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REVIEW ARTICLE

Regenerative Medicine Using Nanotechnology: A Review

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ABSTRACT

Regenerative medicine is considered to have the potential for developing new treatments for previously untreatable, or difficult to treat, diseases. Regenerative medicine is an emerging multidisciplinary field that aims to restore, maintain or enhance tissues and hence organ functions. Regeneration of tissues can be achieved by the combination of living cells, which will provide biological functionality, and materials, which act as scaffolds to support cell proliferation. Mammalian cells behave in vivo in response to the biological signals they receive from the surrounding environment, which is structured by nanometer-scaled components. Therefore, materials used in repairing the human body have to reproduce the correct signals that guide the cells towards a desirable behavior. Nanotechnology is not only an excellent tool to produce material structures that mimic the biological ones but also holds the promise of providing efficient delivery systems. The application of nanotechnology to regenerative medicine is a wide issue and this short review will only focus on aspects of nanotechnology relevant to biomaterials science. Specifically, the fabrication of materials, such as nanoparticles and scaffolds for tissue engineering, and the nanopatterning of surfaces aimed at eliciting specific biological responses from the host tissue will be addressed.

Key Words: Regenerative medicine, Nanotechnology, Nanomaterials.

INTRODUCTION

The general aim of regenerative medicine is to repair, replace or regenerate lost or damaged tissues and organs in vivo through techniques that stimulate them into healing themselves. Tissues and organs can also be grown in vitro for subsequent implantation into the body. Regenerative medicine is a new scientific and medical discipline focused on harnessing the power of stem cells and the body's own regenerative capabilities to restore function to damaged cells, tissues and organs. Researchers in this field seek to understand how and why various kinds of stem cells are able to develop into specialized cells and tissues. Basic scientists and doctors working together are growing stem cells into the specific cell types they hope to transplant into patients to repair or replace damaged or destroyed cells. Researchers also aim to develop tissue replacement therapies that could restore lost function in damaged organs, or perhaps even grow new, fully functioning organs for transplant. In addition to the study and development of stem cells, regenerative medicine also includes the new field of tissue engineering. Bioengineers working with developmental biologists, physicians, nanotechnologists and other specialists can construct connecting tissues and potentially organs on matrices, or scaffolds made of biological materials to resemble cartilage, bone and other supporting structures that support cellular, tissue and organ growth. This 3D approach mimics human anatomical development much better than anything researchers can come up with in a culture dish. It is the next step to testing therapies for safety and effectiveness before trying them in animals and in people.

The rapid expansion of nanotechnology during the past ten years has led to new perspectives and advances in biomedical research as well as in clinical practice. As nanotechnology is defined by the size of a material (generally 1–100 nm) or manipulation on the molecular level, it involves a broad range of nanoscaled materials used in various fields of regenerative medicine, including tissue engineering (TE), cell therapy, diagnosis and drug and gene delivery. The basic strategy of TE is the construction of a biocompatible scaffold that, in combination with living cells and/or bioactive molecules, replaces, regenerates or

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repairs damaged cells or tissue. To promote cell adhesion and growth, the addition of nanotopographies to the biomaterial surface improves its bioadhesive properties, e.g. the surface roughness, aside from the chemistry, is an important factor influencing cell attachment and spreading. The large surface area of nanostructured materials enhances the adsorption of adhesive proteins such as fibronectin and vitronectin, which mediate cell-surface interactions through integrin cell surface receptors [1,2].

By Using drugs and surgery, doctors can only encourage tissues to repair themselves. With molecular machines, there will be more direct repairs [3]. Access to cells is possible because biologists can stick needles into cells without killing them. Thus, molecular machines are capable of entering the cell. Also, all specific biochemical interactions show that molecular systems can recognize other molecules by touch, build or rebuild every molecule in a cell, and can disassemble damaged molecules. Finally, cells that replicate prove that molecular systems can assemble every system found in a cell. Therefore, since nature has demonstrated the basic operations needed to perform molecular-level cell repair, in the future, nanomachine based systems will be built that are able to enter cells, sense differences from healthy ones and make modifications to the structure.

The healthcare possibilities of these cell repair machines are impressive. Comparable to the size of viruses or bacteria, their compact parts would allow them to be more complex. The early machines will be specialized. As they open and close cell membranes or travel through tissue and enter cells and viruses, machines will only be able to correct a single molecular disorder like DNA damage or enzyme deficiency. Later, cell repair machines will be programmed with more abilities with the help of advanced AI systems. Nanocomputers will be needed to guide these machines. These computers will direct machines to examine, take apart, and rebuild damaged molecular structures. Repair machines will be able to repair whole cells by working structure by structure. Then by working cell by cell and tissue by tissue, whole organs can be repaired. Finally, by working organ by organ, health is restored to the body. Cells damaged to the point of inactivity can be repaired because of the ability of molecular machines to build cells from scratch. Therefore, cell repair machines will free medicine from reliance on self repair alone.

