Role of T Follicular Helper (Tfh) Cells Plasticity in Autoimmune Thyroiditis among Hepatitis C Virus Infection

Abstract

T follicular helper (Tfh) cells are a new subset of CD4+ T cells located in tonsils and circulating in the blood. Thf cells are required for maintenance of the germinal center reactions and generation of humoral immunity via their expression of many molecules as CD40 ligand, IL-21, IL-4, and others. Tfh cells provide the help to B-cells to differentiate to plasma cells. It has a unique phenotype CXCR5+ and express a master regulator BCL-6.

IL21is the key feature of TFH cells as they secret high levels of IL21 and express IL21R which in turn play pivotal role in pathophysiology of autoimmune Thyroiditis (ATA).Several studies have observed a high prevalence of circulating Tfh cells expressing CD4, CXCR5, PD-1, CXCR3, ICOS among active HCV and HBV patients. Also it was proved that HCV can infect thyroid cells directly by binding of E2protein to CD81 which is highly expressed on thyroid cells which could trigger thyroid inflammation through activation of autoreactive CD4 T helper cells and autoantibodies production.

There is increasing evidence of the high flexibility between T- helper cells depending on the matched transcription factors, cytokines and the nature of infection. Mi-RNA is a functional single strand RNA involved in regulation of development and differentiation of Tfh cells. On the other hand, recent studies reported the role of definite mi-RNA associated with autoimmune thyroiditis patients. In this review, we will highlight plasticity between Tfh cells and other CD4 T helper cell, and how this will affect autoimmune thyroiditis in case of HCV infection.

Keywords: T Follicular helper cells; Autoimmune; Thyroiditis; Plasticity

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Abbreviations: TFH: T Follicular helper; HCV: Hepatitis C virus; GC: Germinal Center; AITD: Autoimmune Thyroid Disease; ICOS: Inducible Costimulator; Bcl6: B cell Lymphoma 6 Transcription Factor; TSLP: Tthymic Stromal Lymphopoietin

Introduction

The term T follicular helper (Tfh) cells were first used in 2000, it describes anew subset of CD4+ T cells located in tonsils. Tfh cells are subsets of CD4+ T helper cells that are required for maintenance of the germinal center reactions and generation of long-lived humoral immunity. They induce differentiation of B-cells into plasma cells. Tfh cells provide a help to cognate B cells via their expression of many molecules as CD40 ligand, IL-21, IL-4, and others [1].

T Follicular Helper cells origin

It was confirmed from decades that CD4+ T cells are required for formation of germinal center (GC), antigen -specific memory cells and plasma cells. It was thought that TH2 cells are responsible for isotype switch and Ig secretion, IL4 secretion. However, studies show that mice lacking the regulators of TH2 development are still able to form GC [2].

The discovery of Tfh cells in the recent years make it the key cell in formation of GC and generation of memory cells.Tfh as other CD4+ T cells require signals pathways to activate cytokines and cell surface molecules which in turn can activate their specific transcription factors [3].

Tfh are located in tonsils; its unique phenotype is chemokine CXC receptor 5 (CXCR5). Tonsils are secondary lymphoid organs found in lymph node. It has a large GC in which B cell follicles are developed. In GC, B cell affinity maturation include (hyper mutation and selection, Class switching, plasma cell differentiation, memory B cell formation) [4].

Similarly to B cells which express a high level of CXCR5 and required for migration to form follicles, the Tfh cells also express CXCR5 which make them able to migrate and localize in B cell follicles in response to high expression of CXCR3 and low expression of CCR7 on CD4 T cells in T cell zone. At the follicles an T-B interaction start by engagement of TCR and MHCII, which

support the expansion and differentiation of B cells [5]. The heterogeneity of Tfh was regarded to the, phenotype, function and localization [6]. The ability of Tfh cells to differentiate into multiple subtypes depend on the type of infection and the cellular microenvironment [7].

According to localization there are two main subtype; Tonsillar Tfh cells and circulating Tfh cells. Tonsillar Tfh can be further classified to Pre Tfh or early Tfh, which localized in T-B line between T cell zone and B cell follicles and GC Tfh which localized in germinal center inside B cell follicle.

Follicular T helper cell Differentiation

There are different requirements for differentiation of Tfh cells:

Cytokines: IL21 is the key feature of TFH cells, IL6 and IL21 and IL27 mainly induce production of IL21 in a STAT3 dependent manner. Also IL12 which is associated with STAT 4 activation can induce production of IL21 via STAT3 dependent manner. Activation of IL21 producing CD4 T cells result in activation of CXCR5, ICOS and BCL6 [8].

