Anti-fungal role for type I IFN as dectin-1 triggers non-pathogenic T_H17 cell development

The fungal pathogen receptor dectin-1 instructs the development of non-pathogenic T_H17 cells via TGFβ activation. This process requires strict control of the expression of type I interferon to ensure a delicate balance in the expression of its effector genes that control the release of active TGFβ.

This is a summary of:
Gringhuis, S. I. et al. Fungal sensing by dectin-1 directs the non-pathogenic polarization of T_H17 cells through balanced type I IFN responses in human DCs. *Nat. Immunol.* https://doi.org/10.1038/s41590-022-01348-2 (2022).

Published online:
Published online: 2 December 2022

The question

Although the anti-viral role of type I interferon (IFN) responses has been appreciated for several decades[1], we were interested in whether and how these responses contributed to anti-fungal immunity. Our first observation was that dectin-1, the main fungal receptor, induced a very brief and small wave of IFNβ and its effector genes, especially when compared with the huge amounts of type I IFN that are released in response to viral infections through RIG-I-like receptors. We found this observation intriguing, particularly as our previous research on dectin-1 signaling had already uncovered how well balanced its signals are to ascertain the appropriate responses for clearing invading fungi[2]. Hence, we felt that furthering our knowledge of dectin-1 signaling might help us to understand anti-fungal responses better — particularly for diseases in which fungal infections are uncontrolled for unknown reasons.

The discovery

As dectin-1 induced such a restrained type I IFN response, we first investigated what would happen in the absence of type I IFN signaling, by blocking its receptor with neutralizing antibodies, as well as in the presence of excess type I IFN through the addition of supplementary IFNβ. Our readout was an in vitro assay in which dendritic cells, on which dectin-1 is present, instruct CD4 T cells to mount an immune response. We determined this response by measuring the intracellular cytokine levels in the T cells. Our results showed that in normal circumstances, T cells developed that predominantly co-expressed IL-17 with IL-10 (non-pathogenic T_H17 cells), which is the appropriate immune response to clear fungal infections without causing damage to tissues. However, when we blocked type I IFN responses or added high amounts of type I IFN, we found that an increased number of T cells developed that co-expressed IL-17 and IFNγ (pathogenic T_H17 cells) (Fig. 1); these cells are known to cause inflammation and tissue damage. We also found that the dendritic cells did not induce the release of active TGFβ when we either blocked or enhanced type I IFN. TGFβ is known to block the production of IFNγ in T cells, and we showed that the release of active TGFβ was the key to the development of non-pathogenic T_H17 cells through dectin-1 signaling. We then investigated in detail which IFN-responsive genes were required for the release of active TGFβ, and which genes counteracted this process. We concluded that the delicate balance in type I IFN responses induced by dectin-1 signaling was to ensure TGFβ activation and the development of non-pathogenic T_H17 cells.

The implications

In a broader context, our results point toward an important role for aberrant type I IFN responses and the suppression of TGFβ activation in diseases that are driven by pathogenic T_H17 responses, such as rheumatoid arthritis, Crohn's disease[3] and some cases of severe COVID-19[4]. Hence, restoring type I IFN responses, while keeping in mind that both heightened and suppressed type I IFN levels are harmful, might attenuate pathogenesis.

We cannot simply conclude that severe fungal infections are caused by aberrant dectin-1 signaling and/or type I IFN responses, as other errors could also lead to pathogenic T_H17 cell development or even the absence of overall T_H17 cell-mediated immunity, and we next plan to investigate these questions. We also aim to determine the role of other fungal receptors, and whether or how these receptors cooperate with dectin-1 or sabotage dectin-1 signaling to prevent fungal clearance.

Sonja I. Gringhuis &
Teunis B. H. Geijtenbeek
Amsterdam UMC, Department of Experimental Immunology, Amsterdam, The Netherlands.

