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Review Article

Regenerative Medicine: Highlight on the Significance of Therapeutics with Novel Strategies

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ABSTRACT

Background: There is a worldwide effort to present novel approaches for the development of tolerance-induction treatments in regenerative medicine, after years of investigation in clinical transplantation. Particularly, novel approaches are based on controlling the immune response, including the application of biomaterials or imitation of antigen-specific peripheral tolerance in either solid-organ or allogeneic hematopoietic stem cell transplantation (HSCT).
Methods: New biomaterials have been designed to alter the cell behavior in tissue-engineered creatures and also suppressing immune responses against cells and biomaterial scaffolds. Blunting immune responses has been evidenced to be a wise strategy in regenerative medicine. Incorporation of stem cell biologists, material scientists, and transplantation immunologists can lead to the most innovative solutions.
Results: Replacing damaged tissues is the main goal of regenerative medicine. To reach this goal, it is vital to have a comprehensive understanding of the whole regeneration process; for example, the mechanisms of dedifferentiation of cells to progenitor cells or trans-differentiation into another cell types, and rescheduling of somatic cells to pluripotent cells.
Conclusions: Exploring the regenerative processes under in vitro and in vivo situations sheds lights on the underlying molecular and cellular mechanisms and thereby helps to pave the way toward describing novel regenerative strategies to combat human diseases and finally to strengthen the regenerative medicine.

Key words: Immune system, Mesenchymal stem cells, Microfluidics, microRNAs, Pluripotent cells, Polymeric delivery systems

Introduction

Restoring the normal function of damaged tissues, organs, or body parts is the principal purpose of regenerative medicine (RM). Unlocking the therapeutic probability of stem cells has been focused for years, and it has explained that understanding the in vivo context in regeneration is the key to that lock. It has been identified for a long term that just as degenerative aging, the capacity of regenerating injured or lost body parts of the animal kingdom differs among various species. As a result, animals with exceptional regenerative capabilities and insignificant aging have been considered as more attractive candidates for exploring the regenerative processes compared with humans. The potency of animals to regenerate injured or lost organs is the ancestral situation, which has been lost in a variety of lineages, such as amniotes and regained in other species.

In conclusion, regeneration involves conserved and species-particular mechanisms and gene regulatory networks which require astute scrutiny. Regenerative medicine is faced with several complicated necessary questions to be resolved: How can regenerative medicine help us to promote human regenerative capacity? Why is the regenerative ability of mammals such as humans relatively weak? This is while some vertebrates and invertebrates possess an extraordinary capacity of regeneration which is also visible in highly complex tissues. Epimorphic regeneration is the default regeneration mode of non-amniotic vertebrates, including frogs, salamanders and tadpoles, by which a multiplying blastema creates novel tissues, whereas this rarely happens in mammals in which a tissue injury typically stimulates scar formation. Monitoring this process in living animals is the final key to understanding tissue healing (Coffman *et al.,* 2016).

Materials and methods

Regeneration of animal

Regeneration of animal refers to the regeneration of injured or diseased sections of the body to completely return its normal function (Brockes and Kumar, 2008; Lucendo-Villarin *et al.,* 2017). It contains stem cells capable of differentiating into a diversity of mature cell types reelevating the power of the stem cell and the organism. The potency to regenerate enormously differs among the animal kingdom. In metazoans, animal groups such as planaria, starfish and some worms can regenerate their whole body from a small body fragment (Sanchez Alvarado, 2000), while in birds, leeches, and nematodes there is a minimum ability for self-regeneration (Lucendo-Villarin *et al.,* 2017). The potency of human tissues and organs to have defined self-regeneration and real renewal should not be disorganized with compensatory growth. Animals with strong regenerative capacities accomplish the progression using the regenerating cells prepared by extra- or intracellular and signals that raise and control that response. In contrary, animals with inadequate regenerative capacities may lack the prerequisite microenvironmental status or the valence to build it due to cooperating genetic or epigenetic elements.

