Re-educating the post-injury microenvironment to induce tolerogenic dendritic cell subsets and pro-regenerative macrophages

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Advances in transplantation surgical techniques and immunosuppression regimens (IS) have significantly reduced the rate of postoperative morbidity and graft loss following organ transplantation. However, systemic IS regimens are associated with an increased risk of tumor formation, opportunistic infection, and organ toxicity. One potentially successful strategy to address this problem is to deliver immunomodulatory factors to induce transplant tolerance through the local recruitment of tolerogenic subsets of immune cells. In this study, we engineered an enzymatically poly(ethylene) glycol (PEG)-based hydrogel system to release thiolated recombinant human interleukin 10 (IL-10) and aspirin-triggered resolvin (AT-RvD1). Hydrogels were reacted with the cell adhesion peptide RGD and crosslinked with the degradable peptide VPM. Internally controlled in vivo studies show that recruitment and re-education of mononuclear phagocytes by combined delivery IL-10 and AT-RvD1 localizes tolerogenic immune subsets to the hydrogel, including regulatory CD25+ T regulatory cells (Treg), CD206+ macrophages (M2a/c), and IL-10 expressing dendritic cells. Intracellular staining also showed that induced immune subsets express significantly lower levels of pro-inflammatory cytokines such as TNF-alpha while increasing production of pro-tolerogenic cytokines such as IL10 staining. We also utilized immunomodulatory hydrogels in a murine model of skin transplant to track the modulation of the immune response over time and examine graft tissue integration and acceptance. Our studies demonstrate the potential of combined delivery enhance alloimmunity by dampening immune activation and cytokine production of factors involved in rejection.