Receptor - ligand interaction: TCR, CD28, ICOS, CD40L signals are required for up-regulation of CXCR5 and any failure in this signals engagement result in reduction in the number of Tfh cells and impairment of GC formation. SLAM family of receptors are also required for T-B interaction, Also SAP-associating receptors especially CD84 are required for Tfh formation.

Antigen presenting cells: Generation of Tfh cells is initially B-cell independent and it is driven by dendritic cells DCs and Naïve CD4 T cells. This type of antigen presentation facilitates the relocation of primed CD4 T cells from T cell zone to B cell follicles to form Pre-Tfh cells. However B-cell play a great role as a secondary stage in reinforce the Tfh phenotype and promoting their survival through B-cell signals [9]. As we mentioned above that engagement of ICOS-L on B cells with ICOS on CD4 T cells induce expression of IL21 BCL-6 and MAF. Also SAP and SAP-associated receptors is required for Tfh formation and function.

Transcription factors: BCL-6 is considered the master regulator of Tfh cells. It's originally expressed on tonsillar CD4 T cells in GC. Tfh cells express a high level of BCL-6 which antagonize Blimp-1 which expressed on non-Tfh cells (TH1, TH2 and TH17) and suppress its expression. This results could explain the bimodal fate decision by activated CD4 T cells to become either BCL-6+ Tfh cells or Blimp-1 NON-Tfh cells [10].

BCL-6 also can antagonize transcription factors required for TH1, TH2 and TH17 (T-bet, GATA-3 and ROR function) respectively, so suppress differentiation of other CD4 T cells [11]. Tfh cells can produce IFN-γ, IL-4, or IL-17. Tfh cells responding to an acute viral infection express less IFN-γ than do non-Tfh effector CD4 T cells, which is consistent with different levels of T-bet expression and with the different roles of IFN-γ produced by these CD4 T cell type [12].

C-MAF induce production of IL21 by CD4 T cells, MAF its self is induced by IL6.Expression of MAF by CD4 T cells is highly correlated with expression of PD-1 , CXCR5 and ICOS [13]. BATF is required for induction of BCL-6 and MAF and so it's required for Tfh differentiation BATF and STAT-3 related cytokines induce expression of BCL-6 and MAF.

Memory TFH cells in blood

As we mentioned above, there is two types of follicular T cells; circulating and tonsillar Tfh cells. A recent study concludes phenotypic and functional profile of human circulating TFH cells. The three major TFH across blood and tonsils; CXCR5lo CCR7lo PD-1loICOSlo cells found in both tissue which suppose that this phenotype is intermediate between blood and tonsils. Expression of CCR7 in this population is always negative correlated with PD-1, CCXCR5, ICOS. Since CCR 7 downregulation is required for migration of active CD4 T cells from T cell zone to B cell follicle which is concomitant with up-regulation of CXCR5.Their data support the hypothesis that circulating TFH might be memory cells counterpart Tfh cells in secondary lymphoid organs. The difference in the phenotypes of circulating TFH is highly depend on immune response. They described TH1- (TFH1), TH2- (TFH2), and TH17-like (TFH17) TFH cells in the blood based on differential expression of CXCR3 and CCR6The circulating human memory Tfh cells have hitherto been divided into three subsets: Tfh1 (CXCR3+CCR6−), Tfh2 (CXCR3−CCR6−) and Tfh17 (CXCR3−CCR6+). According to their results they proved the evidence of T cells are plastic but that heterogeneity in terms of cytokine production is mostly restricted to CXCR5lo PD-1lo subsets that may represent intermediately differentiated Tfh cells [6].

T Follicular helper cells and HCV infection

There is a weak CD4 T Cell responses in chronic HCV infection due to T cell dysfunction. The viral persistence can promote expansion of TFH cells as majority of CD4 T cell express surface markers of TFH cells [14]. It was evaluated in a previous study a high frequency of distinct phenotype of Tfh cells expressing CD4, CXCR5, PD-1, CXCR13 in chronic hepatitis B patients and it was a biomarker of active immune stage [14,15].

Raziorrouh B et al. [16] have observed a high level of IL21 and high frequency of ICOS expression on specific CD4 T cells. Their study depended on intracellular cytokine staining from HCV-specific CD4 T cells. They explained that Ab production and B cell activation is attributed to HCV- specific CD4+ ICOS+T cells [16].

