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Research review paper

Biocompatibility of hydrogel-based scaffolds for tissue engineering applications

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ABSTRACT

Recently, understanding of the extracellular matrix (ECM) has expanded rapidly due to the accessibility of cellular and molecular techniques and the growing potential and value for hydrogels in tissue engineering. The fabrication of hydrogel-based cellular scaffolds for the generation of bioengineered tissues has been based on knowledge of the composition and structure of ECM. Attempts at recreating ECM have used either naturally-derived ECM components or synthetic polymers with structural integrity derived from hydrogels. Due to their increasing use, their biocompatibility has been questioned since the use of these biomaterials needs to be effective and safe. It is not surprising then that the evaluation of biocompatibility of these types of biomaterials for regenerative and tissue engineering applications has been expanded from being primarily investigated in a laboratory setting to being applied in the multi-billion dollar medicinal industry. This review will aid in the improvement of design of non-invasive, smart hydrogels that can be utilized for tissue engineering and other biomedical applications. In this review, the biocompatibility of hydrogels and design criteria for fabricating effective scaffolds are examined. Examples of natural and synthetic hydrogels, their biocompatibility and use in tissue engineering are discussed. The merits and clinical complications of hydrogel scaffold use are also reviewed. The article concludes with a future outlook of the field of biocompatibility within the context of hydrogel-based scaffolds.

1. Introduction

Tissue engineering, a rapidly evolving field, has changed the therapeutic approach to tissue regeneration and replacement. The recent development of this field stems from reparative medicine in addition to the need for tissues and organs required for transplants. According to the U.S. Department of Health and Services, in 2009 only 28,463 patients received a transplant while over 100,000 patients remained on the waiting list (OPTN/SRTR Annual Report, 2009). Tragically, even after the transplant, patients are treated with immunosuppressants to prevent rejection of the transplanted tissue or organs for the remainder of their lives (Anderson, 2010; Marshall and Browner, 2007). This has led to the conclusion that allotransplantation is only a partial solution (Langer and Vacanti, 1999). The ideal way to circumvent these shortcomings is to use the patient's own cells or a biodegradable material which can promote the ingrowth of neighboring tissues and cells or to serve as a provisional scaffold for transplanted cells to adhere, proliferate, and differentiate within. This strategy is expected to reduce the long waiting time for organ transplants while minimizing the risk of transplant rejection and the necessity for high-risk surgery.

Consequently, this led to the creation of a new branch of research called tissue engineering, first introduced by Langer and Vacanti

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(Langer and Vacanti, 1993; Russell and Monaco, 1964). This interdisciplinary science arose from the combination of cell and developmental biology, basic medical and veterinary sciences, transplantation science, biomaterials, biophysics and biomechanics, bioimmunology and biomedical engineering (Langer and Vacanti, 1993; Lee et al., 2001). Expertise from these fields combined to undertake the immense task of creating living tissues from only a few cells and combining them with biomaterials such as poly(ethylene glycol)(Viola et al., 2003; Zhu, 2010), collagen (Gorgieva and Kokol, 2011), poly(lactic acid) (Majola et al., 1991) or de-cellularized extracellular matrix (ECM) (Badylak, 2004; Sreejit and Verma, 2013). These biomaterials can be used to compensate for donor shortages and allow patients a faster recovery time with fewer complications, increasing quality of life (Slaughter et al., 2009).

The key characteristic that differentiates biomaterials from other materials is their ability to coexist and interact in the presence of specific tissues or physiological systems such as blood, interstitial fluids, and immune cells and molecules without inflicting an intolerable amount of damage (Tronci, 2010). A key concept in tissue engineering is selecting the proper biomaterial to design and produce an appropriate scaffold which induces no or minimal immune reaction from the recipient. Following recent technological advances and interests for the design and development of engineered biodegradable scaffold systems, tissue engineering has moved into a modern innovative era. Nevertheless, many, or perhaps most, of these bioengineered systems are being challenged mainly due to a lack of adequate data regarding their toxicity and biocompatibility.

Key to understanding biocompatibility is the comprehension of which chemical, biochemical, physiological, physical or other mechanisms are activated by the contact of the biomaterial with the cells in the body and also to understand the consequences of these interactions (Williams, 2008a). Herein, this paper's focus is to collect and review existing knowledge on the biocompatibility of hydrogel-based scaffolds.

