


Functional differentiation and regulation of follicular T helper cells in inflammation and autoimmunity

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INTRODUCTION

Effector CD4⁺ T helper cells (T_H) include multiple cell subsets, such as type 1 T helper (T_H1) cells, T_H2 cells,

T_H9 cells and T_H17 cells, regulatory T (T_{reg}) cells and follicular T helper (T_{FH}) cells.^{1–4} (Figure 1). These cells are divided into different subgroups according to the different effector cytokines secreted and the specific

Summary

Follicular T helper (T_{FH}) cells are specialized T cells that support B cells, which are essential for humoral immunity. T_{FH} cells express the transcription factor B-cell lymphoma 6 (Bcl-6), chemokine (C-X-C motif) receptor (CXCR) 5, the surface receptors programmed cell death protein 1 (PD-1) and inducible T-cell costimulator (ICOS), the cytokine IL-21 and other molecules. The activation, proliferation and differentiation of T_{FH} cells are closely related to dynamic changes in cellular metabolism. In this review, we summarize the progress made in understanding the development and functional differentiation of T_{FH} cells. Specifically, we focus on the regulatory mechanisms of T_{FH} cell functional differentiation, including regulatory signalling pathways and the metabolic regulatory mechanisms of T_{FH} cells. In addition, T_{FH} cells are closely related to immune-associated diseases, including infections, autoimmune diseases and cancers.

Keywords: follicular T helper cells; metabolic reprogramming; signalling; infectious diseases; cancer; inflammation.

Abbreviations: AITD, autoimmune thyroid disease; AMP, adenosine 5'-monophosphate; AMPK, activated protein kinase; APCs, antigen-presenting cells; ApoAI, apolipoprotein AI; AS, atherosclerosis; BC, breast cancer; Bcl-6, B cell lymphoma 6; BTLA, B- and T-lymphocyte attenuator; CIA, collagen-induced arthritis; CRC, colorectal cancer; CXCR 5, chemokine (C-X-C motif) receptor 5; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; FDCs, follicular dendritic cells; Foxo, forkhead box O; GATA-3, GATA-binding protein 3; GCs, germinal centres; GD, glucose deprivation; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; ICOS, inducible T cell co-stimulator; IFN- γ , interferon- γ ; IRF4, interferon regulatory factor 4; JDM, juvenile dermatomyositis; LCMV, lymphocytic choriomeningitis virus; LZ, light zone; MS, multiple sclerosis; PAMPs, pathogen-associated molecular patterns; PD-1, programmed cell death protein 1; PKC, protein kinase C; PPs, Peyer's patches; pSS, sjogren's syndrome; RA, rheumatoid arthritis; ROR γ t, retinoid-related orphan nuclear receptor γ t; S1PR1, sphingosine-1-phosphate receptor; SAP, SLAM-associated protein; SLE, systemic lupus erythematosus; STATs, signal transducers and transcriptional activators; T1D, type 1 diabetes; TCR, T cell receptor; T_{FH}, follicular T helper; T_H1, type 1 T helper cells; TNF- α , tumour necrosis factor- α ; Tox, thymocyte selection-associated high mobility group box protein; WT, wild-type

transcription factors expressed, which play decisive roles in each subgroup.³⁻⁵ In response to stimulation by antigens and cytokines, naïve T cells differentiate into T_H1, T_H9, T_H17 and other cell subsets (Figure 1). The main effector factors secreted by T_H1 cells are interferon- γ (IFN- γ) and tumour necrosis factor- α (TNF- α), and T_H1 differentiation is mainly regulated by the transcription factor T-Box transcription factor (T-bet); T_H2 cells are regulated by the transcription factor GATA-binding protein 3 (GATA-3) and produce the cytokines interleukin (IL)-4 and IL-13; T_H17 cells express the transcription factor retinoid-related orphan nuclear receptor γ t (ROR γ t) and produce the cytokine IL-17; and T_H9 cells express the transcription factors PU.1 and interferon regulatory factor (IRF) 4 and produce the cytokine IL-9.³⁻⁷ T_{reg} cells express the specific transcription factor Foxp3, produce the cytokine TGF- β and play immunosuppressive and immunomodulatory roles.^{8,9} The differentiation of T-cell subsets is determined by the cytokines expressed during T-cell activation.¹⁰ For example, IL-12 induces T-bet in T_H1 cells, and IL-6 or IL-23 can induce ROR γ t activation during T_H17 cell differentiation.^{8,11-13}

T_{FH} cells develop differently from other subsets of effector CD4⁺ T helper cells, express the main regulatory transcription factor B-cell lymphoma 6 (Bcl-6) and produce the cytokine IL-21.¹⁻⁴ T_{FH} cells are a newly

discovered subset of T cells that play an important role in regulating B-cell-mediated humoral immunity (Figures 1 and 2). T_{FH} cells were originally characterized as unique activated CD4⁺ T cells in the germinal centres (GCs) of the human tonsil that express chemokine (C-X-C motif) receptor (CXCR) 5 and promote the differentiation and function of B cells.¹⁴ Subsequent gene expression and phenotypic analysis showed the anatomical localization and upregulated expression of cell surface proteins, including inducible T-cell costimulatory molecule (ICOS),^{15,16} programmed cell death (PD)-1,¹⁷ B- and T-lymphocyte attenuator (BTLA) and CD40L,^{18,19} which indicate that T_{FH} cells are different from other T helper cell populations. T_{FH} cells express the master transcription factor Bcl-6 and the cytoplasmic adapter and signalling molecule SLAM-associated protein (SAP), which are required for T_{FH} cell differentiation, and secrete the cytokine IL-21.^{18,20}

T_{FH} cells, as a specific subset of CD4⁺ T cells, can be classified by chemokine receptor expression. CXCR3 and CCR6 are characteristic receptors used to define subgroups of T_{FH} cells.²¹⁻²³ CXCR3 is a chemokine receptor that is highly expressed on the surface of T_H1 cells, while CCR6 is expressed in T_H17 cell subsets.^{24,25} T_{FH} cells can also be further divided into subgroups according to the chemokines expressed on the cell surface. Studies have

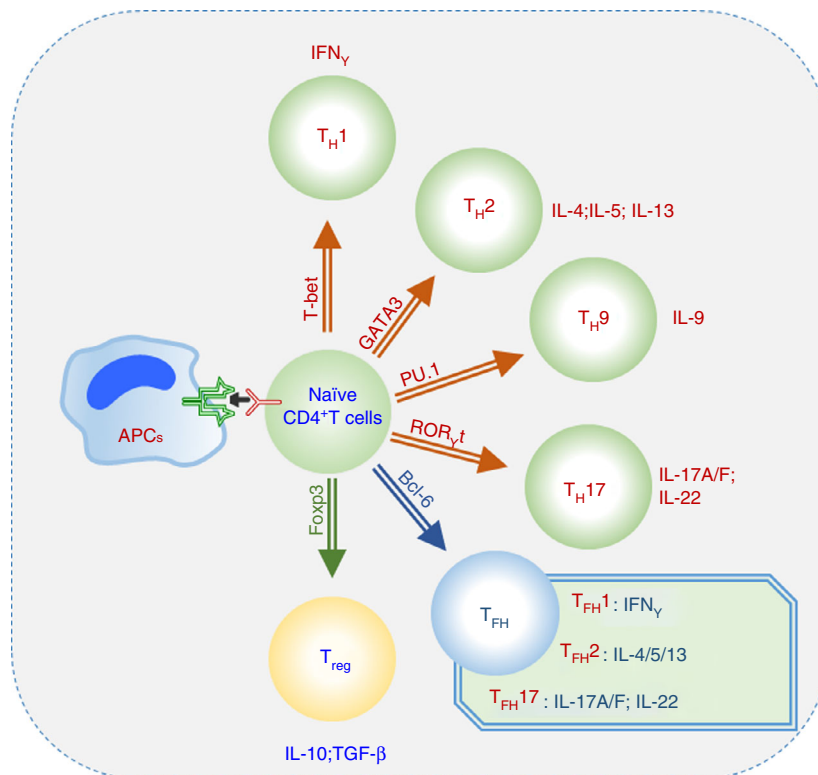


Figure 1. Different T helper cell subsets. Effector CD4⁺ T-cell lineage differentiation and the expression of transcription factors.

