Summary

Repair of damaged tissue requires the coordinated action of inflammatory and tissue-specific cells in time and space. Our group and others have previously shown that perturbation of these interactions leads to unsuccessful healing. Infiltrating immune cells of the monocyte-macrophage lineage and mast cells sense a variety of environmental cues of injured tissue and integrate those into a repair response. The molecular determinants that precisely control the dynamics of immune cell function during healing progression or its failure are largely unknown. In this study we examined the mechanisms how monocytes/macrophages and mast cells coordinate their functional complexity during the sequential repair stages. First, we were aiming at a better understanding of the mechanism regulating the recruitment of blood monocytes into the site of skin damage. For this purpose a new CCR2-eGFP reporter mouse model as well as mouse models of complete or myeloid cell-restricted *CCR2* gene inactivation were established and investigated. Second, to study the role of mast cells in skin regeneration a new mouse model of selective and inducible mast cell depletion was developed and examined.

The presented study revealed that upon mechanically induced excisional skin injury a high number of inflammatory $CCR2^{+}Ly6C^{+}$ monocytes is recruited from the blood stream to the site of injury and that signaling through CCR2 is critical for this process. Furthermore, wound macrophages were characterized by distinct gene expression profiles and exhibited distinct activation phenotypes during the transition of an inflammatory towards a resolution phenotype. Whereas inflammatory and pro-angiogenic mediators were a hallmark of early wound macrophages, immunosuppressive signals characterized late stage wound macrophages. During early stage repair, $CCR2^{+}Ly6C^{+}$ monocytes gave rise to pro-angiogenic macrophages, which had non-redundant functions for the initiation of vascularized granulation tissue and the induction of myofibroblast differentiation. In contrast, genetic ablation of mast cells did not significantly impact overall kinetics of wound closure, formation of vascularized granulation tissue and the quality of scar tissue. However, mast cell ablation resulted in impaired wound contraction and recruitment of polymorphonuclear cells during the early phase of repair. In a bleomycin-induced skin fibrosis model, genetic ablation of mast cells failed to prevent development of skin fibrosis.

Collectively, our findings provide new mechanistic insights into CCR2-mediated recruitment of blood monocyte subsets into damaged tissue, dynamics and functional consequences of macrophage plasticity during the sequential repair phases, and the complementary role of macrophage-derived VEGF-A coordinating effective tissue growth and vascularization in the context with tissue-resident wound cells. Our findings might be relevant for novel monocyte-based therapies to promote tissue vascularization.