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Review

Development of T follicular helper cells and their role in disease and immune system

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ABSTRACT

The T follicular helper cells (TFH) are a subset of CD4+ T cells specialized to regulate antibody responses. The production of these cells is associated with the dendritic cells (DCs) and B cells. TFH cells help B cells form germinal centers (GC) differentiate into memory and plasma cells (antibody-secreting cells) as humoral responses. In addition, there is strong evidence that TFH cells play a pivotal role in the development of long-lived humoral immunity. Molecular factors such as transcription factors, surface receptors, cytokine and micro RNAs are involved in the formation of TFH cells. Such TFH cells are diagnosed by transcription factor (BCL-6), surface marker expression (including CXCR5, PD-1, ICOS and CD40L) and a unique cytokine production pattern (such as IL-21 and IL-6). Memory TFH cells, accompanied by memory B cells, are known to be formed during antibody responses. It is now clear that the precise control of TFH cells is critically important for both inducing the optimal affinity maturation of antibody responses and preventing self-reactivity. Exclusive controls of TFH cell function and production are essential for human health. However, it is important to note that excessive activities may lead to autoimmune diseases, while reduced activity often results in immunodeficiency. It has also been shown that TFH cells are associated with cancers such as angioimmunoblastic T-cell lymphoma (AITL), follicular T-cell lymphoma (FTCL) and nonspecific Peripheral T-cell lymphomas (PTCLs). The biology of TFH cells, including their differentiation and transcriptional regulation will be described in the present review. Some of The developments of these cells in immunodeficiency diseases, autoimmunity and cancer will also be taken into account.

Contents

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1. Introduction

More recently, T follicular helper cells (TFH) have been a new topic for immunologists due to the central role in immune responses associated with antibodies. TFH cells can be identified by unique expression of surface markers (CXCR7^{lo}, CXCR5^{hi}, ICOS^{hi} and PD-1^{hi}), cytokines (IL-21, IL-6) and, more importantly, expression of transcription factor (BCL-6). TFH cells have the ability both to migrate into secondary lymphoid tissues in B-cell follicles, and to expand germinal centers (GC) that have a close interaction with B cells. In general, there is a stable interaction between B and TFH cells in GC, which is necessary to increase their performance. It is well-known that long-lived humoral immunity depends on the assistance provided by TFH cells, mediating the differentiation of antigen-specific B lymphocytes into memory and plasma cells. While highly regulated TFH cells exhibit an aberrant activity in immune pathologies such as autoimmune diseases, immunodeficiency and lymphoma. Effective protection against pathogens after infection or vaccination depends on the development of appropriate immune responses. Naïve CD4$^+$ T cells, relying on high flexibility and different subgroups, are able to inhibit infections by different specific mechanisms [1] (Fig. 1).

The main function of TFH cells is to regulate clonal selection of germinal center B cells, and to generate antibody signals, class switching and somatic mutations in the B-cell. However, other TFH sub-classes exhibiting FOXP3$^+$ (Forkhead box p3) may inhibit the germinal center reaction [2,3]. Antibody production plays a critical role to induce serological memory and long-lasting immunity against pathogens. The fundamental role of T cells in B-cell differentiation was first described 50 years ago, but TFH cell biology has clearly been achieved over the past decade. In human, TFH cells were first described in the secondary lymphoid tissues as CD4$^+$ T cells displaying the chemokine receptor CXCR5 in the B-cell region, suggesting that they could be localized in B cell follicles. The name “TFH cells” refers to their migration to the follicles, followed by interaction with antigen-specific B lymphocytes to help differentiate B-cells (Fig. 2). The aim of the present study is to summarize the recent advances in understanding the cellular and molecular mechanisms of TFH cell regulation and discuss some of the latest developments of these cells in a range of diseases. It will help to provide deeper insights about the development of therapeutic strategies in immunodeficiency diseases, autoimmunity and cancer.

2. The role of dendritic (DCs) and B cells in generating TFH cells

The production of TFH cells from naive T CD4$^+$ cell precursors clearly involves a constant interaction with some APCs (antigen-presenting cells) such as DCs in T cell zones of lymphoid tissues, and activated B cells at the border of T cell zones and follicles [4]. Recent advances in TFH cell biology have made the clear need for antigen presentation by DCs to produce committed TFH [5]. However, in most cases antigen presentation by B lymphocytes is ultimately responsible for induction of completed TFH-cell differentiation. TFH differentiation pathways depend on the expression of BCL-6 (B-cell lymphoma-6) transcription factors, whose expression leads to suppression of other transcription factors specific to T-cell, as well as upregulation of CXCR5. Recent studies have shown that expression of BCL-6 in the TFH cells requires the communication of naïve T CD4$^+$ with antigen-presenting B lymphocytes. Some studies suggested that the relationship between T CD4$^+$ and DCs is out of the follicles [6,7], some of which express low levels of CXCR5 and BCL-6, so-called Pre-TFH cells. It is widely-established that pre-TFH cells migrate to the areas between the follicle B and T zones, encounter antigen-activated B cells and receive their own specific differentiation and survival signals requiring for complete differentiation and sustained TFH-cell responses [8,9] (Fig. 3).

3. Molecular factors involved in creating TFH

3.1. Transcription factors

3.1.1. BCL-6

BCL-6 is a transcription factor stimulating FH cell differentiation (Ma [10]). BCL-6 expression is induced in two ways: first, after interaction between naive T cells and dendritic cells and second, during interaction with B-cells. IL-12 production by DCs is a potential inducer of BCL-6 in humans, and on the other hand IL-21 and IL-6 can also induce unregulated BCL-6 [10,11] (Fig. 4). BCL-6 is needed to develop TFHs and GC responses associated with T cells. This factor expresses AP, CD40L, PD-1 and ICOS which are essential for interaction between B and T cells [12,13].

3.1.2. BLIMP1

BLIMP1 (B lymphocyte-induced maturation protein 1) directly limits the production of TFH cells through the suppression of the