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Editorial

Back to the T Cell: Basic and Clinical Application

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Since the first vaccine was tried in human medicine in the 1700s, immunity has been a central focus for protecting our health and lives. However, the key players in the immune system were not discovered until the 1960s, when Good and his colleagues identified 2 types of lymphocytes in chickens (1). These groundbreaking findings opened up a new field in immunology, but it took another decade for Zinkernagel and Doherty (2) to determine how T cells recognize antigens. Since then, much progress has been made in understanding the fundamental functions of T cells in health and disease.

In addition to these foundational research findings, there have been significant advances in the clinical implications of T cells. The most prominent T cell-based immunotherapies include, but are not limited to, immune checkpoint therapy, chimeric antigen receptor-T cell therapy, and vaccines (3). Other immunotherapies indirectly or directly modify T cells for therapeutic purposes. Since the current coronavirus disease 2019 pandemic, interest in T cell responses to disease has never been higher. In particular, the importance of vaccine or infection-induced T cell responses in controlling viral infections has been increasingly emphasized, especially after reports of neutralizing antibodies against severe acute respiratory syndrome coronavirus 2 variants. These recent developments have encouraged us to re-evaluate T cells to gain a deeper understanding of their precise roles in these immunotherapies and to engineer T cells to achieve better therapeutic outcomes.

In this special issue of the Immune Network, a collection of review articles provides a comprehensive overview of T cells and their regulation. It begins by examining the heterogeneity of naïve T cells, which is crucial for T cells to respond to a wide range of antigens. This review article presents the current knowledge on how the diversity of naïve T cells can lead to the formation of various effector and memory subpopulations in response to antigenic stimulation, and how the fate of T cell responses is determined (4). Additionally, a manuscript explores recent findings on T cell microvilli, which can release TCR after interacting with antigen-presenting cells, and their role in regulating immune responses to antigens (5).

The development of effector and memory T cells is vastly different between $CD4^+$ and $CD8^+$ T cells. While $CD4^+$ Th cells can be classified into various types of subpopulations based on the cytokines they produce, the diversity of effector $CD8^+$ CTLs is limited. Since the first description of the Th1/Th2 paradigm, many different subsets of Th cells have been discovered, and the key factors influencing their formation and functions, including cytokines and transcription factors, have been intensively studied. The current

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understanding of these factors is described in a review article (6). Other crucial factors for metabolic and epigenetic regulation and fate decision, as well as factors related to the plasticity and heterogeneity of Th cells, are also summarized (7). Among these subsets, the specific plasticity between Th17 and Treg has been a point of interest in the gut, primarily due to the factors produced by microorganisms in the organ (8). These microorganisms have also received attention because they produce metabolites that modulate the differentiation and functions of Th cells (9).

$CD8^+$ T cells have also attracted much attention for their potential to kill abnormal cells in immunotherapies for tumors and viral infections. CTLs are a heterogeneous population, and it is crucial to understand the characteristics of each subpopulation for clinical implications. One review article focuses on the regulation of CTL function based on the expression of NK receptors, which determines the functions and regulations of CTL subsets (10). Another article highlights the importance of metabolic switch in the tumor microenvironment for regulating CTL function, as nutrients and critical metabolites are limited (11).

Small subsets of effector T cells differentiate into memory T (Tm) cells after clearing the antigen, which are long-lived and respond robustly to the same antigens. However, Tm cells are also heterogeneous, so they must be carefully selected for application in human diseases (12). Another recent discovery, the "memory-like" T cell population called virtual memory T (Tvm) cells, which acquire a memory phenotype in the absence of foreign Ag, is reviewed. The article outlines the distinct characteristics, immunological properties, and potential application of Tvm cells in immunotherapy (13). In conclusion, these review articles provide a comprehensive overview of T cell biology and offer ideas for further implications in human diseases.

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