating on their surface by culture of osteoblasts.

An osteoblast conditioned Nano-hydroxyapatite/gelatin ([HA/GEL/OC) composite scaffold are utilized for bone tissue regeneration [17].

Bovine gelatin as scaffold is a natural polymer. The ability to promote cellular attachment migration and differentiation into tissue depend on the scaffold‘s surface properties and composition [18].

Expression bone morphogenetic protein 2 (BMP2) in mesenchymal stem cell is efficacy in NBF so delivery system play important role in this process. Bioactive glass nanoparticles (BGN) system for gene delivery showed excellent capacity for advancing the therapeutic potential of stem cells through genetic modification targeting bone defects and disease [19].

The regulation of osteoblast differentiation is important for bone regeneration therapy. MicroRNAs regulate and control variety of cellular process including differentiation, proliferation, apoptosis and play important role in the pathogenesis of human disease. MiRNA therapy will enable development of bone regeneration therapy [20]. Wnt signaling promote differentiation from Mesenchymal stem cells to osteoblast. Wnt inhibitors (SOST, DKK2, SFRP2) can block with miR218 and increase effect of Wnt. Effect of wnt3a delivery in critical size calvarial defect at 7 days of healing promote bone formation [21].

There are several factors that promote bone regeneration such as role of IL-17A in regeneration process after injury [22].

Regenerative therapy for bone defects comprise various strategies such as cell therapy, Mesenchymal stem cell, tissue engineering (use of cells, scaffolds, and bioactive factors), cell-based scaffolds, cell-free scaffolds and gene therapy [23].

Liver Regeneration

The liver is one of the critical organs in the body and plays many important roles including homeostasis, synthesis and storage of glucose and proteins, detoxification and immune defense. The liver is a naturally regenerative organ, at the end stage failure of liver disease therapeutic intervention is necessary [24].

Stem cell therapy have some steps. First, isolation and differentiation of stem cells are performed in specific medium containing growth factors. Stem cells include embryonic stem cells, adult stem cells. Mesemchymal stem cells induced pluripotent stem cells (IPSC). Second step is homing and engraftment of transplanted cells to target organ in cell therapy [25].

Mesothelial cells (MCs) cover the surface of visceral organs and play roles in liver regeneration. MCs express cell adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1), and cytokines, such as SDF-1/CXCL12, MCP-1/CCL2, and IL-8 and Differentiation of MCs into Hepatic stellate cells (HSCs) has been reported in chick and zebra fish livers. MCs act as progenitor cells for liver mesenchymal cells during liver development [26].

Hepatic cell sheet derived from MSCs for treatment liver failure. Knockdown of signaling molecular target genes of WNT/β-catenin signal resulted in hepatic differentiation of human MSCs. Suppression of WNT/β-catenin signal with hexachlorophene induce hepatic specification of MSCs [27].

The effects of the human amniotic membrane (HAM) are assessed on regeneration of resected liver. HAM is mesenchymal stem cell source that express factors play roles in growth of liver mass and cell differentiation but experience don't show positive effect on liver regeneration [28].

Cirrhosis is liver disease that is healed by liver transplantation but there are limitations in transplantation such as scarcity of liver donor organs .bone marrow mesenchymal stem cells act in liver regeneration via differentiation. Fibroblast growth factor 4 (FGF4) could induce bone marrow derived monocyte into hepatocytes *in vitro*. FGF elicit a variety of biological response including cell proliferation, differentiation and migration [29]. One of the molecular factors that effect on liver regeneration after partial hepatectomy (PHT) is carbon monoxide (CO) are produced by hemeoxygenase (HO). HO-1 and CO are hepatoprotective molecules. CO induce a more rapid induction of hepatocyte proliferation after hepatectomy [30]. Besides CO, IL22 effecton hepatocyte and repair injuryvia STAT3 activation after PHT [31]. Several factor have been reported to promote hepatocyte proliferation such as zinc finger transcription factor Egr-1 (early growth response 1) [32], translationally controlled tumor protein (TCTP) [33].

Several molecules regulate various downstream targets independently during liver regeneration. Franesoid x receptor (FXR),a nuclear receptor of ligand-activated transcription factor, is highly expressed in the liver. BA-FXR (BA: ligand of FXR) interaction is highly involved in the pathophysiology of liver regeneration [34].

E2F family members could be mediating liver regeneration and disrupt of E2F2 Leads to impaired this process [35].

Some molecules involved in liver regeneration process after liver injury such as SOX9, Lgr5 and serotonin. Serotonin act as neurotransmitter with essential extraneuronal function [36].

CXC family of chemokine induced activation of signaling pathway involved in the mechanisms of liver repair through their effects on hepatocytes [37].

