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Regenerative Medicine: Strategies and Potential benefits

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ABSTRACT: The most efficient and successful way of treating a patient suffering from failed or diseased organ is to transplant a donated one. This approach, although very popular and safe, has its limitations. The most concerning of which are the lack of sufficient donors and the immune-system mediated rejection of the new organ, and the solutions to these issues seem non-existent. This has prompted experts to look towards a relatively new alternative– Regenerative medicine that deals with the unification of cellular transplantation and tissue engineering with stem cell biology to regrow, revive, and repair living organs *in-vivo*. Over the last 3 decades, regenerative medicine has improved leaps and bounds and the current moment stands as the most viable alternative to organ transplantation. However, the advance of regenerative medicine is hindered by the lack of a consensus on its efficacy and the high costs of research and production that need to be addressed in the coming time.

Keywords: Regenerative Medicine – Organ Transplant – Mesenchymal Stem Cells – Biomaterials – Bioprinting – Stem Cell Therapy.

INTRODUCTION

Stem Cells: Origin and Types. Stem cells are undifferentiated cells with self-renewal potential capable of undergoing morphological and physiological changes and undergoing non-oncogenic widescale proliferation to generate a plethora of progenitor cell lineages(Rajabzadeh *et al.*, 2019). The history of stem cells dates back to the 1960s when hematopoietic stem cells (HSCs) were discovered and their use was authorized as a curative therapy for several congenital and blood-related disorders (Friedenstein *et al.*, 1974), (Ghimire *et al.*, 2017). Stem cells are classified primarily based on their potency or differentiation ability. Totipotent stem cells are capable of forming all the cell types found in a species (Zakrzewski *et al.*, 2019). Pluripotent stem cells can form every single cell type found in an individual, and under natural conditions cannot form the extra-embryonic tissues (Zakrzewski *et al.*, 2019). Multipotent stem cells are derived from the pluripotent stem cells, these can form all the cell types found in a single germlayer like the mesenchymal stem cells (MSCs) or can be the predecessors of a single lineage of cells like the HSCs. Unipotent stem cells are adult stem cells that exist adjacent to various differentiated tissues and act as the source of new cells to replace the old, dead, or damaged cells (Zakrzewski *et al.*, 2019).

Strategies involving Stem Cells. MSCs and HSCs represent the most commonly used types of stem cells for regenerative purposes, out of these; MSCs have the most distinct applications in the field of regenerative medicine. MSCs first came to the fore in 1924, when a single precursor cell was identified that gave rise to various types of blood cells within the embryonic mesenchyme (Rajabzadeh *et al.*, 2019). Later it was identified that the embryonic connective tissue, the mesenchyme, maintained very close contact with the germinal layers and formed all the adult connective tissues. Human MSCs (hMSCs) originate as embryonic perivascular cells and are characterized by the cellular markers CD10, CD13, CD44, CD73, CD90, CD105, and CD107 (Crisan *et al.*, 2008). *In-vivo*, it is often argued, that hMSCs do not function as stem cells and regenerate lost tissues, instead, they act as directors of repair by secreting a host of immunomodulatory and trophic factors that stimulate the tissue-specific progenitors to undertake the repair (Guimarães-Camboa*et al.*, 2017). When introduced to any exogenous location, the hMSCs initiate and support the regeneration of the damaged parts making them very lucrative for organ repair and regeneration.

There are multiple sources of hMSCs and these are primarily divided into two types based on their origin – Adult Stem Cells exemplified by the bone marrow, adipose tissue, peripheral blood cells, and dental pulp, and Neonatal Stem Cells derived from the amnion, placenta, and umbilical cord (Rodríguez-Fuentes *et al.*, 2021). Each one of these has unique immunotypic characteristics which lead to differential responses when introduced to exogenous sources for example the dental MSCs can differentiate into neurons, an ability that is unique among all MSCs (Suchanek *et al.*, 2009).