The main subject in both regeneration and aging is that support systems, especially the immune system, have a significant part in creating a pro-regenerative milieu. In the animals undergoing degenerative aging, the regenerative system impairs as the animal ages (leading, for instance, to the hurt of proteostasis and enhancement stages of unsolved tissue inflammation), although in animals with insignificant senescence those systems are upheld or even completed with age (Coffman *et al.,* 2016). In spite of the fact that the expansion of regenerative medicine will play a

vital part in meeting future healthcare challenges, the promises of regenerative therapies stay mainly unrealized. In specific, a hurt tissue is commonly related to an immune response, which is the greatest possibility for a main controller of the healing progression. Therefore, in-depth comprehension of the involvement of the immune system for the duration of tissue regeneration could prepare signs to therapeutic avenues for returning injured tissues. Moreover, the regulatory action of the immune regulations through tissue healing might be an appealing selection in regenerative medicine (Aurora and Olson, 2014; Forbes and Rosenthal, 2014).

The immune system and its role

The physiological and stress responses are also general themes connected to regeneration and aging. The performance of the immune system in tissue regeneration and regulating inflammation following damage has been discussed by Nadia Rosenthal (Godwin *et al.,* 2013). Her laboratory's work with axolotls showed the significance of macrophages through regeneration and the critical significance of inflammation and its clarity in the regenerative response. She proposed that interventions designed to simplify resolution may promote the tissue regeneration in adult mammals (Forbes and Rosenthal, 2014). To address the complexity in a mammalian model, she and her colleagues at the Jackson Laboratory are using the variability in cardiac recovery following heart attack damage among inbred mouse strains to detect genetic interactions which play an essential role in regulating and resolving inflammation, with an eye toward determining novel therapeutic targets. There is collecting epidemiological proof that chronic stress and difficulty in life correlates with the expansion of inflammatory conditions and degenerative illnesses of aging later in life, a phenomenon usually discussed as progressive programming (Harris and Seckl, 2011; Khulan and Drake, 2012).

Bone regenerative therapies

Bone contain an inherent ability to regenerate the following damages. Most of the bony harms heal without a constant wound when treated adequately by re-apposition. Nevertheless, numerous clinical symptoms remain which need therapeutic intervention to accelerate bone regeneration; for example, bone degeneration in patients with osteonecrosis, distal tibial breaks and periodontal illness (Grayson *et al.,* 2015; Trofin *et al.,* 2013). Hence, wide attempts have been made to improve bone regenerative approaches using different mixtures of cells, growth factors, and biomaterials. Nevertheless, only a few of these plans have translated into clinical repetition, and none of them has become a standard in regenerative medicine. Practical barriers, safety, efficacy, price, usefulness, and regulatory issues often inhibit the extensive therapeutic use of bone regenerative therapies. Besides, one of the significant challenges lies in a clear perception of the cellular and molecular mechanisms that should be aimed to uphold bone regeneration. Mainly, deciphering and consequently the immune regulations of bone regeneration could be crucial steps to develop novel methods in bone regenerative therapies (Aurora and Olson, 2014; Forbes and Rosenthal, 2014; Jones and Yang, 2011).

Cardiac repair and cell therapy

Around the world, numerous thousand patients have been treated using autologous cell-based therapy. The safety and possibility of this method has been established, pitfalls have been recognized, and optimization methods are anticipated. Additionally, the beginning of step III

trials to further validate the therapeutic assessment of cell-based regenerative medicine and addressing the barriers to effective clinical performance need to cause the resurgence in the enthusiasm to accept the treatments between patients and health-care suppliers. In the unique, low description of cell types used, variety in cell-handling procedures, and practical variability inherent to autologously-derived cells have been recognized as the chief factors as restrictive in the adoption of cell-based therapies. The epidemy of heart failure (HF) is a result of a progressively aging population in the field of advanced diagnostic tools joined with impressive percutaneous and surgical coronary revascularization therapies. Also, individuals are progressively more able to survive for substantial phases after an acute cardiovascular harm, just to progress chronic HF at a later date (Ezekowitz *et al.,* 2009). Cardioprotective therapy is proposed to limit the amount of injury persistent as a consequence of ischemic, and thus avoid organ failure by changing the innate myocardial damage reply (Gerczuk and Kloner, 2012). Patients with HF are treated with regenerative cell-based therapy at returning normal myocardial function through direct cell-mediated and indirect paracrine-mediated maintenance mechanisms (Figure 1).

