Th17 cells: a third subset of CD4+ T effector cells involved in organ-specific autoimmunity

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concluding remarks

The recent discovery of Th17 cells as a third type of effector T cells has added a further layer of complexity to our understanding of T-cell differentiation. On the other hand, we have learned about a new pro-inflammatory mechanism that appears to be centrally involved in distinct types of tissue-specific autoimmunity, infection and cancer. The eruption of numerous studies published in the leading scientific journals (see the Reference list) highlights that time was ripe for an overhaul of the Th1/Th2 paradigm that served immunological research so long and so well. Although the exact role of Th17 cells in anti-infectious immunity is far from being understood, there is evidence that these cells may contribute to the defence against bacterial, protozoal and fungal pathogens [24] that were not really covered by the Th1/Th2 theory.

In the field of immune-mediated diseases, the Th17-extended concept offers answers to long-known discrepancies resulting from the Th1/Th2 paradigm. Thus, it has been difficult to understand why inhibition of TNFα or IFNγ was beneficial in rheumatoid arthritis, but detrimental in multiple sclerosis [36] (resulting even in a warning of the US Food and Drug Administration about the potential for worsening demyelinating disorders such as MS), although both diseases were viewed as Th1-dependent delayed type hypersensitivity. The involvement of Th17 cells can explain why targeting Th1 mechanisms was counterproductive. Furthermore, the breakthrough that TNFα blockade represents in treatment of rheumatoid arthritis and Crohn’s disease may partially be due also to inhibiting Th-17 cells, which also produce some TNFα. The effectivity of IL-6-targeting therapies in rheumatoid arthritis [35,45] may be explained by mechanistic knowledge on the induction of Th17 cells. However, despite the abundance of recent publications on Th17 cells in autoimmunity, one must not dismiss previous data demonstrating the role of Th1 cells in autoimmune diseases such as type 1 diabetes or crescentic glomerulonephritis [21,41]. Since Th1 and Th17 cells appear to cooperate in anti-infectious immunity [7,26,39], it appears conceivable that these cell types might liaise also in organspecific autoimmunity with varying contributions of either subset. In kidney disease, the role of Th17 cells is completely unresolved, but undoubtedly will be addressed in the near future.

A further open question pertains to the regulation of human Th17 cells. Very recent findings showed that their differentiation required cooperation of IL-6 with IL-1, but
not with TGF-β [1,44], questioning whether the notion of compromised TGF-β-mediated T<sub>reg</sub> induction as the cause of Th17 generation [7] is valid in humans. Finally, the nature of the pathogen-associated patterns driving Th17 development awaits elucidation.

It can be expected that the Th1/Th2/Th17 trinity will undergo further modifications, as immunologists resolve the mechanistic details underlying CD4+ T-effector-cell polarization, possibly resulting in an even more intricate picture. Nevertheless, the effort will be worthwhile as it promises new avenues for the development of specific therapies against immune-mediated diseases associated with less immuno-suppressive side effects.