RESEARCH HIGHLIGHT

Add on the next level—the time point of the type I IFN response orchestrates the immune response

Angela Wedekind[1], David Fritzsch[1] and Andrea Kröger[1,2]

Cellular & Molecular Immunology _####################_; https://doi.org/10.1038/s41423-020-0442-7

The directed control of an effective cellular or adaptive immune response is the aim of vaccine strategies and tumor therapy. Neutralizing antibodies prevent the spread of pathogens, while efficient cellular immunotherapy is used to overcome T-cell exhaustion and unresponsiveness toward self-antigens. In such settings, the type I interferon (IFN) system mediates pleiotropic effects of the immune system that can be either immunostimulating or immunosuppressing. In a recent work, De Giovanni et al. identified a novel regulatory checkpoint by which type I IFN regulates $CD4^+$ T-cell polarization. This study dissects the time point of type I IFN induction as a central regulator of the adaptive immune response that determines the balance between humoral and cellular immunity. These findings identify an intriguing and previously undescribed checkpoint that can potentially be manipulated for immunotherapy. Furthermore, the authors demonstrate that $CD4^+$ T-cell polarization could be influenced by manipulating the IFN response during infection.

When pathogens are detected by cells of the innate immune system, such as macrophages and dendritic cells (DCs), the expression of type I IFNs is induced. In infected and neighboring cells, type I IFNs cause the expression of IFN-stimulated genes (ISGs) that have antiviral properties and can inhibit the spread of infectious agents. Cells of the innate immune system respond to type I IFNs by enhancing antigen presentation and the production of cytokines and chemokines. Furthermore, parts of the adaptive immune system, such as antibody production by B cells and the effector function of T cells, are also affected by type I IFNs.[1]

Viral infection mostly leads to the generation of type 1 helper T cells (T_H1) and follicular helper T cells (T_{FH}), which are subtypes of $CD4^+$ T cells and have an impact on adaptive immunity.[2,3] The mechanisms by which pathogens lead to generation of various effector cells are incompletely understood. De Giovanni et al. analyzed the impact of two different virus infections on the polarization of $CD4^+$ T cells. They used vesicular stomatitis virus (VSV), a cytopathic virus that induces potent neutralizing antibodies, and lymphocytic choriomeningitis virus (LCMV), a noncytopathic virus that elicits a robust cellular response.[4] Antigen-specific Tg7 or SMARTA $CD4^+$ T cells were adoptively transferred prior to the infection of mice with VSV or LCMV, respectively. In VSV-infected mice, >40% of antigen-specific $CD4^+$ T cells differentiated into T_{FH} cells, whereas upon LCMV infection, $CD4^+$ T cells differentiated into mostly T_H1 cells. Although the binding affinity of a T-cell receptor to an antigen influences T-cell fate, the authors showed that this effect on $CD4^+$ T-cell polarization was independent of antigen affinity.

Microscopy recordings showed that the infection influenced the dynamic behavior of antigen-specific $CD4^+$ T cells. After VSV infection, antigen-specific $CD4^+$ T cells were found primarily in B-cell follicles, while most antigen-specific T cells were outside these structures after LCMV infection. To investigate differences during $CD4^+$ T-cell priming, the cellular and molecular composition of the "priming-niches" were analyzed by NICHE-seq.[5] This method combines the marking of areas in the lymph nodes (LNs) that contain antigen-specific $CD4^+$ T-cell clusters by photoactivation and single-cell RNA sequencing to spatially reconstruct immune niches. The priming niches of VSV- and LCMV-infected mice differed in their cellular composition. After VSV infection, B cells and $NKp46^+$ cells were overrepresented, and LCMV infection led to the accumulation of $CD8^+$ T cells and $CCR2^+$ inflammatory monocytes. By using different conditional knockout and transgenic mice, the researchers determined that the different cellular compositions of the priming niches did not initially influence $CD4^+$ T-cell polarization. Instead, they identified the interaction between DCs and cognate $CD4^+$ T cells as the main stimulus for the differentiation of both T_{FH} and T_h1 cells. It is known that IL-6 promotes early T_{FH} differentiation[6,7] and that this effect depends on the induction of type I IFN.[8] Kinetic analysis of different IFNs and two representative ISGs isolated from the priming niches of the LNs after infection with VSV and LCMV was performed. The magnitude of type I IFN induction did not significantly differ between the two infections, but VSV induced an earlier wave of type I IFN, whereas LCMV induced a delayed and prolonged wave of type I IFN. To examine the impact of the general existence of a type I IFN response on $CD4^+$ T-cell polarization, the type I IFN response was either blocked by specific anti-IFNAR-1 antibodies or induced by poly(I:C) treatment.

