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Research review paper

Three-dimensional biomaterial degradation — Material choice, design and extrinsic factor considerations

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ABSTRACT

The apparent difficulty to precisely control fine-tuning of biomaterial degradation has initiated the recent paradigm shift from conventional top-down fabrication methods to more nature-inspired bottom-up assemblies. Sophistication of material fabrication techniques allows today's scientists to reach beyond conventional natural materials in order to synthesise tomorrow's 'designer material'. Material degradation into smaller components and subsequent release of encapsulated cells or cell-signalling agents have opened medically exploitable avenues, transforming the area of regenerative medicine into a dynamic and self-propagating branch of modern medicine. The aim to synthesise ever more refined scaffolding structures in order to create micro- and nanoenvironments resembling those found in natural tissues now represents an ever growing niche in the materials sciences. Recently, we have developed and conducted the world's first in-human tracheal transplantation using a non-degradable completely synthetic biomaterial. Fuelled by such clinical potential, we are currently developing a biodegradable version suitable for skin tissue engineering and paediatric applications. However, despite enormous efforts, current, as yet insurmountable challenges include precise biomaterial degradation within pre-determined spatial and temporal confines in an effort to release bio-signalling agents in such orchestrated fashion as to fully regenerate functioning tissues. In this review, the authors, almost anti-climactically, ask the readers to step out of the artificially over-constructed spiral of ever more convoluted scaffold fabrication techniques and consider the benefits of controllable bottom-up scaffold fabrication methods. It will further be investigated how scaffold designs and fabrication methods may influence degradation and subsequent release of incorporated elements. A focus will be placed on the delivery of growth factors, stem cells and therapeutic agents alone or in parallel. The difficulties of designing a delivery vehicle capable of delivering multiple factors whilst maintaining distinct release kinetics will be highlighted. Finally, this review will be rounded off with an insight into current literature addressing the recurring issues of degradation product toxicities and suggests means of overcoming those.

Contents

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Introduction

The apparent difficulty to precisely control fine-tuning of biomaterial degradation has initiated the recent paradigm shift to gradually replace conventional top-down fabrication methods with nature-inspired bottom-up assemblies. Traditionally, top-down approaches involving direct cell seeding into pre-made porous scaffolds are limited by slow vascularization, slow diffusion and low cell density as well as non-uniform cell distribution. Bottom-up fabricated scaffolds, on the other hand, benefit from controllable modular assemblies of cell-laden components, thus potentially eliminating the shortcomings of the traditional approach (Tiruvannamalai-Annamalai et al., 2014). Such sophistication of material fabrication and construction techniques allows today's scientists to reach beyond conventional natural materials in order to synthesise tomorrow's 'designer material'. Biodegradable materials have undergone extensive research and represent a popular platform for tissue engineering bone (Cui et al., 2012), skin (Yildirimer et al., 2012), cardiovascular tissues (Ahmed et al., 2011; de Mel et al., 2008; Ghanbari et al., 2009; Salacinski et al., 2003) and nerves (Kannan et al., 2005; Pabari et al., 2011; Sedaghati et al., 2011; Tan et al., 2012) amongst many other organs and tissues. Conceptually, degradation is defined as a molecular change due to chemical chain scission within a polymer matrix. The subsequent breakdown into smaller material components and potential release of encapsulated cells or cell-signalling agents have opened medically exploitable avenues, transforming the area of regenerative medicine into a dynamic and self-propagating branch of modern medicine. The aim to synthesise ever more refined scaffolding structures in order to create micro- and nanoenvironments resembling those found in natural tissues now represents an ever growing niche in the materials sciences. Despite enormous efforts, current, as yet insurmountable challenges include precise biomaterial degradation within pre-determined spatial and temporal confines in an effort to release bio-signalling agents in such orchestrated fashion as to fully regenerate functioning tissues. It thus appears almost anti-climactic to be asked to step out of the artificially over-constructed spiral of ever more convoluted scaffold fabrication techniques and consider the benefits of controllable bottom-up scaffold fabrication methods.

