NKTreg-MIME 2007-
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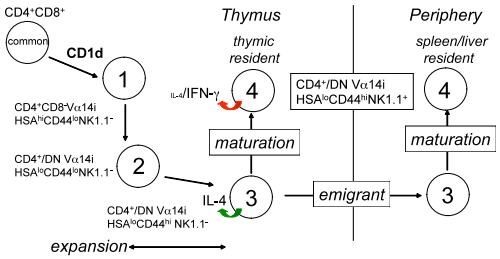
Molecular and cellular aspects of regulatory iNKT cell development

Context

Upon stimulation NKT cells secrete promptly and in large quantity Th1 and Th2 cytokines and have been implicated in the regulation of immune responses associated with a broad range of diseases such as infections, tumor rejection, and autoimmune conditions. During their development immature NK1.1neg NKT cells secrete exclusively Th2-type cytokines and only secondarily, in the thymic medulla and after emigration to the periphery, acquire the capacity to secrete Th1-type cytokines after several differentiation steps leading to the NK-like stage.



Sequential stages of mouse iNKT cell development leading to CD4pos or Double negative (DN) NK1.1pos iNKT cells. Vα14i: invariant Vα14 α chain. (Benlagha et al Science 2002).

Objectives

Our aims are to dissect at the molecular and cellular levels the mechanisms underlying their differentiation program.

Results

In collaboration with Julien Marie's laboratory (Lyon, France), we showed that TGF-β signalling finely and specifically orchestrates several steps of iNKT cell development The Tif-1γ pathway promotes responsiveness of early precursors to IL-7 allowing proliferation, while the Tif-1γ/Smad4-independent pathway represses IL-15 responsiveness and maturational transition. The Smad 4 pathway promotes responsiveness to IL-15 and terminal differentiation. Downregulation of TGF-β signalling at the CD44hiNK1.1neg stage 3 allows a concerted action of these signalling pathways

In addition to thymic maturation of iNKT cells, we have also invested long time effort to study their peripheral maturation. We found that, contrary to spleen and liver iNKT cells that are mainly mature NK1.1pos, PLNs lack NK1.1pos iNKT cells but contain a major stable mature NK1.1neg iNKT cell population expressing RORγt and producing IL-17.
We further showed that IL-1 and IL-23 produced by APC promote PLN RORgtpos iNKT cells production of innate Th17-related cytokines during bacterial infections, and support the hypothesis that they are able to provide an efficient first line of defence against bacterial invasion.

Conclusion

Through this ANR project we have been able to provide new insight into the molecular mecanisms controlling NKT cell maturation and function.

Prospective and impact

Our findings open new area of research regarding the fundamental aspects of RORgtpos iNKT cells maturation and their response *in vivo* in PLNs, as well as their potential use in immunotherapeutic applications.

Publications

Cutting Edge: Crucial Role of IL-1 and IL-23 in the Innate IL-17 Response of Peripheral Lymph Node NK1.1- Invariant NKT Cells to Bacteria. Doisne JM, Soulard V, Bécourt C, Amniai L, Henrot P, Havenar-Daughton C, Blanchet C, Zitvogel Ryffel B, Cavaillon JM, Marie JC, Couillin I, **Benlagha K.**
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Skin and peripheral lymph node invariant NKT cells are mainly retinoic acid receptor-related orphan receptor (gamma)t+ and respond preferentially under inflammatory conditions.nDoisne JM, Becourt C, Amniai L, Duarte N, Le Luduec JB, Eberl G, **Benlagha K.**
J Immunol. 2009 Aug 1;183(3):2142-9. Epub 2009 Jul 8

iNKT cell development is orchestrated by different branches of TGF-beta signaling. Doisne JM, Bartholin L, Yan KP, Garcia CN, Duarte N, Le Luduec JB, Vincent D, Cyprian F, Horvat B, Martel S, Rimokh R, Losson R, **Benlagha K**, Marie JC.
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