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Review
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TFH AND TFR CELLS IN AUTOIMMUNE DISEASES

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Abstract: An immunological condition known as autoimmunity causes the excessive generation of autoantibodies against self-antigen and is characterized by enhanced T-cell activation and extra-stimulated B-cells. The development of lymphatic follicle germinal centers (GCs), the maturation of B cells, and differentiation into plasma cells are all significantly aided by follicular helper T cells (Tfh). Tfh cells express the transcriptional regulator B cell lymphoma 6 (BCL-6), C-X-C chemokine receptor 5 (CXCR5), inducible T cell co-stimulator (ICOS), and programmed cell death protein 1 (PD-1). The production of interleukin (IL)-21 and low expression of the chemokine (C-C motif) receptor 7 (CCR7) define Tfh cells. Additionally, Tfh cells are a diverse population of cells with the potential to co-express minute quantities of transcription factors, such as T-box expressed in T cells (T-bet), GATA-binding protein 3 (GATA-3), and retinoic acid receptor-related orphan receptor (ROR-t). Tfh cells that also produce IL-21, IL-4, IL-17, and IFN-γ are referred to as Tfh1, Tfh2, and Tfh17 cells, respectively. The control of humoral immunity is carried out by follicular regulatory (Tfr) cells that express Forkhead box protein 3 (Foxp3). Tfr cells can, however, decrease T-B cell interactions through the cytotoxic T lymphocyte-associated protein 4 (CTLA-4) while promoting B cell maturation through IL-10. In the context of autoimmunity, the role of Tfh and Tfr cells is still not fully understood. We intend to present the most recent data on the characteristics and function of Tfh and Tfr cells under conditions of autoimmunity in this review.

Keywords: Tfh, Tfr, IL-21, Autoimmune disease

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1. Introduction

Autoimmune disease is a common trait of the varied group of disorders that loss of immunological tolerance to self-antigens (Wojciechowicz et al., 2022) Continuous irregular functioning of the immune system reveals autoimmune disease. Pathogenesis of autoimmune diseases is started by the interaction of environmental variables and genetic predisposition (Goverman et al., 2021). There are still a lot of unanswered concerns about the etiology of these diseases due to the variety of their pathophysiology. Follicular helper T cells (Tfh) are a more recent name for the fraction of helper T cells that are distinguished by surface expression of chemotaxis cytokine receptor (CXCR)5 (Breitfeld et al., 2000; Schaerli et al., 2000). Tfh has been shown to play a significant part in the development of high-affinity, class-switched antibodies (Laguna-Goya et al., 2019). Autoimmune disorders frequently exhibit increased interleukin (IL)-21 expression, and Tfh cells are the main sources of IL-21 (Ren et al., 2021). It has been demonstrated that excessive Tfh activation can cause autoimmunity; as a result, differentiation and functions need to be carefully controlled. T follicular regulatory cells (Tfr), a subpopulation of Foxp3-expressing regulatory T cells, regulate the germinal center (GC) reaction (Sage et al., 2020). According to recent research, Tfr cells are crucial in reducing the presence of self-reactive B cells in the GC (Sage et al., 2020). In this review, we will aim to share the latest knowledge about the characteristics and function of Tfh and Tfr cells in autoimmunity settings.

2. Follicular Helper T Cells

When the $CD4^+$ T cell interacts with a dendritic cell (DC), the antigen-presenting cell (APC), Tfh differentiation begins. A naive $CD4^+$ T cell's activation is started by co-stimulatory molecules, which DC generates, MHC-II expression, and cytokine production (Jogdand et al., 2016). The expression of the transcriptional repressor B cell lymphoma 6 (Bcl-6) and early Tfh development are influenced by the molecules inducible T cell co-stimulator (ICOS) and interleukin-6 receptor (IL-6R). Pre-Tfh cells, which develop from $Bcl\text{-}6^+CD4^+$ T cells, engage with B cells and supply extra signals to promote GC-Tfh development (Crotty, 2019).

Tfh cells are mostly present in lymph nodes, which are secondary lymphoid organs, and in chronically inflamed tissues that develop into lymphoid follicles (Hutloff, 2018). CXCR5, ICOS, programmed cell death protein 1

(PD-1), BCL-6, and IL-21 are all expressed by Tfh cells. Tfh cells also control the development or responses of GCs and the activation of B cells (Vinuesa et al., 2016; Tangye et al., 2013). Pre-Tfh cells can move into B cell regions in the lymph node by upregulating the CXCR5 and downregulating the C-C chemokine receptor 7 (CCR7) (Webb et al., 2017). Pre-Tfh cells interact with pre-activated B cells to help them fully develop into Tfh by presenting antigens at the T-B cell boundary (Ma et al., 2012). Tfh cells initiate and sustain GC responses in addition to mediating the positive selection of particular GC B cell clones for terminal development. Additionally, Tfh cells aid GC responses, create effector cytokines including IL-21, and direct B cells to develop into plasma cells (Kräutler et al., 2017). Additionally, Tfh cells suppress Tfr cells by secreting IL-21, inhibiting Tfr cell growth (Sage et al., 2020).