As of February 2022, 1266 clinical studies are either undergoing or are completed on the applications of

MSCs. 452 studies have already completed the four phases of trial and are in various stages of production (*Home - ClinicalTrials.Gov*, n.d.).Most of these studies are focused on finding cures or preventive measures for diseases that currently don't have any cures (Rodríguez-Fuentes *et al.*, 2021). The most significant results have been found in the field of cardiology. Diseases like cardiomyopathy and ischemic and non-ischemic heart failure have seen substantial improvements due to the new hMSC interventions (Rodríguez-Fuentes *et al.*, 2021). Another important improvement is seen in the field of osteoarthritis, especially in the knee. Two treatments have shown optimistic results, one involves intra-articular injections of bone marrow MSCs and the second involves administration of a fibrin-glue (Gel-one®) along with bone marrow MSCs to the affected region (Kalamegam *et al.*, 2018), (Ruane, 2019). Another cellular intervention is CARTISTEM® for the repair of degenerated articular knee cartilage, it involves the administration of umbilical cord-derived MSCs along with sodium-hyaluronate to repair the damaged tissue (Medipost Co Ltd., 2021). With the onset of the COVID pandemic, MSCs have shown potential in curing the complications seen in patients due to acute lung injury (Ricordi, 2021; Matthay, 2017).

Tendon Injuries. Another field that has gained a lot of attention in regenerative medicine is tendon injuries and healing. Tendons are connective tissues that are present between muscles and bones and along with ligaments are essential for the proper biomechanical functioning of the body (Vinhas *et al.*, 2018). Tendons are mainly comprised of tenocytes and have some populations of stem and progenitor cells. Tenocytes are the main ECM-forming cells in the tendons and are often supported by a minor population of chondrocytes present in the tendons (Millar *et al.*, 2016). Tendons are very poorly vascularized and innervated and this is the biggest reason that tendon injuries require a long time to heal, and in most cases never heal back to previous mobility (Thomopoulos *et al.*, 2015). In conventional treatment, the focus is mostly on reducing the collateral damage caused due to prolonged inflammation at the site of injury to reduce fibrotic scarring (Vinhas *et al.*, 2018). This approach accelerates the healing but leads to the development of tendinopathies. Tendinopathies are usually associated with the change in cellularity in the tendon progenitor niches leading to infiltration of immune cells and upregulation of inflammatory signals like IL-1, IL-6, and COX-2 (Millar *et al.*, 2017). Tendon-derived stem cells (TDSCs) are progenitor cells found in tendons that can differentiate into chondrocytes, osteocytes, and tenocytes *in-vitro*(Lui, 2013). These participate in the regulation of inflammation *in-vivo* at the site of injury, especially CD146 + TDSCs, that secrete anti-inflammatory signals like IL-10 and TIMP-3 to down-regulate pro-inflammatory type-I macrophages (M1) cells (Tarafder *et al.*, 2017). So, these have been used as a method to heal tendons while eliminating the possibility of scarring. It was seen that TDSCs cultured in fibrin glue, when introduced in a patellar tendon window defect rat model, increased the rate of collagen production and tissue regeneration (Ni *et al.*, 2013). In another study on the rabbit model, it was seen that TDSCs entrapped in silk-collagen scaffold improved the rate of rotator cuff regeneration by inducing differentiation in tenogenic cells and providing an anti-inflammatory niche (Shen *et al.*, 2012). These studies highlight that TDSCs have a lot of potentials to act as alternatives to conventional treatment regimens for tendon injuries and can even be better in some cases as they can restore the complete functionality of an injured tendon without any bio-mechanical loss.

Autoimmune Diseases. Autoimmune diseases like Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) are widespread in modern society, but unfortunately, no exact treatment is available for either of these. RA is a systemic autoimmune disease caused due to degradation of joints and expansion of synovial tissue (Shende *et al.*, 2018). The pathogenesis of RA involves major inflammatory cells like macrophages and monocytes along with the T_H1 subset of T-cells. These are incited by pro-inflammatory cytokines, especially TNF-a, IL-1b, IL-6, and IL-18 (Ganesan & Rasool, 2017). This inflammation induces hyperplasia in the synovial tissue mainly due to the active proliferation of Fibroblast-like Synoviocytes (FLSs) causing the characteristic joint pain and degradation in RA (Ganesan & Rasool 2017). In a study, four patients suffering from RA were administered bone-marrow-derived MSCs from allogenic sources and were observed. Two of the four patients suffered from mild EULAR reactions but had significant improvement in their RA (Liang *et al.*, 2012). Following this, a larger study was conducted with 172 RA patients. Out of the 172, 136 received a treatment regime that included the conventional disease-modifying anti-rheumatic drugs (DMARDs) along with an intravenous injection of umbilical cord-derived MSCs (UC-MSCs) and the rest acted as a control group that only received the cell-dissolving media and DMARDs. The patients that received the UC-MSCs along with DMARDs showed no adverse reaction even after 6 months of the administration and only 4% showed any sort of reaction at all and overall showed better improvement in their RA profiles when compared to the DMARDs only control group (Wang *et al.*, 2013). This study showed that UC-MSCs might have the potential to solve the long-standing problem of RA treatment and should be investigated further.