Tissue engineering scaffolds — a bottom-up approach

Tissue engineered scaffolds aim at recuperating lost tissues by guiding cell growth and restoring original tissue architecture whilst gradually degrading into non-toxic by-products. A bottom-up fabrication approach presents several benefits over top-down synthesised scaffolds including (a) a tight control over scaffold architecture down to nanometre dimensions, (b) an ability to incorporate appropriate bioactive factors and stem cells into the scaffold matrix and (c) modulate the mode and rate of scaffold degradation by combining two or more materials exhibiting different degradation patterns. Such that simple and elegant bottom-up combinations may result in staggered material breakdown resulting in the controlled release of incorporated regenerative cues. This approach has found particular resonance in the field of regenerative medicine and controlled particle delivery where breakdown of the delivery vehicle permits particle release and action whilst maintaining a structurally intact 3-dimensional scaffold for tissue ingrowth (Fig. 1) (Biosciences, 2013; Seras-Franzoso et al., 2013; Shmueli et al., 2013; Y. Chen et al., 2011). During unassisted wound healing, cells and cell components release a myriad of trophic factors including growth factors (GF), cytokines and other molecules to minimize wound dimensions and induce spontaneous healing (Yildirimer et al., 2012). However, natural healing is frequently accompanied by scar formation, functional and cosmetic compromise. Accelerated in situ tissue regeneration using scaffold structures supplemented with tissue-specific trophic factors is hoped to be able to induce complete scar-free tissue regeneration with preservation or restoration of function. The major determinants in elucidating the complicated molecular cascade required for true regeneration are (a) finding the correct cocktail of GFs capable of stimulating suitable cellular differentiation and (b) unlocking the correct sequence of GF release.

To date, the delivery of multiple bioactive factors with distinct kinetics to mirror physiological processes remains a challenge (Chapanian and Amsden, 2010; Cheng and Sefton, 2009; Richardson et al., 2001; Weissman, 2000; Yan et al., 2009). Initial studies demonstrated the use of a multi-protein delivery system for accelerated vascularisation and tissue formation in an effort to mimic the synergistic action of cell-signalling molecules (Richardson et al., 2001). Poly(lactide-co-glycolic acid) (PLGA) microspheres encapsulating both vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) were processed into porous scaffolds which were implanted into a murine hindlimb ischaemia model. Dual delivery of GFs resulted in both a high blood vessel density and the formation of thicker and more mature vessels exhibiting typically multilayered structures when compared to vessels exposed to single GFs. Further, the ability to modulate release kinetics for sustained or successive release of bioactive molecules has been found to be of fundamental importance for functional tissue formation (C. Chen et al., 2011). It is generally accepted that in order for regenerative cues to function precisely, their release and activity are subject to a critical window. If release kinetics are timed correctly, natural regeneration of tissues ensues; if released outside this window, previously incorporated biological agents may potentially have antagonistic actions rendering localised factor delivery futile or even harmful.

Richardson's study exemplifies the two main modes of release kinetics of biological molecules incorporated into delivery vehicles (Fig. 2) (Richardson et al., 2001). Mixing of molecular agents with the material before processing into a 3-dimensional scaffold results in the factors being largely associated with the material surface and are thus subject to rapid release. In contrast, pre-encapsulation of molecular agents into polymeric microspheres and subsequent mixing and casting into a scaffold are thought to yield a more even distribution of agents throughout the scaffold with release regulated by material degradation kinetics. A combination of both methods can predictably result in a distinctly multiphasal release profile of more than one factor.

Determinants of scaffold degradation kinetics

Release kinetics may further be influenced by external conditions including temperature (Esteban et al., 1990), presence of a degradative environment (e.g. hydrolytic or oxidative), pH of fluid environment and fluid dynamics surrounding the delivery vehicle (Agrawal et al., 2000). It has further been demonstrated that scaffold degradation kinetics and potential release of adsorbed bioactive molecules can be affected by scaffold-intrinsic features such as porosity, pore size and shape and overall design (Moroni et al., 2008; Yang et al., 2001). It was further suggested that scaffold hydrophilicity may actively influence the extent to which water can diffuse through the scaffold, thereby directly affecting the release kinetic of any molecules adsorbed to the scaffolds (Xu et al., 2013). Precise molecular bottom-up assemblies warrant further and more varied modes of degradation ranging from bulk degradation or surface erosion to more specific and complex designer scaffolds capable of degrading within precise temporo-spatial confines. Degradation rates and mechanisms are primarily influenced by matrix dimensionality, manner of assembly and consequent water penetration efficiency. If water molecules penetrate the 3-dimensional architecture at a higher rate than natural hydrolysis takes place, e.g. potentially influenced by scaffold porosity, thickness and exposed surface area, degradation proceeds throughout the entire material matrix resulting in uniform or 'bulk' degradation. On the contrary, if water permeation is slow, hydrolytic erosion will mainly occur on the exterior surface. The internal matrix remains largely unchanged thus allowing for temporary shielding of any core-integrated trophic factors. The conceptual integration of rapidly and slowly degrading entities within the same scaffold assembly,