Baseline JAK–STAT signaling maintains immune cell homeostasis

Homeostatic immune cells remain perpetually vigilant against pathogens. We found that baseline JAK–STAT signaling supports the characteristic transcriptional and epigenetic state of homeostatic T cells and macrophages in mice. JAK–STAT signaling under homeostatic conditions was driven by signals from healthy tissue and did not require external immune stimuli.

This is a summary of:
Fortelny, N. et al. JAK-STAT signaling maintains homeostasis in T cells and macrophages. *Nat. Immunol.* https://doi.org/10.1038/s41590-024-01804-1 (2024).

Published online: 29 April 2024

The question

Much of what we know about JAK–STAT signaling concerns its role in acute immune responses[1]. Canonical JAK–STAT signaling is initiated by interferons that are recognized by interferon receptors on the cell surface and activate Janus kinases (JAKs). These JAKs then phosphorylate signal transducer and activator of transcription (STAT) proteins, which translocate to the nucleus and activate interferon-stimulated genes (ISGs).

However, already two decades ago it was proposed that weak interferon stimulation induces baseline ('tonic') interferon signaling, which may enhance the alertness of immune cells toward pathogens[2]. Therefore, we investigated what might be the specific functions and implications of JAK–STAT signaling in homeostatic immune cells.

The discovery

To characterize immune signaling in homeostatic cells, the Vienna JAK–STAT consortium established a comprehensive collection of transcriptomes and chromatin accessibility profiles for macrophages and $CD8^+$ T cells from wild-type and JAK–STAT mutant mouse models under homeostatic (unstimulated) conditions. Integrative analysis of this large dataset uncovered low-level expression of various JAK–STAT target genes in homeostatic immune cells from wild-type mice, and this was abrogated in different ways and to different extents in the JAK–STAT mutants.

We validated our findings in primary tissue samples and observed baseline JAK–STAT signaling for wild-type but not STAT1-mutant mice. Moreover, when we removed T cells and macrophages from their native tissue context and cultured them in the absence of any immune signaling input, they lost baseline JAK–STAT signaling activity and resembled cells from JAK–STAT mutant mice.

These results suggest that tissue signals trigger baseline JAK–STAT signaling in homeostatic immune cells in vivo. Indeed, stimulation with type I interferons restored baseline JAK–STAT signaling only partially in T cells and macrophages deprived of their tissue environment.

Bioinformatic analysis of baseline JAK–STAT signaling in homeostatic immune cells identified regulatory patterns that differed from those observed in cells that activate JAK–STAT signaling in response to pathogens. First, we identified STAT2 and IRF9 as the most pronounced transcriptional regulators of transcription in homeostatic immune cells. Second, deletion of the ISGF3 complex members STAT1, STAT2 or IRF9 caused transcriptional changes that were distinct from each other and affected genes well beyond the ISGs, which are the canonical targets of ISGF3 upon interferon stimulation.

Third, in homeostatic immune cells, STAT1 maintained open chromatin in several genes that exceeded those targeted by the ISGF3 complex. This observation further supported the existence of ISGF3-independent roles for members of the ISGF3 complex under homeostatic conditions.

In summary, our study uncovered important and diverse mutant-specific roles of JAK–STAT signaling that are crucial for maintaining the transcriptional and epigenetic state of homeostatic T cells and macrophages in mice.

The implications

Our investigation of JAK–STAT signaling in homeostasis suggests a general mechanism for maintaining cellular plasticity: low-level stimulation within the tissue environment – for example, via cytokines and cell–cell interactions – triggers cell type-specific baseline signaling, and thereby helps to maintain open chromatin and modest gene expression of the pathway's target genes, which determine cellular identity and readiness for stimulation.

There are interesting links between homeostatic JAK–STAT signaling in immune cells and the epigenetic potential for rapid immune responses that we previously observed among epithelial cells, endothelial cells, and fibroblasts[3]. These structural cells also need to sustain immune vigilance and cellular plasticity over long periods of time and react quickly upon pathogen encounter. It will be interesting to test whether homeostatic structural cells maintain their epigenetic potential for rapid immune activation by signaling pathways such as JAK–STAT.

