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Perspectives on the interface of drug delivery and tissue engineering ☆

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ABSTRACT

Controlled drug delivery of bioactive molecules continues to be an essential component of engineering strategies for tissue defect repair. This article surveys the current challenges associated with trying to regenerate complex tissues utilizing drug delivery and gives perspectives on the development of translational tissue engineering therapies which promote spatiotemporal cell-signaling cascades to maximize the rate and quality of repair.

Contents

1. Introduction

Motivated primarily by a desire to improve our general quality of life, tissue engineers have sought for two decades to provide materials-based therapeutic solutions to enhance the rate and quality of tissue defect repair or regeneration. The prevailing paradigm combines the development of appropriate scaffolding materials with the co-delivery of seeded or encapsulated cells and signaling molecules such as peptides and proteins [1]. Within tissue engineering, nearly all applications of drug delivery involve the localized release of molecules of varying sizes and/or co-delivery of entire cells. Delivery schemes have ranged from simple matrix-embedding and encapsulation of drug-loaded microparticles to controlled and stimuli-responsive drug release to immobilization and covalent attachment of drugs to the scaffolds. We first briefly discuss drug delivery applications within each of five current primary challenges in tissue defect repair before turning to our perspective on where the field of tissue engineering research is generally headed.

The most studied application of drug delivery in tissue engineering has long been concerning efforts to induce cells, either recruited from the surrounding host tissue or co-delivered within the scaffold to the defect site, to differentiate down the desired lineage. General and recent reviews on the methods and efficacy of tissue engineering are available for specific topical areas, including bone [2], cartilage [3], neural [4], cardiovascular [5], and general soft tissue regeneration [6].

An emerging application of drug delivery concerns the modulation of the immune and inflammatory response to the implanted scaffold. While it has long been obvious that prolonged inflammation and aggressive foreign body responses due to implanted tissue engineering constructs is extremely detrimental to the successful regeneration and integration of new tissue, only recently has the field come to an understanding that early inflammatory processes within the first week of wound healing can be quite beneficial to the ultimate quality and rate of tissue repair [7]. Current efforts seek to

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modulate and harness the inflammatory process to enhance the rate of tissue regeneration in bone defects using controlled drug delivery [8].

When engineering regeneration strategies for vascularized tissues, the promotion of appropriate angiogenesis must also be considered; as generation of a local blood vessel network that is connected to the host supply is critical for sustained nutrient delivery and tissue functionality. Recent investigations have shown that angiogenesis can be significantly impacted by the mechanical properties of the implant as well as external mechanical stimuli [9]. While these methods likely stimulate local cell populations to generate angiogenic signals, more common approaches involve the localized controlled delivery of such angiogenic factors [10]. One promising avenue of current research involves the creation of three-dimensional perfusable vascular networks, around which a wide array of implantable tissue engineering constructs can be created [11].

While successful angiogenesis in tissue engineering constructs for vascularized tissues such as bone can have the added benefit of promoting integration with the surrounding environment, the complete and functional integration of implants with the native tissue remains a major challenge in avascular and soft connective applications such as cartilage and neural tissues. The current clinical approach is generally to promote integration with sutures or tissue adhesives, such as fibrin glue; however such approaches often display poor biocompatibility and bonding strength, particularly in cartilage applications. Currently evolving approaches to promoting tissue integration include the delivery of peptides and proteins, use of tissue-adhesive interfacial layers, and the development of adhesive structural architectures [12].

Finally, as the field moves toward clinical translation of tissue engineering therapies, the prevention and potential complicating effects of wound infection must be considered. For example, in bone tissue regeneration applications, the challenges associated with infections include decreased blood flow, reduced nutrient delivery, and the formation of necrotic tissues and/or pus [13]. While systemic delivery of antibiotics to treat infections can have a positive impact, there is a need for enhanced localized controlled delivery strategies within a tissue engineering construct to treat and/or prevent infection without negatively impacting the regeneration of new tissue [14,15]. In addition, many tissue engineering applications may require still more advanced drug delivery strategies to combat the formation of antibiotic-resistant biofilms [16].