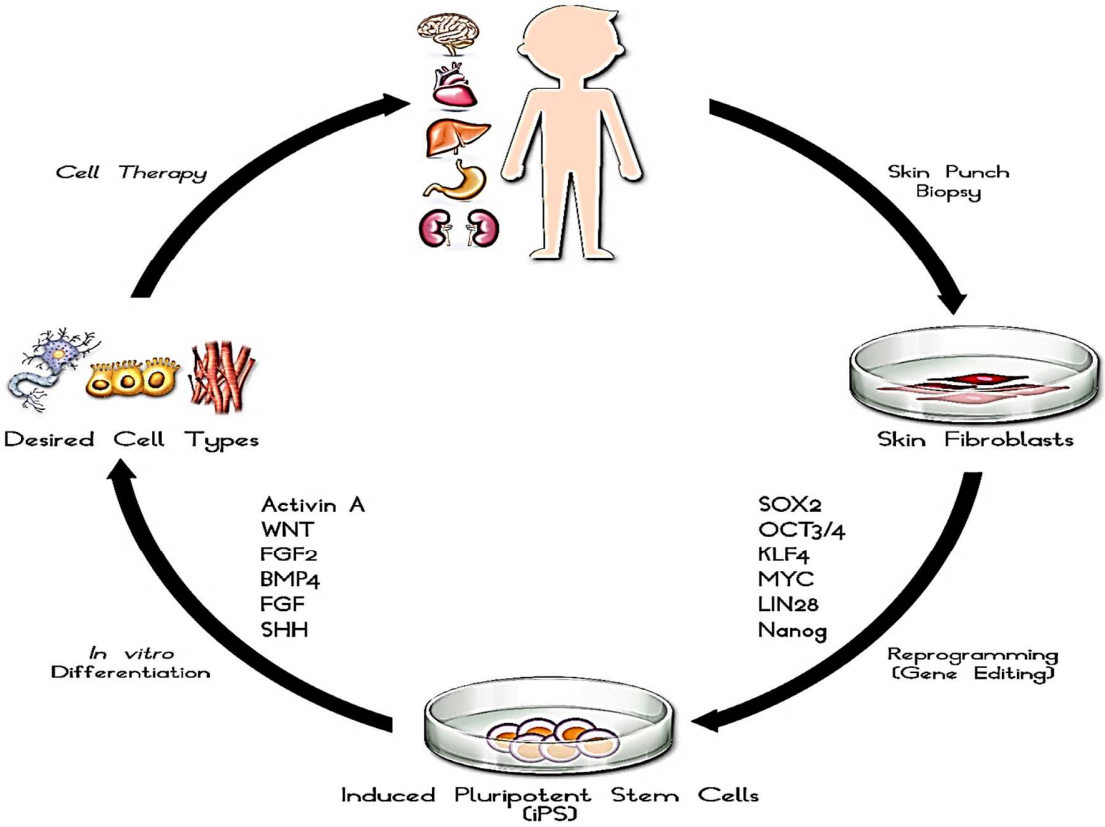

Figure 1. The central cell-based strategy of regenerative medicine
First, cells that can be easily gained from a patient in a non-invasive style are separated and cultured. Second, these cells are reprogrammed into a pluripotent state. Third, the directed variation of those patient-specific pluripotent cells into the cell type pertinent to their disease is done. And, fourth, methods for fixing any intrinsic disease-causing genetic imperfections and transplantation of the fixed, differentiated cells into the patient are applied (Behfar *et al.,* 2014).

