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Review Article

Regenerative Immunology: Pushing Biomaterials Beyond Tissue Repair

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ABSTRACT

In this short review, we discuss how the paradigm in the development of new biomaterials has shifted over the last years and the growing idea that the immune system is of key importance in an effective tissue repair and regeneration. The immune system is currently considered crucial for tissue regeneration, leading to the emerging concept of Regenerative Immunology.

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Introduction

Great progress has been achieved in the use of new biomaterials as scaffolds to repair human tissues and organs. The final purpose of these new biomaterials is to replace defective tissues and/or organs restoring their functions. This ambitious purpose requires perfect biomaterial integration in host tissues together with the ability of restoring function.

Recent advances revealed that the immune system plays a key role both in repair and in regeneration, since immune cells signal through several proteins, either secreted or expressed at their cell surface, and thus modulate tissue repair, for example by stimulating local stem and progenitor cells [1-3]. Different cells of the immune system as well as their secreted cytokines, have been associated to the promotion of tissue regeneration [4]. In fact, in the absence of immune cells, tissue repair is often impaired; a clear example of this phenomenon is the inability of salamanders to regenerate cut limbs without the presence of macrophages [5].

The growing idea that the immune system is also crucial for tissue regeneration supports the emerging concept of Regenerative Immunology i.e., the modulation of the immune system as a tool to rebuild tissues. Thus, new strategies of a biomaterial-directed immune engineering aiming at tissue regeneration are emerging [6, 7]. We are now witnessing a shift in the strategy to develop new biomaterials that modulate the immune response, the so-called Immunomodulatory Biomaterials. In fact, biomaterial innovation is now being pushed to foster endogenous healing and regeneration of tissues, in addition to stimulate the host immune response. We are at the beginning of the creation of the next generation of biomaterials, the Regenerative Biomaterials, those able to promote a pro-regenerative microenvironment at the site of implantation. A clear understanding of the host innates and adaptive immune responses, and their influence in tissue repair and regeneration, is crucial for the development of this next generation of biomaterials [2, 8, 9].

Different strategies have been proposed in this new era of engineering immunomodulatory biomaterials, such as: i) tuning chemical or physical properties of the biomaterial; ii) incorporation of either pro- or anti-inflammatory agents; iii) cell-therapy approaches with the inclusion of immune cells or with the induction of recruitment of these cells upon implantation [10, 11].

The research areas of vaccine development and cancer immunotherapy have greatly helped the development of new biomaterials to engineer the immune system [12]. A few recent successes of this new era of

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regenerative immunology are recalled in the next sentences. Yin *et al.* documented the beneficial effects of biological scaffolds derived from the extracellular matrix (ECM) in corneal wound healing [13]. These ECM immunomodulatory particles reduced inflammatory gene expression, restored tear film production *in vitro*, and reduced scar formation and fibrosis genes in the wounded cornea when they were applied *in vivo*. García *et al.* engineered an injectable synthetic hydrogel with tethered recombinant interferon (IFN)-γ that activated encapsulated human mesenchymal stem cells (hMSCs) thus increasing their immunomodulatory functions [14]. It was underlined that the hMSCs encapsulated in IFN-γ-presenting hydrogels exhibited significantly higher levels of mucosal wound closure compared to untreated controls, as well as wounds treated with hMSCs in hydrogels. In the context of bone tissue regeneration Lee *et al.* have extensively reviewed the biomaterial-driven strategies for modulation of the crosstalk between immune response and osteogenesis [15]. Recently, an important study of Sadtler *et al.* demonstrated divergent myeloid response to biological versus synthetic biomaterial scaffolds, being the biological scaffolds associated with a type-2-like immune response and suggesting a potential role of danger associated molecular patterns (DAMPs) in the pro-regenerative immune activity of these scaffolds [16].

A new and exciting area of innate immunity has been associated with the recent discovery of the inflammasomes. They are intracellular multiprotein complexes that assemble after recognition of pathogens or danger signals and are regulators of the production of the pro-inflammatory cytokines interleukin (IL)-1β and IL-18 [17]. Activation of inflammasomes can go both ways: either run a well-defined and limited course, with resolution of inflammation and healing of the injury, or is continuous, resulting in chronic disease or fibrosis [18]. Thus, inflammasomes are regulators of the type of inflammatory response and of the ensuing tissue repair and regeneration [19]. Discoveries emerging from investigating inflammasome biology promise insights into different pathways regulating immunity, inflammation and homeostasis. Therefore, targeting these complexes appears to be an exciting therapeutic strategy to promote tissue repair and regeneration and may become a milestone in advanced bioengineering.