Fan-Yun kong et al. [17] has reported in his study a high frequency of CD4+ CXCR5+T cells in chronic HCV infected patients, He concluded that activation of CD27 IgG+ B cells is mainly depend on the high level of IL21 and any abnormalities in IgG B cells is associated with autoimmune disorders [18]. He also detected other two different subsets of TFH cells expressing ICOS+ CD4+CXCR5+ and PD-1+ CD4+ CXCR5+ [18].

Also M zhang et al. [18] & Feng et al. [19] studies have evaluated a high frequency of CD4 CXCR5 T cell expression and their associated cytokines in chronic HCV patients. They indicated that CXCR5 CD4 T cells have been activated after HCV antigen stimulation and the phenotype of this T cells is altered in chronic HCV infection [18,19]. M zhang [18] explained that the cause of

failure of specific CD4T cells is attributed to up-regulation of PD-1 on TFH cells which also restrict T-cell receptors signaling that could lead to autoimmune disorders.

Autoimmune thyroiditis and HCV infection

Thyroid gland is considered one of the extrahepatic reservoir for hepatitis C virus. There is a strong correlation between hepatitis C infection and thyroid autoimmunity However, the mechanism by which hepatitis C virus triggering autoimmune thyroiditis in susceptible individuals still unknown. Several suggested mechanisms have been proposed for production thyroid autoimmunity, first by alteration in the immune response or direct effect on thyroid cells or both of them. Other studies concluded that viral antigen itself could induce thyroid autoimmunity by 1-changing self-antigen expression 2-induction of local inflammation (cytokine release) which could activate autoreactive T cells 3-aberrant expression of MHCII on thyroid cells [20].

The two HCV envelop glycoproteins E1 and E2 bind to CD81on different cell types which result in intracellular signals affect hepatocytes and other cells for example engagement of E1 and E2 to CD81 which expressed on T cells lead to increase secretion IL4 and lower IL2 release [21], similarly engagement of virus specific proteins with CD81 on B cells could trigger JNK pathway which increase Naïve B cell proliferation [22-24]. HCV entry in thyrocytes promote local tissue inflammation as occurred in hepatocytes. HCV start replication inside thyroid cells leading to change in self thyroid Ag expression. Engagement of HCV with CD81 result in increase in the secretion of IL8 which is responsible for thyroid inflammation and activation of autoreactive T cells, this mechanism of thyroid inflammation is more likely to occur than thyroid apoptosis [20].

It was found that homology of HCV and thyroid is ranged between 62.5%-100% and it was not restricted to specific HCV genotype. The expression of MHCII on thyroid cells result in activation of autoreactive T cells by bystander activation (cytokines release) [25]. Autoimmune thyroiditis is organ-specific immune disorder, clinically manifested by formation of autoantibodies to thyroglobulin (TG) and TPO, TSHr, pendrin and NIS. Once Helper-T cells activated they induce B cells to secret thisautoantibodies [26].

Three main CD4 T helper cells play a great major role in autoimmune activation through their specific cytokines TH1, TH2 and TH17 and their cytokines IFN-gamma, IL4 and IL17 respectively.

T Follicular helper cells and autoimmune thyroiditis (AITD) in presence of HCV infection

The recent discovery of Tfh cells refutes the first hypothesis that TH1, TH2 and TH17 are the only effector CD4 T helper cells responsible for autoimmune thyroiditis [27]. There is high evidence that both GC-TFH and extrafollicular - T helper cells play role in pathogenesis of autoimmune disease [28].

As we mentioned above distribution of circulating memory Tfh cell subsets (extrafollicular Tfh cells) contributes to the pathogenesis of some autoimmune diseases such as primary sjögren's syndrome, where higher levels of TFH17 were assessed in juvenile dermatomyositis patients, where there are higher levels of TFH2 and TFH17 [29]. A recent study among systemic lupus erythromatus, systemic sclerosis and rheumatic arthritis patients focused on the discovery of circulating CD4^{+}, CXCR5^{+}, ICOS^{high} T cells with a high frequency [2,30].

Zhu et al. [31] has discovered in his study, a high frequency of CD4^{high} CXCR5^{high}ICOS^{high} T cells infiltrated the thyroid gland which indicate that this phenotype of circulating Tfh cells play a role in pathogenesis of AITD. He also found appositive correlation between the frequency of CD4 ICOS CXCR5 T helper cells and percentage of autoantibodies and a positive correlation with age of patients. He found a strong expression of IL21 in circulating CD4 T cells of patients and it was strongly associated with the percentage of CD4 [hi]CXCR5 [hi]ICOS[hi] T helper cells [31].