2. Spatiotemporal control

While each of these complexities have been addressed with varying degrees of success individually, the grand challenge in tissue engineering research going forward is creating therapies capable of addressing each of them in an appropriately controlled manner. A complication in general and in drug delivery strategies in particular is the potential for drug interactions and cross effects. For instance, while preventing infection and prolonged inflammation is critical for translation to wound healing applications, delivery of antibiotics and anti-inflammatory agents can have negative impacts on other regenerative processes, such as reducing the efficacy of osteogenesis in bone tissue repair [17]. Furthermore, a particular drug can have both positive and negative effects on tissue regeneration, depending on the stage of cellular differentiation down a particular lineage. Thus, not only must the drug cocktails to be delivered in a tissue engineering therapy be carefully selected, but a time-dependent drug delivery cascade sequence must be engineered. Early time prevention of wound infection, promotion of beneficial inflammatory processes, and induction of angiogenesis must be followed by longer-term cell proliferation, differentiation, and production of tissue-specific extracellular matrix (ECM). While this can be accomplished to a degree by use of composite scaffolding materials with drugs loaded into varied microparticles for passive release at differing rates, more effective strategies may involve tissue-specific, stimuli-responsive drug delivery.

In addition to temporal control, spatial control of drug delivery will be essential in many cases. In particular, the regeneration of articular cartilage is a major challenge due to the gradient nature of this highly avascular tissue [18]. The majority of cartilage regeneration strategies thus far have led to production of inferior fibrillar cartilage, which lacks the highly organized gradient structure of articular cartilage. Creating concentration gradients of delivered growth factors is one promising strategy to improve functional tissue repair and can potentially be accomplished through gradient incorporation of drug-releasing microparticles or reservoir delivery within multi-layered constructs. Beyond regeneration of simple tissue defects, the realities of clinical applications will necessitate tissue engineering strategies to regenerate complex and inhomogeneous defects [1]. Spatially compartmentalized and/or gradient drug delivery will be essential in successful therapies for such defects. For instance, bilayered scaffolds with compartmentalized drug delivery are being investigated for regeneration of osteochondral defects, where both bone and cartilage must be regenerated in their respective domains for functional repair [19]. Furthermore, spatially-controlled drug release will be an important tool to minimize the quantities of drugs to be used and delivered, both to mitigate potential effects in surrounding tissues and to reduce overall cost.

3. Translation is key

While there are a multitude of essential and interesting research questions still to be answered in the use of complex drug delivery strategies for specific tissue regeneration applications, in particular the establishment of appropriate and effective spatiotemporal drug release cascades, researchers must also keep an eye toward the potential translation of such therapies to clinical use. With the emergence of FDA-approved and commercially successful tissue engineering therapies, the field has begun to move beyond initial scientific discovery. However, the more complex these therapies are made, particularly concerning the number and quantity of drugs to be delivered, the more challenging translation will become. Several recent reviews highlight the regulatory pathways available for and the challenges associated with translation of orthopedic [20–22] and heart valve [23] tissue engineering products.

In addition, the likelihood of patient-to-patient variability needs to be considered in an effort to design robust tissue engineering strategies that can either be easily tuned at the clinical stage as needed or are capable of adapting or overcoming variability in the surrounding tissue environment. Whether this will be most successfully accomplished with more simple or more complex strategies remains to be seen. For example, we have already discussed the importance of the inflammatory immune response in the healing process of tissue defects, however what happens if the patient is immune suppressed or has a hyperactive immune system due to any number of complications, most notably autoimmune and inflammatory diseases? Will the same therapy still work or can it be easily modulated at the clinical stage to suit the needs of a particular patient? While general therapeutic strategy development must initially target ideal conditions for a typical patient, the ultimate robustness and/or tunability of the tissue engineering strategy in a clinical setting is something to consider.

A current widely-pursued approach to increasing the regenerative efficacy of therapies is to co-deliver cells in the scaffolding material. With either the release of appropriate growth factors or the presence of appropriate cell-signaling capability within the scaffold, the cells can act as local drug depots potentially capable of controlling over time the appropriate signaling cascades. New techniques which label cells to allow for long-term *in situ* monitoring of cell fate, including