SLE is a chronic inflammatory auto-immune disease that affects several major organ systems and leads to their failure if left unchecked it is fatal (Lee *et al.*, 2016). The cause of SLE is multi-faceted and includes both genetic and environmental factors that eventually lead to a complete loss of self-tolerance and over-activation of the immune system leading to catastrophic organ damage (Tsokos *et al.*, 2016). It has been noted in patients with SLE that the MSCs derived from their bone marrow have impaired immuno-modulatory functions (Gao *et al.*, 2017). It has also been noted that

these MSCs have increased the production of reactive oxygen species, increased DNA damage and upregulation of p53 and p16 pathways, increased release of pro-inflammatory cytokines, and suppression of Bcl-2 and IDO production, leading to a breakdown of self-tolerance and hence the pathogenesis of SLE (Gao *et al.*, 2017). However, in pre-clinical studies it is seen in the mice model of SLE there is a reduction in proteinuria and serum self-antibody levels and an improvement in renal function and lung function after transplantation of allogeneic MSCs (Xu, 2018). There have been multiple clinical trials as well that have used allogeneic bone marrow-derived MSCs and UC-MSCs to alleviate the symptoms of SLE patients as reviewed by Xu (Xu, 2018). These MSCs when introduced into the patient, decrease the infiltration of $CD3^+$ inflammatory cells and complement C3 in the organs, especially kidneys (Thiel *et al.*, 2015). These MSCs also decrease the serum levels of inflammatory cytokines TNF-α and IL-6, decrease the levels of T_H1 cytokines, namely, IFN-α, IL-2, and IL-17, and simultaneously increase T_H2 cytokines IL-4 and IL-10, causing amelioration of the SLE symptoms (He *et al.*, 2016). The bone marrow-derived MSCs induce apoptosis in T-cells by secreting the monocyte chemotactic factor-1 (Akiyama *et al.*, 2012). This apoptosis causes the macrophages to secrete huge amounts of TGF-α which then upregulates a subset of T_{reg} cells leading to a significant reduction in SLE symptoms and an increase in self-tolerance (Akiyama *et al.*, 2012). The final facet of this therapy is that MSCs have a down-regulatory effect on B-cells, as the MSCs cause the inhibition of follicular T helper cells (Zhang *et al.*, 2017). The most alluring feature of this therapy is that like conventional medication it suppresses the initial symptoms of SLE, but it also goes one step ahead and helps in rebuilding the lost self-tolerance and the damaged tissue in patients without any sideeffects (Xu, 2018).

Biomaterial Assisted Approach

Biomaterials. A substance is defined as a biomaterial if it augments or replaces any part of the body during its time of use and in the process helps in the recovery of functioning of the body (Nii & Katayama 2021). In regenerative medicine, biomaterials have a significant role, they can act as scaffolds that allow cells to grow for tissue engineering (Rahmati *et al.*, 2018), or they can act as *in-vivo* growth promoters, especially when the composition of the biomaterials is similar to ECMs (Lee *et al.*, 2018; Sainio & Järveläinen 2020). The immense popularity of biomaterials is attributed to their bio-compatibility, *i.e.*, their ability to successfully integrate into the recipient body without eliciting any immune responses (Rahmati *et al.*, 2018).