2. Biocompatibility

Biocompatibility is a field that first attracted the attention of researchers in the 1940s in the context of medical implants and their beneficial and harmful interactions with the body. In 1987, biocompatibility was formally defined as "*the ability of a biomaterial to perform with an appropriate host response in the specific application*" (Naahidi et al., 2013; Williams, 1986). In 2010 Kohane and Langer explained biocompatibility in a new context and redefined it as "*an expression of the benignity of the relation between a material and its biological environment*" (Kohane and Langer, 2010; Naahidi et al., 2013). There is a wide variety of biomaterials that are used in tissue engineering that can generally be categorized as natural materials (derived from autologous (Williams, 2008b), allogenic (Chu et al., 1997; Williams, 2008b), or xenogenic (Anderson, 2001; Böstman et al., 1992) sources) and synthetic materials, or a blend of both types called hybrid materials (Bokhari et al., 2005; Kopeček, 2007). These materials can be processed and manipulated such that they have functional properties which form porous scaffolds that can be used for the restoration or modification of tissues (Anderson, 2010). These functional properties are the ultimate goals for biomaterial-based devices *in vivo* and include: restoration of the tissue with appropriate function and cellular phenotypic expression, inhibition of macrophage and foreign body giant cell responses that will degrade the material, inhibition of scar formation that may inhibit the function of the biomaterial, and lastly, inhibition of immune responses that could destroy the functionality of the device (Anderson, 2010; Yang et al., 2008). In the past, tissue engineering has attempted to create materials that will control the fate of the transplanted cell populations included in tissue reconstruction (Hwang et al., 2006; Jeong et al., 2006; Langer and Vacanti, 1993; Miroshnikova et al., 2011; Viola et al., 2003). However, cellular interactions have proven to be extremely complicated and consequently, today researchers have shifted their focus from creating bioactive materials to materials which give greater control over inflammatory and immune responses to reduce the chance of rejection in patients (Ishihara et al., 2010; Ratanavaraporn et al., 2012; Tongers et al., 2011). As a result the long-term co-existence of biomaterials and tissues has been the goal of many scientists. As such, biomimetic strategies taken from nature, such as the mechanisms viruses and bacteria use to evade the immune system, are being developed to create immune invisible biomaterials (Novak et al., 2009). Generally, once a biomaterial has been implanted, the body responds with one or more positive and/or negative reactions. These include blood interactions (hemolysis) (Amarnath et al., 2006; Anderson, 1993), stem cell interactions (Korkusuz et al., 2016), provisional matrix formation (Anderson, 2010; Bélanger and Marois, 2001), temporary inflammation (Clark et al., 1982), wound healing (Clark et al., 1982; Yang et al., 2008), the formation of granulation tissue (Anderson et al., 2008; Tabata et al., 1994), foreign body reaction (Anderson et al., 2008; Böstman et al., 1990) and oxidative stress (Mouthuy et al., 2016). Further, tissue engineered devices can develop a fibrous capsule (scar) that can either surround the implant or infiltrate the porous material (Anderson, 2010). In addition, the body could develop an acquired or innate immune response to the biological component of the device, potentially rendering the biomaterial useless (Anderson, 2010). Therefore, a novel and ideal equation was suggested to quantitatively express biocompatibility (Ratner, 2016). Another problem with preliminary biomaterial testing is that the biomaterial-based implants are generally tested on non-human tissues (*i.e.* rat, mouse or dog). As a result, species-specific immune responses could be triggered when an engineered tissue that is meant for human is tested using a different species or a device tested in other animals is applied in humans. Ideally, the engineered tissue would be made using cells or components from one species and subsequently tested using that same target species. This approach would greatly decrease the probability of an immune response, although it does not completely guarantee the absence of one. As a specific example, Harriger et al. used glutaraldehyde-cross-linked bovine collagen as a scaffold to seed human keratinocytes and fibroblasts and then subsequently placed them on full-thickness wounds of athymic mice (Harriger et al., 1997). The work showed that glutaraldehyde crosslinking resulted in a decrease in the rate of degradation of collagen with no change in immunoreactivity in mice, as measured by HLA-ABC staining. However, this does not guarantee that such an implant will work clinically since athymic mice lack a thymus gland resulting in an inhibited immune system and a low number of T-cells capable of initiating responses.

The goal of evaluating the biocompatibility of any material is to determine any toxic effects to the body. Therefore, a biomaterial must be evaluated to determine the biological responses which could cause damage or unwanted side effects to the host (Anderson, 2010). The three major responses that should be taken into account are: inflammation, wound healing, and the immunological reaction/immunotoxicity (Anderson, 2010). Although standards for biological evaluation of medical devices (ISO:10993) have been published by the International Organization for Standardization, the biocompatibility of a substance can also be affected by other factors such as the nature and quality of the medical intervention, the age, sex, genetic background and health of the patient, as well as the presence of any microorganisms or endotoxins (Kohane and Langer, 2010). Therefore, the Standard Practice for "Evaluation of Immune Responses in Biocompatibility Testing of ASTM" (American Society for Testing and Materials) was withdrawn in 2011 due to its limited protocols with no replacement to date. It is hard to unify a standard approach with the development of implantable materials (Reeve and Baldrick, 2017).

Taken together these data suggest that by using a biocompatible design based on designs seen in nature, advanced biomaterials can be generated to increase efficacy and lifespan of the implant (Novak et al., 2009). Therefore, tissue engineering would be enhanced upon the