defined CXCR3⁺ CCR6⁻ T_{FH} cells as T_{FH}1 cells, which express the transcription factor T-bet and secrete the cytokine IFN- γ ; CXCR3⁻ CCR6⁻ cells are termed T_{FH}2 cells, express the transcription factor GATA3 and secrete the cytokines IL-4, IL-5 and IL-13; and CXCR3⁻ CCR6⁺ T_{FH} cells are termed T_{FH}17 cells, express the transcription factor ROR γ t and secrete the cytokines IL-17A, IL-17F and IL-22.²¹⁻²⁵

DEVELOPMENT AND FUNCTIONAL DIFFERENTIATION OF T_{FH} CELLS

T_{FH} cells are differentiated through three processes (Figures 2 and 3). Because of their tissue-specific anatomical location, T_{FH} cells possess unique functions that differ from those of other T_H subsets. The three-stage differentiation process is divided according to T_{FH} cell migration and localization.^{18,26-28}

The first stage of T_{FH} cell differentiation is the migration of T_{FH} progenitor cells to B-cell follicles.²⁹ Naïve T cells receive antigen signals presented by dendritic cells (DCs) and activate T-cell receptor (TCR) signalling.²⁸ Stimulatory cytokines, such as IL-6, induce the expression of the master transcription factor Bcl-6 and the critical chemokine receptor CXCR5 in T_{FH} progenitor cells.^{29,30} The first stage has been extensively studied and is vital in T_{FH} differentiation.

Currently, research on T_{FH} cells is mainly performed in mice. In humans, most studies on T_{FH} cells are focused on tonsillar and circulating T_{FH} cells in peripheral blood.²⁹ The costimulatory receptor and cytokine signals transduced during the differentiation of T_{FH} cells are almost identical in mice and humans. During the first differentiation stage, naïve T-cell interactions with DCs

are mainly regulated by IL-6, ICOS, IL-2 and the TCR signalling pathways.^{31,32} ICOS plays an important role in regulating the differentiation and migration of T_{FH} cells.^{15,16} ICOSL signalling is necessary for antigen-specific B cells in most cases, except when in the presence of a large number of antigens or during the migration of a large number of antigen-specific B cells.^{15,16} B cells act as not only antigen-presenting cells (APCs) but also the ICOS ligand (ICOSL) in T_{FH} cell differentiation.³³ During acute infection and immune responses, B cells are the main APCs. Antigen presentation is important for antigen-specific CD4⁺ T-cell-required antigen recognition during each cell division.³³ During the migration of activated CD4⁺ T cells from the T-cell zone to the B-cell zone, a series of changes take place in their surface molecules. CXCL13 is the ligand of CXCR5 and is highly expressed in the follicles and germinal centres of B cells. However, CCL19 and CCL21, the ligands of CCR7, are highly expressed in the T-cell region.^{18,33-36} CD4⁺ T cells that are sensitized by DCs upregulate CXCR5 and downregulate CCR7 to induce B-cell migration to the T-B cell junction.^{17,37} ICOS and CXCR5 promote PI3 K signalling, PD-1 inhibits PI3 K activity, and PI3 K signalling determines whether T_{FH} cell precursors enter the follicle. The structural expression of bystander B-cell ICOSL and PD-1 mediates T_{FH} ICOS signalling. ICOS signalling promotes PI3 K activation, T-cell pseudopodia formation and T-cell migration. The interaction of CXCL13-CXCR5 also promotes PI3 K signalling, which stimulates precursor T_{FH} cells to enter the follicular region.¹⁸ miR19-72 promotes the differentiation of T_{FH} cells. miR19-72 downregulates the phosphatases PHLPP2 and PTEN, which inhibit the PI3 K-ICOS signalling pathways.³⁸ IL-2 inhibits the differentiation of T_{FH} cells. Early T_{FH} differentiation is

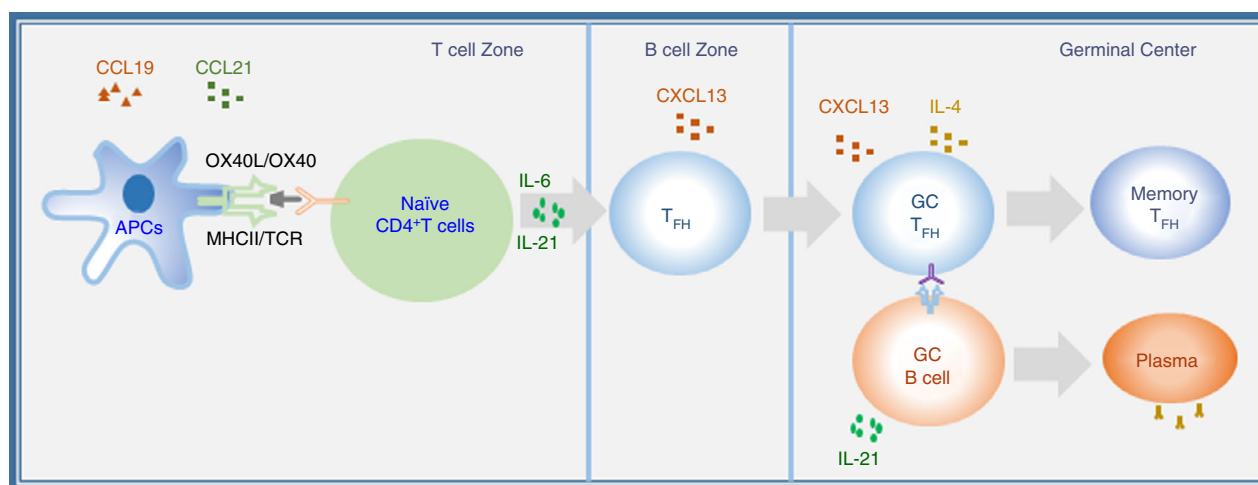


Figure 2. Overview of T_{FH} cell differentiation and localization. The process of T_{FH} cell differentiation highlights the chemokines needed for CD4⁺ T-cell trafficking into the T-cell and B-cell zones. The expression of chemokine receptors on the surface of T cells plays a decisive role in the migration of T_{FH} cells. CXCL13 is the ligand of CXCR5 and is secreted by B-cell follicles and germinal centres. However, CCL19 and CCL21, the ligands of CCR7, are highly present in the T-cell region.

regulated by a variety of signalling pathways, such as the IL-6, ICOS, IL-2 and TCR pathways, mainly by DCs, and by the regulated expression of CXCR5 and Bcl-6.³⁹ IL-6 promotes CD4⁺ T-cell and B-cell activation during *Plasmodium* infection. IL-6 promotes CD4⁺ T-cell activation and B-cell responses during the blood stage of *Plasmodium* infection, which contributes to the production of parasite-specific antibodies. The IL-21 and IL-21 receptors show increased expression and activity levels during the immunopathogenesis of multiple sclerosis. Thus, several related regulators play critical regulatory roles in the early stage of T_{FH} cell differentiation and function.