The thyroid self Ag spread due to HCV E2 engagement to CD81 receptor on thyroid cells lead to generation of autoreactive B-cells then loss of tolerance. Uncontrolled generation of TFH cells shape the outcome of autoreactive B-cells differentiation, resulting in increased production of autoantibodies, inflammation and tissue injury [32] as shown in Figure 1.

Table 1: Difference in surface markers between Pre-TFH and GC-TFH.

Marker Expression	Pre-Tfh	GC-Tfh	Function
PD-1	Low	High	Inhibit TCR signals,CD8 T cell exhaustion
CXCR5	Moderate	High	Migration of Tfh into B cell follicle.
BCL6	Low	High	Tfh differentiation and function
ICOS	Low	High	Regulator of humoral response
CXCL13	Low	High	Chemokine required for B- cell migration into B cell follicle
IL21R	Moderate	High	Germinal center (GC) formation

The process by which TFH cells select mutated B cells and then promote them to differentiate into memory B cells and long-lived plasma cells can sometimes fall into a wrong path and generate self-reactive B cells. Normally, mutated self-reactive B cells that cannot receive the second signal provided by T cells are programmed to die by apoptosis. Once the T cells fail to discriminate self-reactive B cells from the normal antigen-specific B cells, high-affinity autoantibodies will be generated, and thereby autoimmune disease will happen [33]. More deep studies are needed to investigate different phenotypes of circulating TFH cells and their specific roles among autoimmune thyroid patients.

Plasticity of T follicular helper cells

There is increasing evidence of the high flexibility between subsets of T- helper cells. Naïve CD4+ T cells which interact with Ag-presenting DCs can acquire expression of Bcl-6. However, their flexibility to specific effector lineages is governed by additional signals and the coordinated and antagonistic actions of different transcription factors [34]. Sufficient levels of T-bet or GATA3, or potentially RORγt, willoverride the repressive effect of Bcl-6 to yield Th1, Th2, or Th17 cells, respectively.

However, expression of Blimp-1 as transcription factor on other non- Tfh cells (TH1, TH2 and TH17) can stop regulation of BCL-6 as both are antagonist to each other, BCL-6 antagonism of BLIMP-1 is one of the mechanisms by which BCL-6 can stop differentiation of non-TFH cells [35].

The primed naive CD4+ T cells become pre-TFH cells, defined by CXCR5 and Bcl6 expression, which differentiate into GC Tfh cells after interactions with cognate B cells. Th1, Th2, and, presumably, Th17 cells retain flexibility in their differentiation programs such that under conditions of sustained Ag (e.g., persistent pathogen infection) they can down-regulate T-bet, Gata3, or RORγt, upregulate Bcl6, and convert to TFH cells [6,36]. Cytokines which are produced by dendritic cells can regulate the T helper cell lineage. It was found that IL6 and IL21 is required for Tfh cells differentiation. These matched pattern of cytokines and transcriptional factors expression reinforces the concept of the flexibility between Tfh cells and other Th cell subsets [37,38] as shown in Figure 1.