Stem cell therapy

Recently, the center of anticipations in regenerative medicine has used embryonic and adult stem cells in mammalian regeneration and treatment. Clinical and routine applications of hematopoietic stem cells (HSCs) for transplantations, in a non-pure form have been observed since 1959 (Bryder *et al.,* 2006; Horowitz, 2004). Many investigations have been performed to repair damages in several organs: The spinal cord, bone, brain, and other organs using stem cells (Barberi *et al.,* 2003; Haseltine, 2003) . To apply these discoveries, scientists generally have two ways. First, stem cells are isolated, cultured and harvested under in vitro conditions. Then, they are transplanted into definite tissues of patients to stimulate the endogenous signals of differentiation into target cells. Second, those factors activating the patient's stem cells are used by scientists to restoration the hurt. Also, local signaling pathways activating stem cells in normal tissues of youth has an age-related decline (Rao and Mattson, 2001). Thus, stem cell proliferation and variation are controlled by some signals important for stem cells in therapeutic applications.

MicroRNAs and tissue engineering

As a contemporary approach, biodegradable scaffolds can be accompanied by growth factors and donor cells and cultured together. Then the scaffolds can be implanted into the human body to improve or restore damaged cells. Some newer research studies are working on developing human embryonic stem cells (ES cells or ESCs) to create three-dimensional tissues. However, tissue engineers have the problem of controlling the proliferation and variation of seed cells in both strategies. The fundamental understanding of the process of mammalian development determines the solution to this problem. The identification of the first microRNAs in the progress of C.elegans created a novel part of biology and impressed tissue engineers. The ability of microRNAs (miRNAs) in regulating gene expression in mammals, both physiologically and pathologically has been revealed by several studies (Chang and Mendell, 2007; Gusev, 2008; Liu *et al.,* 2012; Motohashi *et al.,* 2013; Zhou *et al.,* 2012). miRNAs are small (19-24 nucleotides), non-coding RNAs evolutionarily conserved which have a part in post-transcriptional regulation of gene expression (Figure 2 'biogenesis of miRNA and mechanisms of action') (Bartel, 2004; Cermelli *et al.,* 2011; Gori *et al.,* 2014; Murata *et al.,* 2010). The recent progress in regenerative medicine, using cutting-edge techniques such as stem cell-based therapies and cell transplantation using miRNAs are summarized. Plans of miRNA inhibition approach are to modulate stem cell differentiation. Anti-miRs include sequences that are supplementary to the miRNA ripe strands and act as competitive inhibitors. DNA sequences with numerous binding sites to the miRNA called miRNA sponges; they could prevent a panel of miRNAs. Finally, miRNA masks could selectively block particular mRNA pathway (Figure 2).

