Advanced Drug Delivery Reviews 149–150 (2019) 1

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Sequential drug/gene delivery in tissue engineering & regenerative medicine

Sing Yian Chew [a,b]

[a] School of Chemical and Biomedical Engineering, Nanyang Technological University, Singapore 637459, Singapore
[b] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore 308232, Singapore

Tissue growth and regeneration require a combination of complex biological signaling. As such, the simultaneous delivery of combinations of biological factors has been evolving in the field of drug and gene delivery for regenerative medicine. However, as our biological understanding of the process of tissue regrowth and restructuring evolves, we recognize that many of these physiological processes happen in a step-by-step and temporally defined fashion. Therefore, it is important to recognize that it may be insufficient to merely deliver a single molecule or a cocktail of critical biological molecules simultaneously at one go, in hope to enhance tissue regeneration. Instead, the intricate timing and duration by which a biochemical signal needs to be followed by another, should be taken into account throughout the tissue regeneration process. In fact, failure to recognize this temporal factor, may in some circumstances, lead to detrimental effects, such that a particular biologic that is delivered at the wrong time may antagonize other factors that are critical at earlier stages of regeneration [1].

While biologists have helped advance our understanding in the involvement of cells and expression of biological factors during tissue development, homeostasis and pathogenesis, the translational use of this knowledge to engineering approaches in regenerative medicine remains limited. With this in mind, this theme issue has been constructed to combine 1) the knowledge of the sequence of events that occur during the natural development, reparative and/or regenerative processes of various tissues and organs after degeneration or trauma/injury with 2) engineering knowledge and approaches of controlled and sequential delivery of drugs and genes to mimic these natural biological processes.

A major difference between sequential delivery vs. combined delivery (as commonly seen in the literature) is the temporal component (i.e. the time sequence by which different biochemical signals should be introduced for ideal regeneration). Depending on the target tissue and organ, unique requirements exist. Many of these sequential events require strong biological understanding before engineers may decide what, when, where and how such biological factors may be delivered to suit the temporal requirement of that particular system.

In this theme issue, starting from the ectoderm, Becker, *et al.* [2] and Chew, *et al.* [3] highlight the importance of sequential biochemical signaling and drug/gene delivery on skin and neural tissue regeneration respectively. Next, a case example of intervertebral disc regeneration, representing a tissue from the mesoderm is presented by Le Visage, *et al.* [4]. Liver tissue regeneration within the endoderm is then discussed by Yu, *et al.* [5]. Importantly, many regenerative approaches involve the reconstruction of tissue architecture, which are largely enabled by scaffold implantation. Hence, this theme issue also covers in detail, the considerations of sequential delivery of biological factors to mediate the foreign body response and improve host-implant integration (Spiller *et al.* [6]), along with directing angiogenesis and blood vessel regrowth (Gerecht *et al.* [7]).

Here, each topic area includes a detailed account of the physiology and problems of healing in an organ-/system-specific manner. In each article, the potential temporal requirements for a regenerative regime is speculated for efficient regrowth of tissues and normalizing diseased conditions. With these spatial and temporal requirements in mind, the authors also suggest potential biomaterials, scaffold designs and drug delivery considerations that are optimal for each system.

Altogether, to achieve sequential drug/gene delivery, one requires knowledge on the development of biological processes. Additionally, one should take into account the practical and translational considerations that are necessary for engineering scaffold designs to achieve temporally controlled sequential delivery of drugs. Through the articles in this theme issue, these unique aspects and requirements for different tissues, organs and biological systems are highlighted. It is hoped that through the collection of these articles, tissue engineers will be inspired to venture into new methods to achieve more biomimicking and temporally defined presentation of biochemicals to provide more efficient treatments for patients.

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https://doi.org/10.1016/j.addr.2019.11.007
0169-409X/