Projekttitel: **Developmental stages and requirements of Innate Lymphoid Cells (ILCs)**

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Hintergrund: The adaptive immune system responds to pathogen infection by employing distinct effector modules, namely type 1 (IFN-γ and TNF), type 2 (IL-4, IL-5 and IL-13) and type 17 (IL-17, IL-22), which are tailored to eliminate the different infectious agents. It is now evident that an emerging family of innate lymphocytes lacking the TCR and collectively known as innate lymphoid cells (ILCs), exhibit a similar heterogeneity of effector programs, which can be activated after pathogen infection as well as in the course of inflammatory disorders, such as inflammatory bowel diseases, psoriasis, atopic dermatitis, asthma and metabolic syndrome. The ILC family comprises of three main groups of cells: group 1 ILCs, including cytotoxic Natural Killer (NK) cells and the IFN- γ producing ILC1; ILC2 producing IL-13/IL-5; ILC3 secreting IL-22/IL-17 (*reviewed in Annunziato et al, JACI 2014*).

Although ILCs can display a large heterogeneity of inflammatory programs as Th cells, the signals that are required for ILC polarization remain completely unknown. Very recent data have identified the progenitor that can give rise in vivo to ILCs with different effector signatures as well as the ILC2-committed precursors in mouse (1-2), thus now enabling to characterize the signals and environmental cues driving the commitment of different ILC subsets. Conversely, the common ILC progenitor and intermediate stages of human ILC differentiation remain undefined. In our previous work, we have identified for the first time a population of human $CD34^+$ hematopoietic progenitor cells (HPCs) expressing RORγt, which are excluded from bone marrow, while residing in tonsils and gut lamina propria. Our data indicate that $ROR\gamma t^+$ $CD34^+$ HPCs represent ILC3-committed precursors and mucosal sites might represent the reservoir not only for mature but also for immature ILCs, especially ILC3. Following this hypothesis, we will further dissect tissue derived $CD34^+$ HPCs in comparison with bone marrow to possibly identify and characterize the common ILC progenitor as well as intermediate stages of ILC subset differentiation. Once the different stages of ILC commitment are clarified, a crucial question that remains to be solved is which signals are driving the differentiation towards the different ILC subset fate and the imprinting of the correspondent inflammatory programs. Along this line, we have started to characterize the cytokines and environmental cues driving the acquisition of human ILC effector programs and showed that commitment towards ILC3 is mainly driven by stem cell factor (SCF) and aryl hydrocarbon receptor (AhR) signalling *(Montaldo et al, Immunity 2014)*. Thus, based on these findings, we would like to further characterize the signals required for the ILC lineage fate decision and their stability. To this aim, we will perform in vitro differentiation cultures in the presence of distinct stimuli (cytokines and/or environmental cues) with FACS-sorted CD34+ precursor subsets isolated from different human tissues, especially tonsils, and

analysis of phenotype and functions of obtained mature ILCs by Multicolour Flow cytometry and PCR/Fluidigm will be performed.
Investigating the developmental history and the signals driving the imprinting of different inflammatory programs in ILCs will enable us to broaden our understanding of the pathogenesis of chronic inflammation and to potentially develop novel targets for the treatment of inflammatory disorders.

External References

[1] Klose et al. 2014. Cell 157:340-56.
[2] Hoyler et al. 2012. Immunity 37:634-48

List of topic-related publications

Annunziato F, **Romagnani C** and Romagnani S. The three major types of innate and adaptive cell-mediated effector immunity. Review. ***J Allergy Clin Immunol.*** **2014** Mar;135(3):626-635.
Montaldo E, Teixeira-Alves LG, Glatzer T and **Romagnani C.** Human RORγt+ CD34+ cells are lineage-specified progenitors of group 3 RORγt+ innate lymphoid cells. ***Immunity.*** **2014** Dec 18;41(6):988-1000.
Killig M, Glatzer T, **Romagnani C**. Recognition Strategies of Group 3 Innate Lymphoid Cells. ***Front Immunol.*** 2014 Apr 1;5:142. eCollection **2014**. Review.
Luetke-Eversloh M, Killig M, **Romagnani C**. Signatures of Human NK Cell Development and Terminal Differentiation. ***Front Immunol.*** **2013** Dec 30;4:499. Review.
Glatzer T[#], Killig M[#], Meisig J, .. and **Romagnani C**. RORγt[+] innate lymphoid cells acquire a proinflammatory program upon engagement of the activating receptor NKp44. ***Immunity.*** **2013** Jun 27;38(6):1223-35. [#]Equal first contribution.