The second stage of T_{FH} cell differentiation occurs during the interaction between T_{FH} cells and antigen-specific B cells at the junction of the T-B cell border and in the follicles and interfollicular region. The chemokine environment of the T-cell region and B-cell region affects the migration of T cells.^{14,18,36,40}

The third stage of T_{FH} differentiation takes place in GCs. GCs are specialized structures found in the B-cell follicles of secondary lymphoid tissues, where B cells produce high-affinity antibodies and differentiate into memory B cells and long-lived plasma cells.^{41,42} GCs are special structures composed of GC T_{FH} cells, GC B cells,

follicular dendritic cells (FDCs), macrophages and stroma.⁴³ The B7 receptor PD-1 is highly expressed on T_{FH} cells and is one of the main markers of T_{FH} cells located in GCs. T_{FH} cell precursors initially express PD-1 during cell activation because of their interaction with antigen-presenting DCs. The expression of PD-1 is enhanced when precursor T_{FH} cells interact with B cells at the junction of the T-B border. The steady interaction between T and B cells leads to the formation of GCs, and the expression of PD-1 on T_{FH} cells peaks in GCs.⁴¹⁻⁴³ Notably, the role of PD-1 in the localization of T_{FH} cells varies with the location and maturation stage of T cells. The expression levels of the chemokine receptors CXCR5 and CXCR4 are high, and the expression levels of PSGL1 and sphingosine-1-phosphate receptor (S1PR1) are low in GC T_{FH} cells during this stage.^{44,45} The expression of G protein-coupled receptor 2 (EBI2), which is induced by the Epstein-Barr virus, requires special attention because EBI2 ligands are present in B-cell follicles but not in GCs. The decreased expression of EBI2 in GC B cells and GC T_{FH} cells is important for their correct localization in GCs.^{46,47} In addition, adhesion molecules play important roles in GC T_{FH} cells, regulating the interaction and localization with GC B cells. The signalling lymphocyte

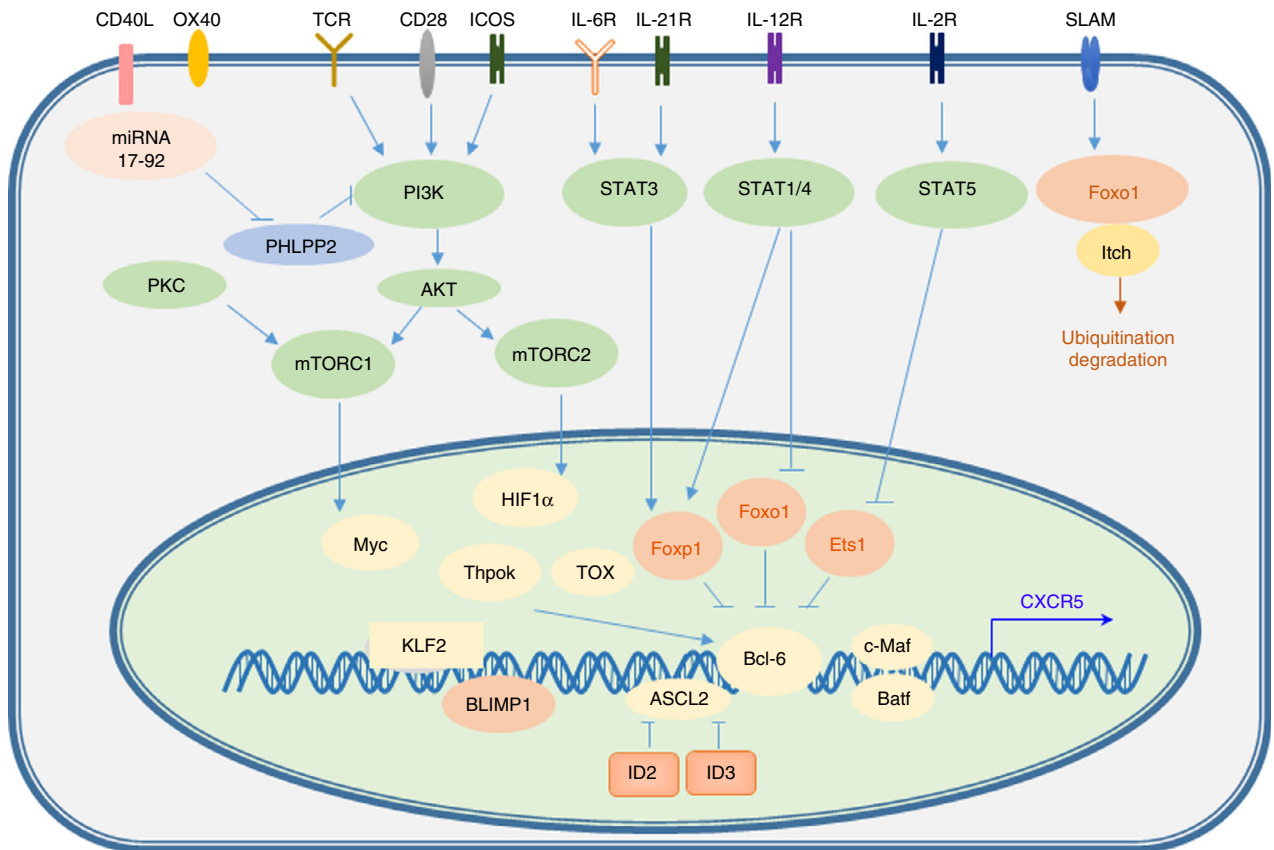


Figure 3. Transcriptional regulation of T_{FH} cell differentiation. IL-6R/IL-21R-STAT3 signalling functions in the differentiation of T_{FH} cells. Bcl-6, c-Maf, Batf and other transcription factors play regulatory roles in T_{FH} cell differentiation.

activation molecule (SLAM) family receptors SLAMF6, also known as Ly108 and NTB-A; CD84 and SLAM, are self-ligands that are differentially expressed in GC T_{FH} cells and GC B cells.⁴⁸ The expression of SLAM-associated protein (SAP) is necessary for the development of GC T_{FH} cells and the production of most memory B cells and memory plasma cells. The absence of SAP weakens the adhesion of T_{FH} cells to GC B cells, making T_{FH} cells unable to remain in GCs and impairing the maturation and function of B cells. The importance of SAP is largely due to its ability to block the powerful inhibitory signals of SLAMF6. After the competitive binding of SAP and the phosphatase SHP-1 to SLAMF6 and SAP, respectively, SLAMF6 transmits a positive T_{FH} cell differentiation signal, which supports the adhesion and function of T_{FH} cells. In contrast, when SLAMF6 binds to SHP-1, a negative regulatory T_{FH} cell differentiation signal is transmitted that inhibits the adhesion of T_{FH} cells and B cells.⁴⁸⁻⁵⁰

However, T_{FH} cell localization to GCs is not the endpoint of T_{FH} cell differentiation. T_{FH} cells migrate from one GC to another or migrate into the blood or lymph for circulation.⁵¹⁻⁵³ On the other hand, the position of B cells in the GCs is fixed; that is, they cannot be removed. After moving out of the GC, T_{FH} cells become memory T_{FH} cells, and the expression of Bcl-6 is downregulated. After T_{FH} cells leave the GC, the activity and polarization of T_{FH} cells decrease, IL-7R α is upregulated, and these cells differentiate into resting memory T_{FH} cells.⁵¹⁻⁵⁵ Memory T_{FH} cells have a central memory phenotype, are located mainly in the spleen, lymph nodes and bone marrow and can be recycled in the blood. Approximately 20% of human central memory CD4⁺ T cells are CXCR5⁺, indicating that memory T_{FH} cells are the main components of the human memory T-cell population. Memory T_{FH} cells are less predominant than reactivated T_{FH} cells and GC T_{FH} cells.^{18,51-55} In humans, memory T_{FH} cells are phenotypically heterogeneous, at least in the blood, and in this population, a considerable number are resting memory T_{FH} cells that express low levels of PD-1. These PD-1^{low} memory T_{FH} cells are the most polarized and powerful memory T_{FH} cells. The expression of Bcl-6 in T_{FH} cells is unstable and requires continuous enhancement.^{18,51-55} Therefore, when GC T_{FH} cells leave GCs, the expression of Bcl-6 is decreased, and as the cells transform into resting memory T_{FH} cells, the expression of Bcl-6 decreases further (Figure 2).