Process of Regenerative Medicine Using Nanotechnology

Regenerative Medicines

Regenerative medicine is a newer approach in medicine aimed at restoring function to damages body organs and tissues. Regenerative medicine represents a global, groundbreaking, and interdisciplinary biotechnological effort with tremendous potential to promote and extend the quality of life of the aging US and world population [4]. Tissue engineering, stem cell therapy, and cloning technologies are subsumed under the rubric of regenerative medicine. Tissue engineering is one of the major components, which, in turn, combines the fields of cell transplantation, materials science, and engineering to acquire medicinal tissues that could restore and maintain normal tissue/organ function, including endogenous regenerative capacity [5]. The widespread promise of regenerative medicine has been recently codified in government publications [4].

The regenerative medicine intends to restore the functions of damaged tissues and organs. Efforts are being made towards artificial tissues, including bone in primes, cartilage, nerve, blood vessels, and skin. Regenerative medicine has brought high expectations for a great number of current worldwide human illnesses. Diseases, such as Parkinson’s disease, Alzheimer’s disease, osteoporosis, spine injuries or cancer, in the near future might be treated with methods that aim at regenerating diseased or damaged tissues. The perspective of regenerating damaged or non-functional tissues by using an off-the shelf synthetic product is a drive for medical science.

Regenerative strategies include the rearrangement of pre-existing tissue, the use of adult somatic stem cells and the dedifferentiation and/or transdifferentiation of cells, and more than one mode can operate in different tissues of the same animal. All these strategies result in the re-establishment of appropriate tissue polarity, structure and form [6]. The dedifferentiation of cells means that they lose their tissue specific characteristics as tissues remodel during the regeneration process. The transdifferentiation of cells means that they lose their tissue specific characteristics during the regeneration process and then re-differentiate to a different kind of cell [6].

Regeneration Process in Human and Animals

Regeneration is a complex biological process by which parts of the body plan are restored after injury or amputation. Every species is capable of regeneration, from bacteria to humans [7,8]. At its

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most elementary level, regeneration is mediated by the molecular processes of DNA synthesis[9,10]. Regeneration in biology, however, mainly refers to the morphogenic processes that characterizes the phenotypic plasticity of traits allowing multi-cellular organisms to repair and maintain the integrity of their physiological and morphological states. Above the genetic level, regeneration is fundamentally regulated by asexual cellular processes [11]. This process requires the concerted action of mechanisms inducing and regulating dedifferentiation, pattern generation and, in certain instances, transdifferentiation events. Although embryos from most vertebrates show a remarkable capacity to regenerate damaged structures, this ability plummets as development proceeds, such that adults generally display very limited regenerative capacity. During the developmental process genes are activated that serve modify the properties of cell as they differentiate into different tissues. Development and regeneration involves the coordination and organization of populations cells into a blastema, which is a mound of stem cells from which regeneration begins.[12]

How nanotechnology helps in regenerative medicine?

Today's interest in nanomedicine keeps growing because the application of nanotechnology tools to the development of structures at the molecular level enables the improvement of the interactions between material surfaces and biological entities. Although cells have micrometre dimensions, they evolve in vivo in close contact with the extracellular matrix (ECM), a substratum with topographical and structural features of nanometre size. The interactions between cells and the ECM influence cell growth, guide cell mobility and affect the general behaviour of cells. Nanotechnologies provide the possibility to produce surfaces, structures and materials with nanoscale features that can mimic the natural environment of cells, to promote certain functions, such as cell adhesion, cell mobility and cell differentiation. This field holds the promise of regenerating damaged tissues and organs in the body by stimulating previously irreparable organs to heal them selves. Regenerative medicine also empowers scientists to grow tissues and organs in the laboratory and safely implant them when the body cannot heal itself. Importantly, regenerative medicine has the potential to solve the problem of the shortage of organs available for donation compared to the number of patients that require life-saving organ transplantation, as well as solve the problem of organ transplant rejection, since the organ's cells will match that of the patient[13,14,15].

The material chemistry and the biochemical technology have progressed from the use of biomaterials that may repair or replace diseased or wounded tissues to the implantable seeded supports. Scientists aim at generating or inducing the formation of a defined tissue in a certain location through selection and manipulation of cells, matrices and biological stimuli. Because these constructs mimic viable tissues, they should be functionally, structurally and mechanically comparable to the healthy tissues. The composites favour cell colonization, migration, growth and differentiation, and in certain cases guide the development of the tissue or deliver drugs and factors. The scaffold, polymers, ceramics or composites must also possess defined porosity, large surface area, adequate structural strength, and timely biodegradability. Significant results have been obtained in the development of surgical techniques for skeletal reconstruction; moreover, regenerative medicine would be an alternative to the conventional autogenic or allogenic bone and cartilage transplants.