TFH express high level IL21R. IL6 is important for induction of IL21 in Tfh cells as well as TH17 in STAT-3 dependent manner. The difference between TH17 and Tfh cells that TGF-βis not required for effector Tfh induction, Also ROR-γ is not expressed on Tfh cells. The over production and excessive amount of IL21 will increase the inflammation and destruction of thyroid cell. As it is known for all IL21 play a great role in pathophysiology of many tumors and autoimmune disease [39]. In a recent study, it was observed that IL-21/IL-21R pathway may be involved in the development of AITD [39].
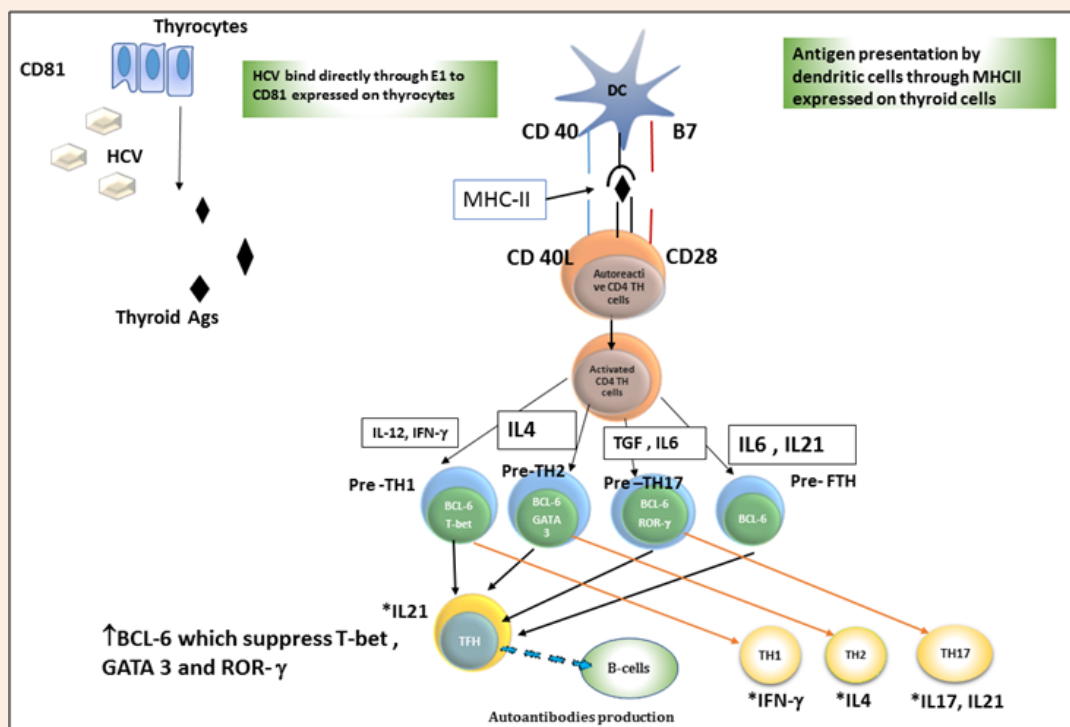

Figure 1: Flexibility between CD4 T helper cells.
Direct engagement of HCV E2 with CD81 which expressed by thyroid cells will lead to initial destruction of thyroid cells and thyroid antigen presentation through MHCII on dendritic cells. Autoreactive CD4 T cell arise and start to acquire BCL-6. However, the Commitment to specific effector T helper cells is governed by specific cytokines and antagonistic action of different transcription factors.

The nature of the infection may detect the fate of CD4 specific T cells, for example in TH2- inducing infection, IL4 expressing TH2 may convert to TFH cells. This persistent infection could induce BCL-6 expressions which in turn suppress GATA 3 [38]. Similarly, In the Th1-mediated infection as Lymphocytic choriomeningitis virus (LCMV) infection, a deviation from Th1 to TFH occur in the chronic stage. This deviation correlate with high expression of BCL-6 which down regulate T-bet and decrease TH1 formation [40].

Role of Circulating Micro-RNA in Regulation of Tfh Cells and Pathogenesis of Autoimmune Thyroid Disease

Mi-RNA are functional single strand RNA which encoded endogenously and involved in immune cells development and differentiation. There were multiple studies reported the role of micro-RNA in different autoimmune disease as rheumatoid arthritis, Crohn's disease, systemic lupus erythromatus and Graves' disease [41]. A recent study reported for the first time a profile of circulating micro-RNA in patients with autoimmune thyroiditis. They revealed a different serum levels of miRNA-16 miR-22, miR-375 and miR-451, were associated with GD or HT, which may play important roles in the pathogenesis of these diseases [42,43].

miR-16 regulates the nuclear factor kappa B(NF-kB) signal pathway, which is associated with production of inflammatory cytokines and chemokines 1. miR-22 targets estrogen receptor alpha (Era) mRNA, resulting in the repression of estrogen signaling, which is required for T cell differentiation. miR-375 regulates thymic stromal lymphopoietin (TSLP), which is a pivotal cytokine linking innate and Th2 adaptive immune function [43].

On the other hand, recent study reported that the miR-17-92 cluster was regulated by Bcl-6 in CD4 T cells [11]. T cells over expressing Bcl-6 demonstrated diminished expression of the miR-17-92, as do TFH cells, which, suppresses the expression of CXCR5. However, MULTIPLE studies have shown that the miRNA-17-92 induces TFH cell differentiation [44].

Also another study found that miR-155 is highly expressed in pre-Tfh and Tfh cells and play a role in generation and function of TFH cells by controlling the cellular proliferation at late stage of TFH cell differentiation [45,46].

Conclusion

In conclusion, further investigations are needed to provide data on the different phenotypes, distribution, clinical relevance and function of TFH cells among autoimmune thyroiditis patients with HCV infection. Also the signaling molecules or pathway which play role in the differentiation of TFH cells which in turn could provide insights for developing some novel therapies for autoimmune thyroiditis.

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