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Research Progress and Challenges in Regenerative Orthopedics

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Abstract

Organ and tissue loss due to disease or injury are generating the evolution of various therapies that regenerate the tissues and lower the dependence on transplantation. The whole summary of regenerative orthopedics is a mutual disciplinary field which applies both engineering and the principles of life science to foster the regeneration, can possibly redevelop the injured or diseased tissues or even the whole organ. There are few imperatively important factors in tissue engineering and regenerative medicine such as growth factors, cells and scaffold. The improvement in the field of science and technology has transferred these fundamental researches into clinical practice. We have also further explored tissue regeneration over the past decade by using the model animals, suffering from musculoskeletal disorders by manipulating the cells, scaffold, and delivery systems that are comparatively much easier to utilize and further develop in clinical settings. Computer simulation or *in silico* models are commonly utilized in regenerative orthopedics and achieved a great success in multiple disease settings. In this review, we would like to introduce, particularly the progress in these models in regenerative medicine. Moreover, we also propose possible tendencies for various therapies on regenerative medicines in the future.

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Introduction

In the recent years, regenerative orthopedics is a growing focus for an expeditious increase in organ and tissue loss caused by any disease or injury. Meanwhile, the term regenerative medicine is developing quickly [1]. It has been practiced in areas of plastic surgery, cardiac diseases and nervous system diseases. This term elicits us the idea of a future inspiration of youth, which can efficiently use cells that can reverse the stages of aging, disease and trauma into a healthy state by cell differentiation. It is widely known that our bodies have the ability to "regenerate" on a daily basis, they create new cells to replace the blood cells, line gastrointestinal tract, reform our skin and maintain the skeletal system [2]. No one would be surprised when our skin heals after a cut or a fracture heals after a trauma. Although the potential and rate of healing slow down along with aging, it does not disappear [3]. Tissues heal/regenerate even in the most elderly people in our population, for instance, cut heals, fractures heal, etc. [4]. Thus, it is an emerging hot topic to trigger the intrinsic capability of healing in humans for treatment of injuries and diseases. There are various ways to promote healing, such as nutritional approaches, regular exercise, invasive measures, and surgical intervention [5].

Recently, regenerative treatments have gone through a huge improvement; including platelet-rich plasma along with autologous theories related to stem cell in orthopedics [6]. The term orthobiologics has been used to describe these diverse biological agents that are extracted directly from our bodies, edging into our own built-in internal efficacy to heal. A series of studies on platelet-rich plasma has shown the healing abilities of chronic refractory tendinopathies and the modulation of pain and inflammation in degenerative arthritis of the knee [7]. There are more studies supporting the potential aid related to the mesenchymal stem cells used in the treatment of cartilage disorders, such as osteoarthritis [8]. The exact mechanism of the consequence after the placement of these biological products in areas of injury is progressing and the scientific evidence to prove the improving local environment and up-regulating the stabilizing and healing factors of the local tissues lead to more benefits as opposed to replacing new tissue in the injured area [9]. Therefore, these biological treatments should be the latest and most desirable treatments to induce an individual's own healing response [10]. Cells, scaffold, carriers and the growth factors are four fundamentals in this field. So, it is essential to choose appropriate fundamentals in the case of tissue regeneration for clinical purpose. This review will elaborate more regarding these essential elements and *in silico* models by presenting a list of all available models in (regenerative) orthopedics; it targets to introduce recent advancement in regenerative orthopedics and discuss more its potential applications.

