

## The Role of Leukocyte-Derived IL-10 on Postoperative ileus and Intestinal Macrophage Differentiation in Mice

**Authors :** Kathy Stein, Mariola Lysson, Anja Schmidt, Beatrix Schumak, Sabine Specht, Hicham Bouabe, Jürgen Heesemann, Axel Roers, Joerg C. Kalff, Sven Wehner

**Abstract :** Objective: Postoperative ileus (POI) is a common complication of abdominal surgery. Monocyte infiltration is a hallmark of POI. The polarization of macrophages/monocytes in this process is not well understood. We aimed to investigate if and how M2 macrophage/monocyte differentiation is involved in POI pathogenesis. Design: POI was induced by intestinal manipulation (IM). C57Bl/6, CCR2<sup>-/-</sup>, IL-10 reporter (ITIB), IL-10<sup>-/-</sup> and LysMcre/IL-10<sup>fl/fl</sup> mice underwent IM. At various points in time leukocyte influx, gene and protein expression of cytokines, chemokines and M2 differentiation markers and intestinal motility were analyzed. Results: IM induced the postoperative expression of the M2 markers Arginase-1 and YM-1, predominantly in F4/80+Ly6C<sup>+</sup> monocytes. Gene expression analyses indicated an IL-10-dependent, IL-4-independent M2 polarization of these monocytes. IL-10 dependency of M2 differentiation was confirmed in IL-10 deficient mice. Leukocytes, in the order of infiltrating monocytes, neutrophils, and resident macrophages were the main IL-10 producers during POI. IL-10 producing monocytes as well as M2 marker expression were almost absent in CCR2-deficient mice. However, postoperative IL-10 expression was not altered in CCR2<sup>-/-</sup> mice. The loss of M2 polarized monocytes neither protected CCR2<sup>-/-</sup> mice from nor affected resolution of POI. In contrast, IL-10 deficiency reduced postoperative neutrophil numbers and ameliorated POI. IL-10Ra expression was strongly induced in neutrophils but not in monocytes. Conclusion: We conclude that IL-10 counteracts POI resolution by activating IL-10Ra-expressing neutrophils in the late phase of disease while IL-10-dependent M2 differentiation is not pivotal to POI manifestation and resolution.

**Keywords :** interleukin-10, macrophages, neutrophils, postoperative ileus

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