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INTRODUCTION

Th17 cells in mucosal immunity and tissue inflammation

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Abstract T helper type 17 (Th17) cells are a distinct lineage of T cells that produce the effector molecules IL-17, IL-17F, IL-21, and IL-22. Th17 cells have been shown to have critical roles in autoimmunity and tissue inflammation. However, emerging evidence also shows these cells are critical regulators of host immunity against bacterial, fungal, and viral infections at mucosal surfaces. Moreover, these cells can be induced following vaccination and have been shown to be critical for vaccine efficacy against both extracellular and intracellular pathogens. In this issue, we summarize recent progress in our understanding of the function of Th17 cells and where these cells fit in protective immunity and immunopathology.

Introduction

CD4+ T helper cells are critical cells that mediated adaptive immune responses. As evidence of this, their progressive loss in the setting of HIV disease is closely linked to the development of opportunistic infections [1, 2] such as Pneumocystis pneumonia. In fact, it was recognized shortly after the initial description of AIDS that the primary immunodeficiency was loss of circulating CD4+ T cells and that the risk of opportunistic infection with many pathogens was directly related to the severity of the CD4+ T cell deficiency [1]. Four years after the initial description of AIDS, Mossmann and Coffman described the first two CD4+ T cells subsets based on the ability of these cells to produce a distinct profile of cytokines [3]. Cells that produced interferon-gamma were termed Th1 cells, and cells that produced interleukin (IL)-4, IL-5, and IL-13 were Th2 cells. This dichotomous paradigm has been validated in several mammalian species. Further evidence that these cells represent distinct lineages is the fact that their differentiation from naive T cells requires distinct transcription factors, STAT 4 [4–6] and T-bet [7] for Th1 cells and STAT6 [8, 9] and GATA-3 [10, 11] for Th2 cells.

This dichotomy of T cell subsets was the basis of T cell immunology for nearly 20 years. However, this dichotomy of T cell subsets could not fully explain the infections seen in congenital or acquired absence of CD4+ T cells such as mucosal candidiasis, *Pneumocystis carinii* pneumonia, or some bacterial pneumonias. For example, mice deficient in Th1, Th2 responses (or both) are not permissive for *P. carinii* pneumonia [12], a hallmark infection in AIDS patients with low CD4+ T cell counts. Moreover, while mice deficient in IL-12p40, a molecule known to drive Th1 responses, were protected against autoimmune inflammation such as experimental autoimmune encephalitis, mice deficient in the hallmark Th1 cytokine, IFNγ, or the other IL-12p35 subunit were not [13]. Taken together, these data suggested that other CD4+ T cell lineages must exist, and these cells must play critical roles in autoimmunity but also in host defenses against opportunistic infections.

Data from a number of laboratories now have clearly changed the traditional paradigm of Th1/Th2 cells. In addition to these effector T cells, a third subset of T cells as emerged referred to as Th17 cells [14–17]. Th17 cells produce the cytokines IL-17A (IL-17) [14, 15] and IL-17F [16], as well as the cytokines IL-21 [18, 19] and IL-22 [20, 21]. This new Th17 cell lineage fills in many of the missing gaps in host immunity not fully explained by the Th1/Th2 paradigm.

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In this issue of Seminars in Immunopathology, we address key issues regarding Th17 cells. What controls their development? What are the positive and negative signals that regulate their fate, survival, and establishment of memory? What regulates the expression of their main effector cytokines IL-17A, IL-17F, and IL-22? What are the requirements for these ligands to signal and in what tissues? What role do these cells play in autoimmune inflammation in the mucosa (gut) and non-mucosal sites such as the central nervous system? Lastly, what is their role in host defense, and can Th17 cells be exploited by vaccination strategies to enhance immunity against various pathogens? In summary, we believe this issue is timely and will be a useful review of our current understanding of Th17 cells and hopefully, will serve as a basis to push the field forward.

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