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The role of T cells in the development of Henoch-Schonlein purpura

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1. ABSTRACT

Henoch-Schonlein purpura (HSP) is an IgA-mediated disorder that most commonly occurs in children. Its etiology and pathogenesis remain unknown. In recent years, numerous studies have pointed to a dysfunction of T cells in the pathogenesis of HSP. Here, we will review the epidemiology, clinical and molecular characteristics of HSP, as well as abnormalities of Th cell subsets in this disorder. Finally, we will discuss the key factors that are involved in Th cell differentiation as potential novel targets for the prevention and treatment of HSP.

2. INTRODUCTION

Henoch-Schonlein purpura (HSP), also known as immunoglobulin A (IgA) vasculitis (1), is an IgA-mediated disorder that causes inflammation of small blood vessels, leading to hemorrhage in the skin, joints, intestines and kidneys. HSP can affect anyone, including elderly people (2), but it is most common in children between the ages of two and six years (3–5). It occurs about twice as often in boys as girls (6). The incidence of HSP in children is about 20 per 100,000 children per year, making it the most common form of vasculitis in children (4). The most striking feature of HSP is a purplish rash, typically on the lower legs and buttocks. HSP can also cause abdominal pain and aching joints. The condition usually improves on its own, but medical care is generally needed if the disorder affects the kidneys (3, 7). Severe HSP nephritis (HSPN) remains the major cause of morbidity and mortality among children with HSP (8). In a systematic review, 34.2% of HSP patients were found to have had renal involvement (9). Cases of HSP may occur anytime throughout the year, but some studies have found that fewer cases occur during the summer months, with most cases occurring in autumn and winter (10).

Multiple standards exist for defining HSP, including the 1990 American College of Rheumatology classification (11–13) and the 1994 Chapel Hill Consensus Conference nomenclature of vasculitides (14, 15). More recent classifications include the 2006 European League Against Rheumatism and Pediatric Rheumatology Society classification criteria (16, 17). Recently, a modified semiquantitative classification was found to be more sensitive than the classical International Study of Kidney Disease in Children system for predicting the outcome in cases of HSPN (18). Like most human illnesses, HSP is an etiologically-complex disease, with environmental factors triggering the disease in genetically predisposed individuals. The current diagnostic criteria have high sensitivity and specificity, and most HSP patients are accurately diagnosed. However, although the prognosis is generally good, the failure of HSP treatment remains a key problem. To reduce associated morbidity and mortality and improve patient quality of life, further research is needed to improve our understanding of the pathogenetic mechanisms underlying HSP.

3. CHARACTERISTICS OF HSP

The pathophysiological features of HSP are not well understood but appear to involve the deposition of immune complexes containing IgA and complement component 3 (C3) in arterioles, capillaries and venules (19). The activation of the complement system, in part through the alternative pathway, may result in increased plasma levels of C3a and C5a; in particular, the increased level of C5a is thought to play a role in disease pathogenesis by activating the endothelium of cutaneous small vessels (19). Increased synthesis of IgA in response to antigens processed by the mucosa-associated immune system also appears to contribute to disease development. HSPN and IgA nephropathy are related diseases, with both resulting from glomerular deposition of aberrantly glycosylated IgA. Although both nephritides present with similar histological findings and IgA abnormalities, they display pathophysiological differences that have important therapeutic implications (20, 21). HSP nephritis is mainly characterized by acute episodes of glomerular inflammation with endocapillary and mesangial proliferation, fibrin deposits and epithelial crescents that can heal spontaneously or lead to chronic lesions. In contrast, IgA nephropathy normally presents with slowly progressing mesangial lesions resulting from continuous low-grade deposition of macromolecular IgA1 (22). Further, IgA nephropathy has a predilection for young adults while HSP is more predominant among children, and IgA nephropathy typically only affects the kidneys, while HSP is a systemic disease (23–25).

The dominant clinical features of HSP are cutaneous purpura (100%), arthritis (82%), abdominal pain (63%), gastrointestinal bleeding (33%) and nephritis (40%) (26). These symptoms can be summarized as four main characteristics (27, 28). The first is rash (purpura). Reddish-purple spots which look like bruises are the most distinctive and universal sign of HSP. The rash develops mainly on the buttocks, legs and feet, but can also appear on the arms, face and trunk and may be worse in areas of pressure, such as the sock line and waistline (29, 30).The second characteristic is swollen sore joints (arthritis). Patients with HSP often have pain and swelling around the joints, mainly in the knees and ankles. Joint pain sometimes precedes the classical rash by one or two weeks. These symptoms subside when the disease clears and leave no lasting damage (31). The third characteristic is gastrointestinal symptoms which many children with HSP develop, including abdominal pain, nausea, vomiting or bloody stools. These symptoms sometimes occur before the rash appears, so they can be helpful in the early diagnosis of HSP (32, 33). The final characteristic is kidney involvement. In most cases, this is revealed by protein or blood in the urine, which may not be evident unless a urine test is performed. This normally dissipates once the illness passes, but in a few cases kidney disease may develop and persist. Before these symptoms begin, patients may have two to three weeks of fever, headache and muscular aches and pains. Other organs, such as the brain, heart and lungs, may also be affected (34, 35).There is a significant correlation between the severity of renal involvement and pathological grading and scoring of HSPN; in particular, the severity of proteinuria is a significant determinant of renal pathologies (36). The exact cause of this phenomenon is unknown. It usually resolves within several weeks and requires no treatment apart from symptom control, but may relapse in a third of cases and cause irreversible kidney damage in about one in a hundred cases.