REGULATION OF T_{FH} CELL FUNCTION AND DIFFERENTIATION

Regulatory roles of cytokines in T_{FH} cell differentiation

Cytokines play important roles in lymphocyte differentiation (Figure 3). IL-6 and IL-21 play roles in T_{FH} cell

differentiation and act directly on B cells. IL-6 transiently induces the expression of Bcl-6 in the early stage of T_{FH} cell differentiation, and it is also an inducer of IL-21 expression in inactivated mouse CD4⁺ T cells. IL-6 is the most important cytokine involved in the early differentiation of T_{FH} cells.³² IL-6 is produced by DCs, macrophages, B cells and other types of cells in response to a series of external and internal pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).¹⁸ In the absence of IL-6, the early differentiation of mouse T_{FH} cells is inhibited, but differentiation is increased in response to supplementation with IL-21 and IL-27. Many kinds of DCs and monocytes regulate the differentiation of T_{FH} cells.^{32,56-58}

IL-2 negatively regulates T_{FH} cell differentiation.⁵⁹ Furthermore, IL-2-STAT5 signalling inhibits the expression of the transcription factor Bcl-6 in T_{FH} cells. STAT5 promotes the expression of BLIMP1, which inhibits the expression of Bcl-6. The expression of PD-1 in GC T_{FH} cells is high, and PD-1 signalling inhibits the production of IL-2, which suggests that IL-2 inhibits the expression of PD-1.³⁹ However, during naive T-cell differentiation, IL-2 signalling is enhanced to different degrees.⁵⁹ Therefore, the regulatory effects of IL-2 signalling on T_{FH} cell differentiation are different and depend on the intensity of IL-2 signalling.

IL-12 is an important cytokine that induces naive CD4⁺ T cells to differentiate into T_H1 cells and promotes the expression of the specific transcription factor T-bet. IL-12 but not IFN- γ is induced during *Salmonella* infection and represses T_{FH} cell differentiation.⁶⁰ T_{FH}1 cells, a subgroup of T_{FH} cells, produce both the T_{FH}-associated cytokine IL-21 and the T_H1 cytokine interferon- γ . IL-12 promotes T_{FH}1 differentiation and function by increasing T-bet and Bcl-6 expression.⁶¹

Type I IFN- α/β participates in the incomplete differentiation of T_{FH} cells and induces the expression of Bcl-6, CXCR5 and PD-1 through STAT1 signalling without producing IL-21.⁶²⁻⁶⁴ Type II IFN- γ plays an active role in the differentiation of T_{FH} cells. As shown in the *Sanroque* lupus model, the accumulation of T_{FH} is the result of excessive IFN- γ . IFN- γ blockade reduces the number of T_{FH} cells in lupus tissue, indicating that IFN- γ plays an important and active role in the production of T_{FH} cells. In terms of mechanism, excessive IFN- γ signalling leads to increased expression of Bcl-6. In contrast, in the late stage of T_H1 cell differentiation, Bcl-6 binds to the IFN- γ gene locus and inhibits excessive *Ifn* mRNA expression.⁶² Thus, Bcl-6 and IFN- γ regulate each other through a negative feedback mechanism.

Therefore, several cytokines show distinct regulatory roles in determining T_{FH} cell lineage differentiation. IL-6, IL-21, IL-27 and IL-12 have positive regulatory effects on T_{FH} cell differentiation, and IFN- γ , IL-2 and IL-10 play inhibitory roles in T_{FH} cell differentiation.

Transcriptional regulation of T_{FH} cell function and differentiation

Multiple transcription factors synergistically promote the development and differentiation of T cells (Figure 3). T cells have different functional subsets, and their transcription factors are expressed in different forms and levels at different stages of development and differentiation. During T_{FH} differentiation, different transcription factors promote or inhibit the differentiation of T_{FH} cells.

Some transcription factors play positive roles in T_{FH} differentiation.⁶⁵ Signal transducers and transcriptional activators (STATs) are also closely related to the differentiation of T_{FH} cells. STAT3 plays an important role in the differentiation of T_{FH} cells in the mouse CD4⁺ T-cell population, and STAT1 and STAT4 are also very important in the differentiation of T_{FH} cells.^{66,67} The expression of STAT3 and IL-21 in mouse CD4⁺ T cells is very important.⁶⁵ Mouse CXCR5 and IL-6 drive STAT3 and STAT1 to interact with Maf and Batf, bind to the promoter and initiate the expression of CXCR5. In contrast to their effects in mice, STAT3 and STAT4 are equally important for the differentiation of T_{FH} cells in humans.^{65,68} STAT5 inhibits the differentiation of T_{FH} cells, and the opposite effects of STAT3 and STAT5 on the differentiation of T_{FH} cells are similar to the effects of STAT3 and STAT5 on the differentiation of T_{H17} cells.^{69,70}

The promoter of Bcl-6 harbours binding sites for the transcription factors STAT and Forkhead box O (Foxo).^{65,71} Under low IL-2 conditions, STAT3 binds to the promoter of Bcl-6, and when IL-2 increases, STAT5 binds to the promoter of Bcl-6. Interestingly, STAT5 replaces the STAT3 complex and excessively recruits the inhibitory complex, which explains why IL-2 inhibits the differentiation of T_{FH} cells.⁷¹ Maf is highly expressed in T_{FH} cells and is related to the expression of CXCR5, IL-21 and IL-4. c-Maf is a basic leucine zipper transcription factor that binds to the IL-4 promoter and plays an important role in the differentiation of T_{H2} cells.^{15,72} The loss of c-Maf leads to a reduction in IL-17 production. ICOS-mediated c-Maf expression is necessary for IL-21 production and T_{FH} cell expansion.⁷²

IRF4 and basic leucine zipper transcription factor (Batf) also play important roles in regulating the differentiation of T_{FH} cells.^{73,74} Batf is a positive regulator of Bcl-6. In the absence of Batf, the coexpression of Bcl-6 and Maf is required for the expression of CXCR5 *in vivo*.⁷³ Although Batf is only moderately increased in T_{FH} cells, *Batf*^{-/-} mice cannot produce T_{FH} cells. Batf directly binds to the promoters of Bcl-6 and Maf. The E protein Ascl2 also promotes the differentiation of T_{FH} cells. Ascl2 is not the only regulatory factor of CXCR5. There is redundancy among several E proteins that are expressed in T cells. Multiple E proteins promote the expression of CXCR5 by

binding to enhanced subregions.⁷⁴ The function of E proteins is tightly regulated by DNA-binding inhibitor 2 (ID2) and ID3 (Figure 3).