Characteristics of Tfh cells

The production of high-affinity antibody responses depends on Tfh cells, which are also crucial to the adaptive immune response. Tfh cells can be identified by the expression of certain markers such as CXCR5, ICOS, PD-1, and BCL-6 as well as by the low levels of CCR7 expression. These indicators' molecular interactions are investigated to understand how they affect Tfh cell migration, development, activation, and cooperation with B cells. Tfh cells express the chemokine receptor CXCR5, which is essential for their migration to lymphoid follicles where they can interact with B cells. Tfh cells can focus on these specialized microenvironments because of CXCR5 expression. Effective antibody responses are aided by Tfh cells, which allow crucial interactions with B cells (Crotty, 2019). The co-stimulatory molecule ICOS, which is expressed on Tfh cells, helps Tfh cells survive and differentiate into a fully functioning state. The Tfh cell activation and good cooperation with B cells are facilitated by the contact between ICOS and its ligand on B cells, which increases the efficiency of the immune response (Vinuesa et al., 2016). An inhibitory receptor called PD-1 that is present on Tfh cells limits Tfh cell activity, avoiding overreactions from the immune system and encouraging the proper selection of high-affinity B cells (Sage et al., 2013). This regulatory mechanism ensures the fine-tuning of the immune response and prevents immunopathology. Tfh cells express BCL-6, a transcription factor, which acts as a key regulator of their ability to differentiate, survive, and perform in the germinal center. It plays a crucial part in the adaptive immune response by orchestrating the connections between B cells and the genes that regulate the production of Tfh cell growth (Johnston et al., 2009). Tfh cells have low amounts of the chemokine receptor CCR7, which is necessary for migration to secondary lymphoid organs. This permits Tfh cells to preferentially cluster within lymphoid follicles, where they are an essential support for B cells that are producing antibodies and maturing into their affinities. The specialization of Tfh cells in fostering efficient antibody responses is facilitated by CCR7 downregulation (Crotty, 2014). Production of IL-21, which is essential for B cells to produce high-affinity antibodies, is one of the primary roles of Tfh cells. B cell survival, proliferation, and the generation of antibodies with higher affinities for particular antigens are all aided by the potent growth and differentiation factor of IL-21 (Linterman et al., 2009).

3. Heterogeneity of Tfh Cells

3.1. Co-expression of Transcription Factors from Other Cell Subsets

Recent research has demonstrated that Tfh cells have an extraordinary level of heterogeneity, which is made possible by the co-expression of transcription factors from different T cell subsets (Choi et al., 2011). For instance, a particular subgroup of Tfh cells is designated as Tfh1 cells because they co-express T-bet, a transcription factor usually connected with Th1 cells. Similar to this, some Tfh cells are classified as Tfh2 cells because they contain GATA3, a transcription factor that is mainly present in Th2 cells. Additionally, Tfh17 cells are Tfh cells that express RORt, a transcription factor commonly connected with Th17 cells (Hogquist et al., 2014). Circulatory Tfh1 cells also express CXCR3 and Tfh17 cells express CCR6, but Tfh2 cells express neither CXCR3, nor CCR6 (Schmitt et al., 2014).

3.2. Tfh1, Tfh2, and Tfh17 Cells

The many Tfh cell subsets perform a variety of functions during the germinal center reaction and antibody production. With their IFN-γ production and T-bet expression, Tfh1 cells support the development of antibody isotypes like IgG2a and cell-mediated immune responses. Tfh2 cells play a key role in boosting humoral immunity and allergic reactions by secreting IL-4, IL-5, and IL-13, which are needed for B cell class switching to IgE and IgG1. Tfh2 cells also play a key role in fostering innate immunity. Tfh17 cells have a role in the production of particular antibody isotypes, such as the IgA and IgG subclasses, by generating IL-17 and expressing RORt. Tfh17 cells have also been linked to the control of mucosal immunity and resistance to specific infections (Hogquist et al., 2014).