Natural Biomaterials and Applications. There are several types of biomaterials. The naturally occurring biomaterials are derived from proteins, and polysaccharides or are decellularized tissue matrices, as these have a plethora of favorable ligands that interact with newly growing cells and prompt them to grow quicker (Rodríguez Patino & Pilosof 2011). These polymers are derived from allogeneic and xenogeneic sources after multiple treatments with detergents and enzymes. The natural polymers are non-toxic and can offer customizable growing platforms for cells used in regenerative medicine (Ige *et al.*, 2012). One of the most common examples of such a material is collagen. Collagen is one of the most abundant proteins in the body and has the role of providing mechanical support (Nii & Katayama 2021). There are five basic types of collagen in the human body, Type-I collagen is the most abundant and is mainly found in skin, tendons, and bones. Type-II collagen is mainly found in cartilage, followed by Type-III collagen which is the reticular form and supports Type-I. Type-IV collagen is mainly found in the basal lamina of the basement membranes. Type-V collagen is the surface collagen and is concentrated on cell surfaces, hair, and the placenta (Ashokkumar & Ajayan, 2021). Irrespective of the type, every form of collagen has a conserved triple helix in the molecule. In the field of regenerative medicine, a composite containing collagen and biphasic calcium phosphate nanoparticles was prepared, and this was used to ensure a puppeteered release of dexamethasone. Dexamethasone promotes MSC differentiation into new bone tissue and when this composite was injected into an athymic nude mouse model, high bone regeneration was observed (Y. Chen *et al.*, 2018). Another group created a collagen hydrogel that encapsulated a multicellular mixture of MSCs and human umbilical vein endothelial cells, This hydrogel was then cultured in form of spheroids that showed a high degree of proliferation and osteogenic differentiation in the MSCs, and this change was attributed to the collagen hydrogel (Heo *et al.*, 2019). Collagen has also been used in the engineering of blood vessels, skin, cancer, and muscles (Nii & Katayama, 2021). The problem with collagen is its insolubility in water and its inertness toward biological stimulation. Hydrolyzed collagen or gelatin has appeared as a prominent solution for regenerative medicine. Unlike collagen, gelatin has around 7-14% (average 10%) water content (Yakimets *et al.*, 2005), this allows gelatin to permeate surrounding water-soluble nutrients and oxygen in significant quantities (Nii *et al.*, 2019), making it more conducive for regenerative medicine.This property also allows gelatin to permeate multiple growth factors, and thus when gelatin hydrogels containing basic FGF were introduced into injured tissue, regeneration was observed (Kawai *et al.*, 2000). Another essential advantage of gelatin is the fact that once hardened, it does not solubilize easily, so to release any entity, for example, a drug, encapsulated inside a gelatin coating, the body has to actively digest it using enzymes, thus ensuring a controlled release of the drug and no remanent gelatin that can hinder with the growth of cells (Nii *et al.*, 2020). Gelatin nanospheres charged with cationic entities and loaded with imaging probes have been designed to detect mRNA *in-vivo*(Murata *et al.*, 2019) and have been used to visualize post-transplantation processes like apoptosis, macrophage phenotypes, and cell

proliferation (Nii & Katayama 2021). A very atypical example of a natural biomaterial is silk, especially the pre-dominantly found crystalline structured protein fibroin which is present in combination with another amorphous protein sericin (Liu *et al.*, 2015). Sericin is often degummed from silk to obtain pure silk fibroin (Sahu *et al.*, 2016), as sericin has immunogenic properties (Jiao *et al.*, 2017) and also reduces the mechanical strength of fibroin (Vepari & Kaplan, 2007). Fibroin is an excellent biomaterial owing to its biological inertness and ease of digestion (Cao & Wang 2009). It has multiple uses in regenerative medicine as reviewed by Nii and Katayama (Nii & Katayama 2021), but it shines the most in bone-related regenerative therapies. It is exemplified by the fact the MSCs grown in silk-fibroin scaffolds achieved an enhanced rate of osteogenesis(Meinel *et al.*, 2006).