T helper cell-inducing POZ/Kruppel-like factor (Thpok) and thymocyte selection-associated high mobility group box protein (Tox) have been reported to regulate other transcription factors that are crucial to T_{FH} cell differentiation, such as Bcl-6 and c-Maf. Thpok and Tox are critical for the development of T cells.^{75,76} It has been shown that these factors bind to the promoters or other transcriptional regulatory regions of T_{FH} differentiation-related transcription factors and regulators (such as CXCR5 and ICOS) to promote their expression. There may be other upstream transcription factors that promote T_{FH} cell development.

Negative regulatory transcription factors in T_{FH} cell differentiation have also been reported in other studies (Figure 3). Foxp1 and Foxo1 are expressed in resting immature CD4⁺ T cells and are necessary for immature CD4⁺ T cells to maintain resting and homing states.⁷⁷ Downregulating the expression of Foxo1 and Foxp1 can positively regulate the differentiation of T_{FH}. For example, itchy E3 ubiquitin protein ligase (Itch) can bind to Foxo1 and accelerate Foxo1 degradation. ICOS and PI3 K-Akt signalling promote the differentiation of T_{FH} cells, while Akt signalling leads to a decrease in Foxo1 transcriptional activity.⁷⁸ Inhibiting Foxo1 and Foxp1 enhances the expression level of ICOS.⁷⁹ E26 transformation-specific sequence-1 (Ets1) downregulates the expression of GATA3 and IL-4. The specific loss of Ets1 in mouse CD4⁺ T cells leads to systemic lupus erythematosus (SLE) and the terminal differentiation of T_{FH2} cells.⁸⁰

Taken together, these data suggest that Bcl-6 is the master transcription factor in T_{FH} cell differentiation; STAT3, STAT4 and STAT1 promote the expression of Bcl-6 and T_{FH} differentiation; and transcription factors such as IRF4, MAF, BATF, Ascl2 and ThpoK also play positive roles in T_{FH} cell differentiation and function. Transcription factors such as Foxo1, Foxo3a and BLIMP1 negatively regulate the differentiation and function of T_{FH} cells.

METABOLIC REGULATION OF T_{FH} CELL FUNCTION AND DIFFERENTIATION

Metabolic regulation plays an important role in the differentiation and function of T_{FH} cells (Figure 4). Some studies of glucose metabolism in T_{FH} cells suggest that glycolysis, which is mediated by mTOR- and HIF1 α -related signalling, is positively regulated during the differentiation process. However, some studies suggest that T_{FH} cells have less robust metabolic functions than other Th cell subsets, such as T_{H1} cells, and oxidative phosphorylation but not glycolysis plays a major role in differentiation.

mTORC1 and mTORC2 are essential for the differentiation of T_{FH} cells and other T_H cell subsets.^{81,82} Specifically, mTORC1 promotes T_{H1} and T_{H17} cell differentiation, whereas mTORC2 favours T_{H2} cell differentiation by orchestrating metabolic reprogramming and lineage-specific gene transcription. It has been reported that mTORC1 and mTORC2 are critical for T_{FH} differentiation based on studies of the phenotype acquired in *Raptor*- and *Rictor*-knockout mice.⁸² The loss of *Rictor* or *Raptor* results in a decrease in the T_{FH} cell population and attenuates the humoral immune response.⁸² Aberrant activation of mTORC1 can lead to autoimmune diseases. The mTORC1-4E-BP-eIF4E axis can promote Bcl-6 protein synthesis.⁸³ In addition, some studies suggest that mTORC1 inhibits the differentiation of T_{FH} cells through the IL-2-mTORC1 axis.⁸⁴ The regulatory effects of mTORC1 on T_{FH} cell differentiation are contradictory, and the precise regulatory mechanisms need to be further

studied. It was recently reported that mTORC2 plays a positive regulatory role in the differentiation and function of T_{FH} cells. Additionally, mTORC1 inhibits the differentiation and expansion of T_{reg} cells. However, some studies have reported that mTORC1 is essential for the differentiation and function of T_{reg} cells by activating the STAT3-TCF-1-Bcl-6 axis.⁵ mTORC1 participates in the regulation of multiple signal pathways, and its regulatory functions on the differentiation and function of T_{FH} cells and T_{reg} cells might differ due to different experimental conditions and external stimuli.

mTOR signalling-related glucose metabolism is critical for T_{FH} cell differentiation. A deficiency in PTEN, a negative regulator of mTOR, promotes T_{FH} cell differentiation and GC formation.^{82,85} mTORC1 and mTORC2 signalling links ICOS to anabolic metabolism and T_{FH} cell-associated transcriptional programmes in Peyer's patches (PPs).⁸² This finding suggests that mTOR activation and

