(Non-)canonical TYK2 - a monarch in signalling into chromatin?

The non-receptor tyrosine-protein kinase 2 (TYK2) is a member of the Janus kinase (JAK) family. In the canonical JAK-STAT signalling pathway, cytokine-activated TYK2 propagates the signal via activation of signal transducer and activator of transcription (STAT) 1-6 into chromatin. TYK2 has been reported to exhibit non-canonical functions, i.e. independent of its kinase activity in both, mice and humans. We have generated mice expressing a kinase-inactive version of TYK2 (Tyk2K923E) and demonstrated that these mice phenocopy complete TYK2 deficiency with respect to type I IFN and IL-12 signalling. However, a novel kinase-independent role of TYK2 was revealed in tumour immunosurveillance involving NK cell maturation and cytotoxicity as well as immune cell cross talks. The Austrian Science Fund FWF Special Research Program (SFB) funded JAK-STAT signalling consortium is dedicated to unravel the STAT- and TYK2-dependent monarchies and hierarchies in shaping chromatin landscapes of myeloid and lymphoid cells by the means of next generation sequencing technologies including ATAC-seq, ChIPmentation, DNA methylation mapping and RNA-seq. Here we present a comprehensive characterization of TYK2 and kinase-inactive TYK2-mediated signalling and their effects on chromatin accessibility and modifications, DNA regulatory elements and transcriptional landscapes in macrophages, NK cells and T cells in homeostasis, upon IFNβ treatment and within a tumour microenvironment. Top listed differentially expressed genes in RNA-seq data sets of homeostatic cells show the indispensable role of TYK2 and its kinase activity in IFN signalling and microbial defense responses in macrophages as well as in maintenance of the MHC class I antigen presentation machinery in NK cells. In addition, we demonstrate an unexpected function of kinase-inactive TYK2 in the metabolism of NK and T cells.

Keywords : JAK-STAT, next generation sequencing, RNA-seq, Epigenetics, metabolism, macrophages
Authors :
References : , , ,

Authors

Anzhelika Karjalainen 1,

1. Animal Breeding and Genetics, Vienna University of Veterinary Medicine, Vienna, AUSTRIA