Irf4-dependent CD103+CD11b+ dendritic cells and the intestinal microbiome regulate monocyte and macrophage activation and intestinal peristalsis in postoperative ileus

Objective: Postoperative ileus (POI), the most frequent complication after intestinal surgery, depends on dendritic cells (DCs) and macrophages. Here, we have investigated the mechanism that activates these cells and the contribution of the intestinal microbiota for POI induction. Design: POI was induced by manipulating the intestine of mice, which selectively lack DCs, monocytes or macrophages. The disease severity in the small and large intestine was analysed by determining the distribution of orally applied fluorescein isothiocyanate-dextran and by measuring the excretion time of a retrogradely inserted glass ball. The impact of the microbiota on intestinal peristalsis was evaluated after oral antibiotic treatment. Results: We found that Cd11c-Cre+ Irf4flox/flox mice lack CD103+CD11b+ DCs, a DC subset unique to the intestine whose function is poorly understood. Their absence in the intestinal muscularis reduced pathogenic inducible nitric oxide synthase (iNOS) production by monocytes and macrophages and ameliorated POI. Pathogenic iNOS was produced in the jejunum by resident Ly6C- macrophages and infiltrating chemokine receptor 2-dependent Ly6C+ monocytes, but in the colon only by the latter demonstrating differential tolerance mechanisms along the intestinal tract. Consistently, depletion of both cell subsets reduced small intestinal POI, whereas the depletion of Ly6C+ monocytes alone was sufficient to prevent large intestinal POI. The differential role of monocytes and macrophages in small and large intestinal POI suggested a potential role of the intestinal microbiota. Indeed, antibiotic treatment reduced iNOS levels and ameliorated POI. Conclusions: Our findings reveal that CD103+CD11b+ DCs and the intestinal microbiome are a prerequisite for the activation of intestinal monocytes and macrophages and for dysregulating intestinal motility in POI.

General information
State: Published
Organisations: National Veterinary Institute, Mucosal Immunology, University of Duisburg-Essen, University Hospital Essen, Weizmann Institute of Science, Lund University, University of Bonn
Pages: 2110–2120
Publication date: 2017
Peer-reviewed: Yes

Publication information
Journal: Gut
Volume: 66
Issue number: 12
ISSN (Print): 0017-5749
Ratings:
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): CiteScore 9.82 SJR 7.44 SNIP 3.832
Web of Science (2017): Impact factor 17.016
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 9.29 SJR 7.074 SNIP 3.946
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 9.1 SJR 6.809 SNIP 3.968
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 8.76 SJR 6.104 SNIP 3.865
Web of Science (2014): Impact factor 14.66
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 7.6 SJR 5.58 SNIP 3.459
Web of Science (2013): Impact factor 13.319
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): CiteScore 6.36 SJR 4.066 SNIP 2.737
Web of Science (2012): Impact factor 10.732