Whereas blocking the early IFN response during VSV infection inhibited T_{FH} polarization, induction of the early type I IFN response during LCMV infection induced T_{FH} polarization, indicating that the time point of IFN stimulation is an important regulator of $CD4^+$ T-cell polarization. Together with previously described results, the authors determined the type I IFN-induced expression of IL-6 in DCs by assessing the composition and transcriptional state of DC subsets after early and late type I IFN sensing. They observed that the IL-6 expression of DCs drove T_{FH} cell polarization in response to early (VSV) but not to late (LCMV) type I IFN signaling. This result indicates that spatiotemporal

[1]Research Group Molecular Microbiology, Institute of Microbiology and Hospital Hygiene, Otto von Guericke University, 39120 Magdeburg, Germany and [2]Research Group Innate Immunity and Infection, Helmholtz Centre for Infection Research, 38124 Braunschweig, Germany
Correspondence: Andrea Kröger (andrea.kroeger@med.ovgu.de)
These authors contributed equally: Angela Wedekind, David Fritzsch

Received: 2 April 2020 Accepted: 7 April 2020
Published online: 28 April 2020

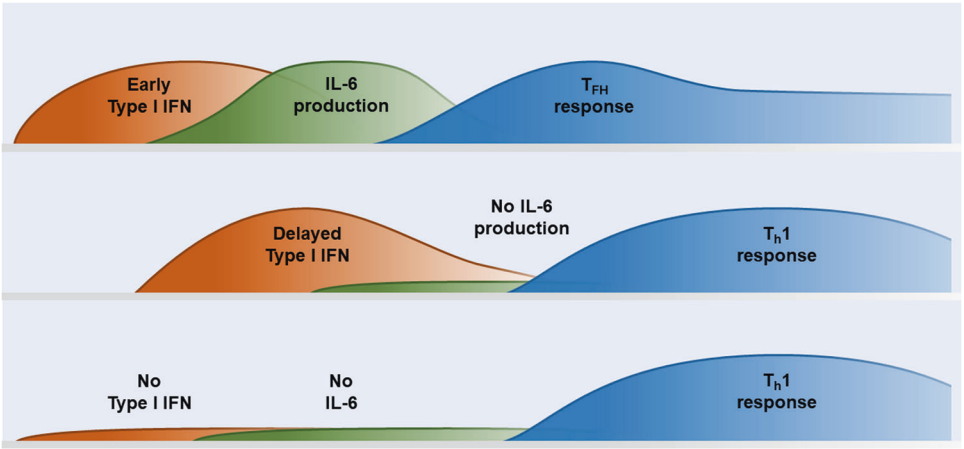

Fig. 1 Different expression of type I IFN and IL-6 leads to different antiviral T-cell responses. In lymph nodes, the early expression of type I IFN during a viral infection leads to a significant production of IL-6 and further to an effective T_{FH} response. The delayed availability of type I IFN does not result in significant IL-6 production and is connected to a T_h1 response. If no type I IFN is available during a viral infection, no IL-6 is produced, but a T_h1 response is still established.

