The role of TLR3/TRIF and type I IFN signaling in the migration of intestinal DC subsets in response to poly(I:C)

Garcia Lopez, A.; Bekiaris, Vasileios; Müller-Luda, K; Hütter, J.; Holzmann, B.; Agace, W.; Lahl, Katharina

Published in:
European Journal of Immunology

Link to article, DOI:
10.1002/eji.201871000

Publication date:
2018

Document Version
Publisher's PDF, also known as Version of record

Link back to DTU Orbit

Citation (APA):

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.
P–227

The role of TLR3/TRIF and type I IFN signaling in the migration of intestinal DC subsets in response to poly(I:C)


1 Technical University of Denmark (DTU), DTU Vet, Kongens Lyngby, Denmark
2 Lund University, Immunology Section, Lund, Sweden
3 Bayer Pharma AG, Pharmaceuticals Division, Berlin, Germany
4 Technical University of Munich, School of Medicine, Munich, Germany

Intestinal dendritic cell (DC) migration to the mesenteric lymph nodes (mLN) is essential for optimal priming of gut-associated T cell responses and different DC subsets are known to prime distinct T cell responses. We here investigated whether migration of intestinal cDC1 (CD103+CD11b−) and cDC2 (CD103+CD11b+) to the mLN differed in response to poly(I:C), a viral RNA mimic which signals through Toll-like receptor 3 (TLR3) and TRIF. Although TLR3 is specifically and highly expressed on migratory cDC1, our results show that cDC1 and cDC2 migrate to the same level in response to intraperitoneal administration of poly(I:C). Pantel et al. previously showed that a type I IFN response rather than TLR3/MDA5 activation of splenic DCs after poly(I:C) stimulation induces massive transcriptional changes in DCs, leading to metabolic shift and maturation. As maturation and migration might require different signals, we decided to analyze the molecular requirements for DC migration. Poly(I:C)-induced migration was fully dependent on TLR3/TRIF, as mice deficient for either molecule showed no DC migration of either subset. Mixed BM-chimeras revealed that cell-intrinsic TLR3 expression was dispensable for migration, but that TLR3 was required on the hematopoietic system. Given the exceptionally high level of TLR3 expression on cDC1, our results show that cDC1 and cDC2 migrate to the same level in response to TLR3/MDA5 activation of splenic DCs after poly(I:C) stimulation induces massive transcriptional changes in DCs, leading to metabolic shift and maturation. As maturation and migration might require different signals, we decided to analyze the molecular requirements for DC migration. Poly(I:C)-induced migration was fully dependent on TLR3/TRIF, as mice deficient for either molecule showed no DC migration of either subset. Mixed BM-chimeras revealed that cell-intrinsic TLR3 expression was dispensable for migration, but that TLR3 was required on the hematopoietic system. Given the exceptionally high level of TLR3 expression on cDC1, we are currently investigating whether TLR3 signaling in cDC1, while not required cell-intrinsically, is nevertheless sufficient to drive DC migration after poly(I:C) injection. To this end, we use novel switch-on mutants that allow to specifically express TLR3 only in cDC1 DCs. Preliminary data suggest that DCs from these mice only partially migrate and become activated in response to poly(I:C), indicating the involvement of other cellular players providing migration-inducing signals in a TLR3-dependent fashion. We next addressed whether type I IFN was among those signals. Type I IFN was indeed required for activation and migration of both subsets, as observed using mice lacking the type I IFN receptor in all CD11c-expressing cells. We are currently investigating whether type I IFN signaling is directly needed on the responding DCs using mouse models specifically targeting receptor expression in the two major DC subsets. Our data suggests that while both TLR3 and IFNAR signaling play key roles in intestinal DC migration and activation in response to poly(I:C), the requirements for cellular sensors of those signals might differ significantly.

P–228

The expression of XCR1 by type 1 conventional dendritic cells promotes NK cell protective functions against cytomegalovirus infection

Ghilas S., Cancel J. C., Massé M., Vu Manh T. P., Dalod M., Crozat K.

1 Centre d’Immunologie de Marseille-Luminy, Marseille cedex 09, France

Conventional dendritic cells (cDCs) are considered as purely dedicated in efficiently priming naive T cells. cDCs have acquired functional specializations to custom shape T cell responses accordingly to the infectious threats they must cope with. Therefore, in all mammals, type 2 cDCs are better in presenting antigens (Ag) to CD4+ T cells, whereas cDC1 favor Th1 polarization, and efficiently prime cytotoxic CD8+ T cells by cross-presenting exogenous Ag. A major breakthrough in this research field was the discovery that, in all species, cDC1 can be univocally identified by their selective expression of XCR1 whatever the tissues examined.

XCR1 is a chemokine receptor with one ligand in mice (XCL1), and two ligands in human (XCL1, XCL2). In both human and mice, Xcl1 transcript is particularly abundant in cytotoxic lymphocytes such as natural killer (NK) cells or activated CD8+ T cells. We used the Xcl1-TEAL-Flox reporter mouse to