Components of tissue regeneration

Endothelial progenitor cell and the mesenchymal stem cell

The patients are not objects like cars or any chemical plant. This treatment has led numerous medical, political, and ethical debates among groups and organizations. As regards to cell origins, endothelial progenitor cell (EPC) and the mesenchymal stem cell (MSC) are commonly used in clinical practices. Under certain circumstances, MSCs tends to separate out into adipogenic, osteoblasts and chondrogenic cell lines, resulting in an efficient source of cells used in regenerative medicine. We can separate out the MSCs from the bone marrow aspirate by their ability to stick to the substrates and collectively form the colony units. MSCs are distinguished by the phenomenon of surface expression markers collectively noted as CD105, CD73, and CD90 as well as CD45- and CD34. MSCs relocate to the damaged sites to proliferate and divide within the repaired tissue through the expression of adhesion molecules and receptors. In addition, MSCs secrete either paracrine or its factors which promote the regeneration of host cells, as well as the stem cells [11]. Some reports have shown that MSCs have the ability of tissue regeneration as it contains complex exosomes that varies from 50-200 nm in size and have two lipid vesicles [12]. These exosomes are composed of the proteins, mRNAs and miRNAs. Additional investigations for exosomes are carried out to validate different therapeutic uses of MSC and also to study the tissue regeneration process through the MSC transplantation [13]. Circulating EPCs have been found in adult peripheral blood, which has the capability of differentiating into endothelial cells and neovascularization *in vitro* and *in vivo* respectively. Because of this feature, a new cell therapy based on the EPC has been utilized particularly for cardiovascular regeneration and ischemic injuries. However, the theory of the EPC is particularly based on the origin of such cellular parts of hemangioblasts; closely related to the hematopoietic stem cells, such as the two antigens, CD34 and CD133

commonly referred to as hematopoietic stem cell surface markers. Therefore, they are reliable markers and are essentially used first. The CD34+ and CD133+ cells have the therapeutic capability to accelerate tissue repair/regeneration also known as neovascularization and to balance the regenerative environment. Those are extracted either from peripheral blood of an adult or directly from the bone marrow thereon transferred to the damaged / ischemic tissues using the systemic and also the topical injections.

Cell-Delivery System

It is necessary for the cells to assemble proficiently at the site of injury for tissue regeneration. Hence, a cell-delivery system or any particular method that can accumulate the cells at the required site is necessarily needed. This mentioned cell-delivery system makes use of the minimally invasive external magnetic devices. MSC's were designated with superparamagnetic iron oxide nanoparticles, which is dextran-coated and is approved by the US food and drug administration as the "magnetic resonance imaging agents" applied in the human liver imaging. External magnetic devices are manufactured, especially to generate the high magnetic forces, and magnetically labeled MSCs (m-MSCs) are built up in the desired area [14]. The adhesion of m-MSCs to cartilage defects and their repair with this new technique is approximately 95%, which is more elevated when compared to that of the local adhesion technique. It is proved that magnetism and magnetic labeling doesn't afflict osteogenic and adipogenic, proliferation and chondrogenesis differentiation of m-MSCs [15]. Researchers are studying the regeneration of bone, cartilage, spinal cord and muscle after injury in animal models for the use of this cellular delivery technology clinically.

Scaffold fabrication process

Scaffold contributes an environment which is 3-dimensional and also the growth factors which provide a proper stimulus for cell proliferation and differentiation. Atelocollagen, which is also referred as type I collagen gel, is a relevant carrier and scaffold used clinically for skin disorders and cosmetic surgery since 1986 and in tissue engineering. Chondrocytes presume to be a dedifferentiated fibroblastic morphology. In a monolayer culture, losing its capability to produce mainly type I collagen compile in the matrix. Chondrocytes embedded in the terminal collagen gel proliferates through which the chondroitin 6-sulfate is originated, which supports the chondrocyte phenotype till four weeks. Atelocollagen is mainly used as a carrier for the repair of nerve cells, muscles and also the articular cartilage. Similarly, for gene delivery, Atelotropin serves as a biomaterial vector both *in vivo* as well as *in vitro*. Atelocollagen-mediated siRNA or miRNA delivery is potent *in vivo* gene silencing because of resistance to nuclease complexed with siRNA or miRNA can be conveniently transduced into cells [16]. Because of their good biocompatibility, hydroxyapatite ceramics have been widely used as bone substitutes. On the other hand, "traditional hydroxyapatite ceramics" have bad osteoconductivity due to their incomplete pore-to-pore connectivity. At an early stage, these features help the cells and tissues to reach the center of IP-Changer and also have a special additional benefit to carry along the cells or growth factors.

MicroRNA

MicroRNAs (miRNAs) have a key role in various human diseases and biological processes as they have the ability to regenerate tissues [17]. MiRNAs, which acts as a group of non-coding RNAs, have the ability to modulate the gene expression by binding mainly 30 of its target mRNAs prior to mRNA degradation or translational repression and are considered as major regulators of various biological processes such as immune function, metabolism and cell cycle [18]. Because of their increasing role in the field of the pathogenesis of human diseases and in orthopedics, these miRNAs are evolutionarily preserved for humans in the identification of Caenorhabditis elegans. As miRNAs tend to play a unique significant character in the development and homeostasis of musculoskeletal components such as muscle, bone and cartilage, has led to the development of new therapeutic strategies in musculoskeletal disorders now a day. Surprisingly, the miRNAs application as biomarkers as they are packed with micro-vesicles (e.g., exosomes) and are secreted from cells that bring the therapeutic attention [19].