Nanomaterials Used For Regenerative Medicine

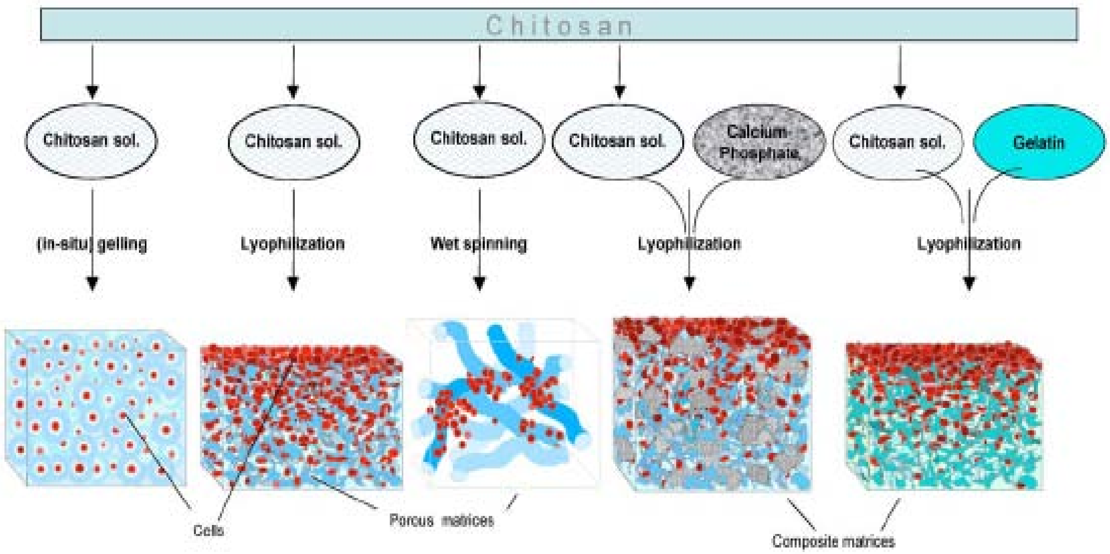
Some examples of commonly-used scaffold materials that either include nanoscale features or that can be functionalized at the nanoscale to provide characteristics suitable to support cell growth include

- collagen and collagen-based materials
- fibrin
- chitosan
- keratin
- peptides
- glycosaminoglycans, e.g. hyaluronic acid
- hydrogels
- silk proteins
- hydroxyapatite
- tri-calcium phosphate
- commonly-used and regulatory-approved medical polymers with known biocompatibility, e.g. - polylactic acid (PLA), polyglycolicacid (PGA), poly DL lactic-co-glycolic acid (PLGA), polycaprolactone (PCL)

Chitosan Used As a Biomaterial in Regenerative Medicine

Biomaterials play a central role in tissue engineering. New materials are required to serve as temporary implantable devices, such as hollow molding chambers, porous tissue scaffolds, and bioactive material delivery devices. An illustration of selected examples of chitosan processing for use in tissue engineering is presented in (**Fig 1**). Thus, cells may be encapsulated in gels or seeded in porous matrices including sponge-like or fibrous structures [16].Combinations of chitosan with other biocompatible materials such as calcium phosphate or gelatin are applied to modify biomechanical and cell-matrix-interaction properties. For example The incorporation of collagen to chitosan as a chitosan-collagen scaffold will enhance its cell attachment ability. Conjugation of chitosan with biologically active containing protein peptides is expected to become a potential technology to develop desirable scaffold materials for the tissue regenerations [17].

Fig 1.Examples of chitosan processing for use in tissue engineering



Keratin Used In Regenerative Medicine

Keratins are a family of structural proteins that can be isolated from a variety of tissues. "Soft" keratins are cytoskeletal elements found in epithelial tissues while protective tissues such as nails, hooves, and hair are composed of "hard" keratins. Hard keratins have been the subject of biomaterials investigations for more than three decades. Numerous methods exist for denaturing these proteins which are characterized by a high sulphur content and extensive disulfide bonding, under either oxidative or reductive conditions, extracting them from tissue and processing them into various physical states such as gels, films, coatings, and fibres. Keratins or keratoses (oxidatively or reductively derived, respectively), alone or in combination with other biomaterials, have been tested in a small number of systems to demonstrate feasibility for medical applications such as wound healing, bone regeneration, haemostasis, and peripheral nerve repair. These investigations have shown generally good compatibility with cells and tissues, but the focus of prior investigations has been fairly narrow, and as a result there is relatively little published data on the general behaviour of keratin biomaterials in biological systems beyond cell culture assays [18].

