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Biomaterials and scaffolds in the medical-surgical area

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ABSTRACT

The use of biomaterials in medicine can change the direction of research in tissue engineering; the goal is the self-repair of the organism with the help of scaffolds that may have growth factors or bioactive molecules. The objective of this review was to provide a general overview on the use of biomaterials such as hydrogels, biopolymers, nanofibers, nanoparticles, flat and tubular scaffolds, bioprostheses, for the experimental replacement of different tissues such as; liver, kidney, cornea, skin, blood vessels, urethra, trachea, bile duct, bone and cartilage. Currently, there is intense work and scientific collaboration to achieve the manufacture of various tissues and organs in tissue engineering, perhaps the use of biomaterials can provide a therapeutic alternative for the treatment of multiple pathologies.

1. Introduction

Biomaterials are structures of natural or synthetic origin, used in biological systems to regenerate, repair or replace the function of a tissue or organ; For decades have been implemented for therapeutic purposes various materials in the surgical field, such as ceramics, metal meshes, osteosynthesis material, prosthesis, to mention some examples that have an extensive application in patients. With the discovery of the morphological and functional properties of the extracellular matrix, as well as the lines of research that integrate the regenerative medicine, have described some essential characteristics to consider for a biomaterial have a good performance in your clinical application, such as porosity (pore size and microstructure) that influence growth, migration morphology and cell adhesion, as well as its mechanical properties, of biocompatibility because you want the host has a lower number of adverse effects (being inert, non-toxic and with the least likelihood of rejection) and degradation of the material because it has to be replaced by natural components of the tissue. The similarity of these structures with the native tissue influences the organization of cells and the compartmentalization for the release of molecules in the implanted tissue. In the last two decades, nanocomposites have emerged as an effective strategy for improving the structure and functional properties of synthetic polymers. Aliphatic polyesters such as polylactic acid (PLA), polyglycolic acid (PGA), Polycaprolactone (PCL), etc. They have attracted broad attention for their biodegradability and biocompatibility in the human body. A logical consequence has been the introduction of inorganic nanofills in biodegradable polymers to produce hydroxyapatite-based nanocomposites, or metallic nanoparticles (carbon nanostructures), in order to prepare new biomaterials with more properties (Armentano et al., 2010). In this review, an overview is presented on some applications of these biomaterials in the surgical field, highlighting their importance as an area of emergent research and with great impact in the clinic (Table 1).

2. Biomaterial implant overview

The implantation of a device of a biomaterial gives rise to a foreign body reaction, an inflammatory response that includes cells such as fibroblasts, macrophages, neutrophils and giant cells of foreign body. The research focuses on the search for biomaterials that by their properties are biocompatible with a reduction of the response by

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the host, among which are considered: chemical composition, wettability, surface roughness and topography of the material. The concept of tissue regeneration in situ has now been introduced, where the guest's response is used as an indirect way to attract specific tissue repair cells. Although several studies choose to modify the surface of implants to reduce the response of the host, biomaterials with surface tuning properties, could be a viable strategy to improve tissue regeneration in situ through a bioreactor in vivo approach (Damanik et al., 2014).