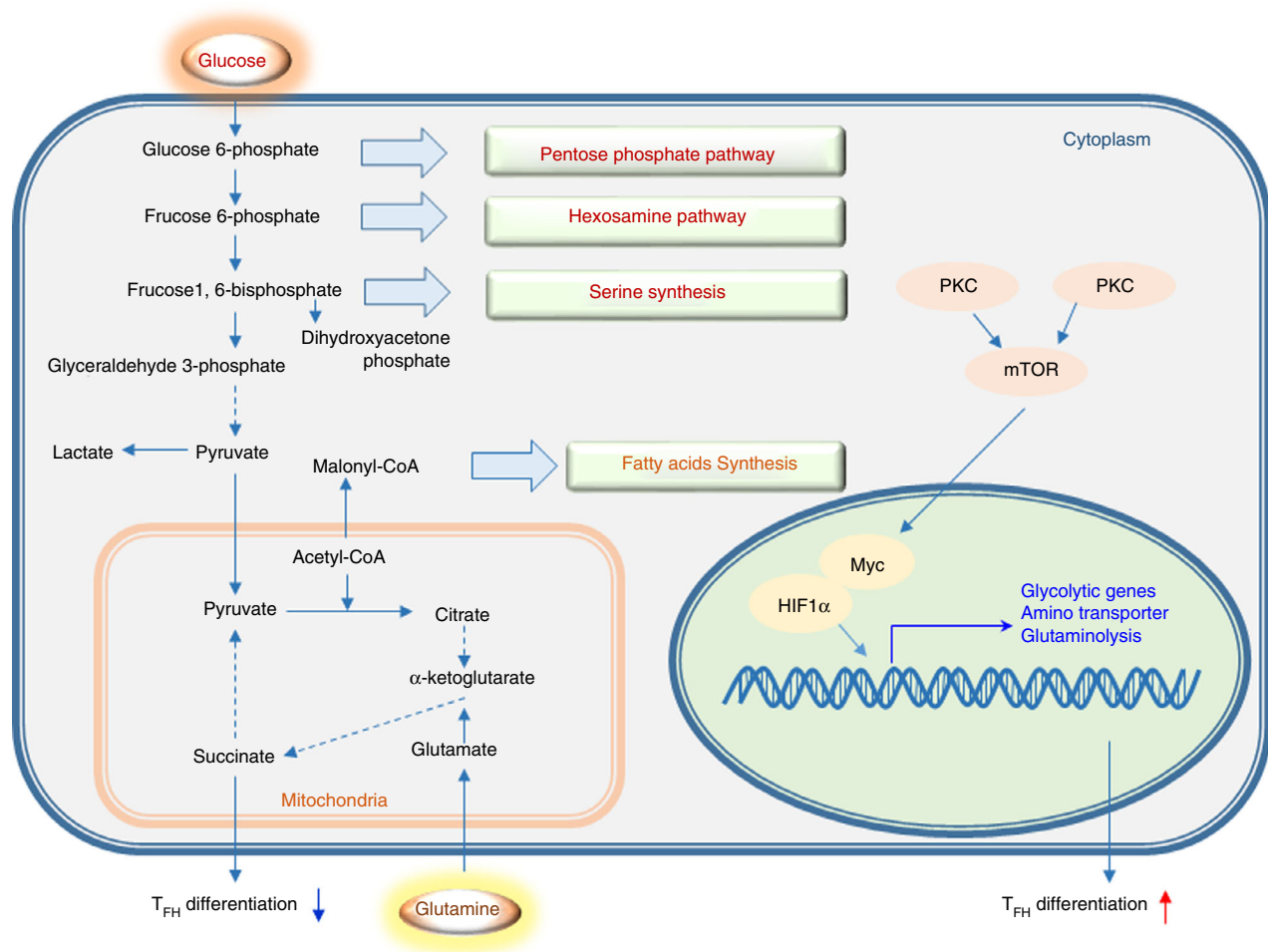


Figure 4. Regulation of metabolism in T_{FH} cell differentiation. Basic processes and correlations of glucose, lipid and amino acid metabolism. mTOR signalling and transcription factors such as Myc and HIF1 α promote T_{FH} cell differentiation related to improvements in metabolism. The differentiation of T_{FH} cells is inhibited by the glycolysis inhibitors 2-DG and succinate, a substrate of oxidative phosphorylation.

glycolysis are required for T_{FH} cell differentiation. K/BxN mice are models of spontaneous rheumatoid arthritis and autoimmune sero-positive arthritis. The production of high levels of anti-GPI IgG requires CD4⁺ follicles to facilitate the expansion of T_{FH} cells. The metabolic activity of CD4⁺ T cells and B cells in K/BxN mice was higher than that in KRN control mice. Prophylactic inhibition of glycolysis with 2-deoxy-D-glucose (2-DG) significantly reduced joint inflammation, the activation of adaptive and innate immune cells, and the production of pathogenic autoantibodies. The self-reactive T_{FH} cells of K/BxN mice exhibit a high level of glycolysis, and their function can be inhibited by downregulating glucose metabolism. The high expression of hexokinase HK2 in joint-infiltrating lymphocytes in patients with rheumatoid arthritis (RA) indicates that the metabolism of these cells is highly glycolytic.⁸⁶ These results suggest that glycolysis and/or mTOR signalling is critical for the differentiation of T_{FH} cells.

Roquin inhibits the PI3 K-mTOR signalling pathway, spontaneous activation of T cells and abnormal differentiation of T_{FH} and T_{H17} cells.⁸⁷ The deletion of Roquin leads to an increase in the ratio of T_{FR} cells to T_{FH} cells, and the inhibition of PI3 K-mTOR signalling restores the increase in T_{FR} and T_{FH} cells caused by Roquin deletion.⁸⁸ The PI3 K-mTOR signalling pathway has been suggested to play an important positive regulatory role in glycolysis; therefore, it is suggested that glycolysis signalling mediated by the PI3 K-mTOR pathway promotes the differentiation of T_{FH} and T_{FR} cells.⁸⁷ T_{FR} cells, similar to T_{reg} cells, play immunosuppressive roles. T_{FR} cells express CXCR5, Bcl-6 and other characteristic factors that function in the germinal centre.⁸⁸ mTORC1 promotes the differentiation of T_{FR} cells, suggesting that mTORC1 positively regulates the expression of CXCR5, ICOS and Bcl-6 in T cells. However, other studies present opposite findings. For example, it was found that T_{FH} cells exhibit reduced glycolysis and mitochondrial respiration, accompanied by reduced mTOR activity compared with those of T_{H1} cells in acute viral infection.⁸⁴ It has been shown that overactivated PI3K δ affects humoral immunity in APDS mouse model (*Pik3cd*^{E1020 K/+}).⁸⁹ In *Pik3cd*^{E1020 K/+} mice, T_{FH} cells and GC B cells are particularly abundant, but the efficiency of the B-cell response to the immune-based conversion of antigen-specific B cells was decreased. T_{FH} cells in *Pik3cd*^{E1020 K/+} mice are typically limited to the light zone (LZ), which specifically targets high-affinity B cells and induces survival and proliferation.⁸⁹ APDS patients present with structural disorders in germinal centres, and the increased invasion of T_{FH} cells impairs humoral immune response.

Protein kinase C (PKC) plays important roles in cell metabolism and signal transduction. The function of mitochondria in B cells is downregulated in *Pkc*^{-/-} mice, and the antigen presentation ability of B cells is inhibited.

It was also found that the reaction of GCs in these mice can be decreased, and the production of plasma cells and immunoglobulin is decreased. The mitochondrial regulation mediated by PKC is partly regulated through the mTOR signalling pathway. Thus, mitochondria are considered to be particularly important for the GC response, which requires the participation of T_{FH} cells.⁹⁰ These findings suggest that PKC also regulates the function of T_{FH} cells by regulating mitochondrial functions.

Bcl-6 is an important transcription factor in the differentiation of T_{FH} cells.⁹¹ The expression of Bcl-6 is significantly upregulated in activated CD4⁺ T cells subjected to glucose deprivation (GD) or 2-DG. Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK), a metabolic sensor, is activated when glycolysis is decreased. The AMPK antagonist compound C inhibits the expression of Bcl-6 induced by glucose deprivation.⁹¹ A study showed that AMPK plays a critical role in the differentiation of T_{FH} cells. Mature T_{FH} cells have a lower metabolic state than T_{H1} cells.⁹¹ These data show that a decrease in cell metabolism is an inducer of T_{FH} differentiation, not merely the result of T_{FH} differentiation.

Resting T cells mainly rely on oxidative phosphorylation in mitochondria to produce ATP. Under antigen stimulation, the downstream AKT signalling pathway is mediated by the TCR pathway and costimulatory receptor CD28, and the AKT signalling pathway has been extensively studied with respect to the positive regulation of glycolysis. Under the metabolic conditions generated by glycolysis, naïve CD4⁺ T cells differentiate into T_{H1}, T_{H17} and other cell subsets. DUSP6, a MAPK phosphatase, connects TCR signalling to activation-induced metabolism that favours glycolysis and attenuates T_{FH} cell differentiation.⁹² Bcl-6 expression is highly upregulated in activated CD4⁺ T cells following glucose deprivation, and this pathway is insensitive to inhibition by IL-2. In a manner similar to glucose deprivation, the glucose analogue 2-DG inhibits glycolysis, and 2-DG induces Bcl-6 expression in activated CD4⁺ T cells.⁹¹ Although these studies revealed that Bcl-6 is induced when glycolysis is inhibited, the inhibition of glycolysis is also detrimental to T-cell activation. Therefore, during robust T-cell proliferation, glucose uptake and glycolysis are required, and Bcl-6 is activated by low-energy signals transmitted by AMPK during high T-cell proliferation and activity.^{86,91,93} These results suggest that the mTOR pathway positively regulates T_{FH} cell differentiation, but the mechanism by which the transcription programme is regulated by mTOR has not been clarified.

Ovalbumin (OVA) sensitization and influenza virus infection are considered to be models for the study of T_{FH} cells. T_{FH} cells are induced to differentiate during OVA sensitization and viral infection. Succinate is a substrate in oxidative phosphorylation. The injection of succinate into wild-type (WT) mice sensitized by OVA

inhibited T_{FH} cell differentiation and the GC response. In addition, 2-DG is an inhibitor of glycolysis. Under OVA sensitization and viral infection, the injection of 2-DG into the body inhibited the differentiation and function of T_{FH} cells.⁹⁴ Therefore, the inhibition of glycolysis or the enhancement of oxidative phosphorylation inhibits the differentiation of T_{FH} cells *in vivo*, suggesting that glycolysis is the main metabolic mechanism regulating T_{FH} cell differentiation.

