



## Review article

## Promoting tissue regeneration by modulating the immune system

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## ABSTRACT

The immune system plays a central role in tissue repair and regeneration. Indeed, the immune response to tissue injury is crucial in determining the speed and the outcome of the healing process, including the extent of scarring and the restoration of organ function. Therefore, controlling immune components via biomaterials and drug delivery systems is becoming an attractive approach in regenerative medicine, since therapies based on stem cells and growth factors have not yet proven to be broadly effective in the clinic. To integrate the immune system into regenerative strategies, one of the first challenges is to understand the precise functions of the different immune components during the tissue healing process. While remarkable progress has been made, the immune mechanisms involved are still elusive, and there is indication for both negative and positive roles depending on the tissue type or organ and life stage. It is well recognized that the innate immune response comprising danger signals, neutrophils and macrophages modulates tissue healing. In addition, it is becoming evident that the adaptive immune response, in particular T cell subset activities, plays a critical role. In this review, we first present an overview of the basic immune mechanisms involved in tissue repair and regeneration. Then, we highlight various approaches based on biomaterials and drug delivery systems that aim at modulating these mechanisms to limit fibrosis and promote regeneration. We propose that the next generation of regenerative therapies may evolve from typical biomaterial-, stem cell-, or growth factor-centric approaches to an immune-centric approach.

## Statement of Significance

Most regenerative strategies have not yet proven to be safe or reasonably efficient in the clinic. In addition to stem cells and growth factors, the immune system plays a crucial role in the tissue healing process. Here, we propose that controlling the immune-mediated mechanisms of tissue repair and regeneration may support existing regenerative strategies or could be an alternative to using stem cells and growth factors. The first part of this review we highlight key immune mechanisms involved in the tissue healing process and marks them as potential target for designing regenerative strategies. In the second part, we discuss various approaches using biomaterials and drug delivery systems that aim at modulating the components of the immune system to promote tissue regeneration.

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## 1. Introduction

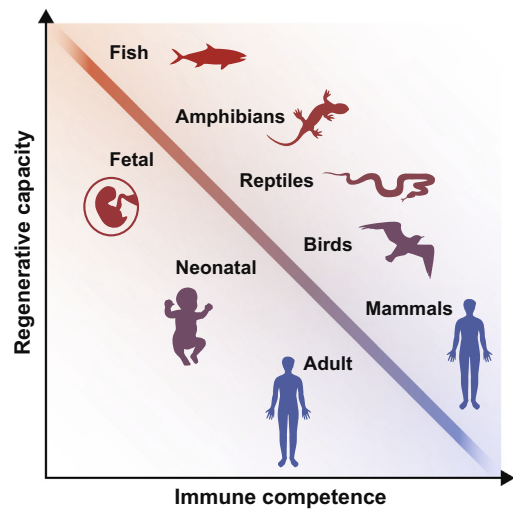
While remarkable progress has been achieved in understanding the cellular and molecular mechanisms of tissue repair and regeneration, it remains unexplained why mammals have a tendency for imperfect healing and scarring rather than regeneration. There is ample evidence in different model organisms indicating that the immune system is crucial to determine the quality of the repair response, including the extent of scarring, and the restoration of organ structure and function. A widespread idea derived from findings in diverse species is that the loss of regenerative capacity is linked to the evolution of immune competence (Fig. 1). Still, there are many situations where the immune response to tissue injury promotes tissue healing. Indeed, the relationship between tissue healing and the immune response is very complex, since there are both negative and positive roles, depending on the tissue, organ and life stage (embryonic, neonatal or adult) [1]. The type of immune response, its duration and the cells involved can drastically change the outcome of the tissue healing process from incomplete healing and repair (i.e. scarring or fibrosis) to complete restoration (i.e. regeneration).

In regenerative medicine, strategies based on stem cells and growth factors have not yet proven broadly effective in the clinic. Here, we propose that immune-mediated mechanisms of tissue repair and regeneration may support existing regenerative strategies or could be an alternative to using stem cells and growth factors. In the first part of this review, we present key immune mechanisms involved in the tissue healing process, in order to highlight potential targets. In the second part, we discuss various approaches using biomaterials and drug delivery systems that aim at modulating the components of the immune system to promote tissue repair and regeneration.

## 2. The main actors of the immune response following tissue injury

An immune response almost always follows tissue damage and this response is usually resolved within days to weeks after an injury. The first phase of the immune response involves components of the innate immune system, which provide instant defense against potential pathogens invading the damaged tissue. However, even in the absence of pathogens, the immune response initially triggered by danger signals released from damaged tissues

produces a so-called sterile inflammation [2,3]. In many if not all tissues, the innate immune response strongly modulates the healing process. For instance, macrophages and their various phenotypes play a predominant role in the restoration of tissue homeostasis by clearing away cellular debris, remodeling the extracellular matrix (ECM), and synthesizing multiple cytokines and growth factors. The innate immune response is then followed by the activation of the adaptive immune system. Although this was originally thought of as a secondary actor in the tissue healing process, the adaptive immune response to tissue injury most likely plays a critical role during tissue repair and regeneration, in particular the activity of T cells. While a large research effort has focused on how transplanted mesenchymal stem cells (MSCs) modulate T cell activities and immune tolerance [4,5], our understanding of how T cells modulate tissue-resident stem cells and the tissue healing process is just beginning. In the next sections, we review the roles and importance of the main actors that shape the immune response following tissue injury.



**Fig. 1.** Apparent inverse relationship between regenerative and immune capacities during evolution or development. Lower vertebrates such as fishes and amphibians have the ability to completely regenerate many of their tissues. In mammals, regenerative capacities depend on the developmental stage (i.e. fetal, neonatal, and adult). Immune competences have increased during evolution and also increase with life stage in mammals.

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