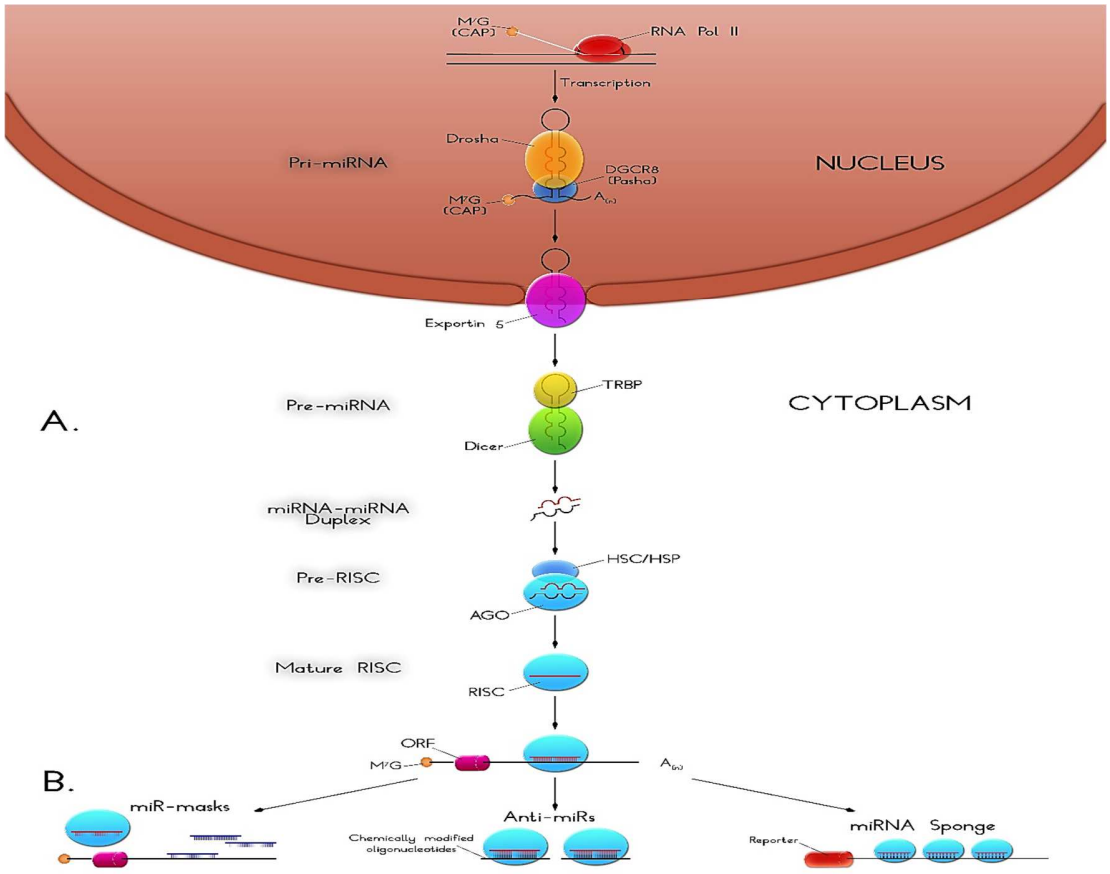

Figure 2. The mechanisms of microRNA biogenesis

A: RNA polymerase II (Pol II) transcribes microRNA genes as pri-miRNA that may have more than one miRNA and start with a 7-methylguanosine cap (m7Gppp) and ends with a 3′ poly (A) tail. The endonuclease Drosha together with its double-stranded RNA [dsRNA]-binding protein partner DGCR8 [mammals] or Pasha [flies] cleave in the nucleus of pri-miRNA. Then, the RNAse III-like nuclear enzyme Drosha processes the pri-miRNA and makes the mini hairpin-like pre-miRNA. The pre-miRNA is exported into the cytoplasm through Exportin5 (Exp 5). The resulting pre-miRNA is exported into the cytoplasm by exportin 5, and then further cleaved by the endonuclease Dicer to achieve a miRNA–miRNA* duplex. This duplex is loaded into an Argonaute (AGO) protein as a dsRNA, supported by the HSC70/HSP90 chaperone machinery. Then, the RNAse III-like Dicer processes pre-miRNA into a 22 nt mature miRNA duplex during maturation step. The duplex is then separated in two strands. One strand is degraded (miRNA*) and the other is the mature miRNA which is finally incorporated into the RNA-induced silencing complex (RISC). Plasma membrane derived exosome microvesicles are able to help the secretion of pre-miRNAs and mature miRNAs into the extracellular environment. At the end, imperfect base pairing of miRNAs to the target mRNAs causes translational suppression (left). Perfect pairing leads to cleavage and degradation of target mRNAs (right). In the particular instance of pre-miR-451, the pre-miRNA defector Dicer processing after nuclear export and is instead directly loaded into the AGO2 protein, which activates its puberty into a single-stranded miRNA. 2′ OH, 2′ hydroxyl group; HSP, heat shock protein; ORF, open reading frame (Adapted from Kim and Nam, 2006; Olena and Patton, 2010).

B: The strategies of miRNA inhibition. A | Sponges of microRNA (miRNA). Multiple miRNA-binding sites are inserted downstream of a correspondent gene. After delivered into cells, the binding sites serve as trap for the targeted miRNA, thereby inverting the suppression of endogenous aim genes. B | Chemically changed miRNA-targeting antisense oligonucleotides (anti-miRs) are planned to be totally complementary to the aim miRNA and bind with a lot attraction (high melting temperature; Tm). After delivered into cells, the anti-miRs bind to the aim miRNA, releasing inhibition of the endogenous aim genes. Many anti-miRs also induce degradation of aimed miRNAs**.**

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are resident in the bone marrow and other musculoskeletal tissues. They play an essential role in the homeostasis of musculoskeletal tissues and also, growth and separation of primitive hematopoietic cells. MSCs have been propounded in regenerative medicine and tissue engineering as a possible source of cells capable of differentiation to a diversity of tissues.