Synthetic Biomaterials and Applications. Synthetic biomaterials trump their natural counterparts due to their cheap costs of production, ease of manipulation, flexibility, and reproducibility (Rahmati *et al.*, 2018). Synthetic biomaterials include synthetic polymers, bioactive ceramics, and composites. Synthetic polymers are exemplified by poly (lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA). PLA is a polyester composed of -[$C_3H_4O_2$]-subunits and is thermoplastic in nature (Nagarajan *et al.*, 2016). Its flexibility, thermoplasticity, and heat resistance along with a young's modulus similar to bones make it a very attractive prospect for tissue engineering (Chen *et al.*, 2018; Grémare *et al.*, 2018). A combination of hydroxyapatite and PLA has been created that act as scaffolds for high-efficiency culturing of mouse embryonic osteoblasts (Si *et al.*, 2019; Zimina *et al.*, 2020). PLA, despite its advantages, has faded out of popularity mainly due to the difficulties in processing it and creating a balanced PLAmix that has considerably high heat tolerance but at the same time is not very brittle (Nagarajan *et al.*, 2016). PLGA is polyester of lactic and glycolic acid and has arrived as an alternative for PLA. It has better biodegradability, biocompatibility, and easier processing when compared to PLA(Astete & Sabliov 2006). PLGA microcarriers containing leuprolide have been used to ameliorate prostate and breast cancer symptoms (Enayati *et al.*, 2017). Neuronal tissue engineering is mostly dependent on PLGA, as exemplified by the successful culture of neurotrophin-3 over-expressing cells that were supported by PLGA microspheres (Moradian *et al.*, 2017). PLGA also is a promising prospect for brain injury remediation as *in-vitro* cultures of neurons and MSCs on PLGA scaffolds showed significant differentiation and growth (Zhou *et al.*, 2018). It has also been observed that a combination of PLGA microspheres containing an anti-inflammatory agent, pioglitazone showed a marked increase in arginase activity and IL-10 secretion of mouse bone-marrow-derived macrophages, which corresponds to an anti-inflammatory polarization of the progeny macrophages (Momotori *et al.*, 2019).

Bio-ceramics have taken the lead on other types of biomaterials in the field of orthopedic and dentistry-related regenerative medicine owing to their superior biocompatibility, mechanical stress tolerance, and aesthetic appeal (Dorozhkin, 2015). Three types of bio-ceramics are currently being used for regenerative medicine, bio-inert ceramics, bioactive ceramics, and bioresorbable ceramics.One example of bioresorbable ceramic is inorganic calcium phosphates (CaP). CaPs are naturally occurring compounds containing both Ca^{+2} ions and phosphate ions (PO_4^{3-}, HPO_4^{2-}, $H_2PO_4^{1-}$, $[P_2O_7]^{4-}$, $[P_3O_{10}]^{5-}$). These are found in bones and teeth tissues. Studies have shown that inorganic CaP coatings on scaffolds can increase bone regeneration, enhance cell adhesion and proliferation, and increase differentiation in MSCs, both *in-vitro* and *in-vivo* (Surmenev *et al.*, 2014). Another study has shown that scaffolds made up of biphasic calcium phosphate (BCP), a mixture of CaP ceramics hydroxyapatite and β-tricalcium phosphate (Suneelkumar *et al.*, 2008), which were loaded with BMP-2 and MSCs showed bone regeneration, and new tissue formation in just 8 weeks after implantation in a rabbit model (Kim *et al.*, 2015). Another study also showed that scaffolds made of BCP mixed with collagen-containing BMP-2 are much better at initializing bone-tissue formation at the initial stages (3-6 weeks) as compared to only BCP scaffolds, making such hybrid ceramics a lucrative option (Lim *et al.*, 2021). Hydroxyapatite (HA) is another promising entry into the list of bioresorbable ceramics. HA [$Ca_5(PO_4)_3(OH)$] is a naturally occurring mineral compound in the bone and teeth. The Ca^{+2} in the HA can be replaced by other metals or even fluoride and chloride to give this mineral a wide variety of applications (Lin & Chang 2015). A study noted that using HA scaffolds with Zn ions induced bone development in rat models in 6-weeks, and the rate of induction was better when compared to collagen scaffolds (Chou *et al.*, 2016).

An example of bioactive ceramics is bioactive glasses. First developed in 1969, bioactive glasses mainly constitute silica (SiO_2), boric acid (B_2O_3), and phosphoric oxide (P_2O_5) along with some modifiers (Rahmati *et al.*, 2018). The first-ever bioactive glass was 45S5, more commonly known as Bioglass®. It contained 24.6% CaO and 6% P_2O_5 embedded in a SiO_2-Na_2O matrix (Hench, 2006). Since then, several other forms of bioactive glasses have been designed. The bioactive glasses S53P4 (Bonalive®) (*Our Story - Bonalive*, n.d.), Bioglass 8625 (Schott VivoTag®) (*VivoTag® RFID Transponder Glass Capsules | SCHOTT*, n.d.), and Bioglass 13-93 (Fu *et al.*, 2008) are some of the newer forms of bioactive glasses. According to a study conducted on a lapine model, the use of low-silica bioactive glasses can induce the new formation and can help repair bone defects (Nommeots-Nomm *et al.*, 2017). Another study has also indicated that the addition of Cu^{2+} ions in bioactive glasses can enhance rates of osteogenesis, and decrease the chances of any foreign invasion, especially opportunistic

bacteria like *Escherichia coli* and *Staphylococcus aureus* (Bari *et al.*, 2017).