T_{FH} CELLS IN IMMUNE-ASSOCIATED DISEASES

T_{FH} cells affect humoral immunity by regulating B-cell development. In recent years, with continuous research on T_{FH} cell differentiation and functions, it has been revealed that T_{FH} cells are closely related to many immune-associated diseases, including infectious diseases, autoimmune diseases and cancers (Figure 5 and Table 1).

Immunoregulatory roles of T_{FH} cells in infection

T_{FH} cells help B cells differentiate into plasma cells to produce antibodies, which are crucial for eliminating viruses and bacteria. In the context of viral and bacterial infection, some investigations have been performed on lymphocytic choriomeningitis virus (LCMV) infection, hepatitis C virus (HCV) infection, human immunodeficiency virus (HIV) infection and group A *Streptococcus* (GAS) bacterial infection.

In mice infected with LCMV Clone 13, a persistent variant of LCMV, persistent viral infection progressively drives $CD4^+$ T-cell development to disfavour T_{H1} cells and favour T_{FH} cells.⁹⁵ In other words, LCMV infection promotes T_{FH} cell differentiation. In addition, in persistent LCMV infection *in vivo*, T_{FH} cells are crucial for viral

clearance.⁹⁶ Cytokine production and other changes were analysed in mice infected with LCMV Clone 13. IL-6 signalling in T_{FH} cells promoted the clearance of LCMV Clone 13 and enhanced the function of T_{FH} cells by upregulating Bcl-6. A similar study also demonstrated that T_{FH} cells were essential in helping B cells produce late-stage antibodies to neutralize LCMV in mice.⁹⁷

T_{FH} cells are also essential in controlling HCV infection in a manner similar to the control of LCMV. During HCV infection, it has been observed that T_{FH} cells also significantly increase the percentage of cells coexpressing CXCR5 and PD-1 in both acute infection and chronic infection.^{98,99} In patients with acute HCV infection, T_{FH} cells express specific markers and secrete IL-21 in response to HCV. Virus-specific T_{FH} cells can be detected in blood samples, and ICOS expression is significantly increased in CXCR3-expressing HCV-specific T_{FH} cells.⁹⁹ In the livers of patients with chronic HCV infection, virus-specific T_{FH} cells are enriched compared with other types of cells.⁹⁹

HIV causes defects in the human immune system, and an increasing number of people die from HIV infection. Research has shown that T_{FH} cells are severely dysregulated in HIV-infected patients.^{100,101} $CXCR5^+PD-1^+Bcl-6^+$ cells harbouring HIV DNA are significantly increased in infected patients. Deregulation of T_{FH} -mediated B cells contributes to diminished B-cell responses during HIV infection, which suggests that T_{FH} cells have a significant impact on the control of HIV infection.¹⁰⁰ GC T_{FH} cells have a higher probability of harbouring HIV infection than other cells *in vitro*, as indicated by the higher frequency of infected cells.^{102,103}

GAS bacterial infection is the main cause of recurrent tonsillitis (RT) in childhood.¹⁰⁴ Aberrant pyrogenic exotoxin A-activated GC T_{FH} cells express granzyme B to kill B cells in RT patients.⁶³

Immunoregulatory roles of T_{FH} cells in autoimmunity

Autoimmunity is closely associated with excessive autoantibody production. The differentiation and function of T_{FH} cells are closely related to autoimmune diseases.¹⁰⁵ Overactive T_{FH} cells were found in subsets of patients with systemic lupus erythematosus (SLE), Sjogren's syndrome (pSS), juvenile dermatomyositis (JDM), autoimmune thyroid disease (AITD) and rheumatoid arthritis (RA) (Figure 5 and Table 1).

SLE is an autoimmune disease that is currently well understood in the field of T_{FH} cell-related diseases. The number of circulating T_{FH} cells is increased in mice and patients with the autoimmune disease SLE.^{51,106,107} T_{FH} cells are closely associated with SLE, suggesting that disordered homeostasis of the T-cell–B-cell equilibrium is a major cause of SLE.^{106,107} In Ets-deficient mice, T_{FH2}

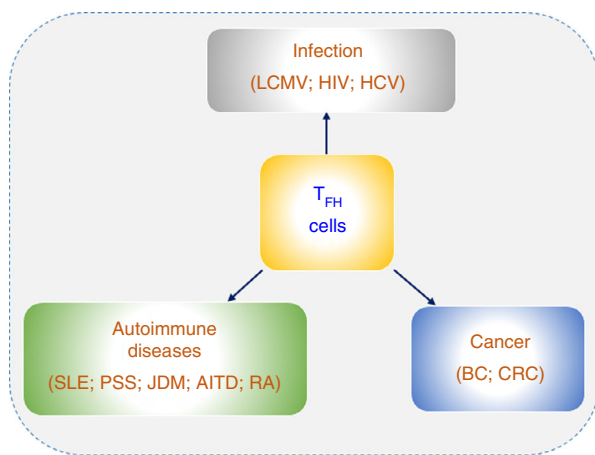


Figure 5. T_{FH} cell-associated immune-mediated diseases. T_{FH} cells play regulatory roles in immune-associated diseases, including infections, autoimmune diseases and cancers.

(Bcl6⁺GATA3^{high}) cells are the main T_{FH} cell subset, and these mice are highly likely to develop SLE.⁸⁰ Similarly, there are more T_{FH2} cells in SLE patients than in healthy individuals.⁸⁰ It has been found that T_{FH} cells play an important role in the severity of pSS.^{108,109} The proportion of peripheral T_{FH} cells is increased in patients. The percentage of T_{FH} cells is positively correlated with the numbers of both activated T cells and Th1 cells.¹⁰⁸ In JDM patients, the T_{FH} cell subset proportions are severely unbalanced, with a profound skewing of the T_{FH} cell subset towards T_{H2} and T_{H17} cells.⁵² Studies have shown that T_{FH} cells play important roles in AITD.^{110,111} In patients with AITD, the frequency of circling T_{FH} cells is increased, and the mRNA expression of IL-21 and Bcl-6 is also enhanced.¹¹⁰ In addition, the chemokine receptor CXCR5 and its ligand CXCL13 are essential in regulating T-cell and B-cell compartmentalization in the thyroid tissue of patients with AITD.¹¹¹ T_{FH} cell and serum IL-21 levels are significantly increased in the RA patient group compared with those of the corresponding healthy control group. Moreover, B-cell proliferation and antibody secretion are increased in RA patients. Research has also shown that IL-21 promotes B-cell activity. Thus, IL-21 may be related to the pathogenesis of rheumatoid arthritis.¹¹² In a collagen-induced arthritis (CIA) mouse model, CXCR5-deficient mice showed strong resistance to CIA, suggesting that CXCR5 is an indispensable factor for inducing autoimmune diseases.¹¹³

T_{FH} cells contribute to metabolic-associated autoimmune disorders, such as diabetes and atherosclerosis. Type 1 diabetes (T1D) is called insulin-dependent diabetes mellitus (IDDM) and is associated with metabolic disorders. T_{FR} cells negatively regulate the function of T_{FH} cells during inflammation. It has been reported that T_{FR} cell deficiency is involved in the pathogenesis of T1D. Thus, it was hypothesized that T_{FH} cells participate in the onset of diabetes.¹¹⁴ Type 2 diabetes (T2D) mellitus is a chronic metabolic disease that is strongly associated with obesity. In mucosal biopsy samples, B cells and plasma blasts from T2D patients exhibited a slight but significant increase in the frequency of cells with surface IgG expression compared with those from healthy individuals. To a large extent, the pathogenesis of T2D is related to obesity, but some patients with T2D have a body mass index (BMI) that is inconsistent with obesity. It was found that non-obese T2D patients exhibited significantly higher levels of faecal IgG and higher frequencies of CD4⁺CXCR5⁺ T (T_{FH}) cells than BMI-matched healthy controls.¹¹⁵ Atherosclerosis (AS) is associated with lipid metabolism disorders and is the main cause of coronary heart disease, cerebral infarction and peripheral vascular disease. T_{reg} cells function in antiatherosclerosis. T_{reg} cells lose Foxp3 expression during inflammation and are then converted into other CD4⁺ T-cell subsets. During atherosclerosis development, T_{reg} cells can switch their phenotype and become pro-atherogenic T_{FH} cells and

Table 1. Immunoregulation of T_{FH} cells in diseases.