The balance between hepatocyte proliferation and apoptosis is critical for liver hemostasis during liver regeneration. Three death receptors FAS, TNFR and DR6 play an important role in the proliferation and apoptosis of hepatocytes [38].

Another regulators on liver regeneration process are MicroRNAs. Microarray analysis showed down-up regulated of some miR in liver. For example miR382 is up-regulated that promotes hepatocyte proliferation and growth factor *in vitro*. miR382 functions negatively correlates with PTEN protein level and positively with increased AKT phosphorylation both *in vitro* and *in vivo* so use of SiRNA-PTEN can help to induce a cell proliferation [39]. miR21 regulates liver regeneration as well by targeting PTEN and can be novel therapeutic strategies in future [40,41].

Chorionic plate-derived mesencymal stem cells (CP-MSC) have been reported as attractive source for regenerative therapy. How CP-MSC decrease the fibrosis and contribute to liver regeneration remain unclear. Hedgehog (Hh) signaling pathway increase after damage. Studies showed transplanted human CP-MSCs induced liver regeneration in carbon tetrachloride (CCL4) inducecirrhotic liver of rat. miR125b is produced by CP-MSCs that regulate the expression of Hh signaling which promote the regression of fibrosis and eventually contribute to liver regeneration [42].

Nerve Regeneration

Following the nerve injury the cell body is signalized and the regeneration process starts. Physiological mechanism of the nerve regeneration is better understood now but the clinical treatment has not remarkably improved. Peripheral nervous system has the regeneration capacity after nerve injury, nonetheless nerve grafting is the gold standard clinical treatment. Types of graft use in peripheral nerve reconstruction included autograft, biological and artificial conduits .some factors influence in capacity of nerve regeneration such as mechanism of injury, level of injury, age of patient [43,44].

Schwann cells have ability to support peripheral nerve system. Schwann cells have poor functional recovery after nerve injury also they are essential for nerve regeneration but they don't support their regeneration [45]. Studies showed Schwann cells–derived extracellular vesicle (exosome) increase axonal regeneration and enhancing neuronal survival after pro-deregeneration stimuli [46]. Schwann-like cells derived from human dental pulp stem cells (hDPSCs) improve peripheral nerve regeneration. Pulsed electromagnetic field (PEMF) has extra effect on hDPSCs, Schwann –like cells *in vitro* and nerve regeneration ability after transplantation *in vivo* [47]. Components such as extracellular matrix that regulate Schwann cells morphology, migration, myelination influence neural repair. Development of stem cells is temporally regulated by ECM expression. The most effectiveness Form of ECM peptide sequence that improve neural regeneration is Arginine-Glycine-Aspartic Acid (RGD) sequence. Nano-particle is the component that is used as the link between molecular of different composite polymer. Surface modification of conventional by incorporating nanoparticles can influence cell attachment, growth and differentiation during tissue regeneration. Nano-fibrous scaffolds mimic native tissue tubular structures including axons, microtubules in the field of neural tissue engineering. They have larger surface area relative to their dimensions that enhance tissue regeneration [48].

Artificial substrates and Bridging techniques have been used inrepairing nerve gaps and stimulating axonal regeneration. Use of artificially aligned fibrous scaffolds facilitate nerve regeneration. They provide directional growth of neurons to bridge the gap. Studies showed a modified electrospinning setup to make differentially aligned fibrous scaffolds with the highly aligned fibers have potential for use in neural tissue engineering [49].

The Neurotrophic factors are family of diffusible protein that mediate neuronal differentiation and cell growth including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin 3 (NT3) and neurotrophin 4/5 (NT4/5). Several signaling pathway such as kruppel like family of transcription factors regulates the regeneration of nerve system [50].

The other factors that can improve neural regeneration are non-coding RNAs. They can affect neural survival, neurotic regrowth by targeting specific mRNA [51]. Pharmacological manipulation of implicated signaling pathways is one of the strategies to stimulate exon growth in injured neurons. Central nerve system has poor capacity for regeneration of exon. Evidences showed some kinase play a role in regulating axon growth. Kinase inhibitors such as Y-27632 AND go6976 can promote exon growth *in vivo* [52,53].

Kidney Regeneration

Kidney is a complex tissue with several different cell types and complicated anatomical structure so de novo regeneration of kidney is more difficult than other tissues. pluripotent Stem cells have been used for kidney regeneration are Embryonic Stem Cells, induced pluripotent stem (IPS) cells, Mesenchymal StemCells (MSCs), Renal Stem/Progenitor Cells. Studied showed that these stem cells were not suitable for kidney regeneration therapy for different reasons. Bioengineered and decellularized cadaveric as artificial scaffolds and biastocyte complementation and metanephros of growing exenoembryos strategies have been used for de novo kidney regeneration process [54,55]. Some factors that effect on kidney regeneration including granulocyte colony-stimulating factor (GCSF) that can increase proliferation of renal tubules [56] and 17β estradiol that how it is involved in regenerating tubular cells is unknown [57].