Growth factor/cytokines

Growth factor/cytokines promote cell proliferation or extracellular matrix production. In the three-dimensional structure of chondrocytes, the hyaluronic acid can enhance the cell proliferation along with the production of chondroitin sulfate. In tissue regeneration, it is to be considered that the change in the environment or the use of growth factors promote the regulation of growth factors or cytokines.

Silico models and classification

In silico are defined *in vitro* and *in vivo* by computer stimulation or directly done on the computer. The computer simulation model, based on the length (and time) of the described process is a classified way which is being widely used. As an introduction to general computer orthopedics, we will deliberate the two categories and give their respective examples. The minimum level model is designed in such a manner to study the interactions among different biological pathways under various experimental conditions, such as a robust network of attractor basins. At a higher level, in relation to either their mechanical or biological behavior (or both), the simulated model developed focuses on a single cell or group of cells. Previous studies used a single cell-based modeling framework to study the growth in cell culture [20]. Since cells have few biological variables, computer modeling or simulation has an advantage of studying aging on stem cells and the effects of cell differentiation [21]. At the tissue level, the cells, growth factors and extracellular matrix (ECM) are presented by concentration or density (weight of a unit volume of growth factor or amount of cells per unit volume). Numerous articles describe the use of computer simulation in bone biology and regeneration basically focusing on distinct aspects regarding the process of fracture healing, including angiogenesis, soluble growth factors or in mechanical loading [22]. In fracture healing process, models that focus on the angiogenesis are called as mixed models or hybrid models as they fuse cell level and tissue level [23]. This enables each of the biological variables to be represented in the nearest correspondence to physical reality, i.e., the density of ECM as well as individual blood vessels in terms of angiogenesis. For example, at the organ level, in case of the entire bone, how damage affects its behavior and remodeling process or how does it behave under mechanical loading [24]. To assess the major risk of fracture in patients with osteoporosis, organ level models can be used [25]. Therefore, the muscle tissues and the entire bone are carried out on the patient-level model. Gait analysis models may be used to depict the bone remodeling and pathology such as the osteoarthritis [26, 27]. The model developed in one patient can then be used to model the behavior of all patients. Highlighting changes to the parameter set allow us in the testing of a vast variety of virtual patients. *In silico*, allows the better delamination of patients, resulting in the reduction of resources and time required as clinical trials may be performed before (or during) *in vivo* clinical trials [28-30].

The other commonly applied classification is based on the information contents. Basic models work only along the experimental data [31]. There is no mechanistic assumption made on how those observed phenomena resulted out. Empirical modeling is fit for its ability to discover biomarkers in a wide range of datasets linking, e.g., *in vitro* observations to desired *in vivo* behavior [32]. To capture the effects of various behavior pathways of cells, the simple network models can be used. Boolean network models can be applied to investigate the power and attractor basins of the networks, and to identify lost connections. For example, in a simple network model representing variables as either 'on' (active, 1) or 'off' (inactive, 0), allowing one to add a dynamical component to the models without adding a number of parameters [33].

Application to regenerative orthopedics

Regenerative orthopedics basically requires four key elements to achieve successful treatment: cells, vectors, growth factors, and appropriate mechanical conditions [34, 35]. In this particular review, we have differentiated the major key elements of a tissue engineering strategy into four basic components: cells, culture (both with and without growth factors), carriers, and clinics (binding mechanics and blood vessel regeneration). Therefore, these models are based on the size of the length and the content of the information, depending on the clinical issue / particular research assigned.

