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Difficulties in the Translation of Functionalized Biomaterials into Regenerative Medicine Clinical Products

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Abstract

There are many ways to influence cell activities, and biomaterials with functional groups attached is an attractive method that clearly has the ability to modulate cell behavior. The evidence is clear that biomaterials, with or without growth factors and cells, have resulted in numerous products for the regenerative medicine field. In contrast the functionalized biomaterial products remain in the development phase.

1. Introduction

The primary importance of tissue engineering and regenerative medicine is the opportunity to impact the treatment of patients, either to improve on already available therapy or to address previously unmet clinical needs. A measure of value for a technology in this field therefore can be the impact that technology has had, or may have on clinical treatments. The objective here is to discuss the value that biomaterials, with and without functional biomimetic groups, have brought to clinical treatment in the tissue engineering and regenerative medicine fields.

2. Biomaterials with Functional Biomimetic Groups

Biomaterials, either alone or in combination with other factors (active groups, soluble mediators, cells) are an integral component of the products that have been made, and continue to be developed, in the field. As a subset of the biomaterials toolbox, the use of functional sequences or groups (or even complete signaling molecules) attached to a biomaterial to modulate cell behavior is scientifically attractive. The use of biomaterials without addition of alternative functional components can frequently be relatively mundane. However, it is interesting to assess these different approaches to regenerative medicine in terms of products that have been brought to market and are having an impact on patient care.

The addition of functionalized biomaterials has been demonstrated to have the capacity to modulate cell activities. Components of the extracellular matrix (proteins, carbohydrates), together with soluble mediators and other regulatory molecules, can control or direct cell function, and this capacity has been demonstrated even when attached to materials, modifying the structures to become biomimetic. An early example is the use of the RGD peptide, found in many cell adhesion proteins and binds to integrin receptors on a wide variety of cell types [1]. Cell differentiation has been modulated successfully, by the collagen I-derived GFOGER peptide attached to a hydrogel and supporting osteoblast

differentiation, and the peptide P-15 from collagen I attached to hydroxyapatite increased osteogenic activity of mesenchymal stem cells [2]. BMP2 as a complete molecule, or a fragment of the factor, when attached to a scaffold or solid surface has enhanced osteoblastic activity [3] and bone repair [4]. The attachment of VEGF to gelatin scaffold induced endothelial cell proliferation [5]. These and many other examples serve to demonstrate the feasibility of the approach.

The efforts to translate this technology to product began in the early 1990's, in particular by the company Telios, who used the RGD peptides, including peptides attached to scaffolds [6] in a series of studies with clinical targets including wound healing, ophthalmic treatments, and coatings for implants. Unfortunately their efforts to advance the technology to products were not successful, and to date commercialization of the biomaterial-functional group technology has not been successful.

3. Biomaterials as Cell-Modulating Matrices

Biomaterials that have capacity to direct cell activities are numerous, and many have become products that are of substantial value in regenerative medicine. An early example is calcium phosphate and its carbonate-rich hydroxyapatite; they are a major component of bone and teeth, and as a biomaterial in tissue repair have been used because of their ability to bind to bone and support osteoconduction. Since the early 1970's calcium phosphate ceramics have been used in dentistry to support mandibular bone growth and repair, and in the 1980's it has been used in orthopaedics [7]. Today it is commercially available in many forms, and is used to coat prosthetics to assist in attachment, as a bone void filler, spinal fusion, and for fracture repair. The various products appear to be a staple for many orthopaedic companies, large and small. Alternative biomaterials have also been used for bone repair, including bioglass [8], which has been used over decades for non-loadbearing bone related repair, and continues to be developed into next generation bone-related products.

The use of a natural extracellular matrix (ECM) has been particularly successful in modulating complex cell activities in the field of regenerative medicine. ECMs consist of a variety of molecular components, including collagens, non-collagenous proteins (for example fibronectin, elastin, fibrin) and glycoproteins and proteoglycans. These components can modulate cell attachment, proliferation, migration, differentiation, matrix deposition and organization, and secretion of agents responsible for a vast array of cell activities that may result in tissue repair and regeneration.

An early example of ECM being used commercially is Biobrane, a silicone-nylon sheet to which collagen is bound, and is used to treat wounds including burns [9,10]. The material acts relatively passively but the collagen does appear to play an active supporting role in encouraging some aspects of the wound repair cascade. A more complex ECM is presented to a wound by the product Transcyte, formed by human dermal fibroblasts depositing an ECM onto a membrane, and then the cells are removed by freezing. This product has had remarkable success in use for treatment of third and second degree burns [11,12], with the complex ECM presumably functioning by supporting a wound repair cascade.

A variety of ECM-based products are now being used clinically to support cell attachment and a variety of cell activities, with the ECM being derived from various tissues including skin, intestine wall, bladder wall, and perichondrium. These ECM products are primarily used to support soft tissue repair during surgery.

The combination of scaffold, ECM and live cells has added a new dimension to the ability of the product to influence wound repair. Dermagraft and Apligraf both contain functional

dermal fibroblasts, and the products are used to treat hard-to-heal and chronic wounds [13,14]. The cells appear to play an active role in the repair of these wounds, assisted by the ECM and supported by the relatively inert scaffolds [15].

The most widely used and commercially successful tissue engineering product is Infuse, a combination product consisting of the growth factor BMP2 embedded within a collagen mesh, used for spinal fusion [16], inducing mandibular bone growth [17] and fracture repair [18]. The collagen mesh was found to be important in regulating release of the growth factor, and the BMP2 has been revolutionary in inducing new bone formation.

4. Commercialization of Products for Regenerative Medicine

There are many features of biomaterials, ECMs, cells, active molecules and functional groups that present interesting and functional properties of potential value to regenerative medicine. However, translation of one or more of those features into a product that can be used clinically involves a new set of challenges frequently overlooked when research is the primary objective. A ‘rule of thumb’ is that the more complex the product the more challenges there will be to overcome before regulatory agencies allow a product to be used. The more complex product designs will invariably be more expensive to manufacture and therefore more difficult to motivate investment. Biomaterials with functional attachments represent a relatively complex product concept with obvious biologic features, compared to biomaterials without those added complexities. The costs associated with the technical hurdles, timelines and regulatory challenges may be difficult to motivate, the commercial opportunity may be lost. In comparison, a relatively simple biomaterial may face a straightforward and rapid pathway to market, requiring less investment and shorter development time.

5. The Future

New regenerative medicine concepts will continue to be developed, and clinical need and market opportunity will rationalize what ultimately will be developed into product. It seems likely that the biomaterial-functional group set of potential products may result in some new products, but their introduction will be slow. In contrast, biomaterials that have the capacity to modulate cell activities will continue to be introduced relatively quickly, addressing the easier clinical issues, and leaving the more complex problems to the more complex products.

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