Muscle Regeneration

Evidence showed muscle fiber may regenerate even after repeated damage in the absent of nerve [58]. Results of studies on human tonsil-derived MSCs (T-MSCs) demonstrated that T-MSCs express muscle-related genes under conditions that induce myogenic differentiation. Using ES/IPS cells and muscle stem cell therapy in order to promote SKM regeneration but they have limitations. T-MSCs have myogenic potential and may thus increase muscle regeneration through either direct de novo muscle differentiation or by a paracrine mechanism [59].

The other factor that help to myogenic differentiation is Stablin 2 as downstream target of calcineurin/NFATc1 signaling for regulation of muscle regeneration. The phosphatidylserine receptor stabling 2 acts as membrane protein or myoblast fusion during muscle regeneration and myogenic differentiation [60].

(OPN) is an inflammatory cytokine and myogenic factor that is expressed in immune cells, myoblasts, damage and regenerating

muscle fiber and its functional involved in muscle regeneration and fibrosis in Duchene Muscular Dystrophy [61].

Heart Regeneration (Cardiac Regeneration)

Stem cell therapy indicates promise for regeneration in heart disease. Regeneration medicine provides an opportunity to increase pharmacologic and hemodynamic therapies through restriction of myocardial structure and function [62].

The most commonly tested active ingredient within regenerative toolkit include standalone and combination techniques relaying on cells/tissue/biomaterial and molecules, stem cells and derivatives. Cardiopoiesis-mediated lineage specification-conditioning stem cells provide therapeutic proficiency in heart failure [63].

Following heart disease, adult heart has a poor capacity to endogenous regeneration and repair. MicroRNA could be used for inducting of cardio myogenic and reprogramming strategies [64]. Fabrication of bioactive scaffold is one of the strategies to regenerate the infarcted myocardium. Polyester urethane urea (PEUU) + gelatin Nano fibrous scaffold could be used for myocardial regeneration [65]. Most of studies about heart regeneration has been performed on zebrafish such as assessing RAC1-PAK2 pathway that play important role in heart development with unknown mechanism [66].

Skin Regeneration

Skin tissue expansion is a clinical method for skin regeneration. the transplantation of mesenchymal stem cells (MSCs) promote skin expansion [67]. Other cells that improve wound healing and quality of regenerating skin are the secretome of peripheral blood mononuclear cells (PBMCs) [68] and human embryonic cells (hESCs) [69].

Platelet rich plasma fractionation enhance platelet-derived growth factors. Produce of hydrogel with fractionated platelet –rich plasma supplemented scaffold improve cellular recruitment and growth and differentiation of dermal–derived stem cells [70] and novel skin substitute are made of pullular and gelatin (PG1 hydrogel)can increase wound healing following burn and chronic wounds [71].

Fibrin play an important role during skin regeneration by its ability to easily bind to cells. Nanostructure material are attractive for cell adhesion and proliferation and improve proliferation of skin cells. The fibrin Nano coating on poly (L-lactin) (PLA) Nano fibrous membrane effect on the function of human dermal fibroblast [72]. There are several cellular and molecular mechanism involved in skin regeneration that can develop local skin therapies such as opioid receptors function [73].

Conclusion

Tissue regeneration has the ability to improve tissues function and structure that are injured by trauma, cancer or congenital disorder. Knowledge about mechanism of regeneration and involved signaling pathway and regulator molecules in this process can help to increase treatment. Also tissue transplantation is used for replace damaged tissue but there are limitations such as rejection because of immune system, so development of regenerative medicine may solve this problem by using of patient's cells for therapy that called as tissue engineering.

Regenerative medicine food and drug –approved products encompass in three category: biological, cell base medical device and biopharmaceutical that are commercially available.

Following injury, innate healing responses occur in body. The group of regulators control this responses are microRNA that are involved in multiple physiological and pathological processes of cell differentiation and function.

MiRNAs-based therapy can be considered as a promising strategy for the treatment. Materials are often an important component of current regenerative medicine strategies because the material can imitate the native extracellular matrix (ECM) of tissues, contribute to the function and structure of new tissue, and positionally present growth factors [4].

The use of components with high efficacy enhances a chance of achievement in manufacturing of tissue. These components include stem cells, scaffolds, bioreactors (growth factor and signaling). In summary, regenerative medicine whirls in tree main base including cell therapy, biomaterial technology and tissue engineering that may became the only strategy for treatment of most of disease in the future.

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