The process of separation, expansion, and variation of MSCs in culture have been well explained, which can be easily performed. Nevertheless, we know little about the biology of stem cells under in vivo conditions and what they precisely do in tissue restoration or regeneration. This perhaps related to the absence of useful cell-specific markers. MSCs can differentiate into cells of linked tissue lineages, such as bone, fat, and cartilage under in vitro situations. Sources of stem cells which have mesenchymal probable are periosteum (Fukumoto *et al.,* 2003; O'Driscoll *et al.,* 2001), trabecular bone (Nöth *et al.,* 2002; Tuli *et al.,* 2003), adipose tissue (De Ugarte *et al.,* 2003; Wickham *et al.,* 2003), skeletal muscle , lung and deciduous teeth (Miura *et al.,* 2003).

Due to the promising features of adult stem cells, many investigations have been handled for their therapeutic applications. Depending on the purpose, mesenchymal stem cells can be used for regeneration or infused systematically. Direct loading, and Systemic infusion are two examples.

Direct loading is properly utilized in clinical strategies with the purpose of local repair or regeneration of bone (Goshima *et al.,* 1991; Richards *et al.,* 1999), cartilage, tendon and fat (Choi *et al.,* 2005; Neubauer *et al.,* 2005). MSCs derived from marrow represent a diversity of progress in cardiovascular repair, lung fibrosis, and spinal cord injury treatment. Bone marrow-derived mesenchymal stem cells are infused into bone marrow stromal sites for a selective homing (Hardy, 1995). Engraftment and variation of hematopoietic stem cells are facilitated by the homed mesenchymal stem cells, and thus the function of the hematopoietic-supporting stroma is improved (Almeida-Porada *et al.,* 2000; Koc *et al.,* 2000).

Results

Polymeric delivery systems in regenerative medicine

Use of hydrogels for tissue engineering and RM

Several features have made injectable hydrogels incredibly applicable in tissue engineering and regenerative medicine. Those features include mechanical resemblance to natural tissues, high water content, and easy surgical implantation.

Injectable hydrogels

Before injection, a TERM hydrogel should have low-viscosity and quick gel under the physiologic tissue environment where it is needed. Gelation (sol-gel transition) by cross-linking has the most important role in this process. The cross-linking of injectable hydrogels can be done under in vitro conditions while procurement or in vivo events occur after injection. Several hydrogel cross-linking mechanisms exist (Jiang *et al.,* 2014) including physical and chemical cross-linking, ionic cross-linking, and enzyme-initiated crosslinking.

Classifications of bio-conjugated hydrogels

Peptide-conjugated hydrogels

Bioactive domains in some peptides play a role in cell binding and function, including matrix degradation. They are able to conjugate to hydrogels to develop their functionality (Wang *et al.,* 2014).

Some characteristics make PEG hydrogels desirable for TE practical like mechanical properties, porosity, and biocompatibility under in vivo conditions (Mahoney and Anseth, 2006). Unfortunately, PEG hydrogels are unable to provide cell attachment sites and are not biodegradable. Modification with cell-adhesive and enzyme-sensitive peptides can develop functionality and degradation of PEG hydrogels and make them appropriate for the ECM (Zhu, 2010). Recently, photopatternable peptide conjugated hydrogels with the ability to be tailored for cell culture and tissue fabrication has been highlighted. For instance, Mosiewicz *et al.,* used photopatterning peptide-conjugated PEG to achieve the organized spatiotemporal connection of primary human mesenchymal stem cells.