4. Follicular Regulatory Cells

Tfr cells are a subset of regulatory T cells that develop from thymic progenitors that express both Foxp3 and Bcl-6 (Chung et al., 2011), and control the role of Tfh cells as well as the formation of GCs in secondary lymphoid organs, which implies they control autoimmunity (Stebegg et al., 2018). Tfr cells are characterized by an expression of FoxP3+ and initiate interaction with natural Treg cells by DCs. Through contact with B cells, Tfr cells get differentiation signals within the B cell follicle, which improves the transcriptional program of Tfr cells and promotes repression. Tfh cells require achaete-scute homolog-2 (Ascl2) for CXCR5 expression,

while Tfr cells show a dependence on activated nuclear factor T cells (NFAT)-2 (Liu et al., 2014).

Autoimmunity may be brought on by Tfr cells that are malfunctioning, according to recent findings. For extremely selective autoantibody synthesis suppression, Tfr cells are crucial (Botta et al., 2017). The main function of Tfr cells is to inhibit cytokine production of Tfh cells and to reduce B cell-mediated antibody production. IL-21, on the other hand, inhibits Tfr cells (Linterman et al., 2011).

4.1. Involvement of Tfr Cells in Declining Autoreactive B Cells in GCs

By preventing autoreactive B cells from activating within the GCs, Tfr cells serve a vital role in sustaining immunological tolerance (Sage et al., 2015; Wing et al., 2018). To avoid the production of self-reactive antibodies and the emergence of autoimmune disorders, Tfr cells use a variety of strategies to inhibit the activation and proliferation of autoreactive B cells.

One of the ways Tfr cells carry out their suppressive activity is by direct interaction with autoreactive B cells (Sage et al., 2013). Through this interaction, autoreactive B cells can receive inhibitory signals from Tfr cells, which reduces the intensity of their activation and subsequent differentiation. Tfr cells suppress the production of self-reactive antibodies by directly interacting with autoreactive B cells to restrict their contribution to the antibody repertoire.

Interleukin-10 (IL-10) is a crucial cytokine released by Tfr cells and has powerful immunosuppressive effects (Laidlaw et al., 2017). IL-10 can reduce the pathogenic potential of autoreactive B lymphocytes by preventing their activation, proliferation, and differentiation. The production of transforming growth factor-beta (TGF-β), a different immunosuppressive cytokine that can reduce the activity of autoreactive B cells within the GCs by Tfr cells has also been demonstrated (Wollenberg et al., 2011).

Tfr cells help to maintain immunological tolerance and ward off autoimmune disorders by actively regulating the activation of autoreactive B cells in the GCs. Tfr cell dysregulation or depletion can cause autoreactive B cells to activate and differentiate unchecked, producing self-reactive antibodies and triggering the onset of autoimmunity (Sage et al., 2015).

5. Suppression of T-B Cell Interactions through CTLA-4

CTLA-4 is a crucial component involved in this regulatory pathway, which is how Tfr cells carry out their suppressive function by reducing T-B cell interactions (Sage et al., 2015; Sage et al., 2016). Tfr cells contain CTLA-4, which is widely regarded as a key negative regulator of T-cell activation and is essential for regulating humoral immune responses.

The contact between Tfr cells and B cells in the germinal centers is prevented by CTLA-4 expression on Tfr cells (Wing et al., 2019). The competitive inhibitory effect of CTLA-4, which is mostly expressed on B cells and interacts with its ligands CD80 and CD86, limits the co-stimulatory signals required for T-B cell cooperation. The generation of high-affinity antibodies is downregulated as a result of CTLA-4 expression on Tfr cells suppressing T-B cell interactions.

It is crucial to understand CTLA-4's inhibitory function in the context of Tfr cell-mediated humoral immunity control. Unchecked interactions between T-B cells and germinal centers, increased germinal center reactions, and dysregulated antibody responses can result from disruption or lack of CTLA-4 expression on Tfr cells (Watanabe et al., 2007). Such dysregulation may contribute to the development of autoimmune diseases or compromised immune tolerance.

6. Enhancement of B Cell Maturation Via IL-10

Tfr cells perform additional tasks in addition to inhibiting T-B cell interactions, as evidenced by the fact that they help B cells mature by secreting the anti-inflammatory cytokine IL-10 (Laidlaw et al., 2017; Simpson et al., 2010). A crucial mediator in preserving immunological tolerance and delaying the onset of autoimmune disorders is IL-10. The survival, proliferation, and differentiation of B cells are significantly aided by the release of IL-10 by Tfr cells. Tfr cells' IL-10 production creates a regulatory loop in the germinal centers, where it directly influences B cells (Laidlaw et al., 2017). IL-10 works by increasing B cell survival, promoting their growth, and assisting their differentiation into plasma cells that secrete antibodies.

