

Developmental Immunology



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Innate immune regulation and lymphoid tissue induction

The innate lymphoid cell (ILC) family has emerged as the first line of defense against various pathogens. In addition, ILCs regulate tissue homeostasis and repair through the release of cytokines. Based on effector cytokines and transcriptional regulation they can be divided into three populations: group 1 ILCs, group 2 ILCs and group 3 ILCs including lymphoid tissue inducer (LTI) cells (Fig. 1). Studies in mouse and men clearly demonstrate that each subset has defined immune functions that depend on the tissue localization, type of activation and disease status. The molecular mechanisms underlying the tissue-specific regulation of ILCs are not fully understood. In particular, the exposure to environmental signals from commensals and nutrition factors has an effect on local expansion and activation of ILC subsets. Our work focuses on understanding the developmental requirements for generating ILCs and for regulating their activation and immune response in situ.

One major topic of investigation is assessing the molecular pathways that coordinate ILC development and tissue homeostasis. In recent years we have identified cytokines that act as master regulators of ILC and lymphoid tissue development. Notably, IL-7 and Flt3L are key cytokines in promoting the development of ILCs from fetal liver and common lymphoid progenitors in the bone marrow. Deletion of flt3l severely reduces the number of LTI cells in the neonatal intestine, resulting in impaired development of Peyer's patches, whereas IL-7 is critical for lymph node development (Fig.2). In adults, both Flt3L and IL-7 regulate the generation of ILCs, although both cytokines operate at different developmental stages of progenitor cells. The complex network of cytokines in various tissues and stages of development may explain how ILCs can further mature in peripheral tissues.

A second focus of our research is the regulation of adaptive immune responses by group 3 ILCs. ILC3s respond to various "danger signals" with a specific profile of cytokines, which contribute to T cell polarization and activation of innate immune

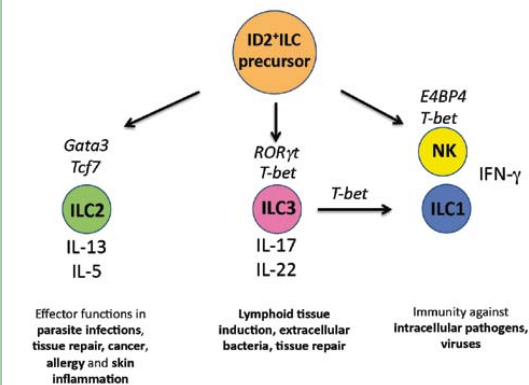


Fig. 1: Innate lymphoid cell (subsets): transcriptional regulation, cytokine release and effector functions.

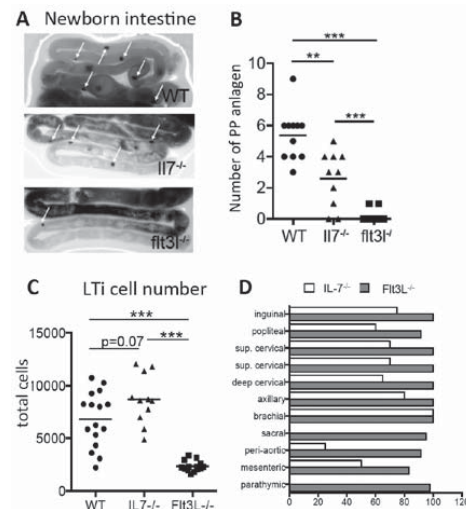


Fig. 2: (A) and (B) Peyer's patch antigen in the small intestine of day 0.5-old WT, IL7^{-/-} and flt3l^{-/-} mice visualized by VCAM-1 whole-mount staining. Representative pictures of VCAM-1⁺ spots (indicated by arrows) are shown. (C) Total number of LTI cells in the small intestine of day 0.5-old WT, IL7^{-/-} and flt3l^{-/-} mice. (D) Presence of LNs in adult IL7^{-/-} and flt3l^{-/-} mice compared with WT set as 100% (n=6-10).

cells. We have reported that ILC3s have the capacity to internalize antigens (Fig. 3) and to present MHC-peptide ligands to T cells. Interestingly, according to their tissue of origin, splenic and intestinal (lamina propria (LP)) ILC3s have opposite antigen-presenting functions. Comparable to dendritic cells, splenic ILC3s are able to undergo a process of maturation (activation) upon IL-1β stimulation and induce antigen specific T-cell proliferation. By contrast, LP ILC3s lack co-stimulatory molecules after IL-1β stimulation and induce only very weak T-cell proliferation. In addition, a role in the negative regulation of T-cell responses against the gut microbiota was assigned to LP ILC3s. Hence, differences in the antigen-presenting function of splenic and LP ILC3s are that the former could be considered as immunogenic and the latter tolerogenic. The genetic analysis of both subsets has demonstrated subset-specific transcriptional profiles under steady-state and inflammatory conditions. We could further demonstrate that ILC-T cell interactions are bi-directional and that Ag-activated T cells provide feedback signals for activation of ILCs. Our current interest is to better understand the molecular pathways, which shape the tissue-specific ILC subset repertoire and immune function in the presence and absence of an adaptive immune system.

A third topic of interest is to understand the regulation of early and late effector cytokine responses of ILCs in health and disease. The tissue protective role of IL-22 produced by ILC3s has been well documented. On the other hand, ILC3s can convert into pro-inflammatory IFNγ-producing ILC1s (Fig. 1) thus demonstrating a high degree of plasticity. Using gene-targeting strategies we study key pathways promoting pro-inflammatory ILC responses in intestinal inflammation and cancer. Together, we use systematic molecular and functional analysis of ILC subsets in genetically modified mouse models and models for human inflammatory diseases to gain insights into the role of ILCs in chronic inflammation and tumor diseases.

Selected Publications

- Baerenwaldt A, von Burg N, Kreuzaler M, Sitte S, Horvath E, Peter A, Voehringer D, Rolink AG, Finke D. (2016) Flt3 Ligand regulates the development of innate lymphoid cells in fetal and adult mice. *J. Immunol.*, 196 (6):2561-71
- Von Burg N, Turchinovich G, Finke D. (2015) Maintenance of immune homeostasis through ILC/T cell interactions. *Frontiers in Immunology*, 6, 416
- Schmalzer M, Broggi MA, Lagarde N, Stöcklin BF, King CG, Finke D, Rossi SW. (2015) IL-7R signalling in regulatory T cells maintains peripheral and allograft tolerance in mice. *PNAS*, 112 (43):13330-5
- Brasseit J, Althaus-Steiner E, Faderl M, Dickgreber N, Saurer L, Genitsch V, Dolowschiak T, Li H, Finke D, Hardt WD, McCoy KD, Macpherson AJ, Corazza N, Noti M, Mueller C. (2015) CD4 T cells are required for both development and maintenance of disease in a new mouse model of reversible colitis. *Mucosal Immunology*, 9, 689-701
- Von Burg N, Chappaz S, Baerenwaldt A, Horvath E, Dasgupta SB, Ashok D, Pieters J, Tacchini-Cottier F, Rolink H, Acha-Orbea H, Finke D. (2014) Activated group 3 innate lymphoid cells promote T-cell-mediated immune responses. *PNAS*, 111(35): 12835-40

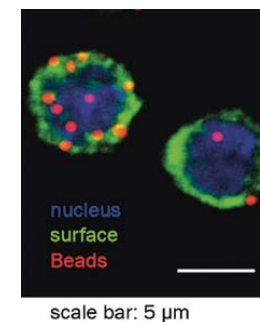


Fig. 3: Representative immunofluorescence image of red fluorescent latex bead uptake by sort-purified *in vitro* generated ILC3s.