Protein-conjugated hydrogels

The sensitive chemical structures of proteins make them limited for the direct use in regenerative medicine (Sheridan *et al.,* 2000). The other limitations of proteins are their poor chemical stability under certain conditions and aggregation, which cause the stimulation of the immune system and the loss of their bioactivity (Vermonden *et al.,* 2012). Thus, further investigations in TE and regenerative medicine are necessary to maintain protein practical during their processing or sending (Mikos *et al.,* 2006). Binding proteins with other macromolecules, such as heparin is an appropriate approach to protect them from degradation and to prevent immunogenic reactions (Freeman *et al.,* 2008). A variety of protein carriers have been developed to ease their organized release in medium, such as particles and cross-linked polymer networks.

Hydrogel-hydrogel conjugates

Hydrogel-hydrogel conjugates comprise chemically bonded hydrogels which are natural and synthetic and are widespread in the hydrogel network randomly or selectively. These hydrogels demonstrate alterable structural, and biological features. The synthetic hydrogels are responsible for controlling the mechanical and structural characteristics of hydrogel-hydrogel conjugates. Natural hydrogels regulate cellular attributes of gels containing proliferation, adhesion, matrix manufacture, and enzyme activity (Lau and Kiick, 2014). PEG hydrogels seem

to be proper candidates for the construction of hydrogel-hydrogel conjugates (Harris, 2013; Hubbell, 2003).

Fabrication techniques of bio-conjugated hydrogels

Electro-spinning

Electro-spinning is the process of extraction of micro-, and nanofibers from a polymer solution and deposition of them on a collector after ejection by using an electric field. It makes fibrous structures from numerous polymers in a multipurpose, easy, and reproducible process (Greiner and Wendorff, 2007). Electrospun fibers derived from bio-macromolecules such as hydrogels have been applied for wound dressing, (Zahedi *et al.,* 2010) enzyme immobilization, (Wu *et al.,* 2005) artificial blood vessels production, (Buttafoco *et al.,* 2005) as drug or gene carriers and TE scaffolds (Ostrovidov *et al.,* 2014). Aligned electrospun fibers can be possibly made by containing a rotating disk or mandrel into the electrospinning setup (Bellan *et al.,* 2012).

Photopatterning

Photopatterning or (photolithography) is a well-known process of fabrication of hydrogel structures in which a photomask with the favorite pattern is made. This photomask has some covered areas to block light display and some transparent areas to permit passage of light. When a photomask hydrogel is exposed to light, transparent areas are cross-linked and form the negative of the mask pattern, while the parts under the opaque regions stay uncross-linked and washed out (Selimović *et al.,* 2012).

Bioprinting

Fabrication of tissue constructs has brought main advances. However, a considerable gap among fabricated tissues and clinically related ones exist (Sadri-Ardekani and Atala, 2015). Recently, bioprinting has considered as a powerful technique able to produce large-scale and complicated tissue structures (Kolesky *et al.,* 2014). Mainly, cell-laden and bioprinting hydrogels cooperate with reproducing 3D and hierarchical architecture of native tissues and deposit hydrogel layers sequentially. Recent bioprinting methods can create custom-made cell-laden architectures which have high cell feasibility (Derby, 2012).

Microfluidics

Microfluidics is a multidisciplinary arena of investigation which involves manipulating small capacities of fluid at a micro-scale level. It was first applied in the early 1980s and nowadays is applicable in diverse areas of science and technology (Tabeling, 2005). Also, microfluidics is capable of making functional hydrogels which have 3D morphologies and tunable chemical structures (Nichol and Khademhosseini, 2009).

Microfluidics may be a process for a new way of research and progress in regenerative medicine where it can for example help to realize high throughput screening platforms. Furthermore, microfluidics has other benefits, including the probability of making in vivo conditions like microenvironments. In addition to the complication of organs or tissues which should be regenerated, regenerative medicine has challenges of complicated regeneration developments and plans. Microfluidics can be combined with microarray technology to develop HTS systems.

In particular, this method is applicable when microfluidics is adaptable with conventional laboratory equipment for well-plate culture techniques (Zheng *et al.,* 2012).

