The role of Tyk2 in Dendritic Cells

The non-receptor tyrosine kinase TYK2 is a member of the JAK family and an important determinant of host immunity both in man and mice. TYK2 deficiency leads to a high sensitivity to microbial infections and an increased tumour growth but improves clinical symptoms in several autoimmune diseases. Canonically, cytokine-activated TYK2 amplifies the phopshotyrosine-mediated activity of signal transducer and activator of transcription (STAT) proteins resulting in altered transcriptional profiles. There is also evidence of kinase-independent, i.e. scaffolding functions of TYK2.

Using mice deficient for TYK2 (Tyk2-/-) and mice expressing a kinase inactive version of TYK2 (Tyk2K923E) we are able to explore the kinase-dependent and independent functions. Tyk2K923E phenocopies complete loss of TYK2 with respect to canonical cytokine signalling. Loss of TYK2 leads to an impairment in NK cell maturation that is partially restored in Tyk2K923E mice. Conditional mouse models showed that NK cell-intrinsic TYK2 is not required for maturation and anti-tumor activity, while deletion of TYK2 in DCs results in impaired NK cell functionality as observed in complete TYK2-deficient mice.

We hypothesise that the restored NK cell maturation in Tyk2K923E mice is governed at least in part by kinase-independent functions of TYK2 in DCs. Furthermore, we hypothesise that loss of TYK2 and presence of TYK2K923E differentially alter the chromatin landscape and the transcriptional profile of DCs as well as the DC subset composition or functionality. In a first step we use next generation sequencing technologies (ATAC-seq, ChIP-seq, SMART-seq2) to characterise chromatin accessibility and the activity of splenic cDCs derived from wild-type (WT), Tyk2K923E and Tyk2-/- mice. Additionally, we have completed single cell RNA-seq on DC-enriched splenocytes (MACS lineage negative selection) of WT, Tyk2K923E and Tyk2-/- mice, comparing the role of TYK2 among subsets of DCs (cDCs, pDCs and monocyte derived cells).

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Authors :
References : , , ,

Authors

Stephen Shoebridge 1, Sabine Macho-Maschler 1, Katrin Meissl 1, Milica Krunic 1, Matthias Farlik 2, Christoph Bock 2, Nikolaus Fortelny 2, Marlies Dolezal 3, Frank Ruge 3, Caroline Lassnig 4, Birgit Strobl 4, Mathias Müller 4,

1. Institute of Animal Breeding and Genetics, University of Veterinary Medicine Vienna, Vienna, AUSTRIA
2. Research Center for Molecular Medicine (CeMM) of the Austrian Academy of Sciences, Vienna, Vienna, AUSTRIA
3. Platform Bioinformatics and Biostatistics, University of Veterinary Medicine Vienna, Austria, Vienna, AUSTRIA
4. Institute of Animal Breeding and Genetics, University of Veterinary Medicine Vienna, Austria, Vienna, AUSTRIA