Table 1: Use of biomaterials and scaffolds in medicine

Biomaterials	Advantages	Challenges	Experimental application	Reference
Three-dimensional collagen tubes coated with agarose hydrogel 2%	Degraded ducts from 4 weeks. At 3 months, it looks like a native-style biliary pathway	Long-term viability for human implementation	Bile duct replacement	Pérez et al. (2013)
Collagen bioprosthesis coated with ε-caprolactone	Complete resurfacing of scaffolding per month follow-up, with no biliary stenosis or leakage	Long-term viability for human implementation	Bile duct replacement	Montalvo-Javé et al. (2015)
Acellular porcine cornea matrix treated with SDS 0.5%	Corneal reconstruction by culture of human corneal epithelial cells and fibroblasts	Optical refraction features	Previous lamellar replacement	Zhang et al. (2016a)
Decellularized porcine liver tissue treated with Triton X or SDS	It maintains microarchitecture and bioactive signals for the recellularization	Complexity of in vitro growth for complete recellularization	Hepatic replacement	Baptista et al. (2011) Peloso et al. (2015)
Decellularized murine renal tissue treated with Triton X or SDS	It maintains a balance between cellular removal and conservation of the cytoarchitecture with extracellular matrix proteins and growth factors	Presence of more than 30 different types of cells specialized in this organ	Renal replacement	Peloso et al. (2015)
Polyethylene glycol hydrogel bound to phosphate groups	Osteogenic induction from human mesenchymal cells	Cell and microenvironment interactions	Chondrogenic Differentiation	Benoit et al. (2008)
Oakermanita (Ca 2 MgSi 2 O 7)	It induces osteogenic differentiation of osteoclasts, bone marrow stromal cells and stem cells derived from adipose tissue in vitro	Inherent mechanical resistance and limit of superficial cellular activity	Osteogenesis in osteoporotic bone	Xia et al. (2016)
MBG scaffold with amino groups	High in vitro osteogenic capacity, high regeneration rate with low rate of degradation	Inherent mechanical resistance and limit of superficial cellular activity	Osteogenesis	Xingdi et al. (2016)
TRACER	Studies of oxygen gradients in cancer cells	Management of in vitro microenvironment variables	Oncology	DelNero and Fischbach (2016)
Nanoparticles: drug release	Local administration of pharmacological therapy in places of difficult access	Porous structure dependent on the particles administered	Oncology Psychiatry	López et al. (2013)

In tissue engineering, artificial scaffolding has been studied containing living cells for tissue repair and regeneration. Notably, the performance of these cells in scaffolding, in terms of cell viability, proliferation and expression of function during and after the manufacturing process, has not been well documented because of the influence of physical properties, chemical and the mechanics of substrate materials for scaffold design. Therefore, the characterization of these devices results in a fundamental element added to the reaction of the organism at the moment of being implanted, since the intrinsic properties of the scaffold affect the cell adhesion (cell-scaffolding, cell-cell) the analysis of the viability, proliferation, morphology and expression of proteins that constitute the extracellular matrix in both 2D and 3D structures that are fundamental to assess the application of these devices in the regeneration and/or repair of a tissue (Ning et al., 2016).

The current treatment of damage to the extrahepatic biliary pathway affected by multiple circumstances such as cancer, congenital malformations and surgical lesions consists of an anastomosis of the hilar-biliary plaque to the small intestine in the most severe cases. The development and use of tubular scaffolding whether biological or synthetic, represents an area of opportunity as a viable therapeutic alternative for this type of injury. (Pérez et al., 2013; Montalvo-Javé et al., 2015)

Pérez et al. (2013) built three-dimensional collagen tubes coated with 2% agarose hydrogel. This material was implanted in 40 experimental animals substituting the native bile duct. The artificial conduits are mostly degraded from 4 weeks, persisting even adhesions and light inflammation of the adjacent tissues. From the 3 months, a biliary

pathway similar to the native and complete resorption of the scaffold was found. We observed the entire path of reepithelialized neoconduct with glandular tissue under the biliary epithelium. In specimens of 3 and 6 months, the tube was undetectable because the collagen scaffold was replaced by dense connective tissue, with an internal total cover of simple cylindrical epithelium. The integration of the implanted conduit was completed from 4 weeks, maintaining the functions of bile conduction.

2.1. Bioengineering applied to the corneal tissue

Once corneal damage is generated by trauma, inflammation or degeneration, the cornea loses its normal function, leading to a deficit in visual acuity. Although blindness is a frequent occurrence worldwide, accounting for more than 10 million people affected by corneal blindness, the only effective treatment to date is human donor cornea transplantation, with adverse factors being donor scarcity and high risk of tissue rejection. Currently, scientific efforts are being made to achieve the fabrication of a cornea through tissue engineering, in order to overcome the current disadvantages in allografts and provide a further option for patients with this involvement. The characteristics pursued in this type of tissue, due to their main function within the eye lens apparatus, are good biocompatibility, high optical clarity, resistance to surgical manipulation and immunogenic properties. In their study, Zhang et al. (2016b) compared scaffold preparations from fresh porcine corneas treated with 0.5% sodium dodecylsulfate (SDS) to an acellular porcine cornea matrix to subsequently be treated with fibroblasts and human corneal epithelial cells (both autograft as an allograft) to establish more than 10 layers on the scaffold. The anterior lamellar replacement of the cornea can be reconstructed by culturing human corneal epithelial cells and fibroblasts in an acellular porcine cornea matrix, a viable therapeutic option.