Carbon-based bioinert ceramics like graphene, fullerenes, carbonnanotubes, quantum dots, nanocrystalline diamond films, diamond-like carbon, mesoporous carbon nanomaterials, and carbon nanofibers are some very alluring and recent prospects for regenerative applications (Rahmati *et al.*, 2018). For instance fullerenes and nanodiamonds have been used for bioimaging and cancer diagnosis and therapy (Lichota & Krokosz, 2016; Qin *et al.*, 2021). Similarly, multi-walled carbon nanotube blocks containing BMP-2 when inserted into rat muscles led to the generation of ectopic bones (Tanaka *et al.*, 2017). Graphene, a 2-D sheet-like carbon allotrope, has shown potential for tissue regeneration and engineering (Shang *et al.*, 2019), especially neural (Aydin *et al.*, 2018) and liver tissue regeneration (Geetha Bai *et al.*, 2019). Graphene-based scaffolds have also shown the potential to act as *in-vivo* niches for MSC proliferation and differentiation into bone tissue (Crowder *et al.*, 2013).

A composite biomaterial is the macroscopic combination of two materials that have significant discrepancies in their physical, chemical, and mechanical properties and the overall properties of the composite are the net sums of the properties of its constituents (Egbo, 2021). Conventional composites were often created by adding carbonfiber to polymer matrices. One such example is carbon fiber reinforced-polyether-etherketone (PEEK). PEEK has been successfully utilized for orthopedic and dental plate and screw creation (Rahmati *et al.*, 2018). Several other composites have also been designed and utilized for the treatment and replacement of bones, cartilage, and ligaments (Egbo, 2021). A subset of composites are nanocomposites, in which at least one material is at the nanometer scale. These have shown excellent manipulability and bio-compatibility and therefore are one of the most discussed topics in regenerative medicine (Follmann *et al.*, 2017). For instance nanocomposite hydrogels, which are hydrogels with an additional nanomaterial filled in the matrix, giving it more controllable physio-chemical properties as compared to conventional hydrogels (Carrow & Gaharwar, 2015). These are currently highly in demand due to their ability to mimic ECM conditions and provide adequate hydration to nutrients and cells alike, especially in electroactive tissues like cardiac tissue, nerve tissue, and skeletal muscles (Mehrali *et al.*, 2017). Some nanocomposites have shown the ability to self-heal using either external effects like Joule's effect or intrinsic properties like supramolecular interactions, Diels-Alder's reaction, and Au-S exchange, making them very exciting prospects for *in-vivo* regenerative therapies (Orellana *et al.*, 2021; Sanka *et al.*, 2019).

Regenerative medicine- future strategies andtargeted diseases. The loss of organs and tissues due to disease and damage motivates the development of drugs that can regenerate tissues and lessen the need for transplantation. Regenerative medicine is an interdisciplinary field that employs engineering and life science ideas to promote tissue and organ regeneration. Since the field's foundation decades ago, the Food and Drug Administration (FDA) has approved and commercialized a variety of regenerative medicine therapies, including those for wound healing and orthopedics. This article will go through these drugs as well as other regenerative medicine strategies that are currently being studied in both preclinical and clinical settings. The most recent advancements in the production of advanced grafts and tissue mimics, as well as graft technology

Therapies in the Market. Since tissue engineering and regenerative medicine became a business around two decades ago, a variety of therapies have received FDA clearance or approval and are commercially available. The introduction of therapeutic cells that directly contribute to the creation and function of new tissues has been one of the most important concepts of regenerative medicine to date. These treatments use either autologous or allogeneic cells that have been differentiated yet still have the potential to proliferate. Carticel, for example, is the first FDA-approved biologic product in the orthopedic field, and it uses autologous chondrocytes to treat localized articular cartilage defects. Autologous chondrocytes are taken from articular cartilage, expanded *ex vivo*, and transplanted into the damaged region, resulting in patient healing.