In case of cellular compartments, regenerative orthopedics aims to achieve a robust source of cells with predictable and reproducible in both *in vivo* and *in vitro* results [36]. Empirical models recognize the biological status of cells and functional regulators to highlight biological processes *in vivo* and *in vitro*. Mechanistic models that use relevant specific pathways, allows us to study the dynamics in relation to the cell status while using certain growth factors in the cell culture [37]. Moreover, other models to study the cell-specific basins and the attractiveness of regulatory networks provide the precise culture conditions that keep or drive cells in their expected state [38]. In addition, Kerkhofs designed a Boolean model of the osteochondral regulation network, which is large-scale literature-based and the effects of either inhibiting or activating several genes in this network on the further progress of cells in endochondral ossification were studied. This inhibition or activation can thus

be converted to a medium composition for *in vitro* cell culture [39]. The operators OR carrier models concentrate on chemicals, mechanical, and/or morphological aspects in order to further optimize their design by understanding their effect on seeded cell behavior [40-43]. To study the effect of non-elastic microcarrier on cell proliferation, Smeets et al. [44] used a single cell-based model. Based on the combination of experimental hypotheses and experimental data proposed by the collaborators, the model captures various perspectives of the process of calcification of bone. This model has been widely used in designing a combination of cell seeding density (or one of the cellular characteristics such as growth rate) and calcium release rate to produce ideal bone formation [44].

Future perspectives

However, the use of these models is limited clinically, but the application of these research tools in industrial and educational fields is gradually increasing. In areas of oncology and related cardiac diseases, the latest versions of computational models are being developed as the newest therapeutic strategies that are being evaluated in clinical trials (i.e., Phase I and Phase II clinical trials). In the areas of diabetes, the US food and drug administration (FDA) has approved the use of these latest computational models as one of the most valid preclinical evidence for implantable insulin pump files [45]. In addition, computer simulation models are now considered as a significant tool for addressing many of those "science priorities of medical product regulation" of the FDA. Moreover, increasing interest in the biomedical research ethics of laboratory animals has provided a powerful incentive for computer research. The wide uses of computer models as an intrinsic part of the research process is denoted by 3R (shrink, improve, replace). In addition, computer simulations can help translate animal-derived research into clinical opportunities for humans. The *in silico* medicinal community is getting a benefit from the large-scale initiatives such as the virtual physiological human along with the Physiome. The main aim of these initiatives doesn't include the development of one integrated model of a complete human, but rather to develop an integration of different organ systems on different length/time scales that can easily interact with each other. Due to this reason, scientists interested *in silico* medicinal field should agree on a set of standards that will allow the interrelation in between different in silico models, as well as in between *in vitro*, *in vivo* and *in silico* models.

The advancement approaching the personalized and precision medicine demands us for an amalgamation of all available relevant information from the patients, like their genetics, lifestyle and anatomy. The amalgamation and interpretation of all the related information can be achieved by the use of *in silico* models. The simulated physiological human can be varied depending on the users: the digital guinea pig for researchers, the digital patients for clinicians, *in silico* clinical trials for industry and personal health forecasting for patients [46]. As this EPC and MSC have been already applied clinically, these essential cells and the materials will promote more clinical use in the future. Because of the low frequency, a large number of CD34+ or CD133+ cells need to be obtained from the bone marrow mobilization (termed as *in vivo* expansion) and subsequent cytopenia using G-CSF (termed as granulocyte colony-stimulating factor). Therefore, *in vitro* amplification of CD133+ or CD34+ cells using a certain medium which contains a mixture of growth factors/cytokines can demonstrate a less invasive and more economical method of EPC-assisted tissue regeneration. This new treatment will help in more extensive tissue repair/regeneration possible. The main goal is to achieve more efficient and less invasive cell therapy by using external magnetic forces to space-control the transplanted cells. There are several reports on the effective use of cell therapy in the field of tissue regeneration, although its mechanism has not been fully studied.

Analysis of miRNAs / exosomes in cell therapy is likely to exemplify this mechanism, resulting in a newer alternate type of cell therapy for tissue regeneration. Multiple reports show that the treatment of synthetic miRNAs or *in vivo* modified antisense oligonucleotides has been performed in many fields and miRNA therapy will soon be introduced in orthopedics. The use of miRNA with external magnetic devices is better and safer, so any disorder is to be well examined to find the least invasive and also most effective method. We are currently in the clinical stage of achieving a combination of cell therapy and magnetic targeting systems for cartilage and bone damage. In summary, an elaborative analysis of effectiveness, safety and mechanism for the clinical application of tissue regeneration will become more beneficial and assure in a new generation of regenerative medicine treatment.

Conflict of Interest

The authors certify that they have no affiliations with or involvement in any organization or entity

with any financial interest (such as honoraria; educational grants, membership or employment) or non-financial interest (such as personal or professional relationships, affiliations knowledge or beliefs) in the subject matter or materials discussed in the above manuscript.

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