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EDITORIAL

# Rethinking regeneration: empowerment of stem cells by inflammation

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The ontogenetic development and maintenance of tissue homeostasis at the cellular level are accomplished by regulating the activation, renewal, expansion and differentiation of stem cells. The differentiation and regeneration potential of stem cells has been well studied in both preclinical and clinical investigations.[1] In recent years, a series of experiments have revealed that replacement of damaged or defective cells by exogenously administered stem cells is critical in achieving their therapeutic effects in various diseases, such as multiple sclerosis (MS).[2] However, modulation of experimental autoimmune encephalomyelitis (the animal model of MS) by neural progenitor cells (NPCs) has been found to be related to the immunoregulatory properties of these cells, and can be even achieved with irradiated NPCs or just NPC-derived supernatant, indicating that stem cell-based tissue repair can also be promoted by their immunoregulatory and paracrine effects.[3] More persuasive studies of stem cell-mediated immunoregulation have been carried out with mesenchymal stem/stromal cells (MSCs), multipotent cells that can be isolated from many tissues, such as bone marrow, adipose tissue and umbilical cord, which are capable of differentiation into adipocytes, osteoblasts, chondrocytes and myoblasts.[4] Interestingly, MSCs have been demonstrated to suppress an immune response through licensing by combinations of pro-inflammatory cytokines, specifically IFN$\gamma$ in combination with TNF$\alpha$ or IL-1, leading to the concept of bidirectional interaction between MSCs and inflammation.[5] Under inflammatory conditions, ample amounts of growth factors produced by MSCs can facilitate tissue repair through their effects on endothelial cells and fibroblasts, as well as tissue progenitor cells, at sites of damaged tissue. Such concerted actions of MSCs on tissue repair have been termed as 'cell empowerment'.[6] It is important to point out that most biological properties involved in the interplay between stem cells and immune responses are derived from studies with cells expanded *ex vivo*, rather than investigations exploring this interaction *in vivo.*

Skeletal muscle stem cells (MuSCs) are now well known to exist,[7] but their expansion *in vitro* for the treatment of muscle atrophy and muscle damage has been extremely difficult owing to a lack of crucial niche components in the culture systems.[8,9] Recently, Fu *et al.*[10] studied the regulation of MuSCs by T cells during muscle regeneration in mice. Using a cardiotoxin-induced muscle injury model, the authors found that muscle regeneration capacity was severely impaired in *Rag1*$^{-/-}$ mice, which lack both T cells and B cells owing to their inability to generate antigen receptors. Interestingly, adoptive transfer of activated T cells, but not B cells, restored normal muscle regeneration potential in these mice, suggesting a critical role for T cells in facilitating muscle regeneration. It was also demonstrated that addition of activated T-cell culture supernatant leads to an exponential expansion of MuSCs *in vitro*. A detailed analysis revealed that IL-1$\alpha$, IL-13, IFN$\gamma$ and TNF$\alpha$ were the key factors in T-cell supernatant-mediating MuSC expansion. Importantly, addition of the same T-cell cytokine combination in recombinant form was sufficient to mimic the *in vivo* microenvironment to facilitate muscle regeneration *in vivo*. This provocative discovery, which T cells directly influence MuSC expansion during skeletal muscle regeneration, provides convincing support that immune cells modulate stem cell function. Notably, MuSCs expansion driven by these four cytokines can replenish the endogenous stem cell pool, which can be activated in response to another injury. These findings demonstrate that cross-talk between stem cells and immune responses *in vivo* determines the function and fate of stem cells in the process of tissue regeneration.