Hydro gels Used in Regenerative Medicine

In terms of material requirements in regenerative medicine, such as those needed for tissue scaffolds or as therapeutic delivery systems, hydro gels have long received attention because of their innate structural and compositional similarities to the extracellular matrix and their extensive framework for cellular proliferation and survival. Hydro gels are three-dimensional networks formed from hydrophilic homopolymers, copolymers, or macromers (preformed macromolecular chains) cross linked to form insoluble polymer matrices. These polymers, generally used above their glass transition temperature (Tg), are typically soft and elastic due to their thermodynamic compatibility with water and have found use in many biomedical applications.[19] Biological hydro gels have been formed from agarose, alginate, chitosan, hyaluronan, fibrin, and collagen, as well as many others.[20,21]

Many hydro gel types with vastly different chemical and physical properties have been developed over the last several decades from a wide variety of chemical building blocks and using an array of synthetic techniques. This expanse of hydro gel knowledge allows for scaffold properties, such as cellular attachment, molecular response, structural integrity, biodegradability, biocompatibility, and solute transport to be carefully engineered to meet the proliferative demands of the construct [22].

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There are several applications in regenerative medicine where hydro gels have found longer utility and Vacant [23] were among the first to elucidate the basic techniques used in tissue engineering to repair damaged tissues, as well as the ways polymer gels are utilized in these techniques. To date, hydro gels in regenerative medicine have been used as scaffolds to provide structural integrity and bulk for cellular organization and morphogenic guidance, to serve as tissue barriers and bio adhesives, to act as drug depots, to deliver bioactive agents that encourage the natural reparative process, and to encapsulate and deliver cells.

Nanofibers Used In Regenerative Medicine

The first scaffolds were made using biodegradable materials and had a porous structure that would ensure host-cell colonisation. Among the possible structures that could replace the natural ECM, the use of nanofibres as scaffolds has several advantages compared with other techniques. Nanofibres show a high surface area and a highly interconnected porous architecture, which facilitate the colonisation of cells in the scaffold and the efficient exchange of nutrients and metabolic waste between the scaffold and its environment. These nanofibers can be made of synthetic, natural or the combination of both types of materials.

Recent trends in techniques producing nanofibers for TE are the development of biomimetic scaffolds that not only provide structural support for living cells, but also can serve as a delivery system for drugs, growth factors or cytokines that may further promote cell function and tissue regeneration. Various attempts have been made to enhance the bioactive properties of the scaffolds by the immobilization of functional cell-adhesive motifs, such as laminin or fibronectin derived peptidic sequences. Currently, electrospun and self-assembled nanofibers have been studied as potential scaffolds for the regeneration of bone, cartilage, and skin as well as vascular, cardiac, nervous and other tissues.

Applications and Perspectives of Regenerative Medicine

Regenerative medicine has a potential to extend healthy life spans and improve the quality of life by supporting and activating the body's natural healing mechanisms, or by creating an environment that mimics early development or that is more conducive for tissue regeneration. Some examples of clinical application areas of current research in regenerative medicine include:

- replacement of skin for burns patients, wounds, pressure sores or diabetic foot ulcers
- bone and cartilage regeneration
- bladder repair
- the use of stem cells in tissue regeneration
- repair of damaged heart muscle following heart attack
- restoration of peripheral nerve or spinal cord following injury, or of the CNS after tumour
- resection
- regeneration of pancreatic tissue to produce insulin for people with diabetes
- further early stage research on regeneration approaches to replace lost organ function

Regenerative medicine can be applied to form new muscle tissue, heart valves, blood vessels, kidney, bladder or other genitourinary tissue or organs, trachea, breast, liver, bone, cartilage and also to produce new nerve cells or tissues [24]. Regenerative medicine therapies have the potential to treat numerous diseases and conditions, such as diabetes, spinal cord injuries and cardiovascular disease, resulting from damaged or failing tissues. In addition, regenerative medicine is desperately needed to help combat rising health care costs [25].

CONCLUSION

The application of nanotechnology in regenerative medicine has already begun to revolutionize several areas of stem cell research and will continue having great impact on regenerative medicines. However recognizing the optimum potential of nanotechnology in regenerative medicine requires several considerations. First appropriate imaging methods should be designed carefully by considering the specific biological questions regarding stem cells that need to be addressed because each imaging technique has its unique set of advantages and disadvantages. Second, nanomaterials might have undesirable side effects on stem cells owing to their composition, size, and physical properties. In particular, this approach would be beneficial to elucidate the complex cellular spatial temporal dynamics and signalling pathways in more effective ways. Addressing the challenges ahead would accelerate the development of nanotechnology approaches towards regenerative medicine.

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