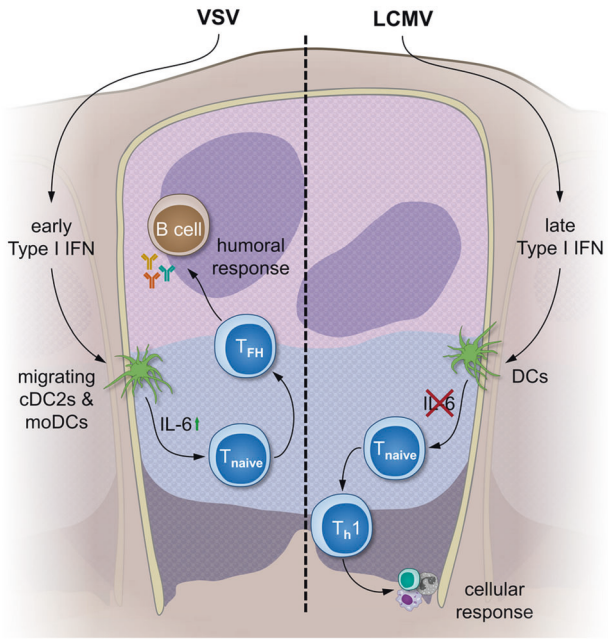

Fig. 2 Different polarization of T cells based on spatiotemporal regulation of type I IFN. In the lymph node, the early availability of type I IFN after a VSV infection leads mainly in type 2 conventional dendritic cells (cDC2s) and monocyte-derived dendritic cells (moDCs) to an increased production of IL-6. This effect drives naive T cells in the paracortical area to differentiate into T_{FH} cells. They migrate into the follicular area and facilitate a strong humoral response by promoting the production of effective neutralizing antibodies. The delayed availability of type I IFN associated with LCMV infection does not influence DCs toward considerable IL-6 production. As a result, a large number of naive T cells differentiate into T_h1 cells and, in contrast to T_{FH} cells, promote antiviral activity facilitated by a cellular response.

regulation of type I IFN expression determines whether DCs in the lymph node produce the cytokine IL-6 and shape antiviral $CD4^+$ T-cell polarization (Fig. 1).

The study conducted by De Giovanni et al. highlights the temporal component of IFN induction for the regulation of $CD4^+$ T-cell polarization toward T_{FH} or T_{H1} cells (Fig. 2). These findings provide new information for understanding the outcome of viral infections and further advances in handling the manipulation of immune responses in the desired direction for vaccine development. However, further investigations are of utmost interest. It remains unclear how other cellular sources of IL-6 influence antiviral $CD4^+$ T-cell polarization. In addition, the preceding relative contribution of all cells in the LN to type I IFN production was itself an unsolved question. Aside from the polarization of $CD4^+$ T cells, the level of induction and the temporal occurrence of IFN have far-reaching consequences. In the case of virus infections, IFN not only limits the viral load but also has beneficial immunostimulatory functions. In the case of influenza infections, the high expression level of type I IFN also leads to the massive induction of proinflammatory cytokines such as TNF, IL-1β, IL-6, and chemokines, which are ultimately responsible for pathological effects in the lung.[9] A temporal effect of IFN-mediated pathology can also be observed during coronavirus infection. Here, only an early induction of type I IFN was beneficial and reduced viral replication, whereas a late induction of type I IFN was associated with dysregulation of inflammatory macrophages and immunopathology.[10] In summary, the work of De Giovanni et al. adds an important piece to an incomplete puzzle of IFN function and adds spatiotemporal regulation as a new dimension. By characterizing the cellular and molecular composition of the LN niches where $CD4^+$ T-cell polarization occurs and identifying the causative cytokine dynamics, this work generated important knowledge with respect to antiviral responses and their possible pharmaceutical utilization.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

REFERENCES

1. Ivashkiv, L. B. & Donlin, L. T. Regulation of type I interferon responses. *Nat. Rev. Immunol.* **14**, 36–49 (2014).
2. Hale, J. S. et al. Distinct memory CD4+ T cells with commitment to T follicular helper- and T helper 1-cell lineages are generated after acute viral infection. *Immunity* **38**, 805–817 (2013).
3. Wu, T. et al. Cutting edge: miR-17-92 is required for both CD4 Th1 and T follicular helper cell responses during viral infection. *J. Immunol.* **195**, 2515–2519 (2015).
4. De Giovanni, M. et al. Spatiotemporal regulation of type I interferon expression determines the antiviral polarization of CD4+ T cells. *Nat. Immunol.* **21**, 321–330 (2020).

5. Medaglia, C. et al. Spatial reconstruction of immune niches by combining photoactivatable reporters and scRNA-seq. *Science* **358**, 1622–1626 (2017).
6. Nurieva, R. I. et al. Generation of T follicular helper cells is mediated by interleukin-21 but independent of T helper 1,2 and 17 cell lineages. *Immunity* **29**, 138–149 (2008).
7. Eto, D. et al. IL-21 and IL-6 are critical for different aspects of B cell immunity and redundantly induce optimal follicular helper CD4+ T cell differentiation. *PLoS ONE* **6**, e17739 (2011).
8. Cucak, H. et al. Type I interferon signaling in dendritic cells stimulates the development of lymph-node-resident T follicular helper cells. *Immunity* **31**, 491–501 (2009).
9. Galani, I. E. et al. Interferon-λ mediates non-redundant front-line antiviral protection against influenza virus infection without compromising host fitness. *Immunity* **46**, 875–890.e6 (2017).
10. Channappanavar, R. et al. Dysregulated type i interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. *Cell Host Microbe* **19**, 181–193 (2016).