Editorial

CD4$^+$ T Helper Cell Plasticity in Infection, Inflammation, and Autoimmunity

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CD4 T helper (T$_H$) cells orchestrate the immune response and play a pivotal role in infection, inflammation, and autoimmunity. CD4 T$_H$ cells can be subdivided into different subsets, which are defined based on a specific network of transcriptional regulators and unique cytokine profiles. This model despite its limitation has proven to be useful to understand the complexity of the immune system and its relationship to different types of immune mediated inflammatory diseases. Interestingly recent findings indicate that some T$_H$ cell subsets have a certain degree of plasticity. They can share characteristics typical of other types of T$_H$ cells and potentially lose their original features to convert into another T$_H$ cell subset. This has been shown for all known T$_H$ cell subset but best studied for T$_H$17 cells [1, 2]. Thus T$_H$17 cells have the capacity to acquire a T$_H$1 phenotype under chronic inflammation [3, 4] but can also convert to regulatory T cells [5–9] and participate in the resolution of the immune response [5, 7–9].

These basic aspects of T$_H$ cell lineages and plasticity are discussed by J. E. Belizário et al. who focused on thymic and postthymic regulation of naïve CD4$^+$ T cell lineage fates in humans and mouse models. Furthermore M. L. Diller et al. described the link between T$_H$17 and regulatory T cells highlighting the mechanisms driving T$_H$17 cells plasticity and discussed the biologic consequences of their unique relationship.

T helper cell plasticity seems to play a key role in amplitude of diseases. Accordingly L. Barbarash et al. analyzed T cell response in patients with implanted biological and mechanical prosthetic heart valves. Their findings suggest that altered composition of T cell subsets correlates with the development of xenograft rejection. Furthermore A. Ni et al. studied T$_H$17 cell response following motor nerve injury in mice. They found that motor nerve injury exacerbates T$_H$17 cell responses, which may contribute to the development of amyotrophic lateral sclerosis. J. Ruhnau et al. reported reduced numbers and impaired function of regulatory T cells in peripheral blood of ischemic stroke patients. C. F. Krebs and O. M. Steinmetz review the role of CD4$^+$ T cell fate in glomerulonephritis. Interestingly, T$_H$17 cells seem to have a relatively stable phenotype and regulatory T cells show heterogeneity rather than plasticity during glomerulonephritis. These findings suggest that the environment plays a key role during T helper cell plasticity.

In conclusion, we hypothesize that the study of T$_H$ cell plasticity could pave the way for future therapies aiming to steer an immune response towards the desired outcome. However, it is unclear at which stage of maturation T$_H$ cells will lose their potential plasticity and if T cell plasticity plays an essential role during physiological immune responses or whether it is merely a tolerable "mistake" which does not provide any physiological advantage. If this latter point would turn out to be true, this will not exclude the possibility of reprogramming the immune system but this reprogramming will probably lead to more side effects.

Nevertheless, it is now obvious that we have to enlarge the original frame of the monolithic model of T helper cell subsets in order to fully comprehend the biology of CD4 T cells. Establishing a simplified model, which integrates the original knowledge and the new findings regarding plasticity, will help to predict T helper cell behavior and it will be essential to overcome the current boundaries limiting the potential clinical applications of this knowledge.

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References

[1] J. Geginat, M. Paroni, I. Kastirr, P. Larghi, M. Pagani, and S. Abrignani, "Reverse plasticity: TGF-β and IL-6 induce Th1-to-Th17-cell transdifferentiation in the gut," *European Journal of Immunology*, vol. 46, no. 10, pp. 2306–2310, 2016.

[2] J. Geginat, M. Paroni, S. Maglie et al., "Plasticity of human CD4 T cell subsets," *Frontiers in Immunology*, vol. 5, article 630, 2014.

[3] K. Hirota, J. H. Duarte, M. Veldhoen et al., "Fate mapping of IL-17-producing T cells in inflammatory responses," *Nature Immunology*, vol. 12, no. 3, pp. 255–263, 2011.

[4] S. N. Harbour, C. L. Maynard, C. L. Zindl, T. R. Schoeb, and C. T. Weaver, "Th17 cells give rise to Th1 cells that are required for the pathogenesis of colitis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 112, no. 22, pp. 7061–7066, 2015.

[5] N. Gagliani, M. C. A. Vesely, A. Iseppon et al., "TH17 cells transdifferentiate into regulatory T cells uring resolution of inflammation," *Nature*, vol. 523, no. 7559, pp. 221–225, 2015.

[6] C. E. Zielinski, F. Mele, D. Aschenbrenner et al., "Pathogen-induced human T_H17 cells produce IFN-γ or IL-10 and are regulated by IL-1β," *Nature*, vol. 484, no. 7395, pp. 514–518, 2012.

[7] N. Obermajer, F. C. Popp, Y. Soeder et al., "Conversion of Th17 into IL-17A^{neg} regulatory T cells: a novel mechanism in prolonged allograft survival promoted by mesenchymal stem cell—supported minimized immunosuppressive therapy," *Journal of Immunology*, vol. 193, no. 10, pp. 4988–4999, 2014.

[8] C. Heinemann, S. Heink, F. Petermann et al., "IL-27 and IL-12 oppose pro-inflammatory IL-23 in CD4$^+$ T cells by inducing Blimp1," *Nature Communications*, vol. 5, article 3770, 2014.

[9] R. Basu, S. K. Whitley, S. Bhaumik et al., "IL-1 signaling modulates activation of STAT transcription factors to antagonize retinoic acid signaling and control the T_H17 cell–iT$_{reg}$ cell balance," *Nature Immunology*, vol. 16, no. 3, pp. 286–295, 2015.