Therapies at the Preclinical Stage and in Clinical Testing. At the preclinical and clinical stages of research, a wide range of approaches are presently being investigated. The numerous techniques, which are grouped into three groups, will be discussed in the subsections that follow: fabricating scaffolds, 3D bioprinting, and self-assembly to replicate organ and tissue structure; (ii) vascularization and innervation to integrate grafts with the host; and (iii) altering the host environment to induce therapeutic responses, particularly through cell infusion and immune system modulation. Finally, regenerative medicine strategies based on newly discovered and developed cell sources will be described.

Recapitulating Tissue and Organ Structure. Because tissue and organ design are so tightly related to function, it's a frequent assumption that the ability to reconstruct structure is essential for successful tissue recapitulation. One method for capturing organ shape and material composition in synthetic tissues is to decellularize organs before transplantation. Decellularization removes immunogenic cells and chemicals while potentially conserving the structure, mechanical properties, and material composition of the native extracellular matrix. This approach has been used in bioreactors and animal models of diseases involving the lungs, kidneys, liver, pancreas, and heart.

The field of regenerative medicine comprises a wide range of strategies for replacing missing tissue, including the use of materials and *de novo*-created cells, as well as diverse combinations of both, both structurally and functionally.

A lot of strategies are being studied at the preclinical and clinical stages of research. The sections will go over the various strategies, which have been divided into three categories: replicating organ and tissue structure through scaffold fabrication, 3D bioprinting, and self-assembly; integrating grafts with the host through vascularization and innervation; and altering the host environment to induce therapeutic responses, particularly through cell infusion and immune system modulation. Finally, regenerative medicine techniques for utilizing recently discovered and developed cell sources will be discussed.

It is also possible to create synthetic scaffolds that have at least some of the material properties and structure of the target tissue. Scaffolds can be made from natural materials such as purified extracellular matrix components or algae-derived alginate, or synthetic polymers.

According to animal studies, the seeded cells in TEVGs did not contribute structurally to the graft once in the host but instead controlled the inflammatory response that helped host vascular cells populate the graft to build the new blood artery. Biodegradable vascular grafts seeded with cells, cultivated so that the cells produce extracellular matrix, and then de-cellularizedis being tested in patients with end-stage renal failure. Scaffolds with a variety of mechanical properties have been developed to provide bulk mechanical support for tissue formation as well as instructive cues to adhering cells. Soft fibrin–collagen hydrogels, for example, have been studied as lymph node mimics, while faster degrading alginate hydrogels aided in the regeneration of critical defects.

In some cases, the mechanical properties of the polymer may be sufficient to provide a therapeutic effect. Injection of alginate hydrogels into the left ventricle, for example, has been shown to slow the progression of heart failure in dilated cardiomyopathy models and is currently being tested in clinical trials. The use of composite polyglycolide and collagen scaffolds seeded with cells as bladder replacements for human patients demonstrated how combining materials with different properties can improve scaffold function. Another study found that an electro-spun nano-fiber mesh loaded with bone morphogenic protein 2 and paired with peptide-modified alginate hydrogel increased bone growth in critically sized defects. Medical imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) can be used to generate 3D representations of substitute tissues on occasion.

In some cases, it may be possible to design new tissues without the use of scaffolds. Cell sheet technology works by removing a confluent sheet of cells from a temperature-responsive substrate while leaving cell-cell adhesion and signaling molecules, as well as ECM molecules deposited by the cells, intact. Layers of sheets can be stacked on top of each other to create thicker structures. This technique has been tried in a variety of applications, including corneal restoration. Autologous oral mucosal cells were grown into sheets, collected, and implanted to epithelialize human corneas. Autonomous cellular self-assembly could also be used to create tissues and as an adjunct to bio-printing.

CONCLUSION

Regenerative medicine can repair or replace tissues and organs that have been damaged by age, disease, or trauma, as well as prevent congenital malformations. To date, promising preclinical and clinical data to support the use of regenerative medicine to treat both chronic diseases and acute insults, as well as maladies affecting a wide range of organ systems and contexts, such as dermal wounds, cardiovascular diseases and traumas, cancer treatments, and more. The current therapy of intact organ and tissue transplantation to cure organ and tissue failures and loss suffers from a scarcity of donors and frequently significant immunological problems, but these limitations could be overcome with the use of regenerative medicine. In the coming years, regenerative medicine will offer an advantageous alternative to classical allopathic medicine, however, it will be subjected to very controversial ethical arguments that need to be tackled gracefully. The most important direction in which regenerative medicine will move forward is toward the affordability and user safety of all the new creations.

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