The ultimate goal of Regenerative Immunology together with the use of regenerative biomaterials is to increase the body natural capacity to repair with the help of the immune system, the first responder to injury, in order to create a local microenvironment favourable for tissue repair and regeneration. It is our task as bioengineers to push biomaterials beyond the current state of the art and to develop new strategies to enhance biomaterial engraftment and tissue regeneration.

With this new concept of Regenerative Immunology, we perceive a shift in the paradigmatic way that we look at immunology. We will no longer see our immune system as something created to fight aggressions but as a system with the ability of participate in regenerative processes. Takin advantage of this feature will be a major breakthrough in modern medicine.

REFERENCES

1. Eming SA, Wynn TA, Martin P (2017) Inflammation and metabolism in tissue repair and regeneration. *Science* 356: 1026-1030. [Crossref]
2. Sadtler K, Singh A, Wolf MT, Wang X, Pardoll DM et al. (2016) Design, clinical translation and immunological response of biomaterials in regenerative medicine. *Nat Rev Mat* 1: 16040.
3. Forbes SJ, Rosenthal N (2014) Preparing the ground for tissue regeneration: from mechanism to therapy. *Nat Med* 20: 857-869. [Crossref]
4. Chung L, Maestas DR, Housseau F, Elisseeff JH (2017) Key players in the immune response to biomaterial scaffolds for regenerative medicine. *Adv Drug Deliv Rev* 114: 184-192. [Crossref]
5. Godwin JW, Pinto AR, Rosenthal NA (2013) Macrophages are required for adult salamander limb regeneration. *Proc Natl Acad Sci U S A* 110: 9415-9420. [Crossref]
6. Sadtler K, Estrellas K, Allen BW, Wolf MT, Fan H et al. (2016) Developing a pro-regenerative biomaterial scaffold microenvironment requires T helper 2 cells. *Science* 352: 366-370. [Crossref]
7. Cravedi P, Farouk S, Angeletti A, Edgar L, Tamburrini R et al. (2017) Regenerative immunology: the immunological reaction to biomaterials. *Transpl Int* 30: 1199-1208. [Crossref]
8. Dziki JL, Huleihel L, Scarritt ME, Badylak SF (2017) Extracellular Matrix Bioscaffolds as Immunomodulatory Biomaterials. *Tissue Eng Part A* 23: 1152-1159. [Crossref]
9. Vrana NE (2016) Immunomodulatory biomaterials and regenerative immunology. *Future Sci OA* 2: FSO146. [Crossref]
10. Vishwakarma A, Bhise NS, Evangelista MB, Rouwkema J, Dokmeci MR et al. (2016) Engineering Immunomodulatory Biomaterials To Tune the Inflammatory Response. *Trends Biotechnol* 34: 470-482. [Crossref]
11. Andorko JI, Jewell CM (2017) Designing biomaterials with immunomodulatory properties for tissue engineering and regenerative medicine. *Bioeng Transl Med* 2: 139-155. [Crossref]
12. De Geest BG (2018) Engineering the immune system with particles, step-by-step. *Mol Immunol* 98: 25-27. [Crossref]
13. Yin H, Lu Q, Wang X, Majumdar S, Jun AS et al. (2019) Tissue-derived microparticles reduce inflammation and fibrosis in cornea wounds. *Acta Biomater* 85: 192-202. [Crossref]
14. Garcia JR, Quiros M, Han WM, O'Leary MN, Cox GN et al. (2019) IFN-γ-tethered Hydrogels Enhance Mesenchymal Stem Cell-Based Immunomodulation and Promote Tissue Repair. *Biomaterials* 220: 119403. [Crossref]
15. Lee J, Byun H, Madhurakkat Perikamana SK, Lee S, Shin H (2019) Current Advances in Immunomodulatory Biomaterials for Bone Regeneration. *Adv Healthc Mater* 8: e1801106. [Crossref]
16. Sadtler K, Wolf MT, Ganguly S, Moad CA, Chung L et al. (2019) Divergent immune responses to synthetic and biological scaffolds. *Biomaterials* 192: 405-415. [Crossref]
17. Jha S, Brickey WJ, Ting JP (2017) Inflammasomes in Myeloid Cells: Warriors Within. *Microbiol Spectr* 5: 10. [Crossref]
18. Artlett CM (2013) Inflammasomes in wound healing and fibrosis. *J Pathol* 229: 157-167. [Crossref]
19. Ouyang X, Ghani A, Mehal WZ (2013) Inflammasome biology in fibrogenesis. *Biochim Biophys Acta* 1832: 979-988. [Crossref]