Summary

Recruitment of immune cells is a hallmark of tissue injury and repair. However, restoration of tissue integrity requires resolution of the inflammatory response. The exact mechanisms and dynamics how immune cells interact with tissue resident cells during the subsequent phases of tissue growth and differentiation during wound healing are elusive. Macrophages are immune cells, that are abundant at the wound site during all different stages of healing. Recent findings have shown that they exert a pro-inflammatory (M1) in the early and an anti-inflammatory (M2) phenotype in the later phase of repair. Mediators directing the M1/M2 conversion in skin repair are largely unknown. To explore the function of Interleukin-4 and -13 (IL-4/IL-13) for macrophage activation in cutaneous repair, the healing response of myeloid cell-restricted Interleukin-4 receptor alpha (IL-4Rα) deficient mice were analyzed. Wound macrophages in myeloid cell-restricted IL-4Rα-deficient mice revealed a disturbed M1/M2 balance during healing, with a shift towards a prolonged M1 and an attenuated M2 activation. Dysregulated macrophage activation was associated with delayed wound closure and massive hemorrhages in the granulation tissue. A combination of multiple *in vitro* and *in vivo* analysis unraveled an unexpected disturbance of extracellular matrix architecture, suggestive for impaired mechanical stability. Mutant mice revealed an abnormal collagen fibril assembly and an altered collagen cross-link pattern in wound tissue when compared to control mice. Whereas granulation tissue in control mice was characterized by a dihydroxy lysinonorleucine (DHLNL) collagen cross-linking pattern, these cross-links were significantly reduced in myeloid-cell restricted IL-4Rα-deficient mice. Interestingly, we identified IL-4/IL-13 mediated expression of Found-in-inflammatory-zone-1 (Fizz-1) in macrophages as a critical regulator of Lysyl hydroxylase-2 (LH-2, *plod-2* gene) expression in fibroblasts. LH-2 is known to play a pivotal role directing the DHLNL collagen cross-link phenotype which is typically found in fibrosis. Consistently, wound macrophages in myeloid cell-restricted IL-4Rα-deficient mice revealed reduced expression of Fizz-1 and, most interestingly, expression of LH-2 was also significantly reduced in wound tissue of mutant mice.
Collectively, these findings provide novel mechanistic insights into the role of IL-4Rα-mediated conversion of an early M1 into a late M2 macrophage activation phenotype during skin repair. This process is crucial for efficient skin repair. Data presented in this thesis work show for the first time, that myeloid cell-restricted IL-4Rα signaling gives rise to a macrophage subpopulation that through a Fizz-1 mediated crosstalk with fibroblasts is critical to develop a functional granulation tissue and matrix architecture important for restoration of tissue integrity following injury.