The good Samaritan effects of the immune system on stem cells was also demonstrated in another elegant study published in *Cell* by Chen *et al.*[11] Although examining the regeneration of hair follicles in response to patterned hair plucking, it was found that plucking hair at different densities leads to a regeneration of up to five times more neighboring, unplucked resting hairs. The authors further found that, in this process, TNF$\alpha$ produced by recruited macrophages could activate hair follicle stem cells and facilitate hair regeneration.[11] In this scenario, plucking hairs at a certain high density led to the apoptosis of hair follicle keratinocytes. These apoptotic cells produced high levels of chemokines and inflammatory cytokines, including CCL2, IL-1$\beta$ and TNF$\alpha$, resulting in an accumulation of M1 macrophages. Subsequently, the augmented production of TNF$\alpha$ by macrophages resulted in the activation of hair follicle stem cells. Ablation of macrophage function by chemical inhibition or genetic deletion verified that macrophage activity was essential for hair

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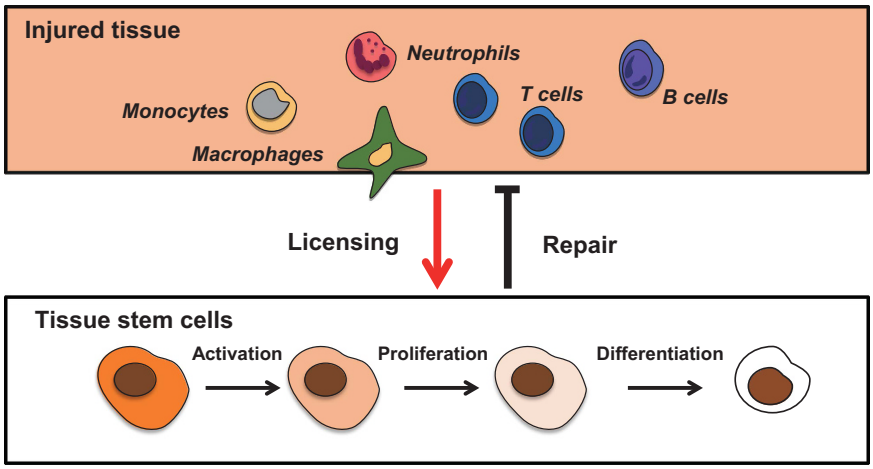


**Figure 1** Stem cell immunology: the interaction between immune cells and stem cells during tissue regeneration. Immune cells at the site of tissue injury, including macrophages and T cells, secrete TNF$\alpha$, IFN$\gamma$, IL-1, IL-13 and other pro-inflammatory cytokines, which in turn can activate stem cells. Once licensed by these cytokines, stem cells can facilitate tissue regeneration through cell differentiation and the release of anti-inflammatory cytokines and growth factors

regeneration. These TNF$\alpha$-secreting macrophages were found to accumulate around the distressed hair follicle and later migrate to healthy hair follicles, resulting in an augmented hair follicle regeneration. Although further investigation remains, this study revealed that macrophages can stimulate hair follicle stem cells directly and promote the regeneration of hair follicles, another demonstration that inflammation is necessary to achieve the regeneration potential of tissue stem cells. Interestingly, such plucking-induced hair follicle regeneration was dependent on the magnitude and extent of skin injury, an example of quorum sensing. Thus, the strength of inflammation invoked by the injury dictates the behavior of stem cells.

Over the several years, studies using different experimental systems have repeatedly confirmed that various kinds of immune cells, including macrophages, T cells and mast cells, actively participate in the tissue repair or regeneration process.[1,2] The two studies described above provide direct support for the importance of the cross-talk between inflammation and stem cells in directing the fate and behavior of stem cells during tissue regeneration. Further investigations in the newly emerging field of stem cell immunology (Figure 1) should greatly improve our understanding of the effects of immune cells and their inflammatory factors, which fluctuate considerably in the microenvironment of a tissue lesion, on the proliferation, activation and immunoregulatory capacity of stem cells. It is anticipated that, in the foreseeable future, details about the interaction between stem cells and immune responses, and their collective actions during tissue repair, will accelerate the development of novel strategies of regenerative medicine.

## Conflict of Interest

The authors declare no conflict of interest.

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