2.2. Bioengineering applied to the liver: Challenges of the function

Globally, 650 million people have liver disease, of which 21 million are chronically affected. As in the case of corneal transplantation, liver transplantation is the only effective treatment for these patients, whereby the donor demand is high. In the United States, 16 000 patients require a liver transplant, but only 6 000 procedures are performed annually. This is why tissue engineering can be very supportive and represent a viable solution. It has been proposed to use decellularized porcine organs previously treated with Triton X or SDS, as it not only maintains its microarchitecture but also retains bioactive signals that are difficult to replicate artificially. The decellularized livers use the perfusion method, since it has been the most efficient in the elimination of the cellular components and minimize the damage to the vascular elements, criteria relevant for the recellularization of the whole organ. Baptista et al. (2011) report the creation of a functioning humanized rat liver by using a bioreactor system for the placement of human progenitor cells on scaffolding (Baptista et al., 2011). Despite the different protocols used for this purpose, liver cells are extremely difficult to grow in vitro, so complete recellularization with all cells found in the liver including Kupffer cells, endothelial and star-shaped, has not been possible to a scale of the human liver with the correct function (Peloso et al., 2015). One of the biggest challenges is an adequate cellular source to repopulate the scaffold.

2.3. Bioengineering in the kidney

Hemodialysis has increased the survival of patients with end-stage renal disease, the only treatment with curative potential being renal transplantation. Despite advances in therapeutics to avoid rejection of the organ, 20% will present an acute rejection within 5 years after transplantation and 40% at 10 years. The most effective strategy for the construction of a scaffold is the use of Triton / SDS to decellularize rat kidneys, in addition to maintaining a balance between cell removal and preservation of the original architecture with extracellular matrix proteins and growth factors. The major challenge for tissue bioengineering in this specific organ is the presence of more than 30 different types of specialized cells, including 2 million glomeruli and its vast vascular network (Peloso et al., 2015). Harari-Steinberg et al. Identified progenitor cells in nephron of human kidneys capable of generating renal structures and functional repair of chronic kidney disease. These cells expressed NCAM1 + and had a high clonogenic potential. When these cells were grafted into the aggregates on a chorioallantoic membrane of the chicken embryo, they generated renal structures (Harari-Steinberg et al., 2013). It was shown showed that human amniotic stem cells integrated into metastatic structures after being injected into embryo kidneys improved repair / recovery of kidneys with acute tubular necrosis (Zambon et al., 2014). The utility of induced pluripotent stem cells was described by Takahashi and Yamanaka (2006) in reprogramming human fibroblasts into pluripotent stem cells by the addition of four different genes: Oct3 / 4, Sox2, c-Myc and Klf4. Despite being a good source of cells, not all adult stem cells can be reprogrammed using the same method, which means that each cell type can have critical factors.

2.4. Relevance of collagen

Collagen is one of the most abundant proteins in the human body, fulfilling a fundamental role in the organization of tissues and organs. It has commonly been used collagen type I as key biomaterial in tissue engineering, while there is research focused on

oncological factors, studying the migratory behavior of cells. Oostendorp et al. (2016) developed a strategy for the detection of freshly deposited collagen on an inert surface with dermatan sulfate with the GD3A12 antibody (single-chain antibody anti-sulfate dermatan), because the identification of this deposit produced from novo by cells in a biomaterial fund is a major problem. Its application is also present in the cancer biology, because the tumor cells invade the surrounding tissues while the remodeling of the extracellular matrix is carried out, which can identify the newly synthesized collagen.