Disease			Prognosis effects	Immune functions
Infection	LCMV	Mouse	Promote viral clearance	IL-6 and Bcl-6 upregulation ⁹⁶ Production of late-stage antibodies ⁹⁷
	HCV	Human	Anti-infection	IL-21 and ICOS upregulation ⁹⁹
	HIV	Human	Anti-infection	Plasma cell and autoantibody production decreases ^{100,102,103}
	GAS	Human	Promote bacterial clearance	Granzyme B expression ¹²⁸
Autoimmune diseases	SLE	Mouse; human	Hyperactive	Autoantibody production ^{51,80,106,107}
	pSS	Human	Hyperactive	Autoantibody production ^{108,109}
	JDM	Human	Hyperactive	Autoantibody production ⁵²
	AITD	Human	Hyperactive	Autoantibody production; IL-21 and Bcl-6 upregulation ¹¹⁰ ; CXCR5 and CXCL13 expression ¹¹¹
Cancers	RA	Human; Mouse	Hyperactive	Autoantibody production; IL-21 upregulation ¹¹² ; Autoantibody production; CXCR5 expression ¹¹³
	BC	Human	Positive correlation with good prognosis	8-gene T _{FH} cell signature ¹²³ ; CXCL13 expression ¹²⁴
	CRC	Mouse; human	Positive correlation with good prognosis	CXCL13 and IL-21 expression ¹²⁵
Other cancers	Other cancers	Mouse	Downregulate antitumour immunity	IL-4 expression ¹²⁶
			Upregulate antitumour immunity	IL-21 expression ¹²⁷

apolipoprotein AI (ApoAI), this conversion can be achieved by reducing the expression of IL-2R α and p-STAT5 levels.¹¹⁶ There is cross-regulation between atherosclerosis and other autoimmune diseases, such as SLE. Dyslipidaemia in atherosclerotic diseases significantly increases the severity of SLE, with enhanced production of autoantibodies, such as IgG2c, and the T_{FH} cell response *via* IL-27.¹¹⁷ STAT4 suppresses Foxp3 expression, regulates T_{FH} cell functions and promotes atherogenesis in insulin-resistant low-density lipoprotein receptor-deficient (*Ldlr*^{-/-}) mice.¹¹⁸ Pre-B-cell leukaemia transcription factor 1 isoform d (*Pbx1d*) can regulate T_{FH} cell expansion and T_{reg} cell homeostasis as a lupus susceptibility gene. Cholesterol favours T_{FH} cell differentiation or maintenance, and the interaction between *Pbx1d* and dyslipidaemia alters T_{FH} cell and T_{reg} cell fates and functions.¹¹⁹

Furthermore, different subsets of T_{FH} cells (T_{FH2} or T_{FH13} cells) are specifically involved in autoimmune diseases. Dysfunction or imbalance in CD4⁺ T cells leads to the pathogenesis of autoimmune diseases. For example, T_{H1} cells play critical roles in insulin-dependent T1D, inflammatory bowel disease (IBD) and RA; T_{H17} cells participate in the pathogenesis of autoimmune encephalomyelitis (EAE); and T_{H22} cells are critical in psoriasis, obsessive-compulsive spondylitis and multiple sclerosis (MS). T_{FH} cells are critical for antibody production and humoral immunity, and their aberrant activity is closely related to the pathogenesis of autoimmune diseases. Among the T_{FH} cell subsets, T_{FH2} and T_{FH13} cells are recognized as crucial participants in the onset and exacerbation of autoimmune diseases. Asthma causes air-flow obstruction and is induced by inflammatory disorders. Circulating T_{FH2} cells are polarized, and the ratio of T_{FH2} cells to T_{FH1} cells is increased in the peripheral blood of patients with asthma.¹²⁰ T_{FH2} cells are polarized in both allergic rhinitis (AR) and AR +asthma cases. In one study, it was found that peripheral blood lymphocytes of patients with AR or AR +asthma diseases were preferentially polarized to the T_{FH2} phenotype. T_{FH2} cells can produce IgE-related cytokines, such as IL-4, IL-5 and IL-13, similar to T_{H2} cells, leading to allergic inflammation.¹²¹ It was reported that the expression of CD23 was enhanced on CD19⁺CD20⁺CD27⁺IgD⁻ switching memory B cells and positively correlated with antigen-specific IgE levels and the T_{FH2} cell ratio in AR patients. T_{FH2} cells have the capacity to promote CD23 expression on switching memory B cells by secreting the cytokine IL-4.¹²²

Immunomodulatory roles of T_{FH} cells in cancer

An increasing number of studies have shown that T_{FH} cells have an indispensable role in a variety of cancers, including breast cancer (BC) and colorectal cancer (CRC) (Figure 5 and Table 1).

It has been observed in breast cancer patients an 8-gene T_{FH} cell signature in tumour tissue who has a significant positive correlation with organized antitumour immunity, long-term patient survival and preoperative response to chemotherapy.¹²³ In addition, researchers have also shown that T_{FH} cells promote local memory B-cell differentiation, thus enhancing antitumour immunity.¹²⁴ In human CRC, T_{FH} cells also have a positive effect on the survival of cancer patients. A study showed that the density of T_{FH} cells increased, whereas the levels of most T cells decreased during tumour progression. CXCL13 and IL-21 expression are also associated with cancer progression.¹²⁵

However, studies have shown that T_{FH} cells expressing IL-4 are associated with downregulated antitumour immunity in other cancers.¹²⁶ CNS2-deleted mice were injected subcutaneously with various tumour cells and exhibited stronger antitumour immunity than control WT mice. In addition to IL-4, IL-21 is another major cytokine that is expressed by T_{FH} cells. However, in contrast to the effect of IL-4, IL-21 enhances antitumour immunity in mouse models.¹²⁷ When PD-1 or CTLA-4 blockade was combined with IL-21, the mice showed improved treatment outcomes.¹²⁷

CONCLUDING REMARKS

T_{FH} cells have been extensively investigated in mouse and human studies. These studies have demonstrated that T_{FH} cells contribute to both humoral immunity and immune-related diseases. However, despite in-depth study, the regulatory factors and mechanisms of T_{FH} cell differentiation, especially in the pathogenesis of various important immune-related diseases, remain unclear and need further study. Further study of T_{FH} cell subgroups, including the T_{FH1}, T_{FH2} and T_{FR} cell subgroups, and other subpopulations may be helpful to further clarify the roles of these cells in immune-related diseases, which will provide the basis for the diagnosis and treatment of diseases in the future.

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AUTHOR CONTRIBUTIONS

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Y.B. and G.L. contributed to writing the manuscript and participated in discussions.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

Not applicable.

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