The relevance of Tfr cells in preserving immunological homeostasis within the germinal centers is highlighted by their dual regulatory role in influencing the function of both Tfh cells and B cells. Tfr cells assist in orchestrating the delicate balance between immunological activation and tolerance by blocking excessive Tfh-B cell interactions while further encouraging B cell maturation through IL-10 production.

7. The Function of Tfh and Tfr Cells in Autoimmunity

The development of autoimmune disease depends heavily on Tfh and Tfr cells, whose imbalance might be harmful to immunological homeostasis (Sage et al., 2016). An imbalance between Tfh and Tfr cells can cause B cells to become abnormally activated, which can result in the creation of autoreactive antibodies and consequent tissue injury.

Due to their excessive stimulation of B cells and generation of autoantibodies, Tfh cells have been linked to the pathophysiology of several autoimmune disorders, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS) (Craft, 2012; Linterman et al., 2009). Tfh cells are crucial

for the development of GCs and the subsequent production of anti-dsDNA antibodies, and they are linked to higher disease activity in SLE (Simpson et al., 2010). In RA, Tfh cells help B cells differentiate into plasma cells, which help to produce autoantibodies and cause tissue damage (Humby et al., 2009). Tfh cells play a role in the production of pathogenic antibodies in MS, which aids in the progression of the disease (Krumbholz et al., 2006).

On the other hand, it has been discovered that Tfr cells play a crucial role in humoral immune regulation and the suppression of autoreactive B cells within GCs (Sage et al., 2014). Tfr cells block T-B cell interactions by expressing CTLA-4, preserving immunological tolerance (Chao et al., 2018). Aside from that, Tfr cells encourage B cell maturation by secreting IL-10 (Wing et al., 2008). Type 1 diabetes (T1D), SLE, and RA are autoimmune disorders that have been linked to Tfr cell dysregulation (Sage et al., 2015). Tfh cell activation and autoantibody production increase in RA due to Tfr cells' impaired suppressive activity (Wing et al., 2018). Tfr cells are essential in T1D because they decrease autoreactive B cell activation and stop the onset of autoimmunity (Wing et al., 2014).

Maintaining a balanced interplay between Tfh and Tfr cells is crucial for the regulation of humoral immunity and the prevention of autoimmune diseases (Sage et al., 2015). The abnormal activation of B cells, the creation of autoreactive antibodies, and consequent tissue injury can all be caused by the dysregulation of this delicate equilibrium.

8. Implications and Future Perspectives

Understanding the functions and regulation of Tfh cells has significant implications for various areas of immunology. Insights into Tfh cell biology may lead to the development of novel therapeutic strategies for autoimmune diseases, where Tfh cells can be targeted to modulate aberrant immune responses. Furthermore, innovative vaccination approaches can be designed to enhance antibody responses by leveraging the unique characteristics of Tfh cells. Continued research into Tfh cell biology holds promise for advancements in immunotherapy and vaccine design. However, understanding the intricate mechanisms employed by Tfr cells to control autoreactive B cell responses is of utmost importance in deciphering the pathogenesis of autoimmune diseases. Further research into the specific molecular and cellular interactions involved in Tfr cell-mediated regulation may unveil novel therapeutic strategies for the treatment of autoimmune disorders.

9. Conclusion

Extensive analysis reveals that autoimmune disorders share the characteristic of overactivated Tfh cells, while self-antigen exposure influences Tfr cell levels. Poor Tfr function relative to Tfh cells can favor self-reactive responses. Targeting these cells holds promise as a therapeutic strategy for autoimmune diseases, highlighting their crucial role in the immune response.

Future research should examine how Tfh cells and Tfr cells interact. In addition, it is important to look into other follicle cell types like follicular DCs, tingle body macrophages, and newly identified follicular cytotoxic T cells. Tfh and Tfr cells will be used to uncover biomarkers in upcoming clinical studies, enabling these applications.

Author Contributions

The percentage of the author's contributions is presented below. The author reviewed and approved the final version of the manuscript.

	G.H.	N.Y.	M.S.
C	40	30	30
D	40	30	30
S	40	30	30
L	40	30	30
W	40	30	30
CR	40	30	30
SR	40	30	30

C=Concept, D= design, S= supervision, L= literature search, W= writing, CR= critical review, SR= submission and revision.

Conflict of Interest

The authors declares that there is no conflict of interest.

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