2.5. Scaffolds for chondrogenic differentiation

The extracellular matrix provides a series of stimuli that influence cellular development. In order to recover these characteristics, it has been proposed the development of 3D scaffolds as templates for regeneration in tissue engineering. The success of such scaffolds depends on the understanding of the basic interactions of the cell in question with the surrounding microenvironment. Benoit et al. (2008) demonstrated that the phosphate group bound to polyethylene glycol hydrogel allows the osteogenic induction from human mesenchymal cells, whereas the tertiary butyl groups of hydrophobic characteristics, allow the adipogenesis. The cellular response to biomaterials is complex, multifactorial and interdependent. Ahmed et al. (2015) report that soft scaffolding with intermediate hydration composed of the biodegradable product PLGA 50:50 and collagen (40:60 and 60:40) are optimal for chondrogenic differentiation of ATDC5 cells, determined by the increase in extracellular matrix production and augmentation of increased gene expression specific for cartilage.

2.6. Bone tissue: Scaffolding and biomaterial

With the increasing number of patients with osteoporosis and car accidents, it is necessary to develop and design synthetic materials for the repair of bone tissue and restitution of limb function, specifically in the sites of weight support, such as the joints of the lower limb. Within the characteristics with which an artificial graft must be fulfilled must be: structural compatibility, morphological, physical, chemical and biological properties similar to the innate, stability, durability and minimal rejection.

Xia et al. (2016) have shown that a material of Ca, Mg and Si ($Ca_2MgSi_2O_7$) induces osteogenic differentiation of osteoblasts, bone marrow stromal cells and adipose tissue stem cells in vitro, improving regeneration bone in vivo. The results demonstrated the possibility of inhibiting the expression of osteoclastogenic factors (including RANKL and TNF-alpha), facilitating the regeneration of osteoporotic bone. Scaffolds with biomaterials that have open pores and channels, are favorable for cell growth and regeneration of tissues, however, the poor inherent mechanical strength and the limit of surface activity limits its applications as load bearing bone tissue and satisfactory osseointegration. The interconnected and porous structure of the macroporous-nanowire titanium graphene oxide scaffolds provides a large surface for cell attachment and migration, as well as showing a high compressive strength of about 81.1 MPa, in addition to a Young's modulus tunable in the range of 12.4 to 41.0 GPa, meeting site-specific requirements for implantation. Cellular affinity is improved with this combination of biomaterials, allowing a unique environment that facilitates vascularization, exhibiting cellular viability with adequate proliferation, differentiation and osteogenic activity, helping tissue regeneration and support of constant loading, main functions necessary for a biomaterial that tries to replace the bone (Dong et al., 2015).

2.7. New materials

Among the novel materials for its application in the regeneration of bone tissue is the mesoporous active glass (MBG) due to its bioactivity due to its highly ordered mesoporous structure and large volume of pores with the capacity to load large quantities of drugs, biocompatibility and osteoconduction. In relation to the structure of the pore, its dimensions range from 20-400 um, which makes it ideal for cell penetration, adhesion and proliferation. Keselowsky et al. Demonstrated that -NH2 possesses the highest capacity to adsorb fibronectin compared to -CH3, -COOH and -OH, taking into account that the ability of a material to adsorb the protein is related to its functional groups. With respect to the above, it has been shown that -NH2 can induce the osteogenic differentiation of human mesenchymal stem cells (Curran et al., 2005).

Zhang et al. (2016b) fabricated a new type of MBG scaffold with amino group grafting (N-MBG) and carboxylic groups (C-MBG), comparing their performance in osteogenic differentiation against stromal cells from the rabbit bone marrow. Due to the positively charged surface, N-MBG presented greater osteogenic capacity in vitro, in addition to promoting higher levels of regeneration with a lower rate of degradation.