Electrospun nanofiber scaffolds

Electrospinning has appeared as an easy, delicate, and scalable method that can be used to manufacture polymeric nanofibers. Natural polymers, also mixtures and composites of both synthetic and normal ones, have been effectively electrospun into nanofiber matrices for several biomedical applications. Tissue-engineered medicinal implants, like polymeric nanofiber scaffolds, are possible replacements to autografts and allografts, which are short in efficiency and transfer dangers of illness conduction. These scaffolds are used to engineer different soft tissues, containing linked tissues, for example, skin, ligament, and tendon, likewise non-linked ones, for example vascular, muscle, and neural tissue (Manoukian *et al.,* 2017).

Clinical research skills development program

Different terms of Cell-based regenerative medicine are quickly developing, such as the number of physicians working, patients, and situation treated (Knoepfler, 2013b; Martín *et al.,* 2014). As regenerative medicine lacks formal physician, training and cell-based therapies for a diversity of illnesses are increasingly used, physical and psychological harms for patients and also preventable conflicts among the governmental controlling agencies like FDA and physicians are predictable. It has been demonstrated that physician training program in the academic setting is a practical approach to enhance compliance in this field (Knoepfler, 2013a).

The role of physiatry: The evolution

Physical medicine and rehabilitation physicians are facing more patients with overuse or degenerative injuries due to a surge in sport participation and physical activity. New treatment techniques like stem cells and PRP have achieved increased media coverage, and these procedures have been exciting for the lay public. Using regenerative treatments must be dependent on sound medical judgment and pathophysiology and current evidence of effectiveness and safety. NSAIDs and corticosteroid injections which are commonly used are unable to provide short-term pain relief and play a role of an adjunct for a comprehensive rehabilitation (Setiawan *et al.,* 2017); their application is challenged in patients with chronic degenerative conditions without inflammation by the current evidence. When other holistic regenerative treatments have been unsuccessful in patients with refractory pain, regenerative treatments like stem cell and PRP therapies might play a part in tissue regeneration and practical rehabilitation. Post-procedure regeneration should be dependent on the tissue pathology and knowledge of the tissue regeneration progression of the patient's harm (Alsousou and Harrison, 2017).

Physiatrists' knowledge of biomechanics, functional anatomy, modalities, and regeneration methods help them to prepare care that improves non-operative treatments in patients with a variety of musculoskeletal injuries, strategically integrating new regenerative therapies when essential.

Regenerative treatments must be recognized as supplementary to a more excellent rehabilitation method. Musculoskeletal specialists determine the probable of regenerative medicine by how they face the regulatory, scientific, and economic challenges of these interventions.

Conclusions

Regenerative medicine meets rapid development by increasing cell sources. Successful investigations are being done in macular degeneration, diabetes, spinal cord injury, and cardiovascular disease. Thus, the most vital issue is to suppress immunological responses. Regarding successful investigations, it is necessary to be optimistic. By the emergence of regenerative medicine, tolerance induction in transplantation is being considered to suppress the immunological barriers (Zakrzewski *et al.,* 2014). Modern progress in the knowledge of the pathogenesis and histogenesis in tissue injury and regeneration has led to significant advances in stem cell biology. Therefore, the success of clinical tissue restoration strategies is an undeniable reality (Kimbrel and Lanza, 2015). Instances are: injection of progenitor cells or stem cells; using biologically active molecules or inductive scaffolds constructed alone or as a secretion by infused cells to induce regeneration; modulating the immune responses, and transplantation of grown tissues and organs under in vitro conditions. While the practice of pluripotent stem cells in regenerative medicine has been considered exciting, the function of endogenous stem cells in various tissues will require to be joined with the biology of tissue restoration. Understanding the recipient tissue stroma and providing a suitable microenvironment for the transplanted cells is necessary alongside the comprehension of the biology of transplanted cells. (Walters and Gentleman, 2015). The development of three-dimensional culture environments under in vitro conditions which elicit self-organization of stem cells into organoids will be relevant to illness modeling and treatment in regenerative medicine (De Waele *et al.,* 2015).

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