Mutations in the JAK–STAT pathway can lead to immunodeficiency, chronic inflammation or cancer, and targeting JAK–STAT signaling holds therapeutic promise for many of these diseases[4]. Our findings highlight the importance of assessing the potential effects of altered baseline JAK–STAT signaling in pathophysiology, disease diagnosis, and targeted therapy.

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EXPERT OPINION

"Using extensive analyses of systematic STAT knockouts followed by transcriptional and epigenomic profiling, as well as ex vivo cell cultures, the authors point towards a crucial role for JAK–STAT pathways in maintaining homeostatic gene regulation in CD8⁺ T cells and macrophages. The experimental and analytical design is robust and thorough, and the study advances our understanding of the role of JAK–STAT in maintaining homeostatic regulatory state in the selected immune cells under non-infected conditions." **Shankar Subramaniam, University of California, La Jolla, CA, USA**

FIGURE

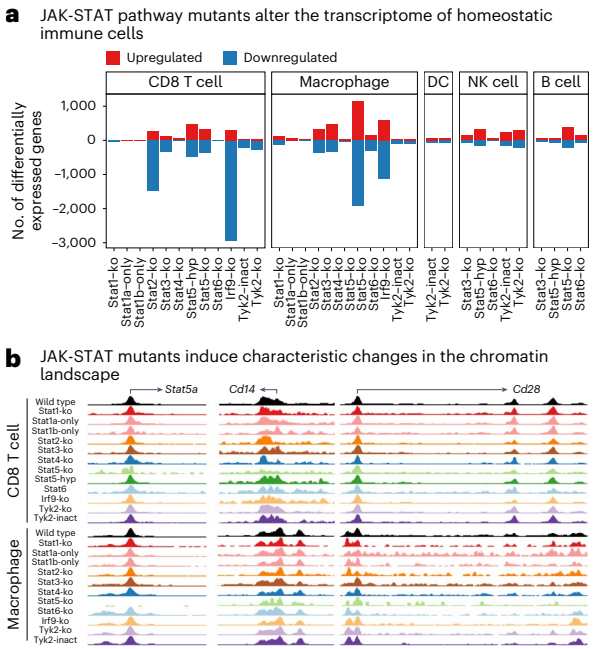

Fig. 1 | Widespread effects of JAK–STAT mutants on homeostatic immune cells. a, Bar plots showing the number of differentially expressed genes in T cells, macrophages, dendritic cells (DC), natural killer (NK) cells, and B cells from JAK–STAT mutant and wild-type mice. **b**, Chromatin accessibility profiles for the promoter regions of the *Stat5a* gene, the macrophage marker gene *Cd14*, and the T cell marker gene *Cd28* in wild-type mice and in mice with 12 different mutations affecting the JAK–STAT signaling pathway. hyp, hyperactivating mutation; inact, inactivating mutation; ko, knockout.

BEHIND THE PAPER

By historical coincidence, Vienna has perhaps the world's highest density of JAK–STAT researchers, supported by a string of 'special research area' grants of Austria's national funding agency FWF. When I came to Vienna with a background in epigenomics and bioinformatics, the coordinators of the Vienna JAK–STAT consortium, Thomas Decker and Mathias Müller, invited me to join their plans for a new grant aimed at connecting the dots and creating a comprehensive genome-wide map of JAK–STAT signaling in immune cells.

Using a collection of 12 JAK–STAT-mutant mice that were available within the consortium, we established and analyzed epigenomes and transcriptomes through the painstaking work of postdocs Matthias Farlik and Nikolaus Fortelny, and with extensive support by eight contributing labs. We put an emphasis on consistent sample handling and high data quality, to be able to see even mild changes in unperturbed, homeostatic cells. In fact, much of the work of the paper revision focused on providing further evidence that baseline JAK–STAT signaling is robustly seen in homeostatic immune cells in vivo. **C.B.**

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FROM THE EDITOR

"This paper provides a thorough analysis of the roles of JAK–STAT signaling in the steady state and suggests that these pathways are crucial for maintaining homeostatic gene regulation in CD8⁺ T cells and macrophages." **Stephanie Houston, Senior Editor, *Nature Immunology*.**