Within the characteristics that must have a scaffold or biomaterial is the basic expression of growth factors, which are fundamental in regulating cell proliferation and migration (fibroblasts, endothelial cells, development of angiogenesis, the formation of connective tissue, etc.) In vivo the average life of these factors is the order of minutes, due to degradation and inactivation, which could be potentially reduced by controlled-release vehicles. Butko et al. (2016) conducted a study where the growth Factor fibroblastic (BFGF) was covered by nanoparticles of chitosan (CS) with and without heparin, conducting studies of release. It was observed that the very variable release profile between the samples and as a matrix of nanoparticles contributed to the greater amount of release of BFGF during the time investigated, giving guideline to biomaterials and scaffolds that have the

regulated release of growth factors to ensure compliance with its functions.

2.8. Contributions to cancer research

Tissue and biomaterial engineering can allow the study of the molecular mechanisms of neoplasms, because they mimic the specific physicochemical properties of tumors in vivo, by recreating the three-dimensional structure of the tissues. Despite the advances in the management of scaffolding, biomaterial and induction factors, the success is relative in the prediction of cell signaling and response to pharmacological therapy, due to the failure of the exact mechanisms that interact in the living subject. McGuigan and collaborators report the application of a biocomposite tape called TRACER, which corroborated that in hypoxia, oxygen gradients are only one of the environmental factors influencing the regulation of tumor metabolism and Malignancy. Likewise, the extracellular matrix plays a fundamental role due to its structural and physicochemical properties, affecting the behavior directly by altering the mechanotransduction and indirectly by modulating phenomena of transport. The microenvironment of cancer is a biological diversity, in which the biomaterials can recreate the appropriate conditions and gradients, to elucidate the adverse parameters and to formulate appropriate managements with the constituent factors of the neoplasm (DelNero and Fischbach, 2016).

The development of technology in the present century has led to the introduction of nanoparticles and nanostructures to cancer therapy, the latter being studied as markers in targeted therapy. Elements such as nano silicon have been investigated as agents in the delivery of drugs, markers, diagnostic chips and photosensitizers against cancer cells through photodynamic therapy. Xia and collaborators created silicon nanoparticles through the electrochemical attack of a single silicon crystal, demonstrating a 45% cancer cell death against 25% cell death (Xiao et al., 2011). In comparison, Erogogbo and collaborators by generating luminous quantum points of silicon by pyrolysis followed by chemical attack until a considerable required size of the area in question is obtained (Erogbogbo et al., 2008).

Regarding its usefulness in the controlled release of medicines, Meng and collaborators developed mesoporous silica nanoparticles through the Sol-GE process, being loaded with doxorubicin and P-glycoprotein SiRNA which can help in eliminating cancer cells (Premnath et al., 2015). Glioblastoma multiforme is one of the most aggressive cancers, with an average survival of about 12 to 15 months. Currently treatment consists of surgery and radiation therapy, but it is due to its local infiltration in high-grade tumors that makes it difficult to complete resection; to which strategies have been proposed such as local drug administration, allowing the penetration of the substance in deep areas of the cerebral parenchyma (Allhenn et al., 2012). López et al. (2013) have proposed the implantation of a drug-releasing material in brain tissue for use in chemotherapy, reporting in previous studies the toxic effect exerted by structures of copper complexes in cancer cells of the brain, when they were released from a biocompatible titanium nanostructure.

In the medical area has also described the use of this type of nanostructured materials are a wide variety of molecules can perform their therapeutic activity to stay and release their assets in more specific sites, being the case of phenytoin by the use of a mesoporous matrix of silica (SBA15) and nanostructured titanium Tubes (TiO2). Phenytoin molecules stay within the mesoporous structures in both templates, in which an initial rapid release phase was identified during the first 10 hours and a later slow release.

3. Conclusion

The recognition of biomaterials based on the characteristics of their natural or synthetic origin, will guide their use for regeneration, repair or replace the function of affected tissues or organs, providing an innovative therapeutic measure with the objective of maintaining the morpho-functional characteristics, as well as to study pathological processes previously misunderstood in oncology. Currently there is intense work and scientific collaboration to achieve the manufacture of various tissues and organs through tissue engineering, in order to overcome the current disadvantages in allografts and provide a more therapeutic alternative to patients.

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