EXPERT OPINION

"This study devises a dectin-1-dependent pathway that gives dendritic cells tight control over the release of TGFβ during antigen-specific priming of T_H17 cells. This pathway could be exploited to reduce immunopathology without weakening host defense against fungal pathogens." **Thomas Korn, Technical University of Munich School of Medicine, Munich, Germany.**

FIGURE

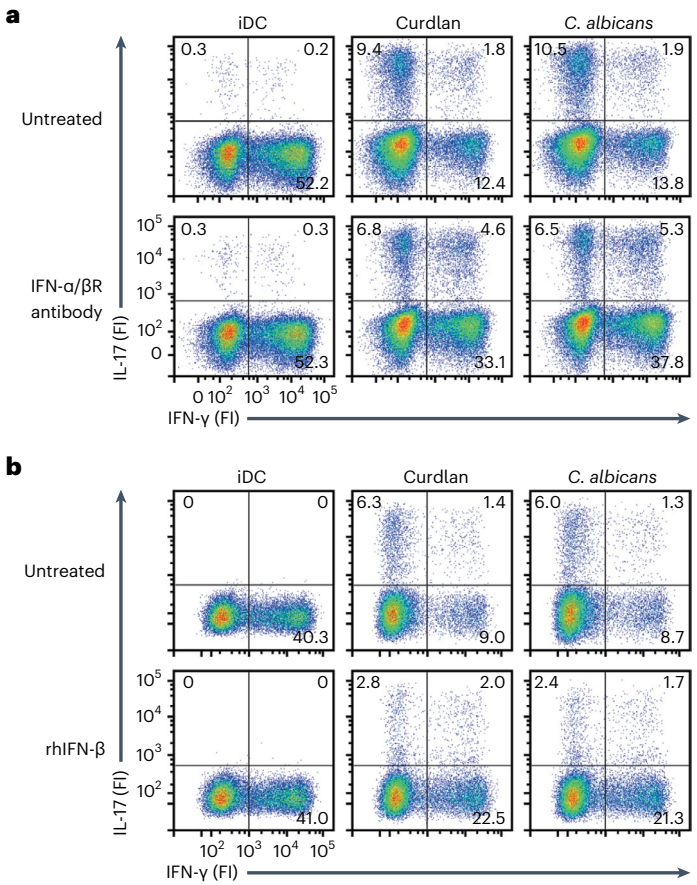

Fig. 1 | Dectin-1 signaling induces non-pathogenic T_H17 cell development via balanced type I IFN expression. a,**b**, Curdlan-primed or *Candida albicans*-primed immature dendritic cells (iDCs) instruct the development of primarily IFNγ$^-$IL-17$^+$ CD4 T cells, which shifts to the development of more IFNγ$^+$IL-17$^+$ cells when type I IFN signaling is blocked by anti-IFNα/βR antibody (Ab) (**a**) or enhanced by the addition of recombinant human IFNβ (rhIFNβ) (**b**).

BEHIND THE PAPER

We first started this research when T_H17 cells were already well known, but their plasticity had not yet been established and embraced. Our first results showed no differences in the overall development of T_H17 cells when we blocked type I IFN signaling and, as such, we hit a dead end. Progress was slow until other labs began to show in mouse experiments that various factors could affect the phenotype of the developed T_H17 cells. When re-examining our data, we clearly saw how the phenotype of the developed T_H17 cells would change from low percentages of IFNγ$^+$ cells to predominantly IFNγ$^+$ cells. When we found that type I IFN had a profound effect on the release of active TGFβ, we could make the connection, and dive into the underlying molecular mechanisms. **S.I.G.**

REFERENCES

1. McNab, F., Mayer-Barber, K. & Sher, A. et al. Type I interferons in infectious disease. *Nat. Rev. Immunol.* **15**, 87–103 (2015).
   A review article that discusses the role of type I IFN and its effector genes in viral and bacterial infections.
2. Gringhuis, S. I. et al. Dectin-1 directs T helper cell differentiation by controlling noncanonical NF-κB activation through Raf-1 and Syk. *Nat. Immunol.* **10**, 203–213 (2009).
   This paper reports how dectin-1 signaling evokes a balance between the activities of the transcription factors RelA (also known as p65) and RelB to induce anti-fungal TH1 cell immune responses.
3. Ueno, A. et al. Th17 plasticity and its relevance to inflammatory bowel disease. *J. Autoimmun.* **87**, 38–49 (2018).
   A review article that discusses how T_H 17 plasticity has a key role in the pathogenesis of IBD.
4. Lee, J. S. & Shin, E. C. The type I interferon response in COVID-19: implications for treatment. *Nat. Rev. Immunol.* **20**, 585–586 (2020).
   A comment article that discusses the role of both heightened and suppressed type I IFN responses at different stages of COVID-19.

FROM THE EDITOR

"T_H17 cells perform important physiological functions, but can also be induced to pathological phenotypes in autoimmune and other inflammatory conditions. This study provides an interesting insight into how the balance between the two could be disturbed by an uncalibrated type I IFN response in the dendritic cells that sense the pathogens." **Ioana Visan, Senior Editor, *Nature Immunology*.**