4. INVOLVEMENT OF $CD4^+$ T CELLS IN HSP DEVELOPMENT

The immune system is believed to play a role in targeting the blood vessels involved in HSP. An abnormal immune response to an infection may be a factor in many cases. In recent years, the role of T cells in the pathogenesis of HSP has become a focus of research. It has been suggested that leukocyturia is associated with post-infectious glomerulonephritis (GN), interstitial nephritis and renal allograft rejection. In addition, prominent infiltration of T cells and macrophages is commonly observed in the renal tissues of patients with GN, accompanied by cellular crescent formation and/or interstitial cell infiltration (37). In urine from patients with different forms of GN, including IgA nephropathy, HSPN and anti-neutrophil cytoplasmic antibody-associated GN, T cells appeared together with macrophages. T cells from urine were mainly $CD45RA^-$, $CD45RO^+$ and CD62L (L-selectin), which are the phenotypic features of effector T cells (37). The findings suggest that the appearance of effector T cells in urine may reflect the cellular immune reaction that occurs in the kidneys of patients with GN, which is accompanied by active cell infiltration.

$CD4^+$ T cells play critical roles in mediating adaptive immunity to a variety of pathogens. They are also involved in autoimmunity, asthma and allergic responses as well as in tumor immunity. Recently, these cells have been found to contribute to the pathogenesis of HSP. Results from 32 HSP patients and 25 healthy donors revealed that freshly isolated $CD4^+$ T cells from patients with HSP expressed higher levels of OX40 than cells from healthy individuals (38). The levels of soluble OX40L (Sox40l) in the sera of patients with HSP were also much higher than in controls. Importantly, significantly elevated levels of OX40 on $CD4^+$ T cells and Sox40L in sera were detected in patients with HSPN compared to patients without nephritis, indicating that both OX40 upregulation and an increase in Sox40l were closely associated with disease activity in these patients (38).

As OX40/OX40L is a costimulatory pathway that can promote T-cell activation and prolong survival, their upregulation indicates the involvement of $CD4^+$ T cells in the pathology of HSP.

During T cell receptor (TCR) activation in a particular cytokine milieu, naive $CD4^+$ T cells may differentiate into different subsets of T helper (Th) cells. There are at least four types of Th cells: Th1, Th2, Th17 and regulatory T (Treg) cells, as defined by their pattern of cytokine production and function. Th1, Th2 and Th17 cells are important for eradicating intracellular pathogens, helminth and extracellular bacteria/fungi, respectively. Th1 and Th17 cells are also involved in many types of autoimmune diseases, whereas Th2 cells contribute to allergic responses (39). Treg cells are critical in maintaining self-tolerance and in modulating immune responses to infections (40). $CD4^+$ T cells are also important in the induction and control of immunoglobulin class switching and somatic hypermutation. These events occur mainly within germinal centers (GCs), and $CD4^+$ T cells that enter GCs to mediate their helper function for antibody production are often designated T follicular helper (Tfh) cells (41). Children with HSP show T-cell disorders and abnormalities in Th cell differentiation.

4.1. Th1 cells

Th1 cells are the host immunity effectors against intracellular bacteria and protozoa. They are triggered by interleukin 12 (IL-12) and IL-2, and their effector cytokine is interferon gamma (IFN-γ). The key Th1 transcription factors are signal transducer and activator of transcription 4 (STAT4) and T-bet. Th1 overactivation against autoantigens will cause type 4 delayed-type hypersensitivity; tuberculin reactions and type 1 diabetes also belong to this category of autoimmunity (39).

There are findings showing that in urine from patients with IgA nephropathy, HSPN or anti-neutrophil cytoplasmic antibody-associated GN, T cells were present along with macrophages. These urine cells expressed mRNA for Th lymphocyte 1 cytokines, IL-2 and/or IFN-γ, indicating the involvement of Th1 cells in the pathology of HSP (37). Furthermore, renal biopsy specimens from 22 pediatric patients diagnosed with HSP were compared to normal renal tissue taken during nephrectomy in 20 pediatric patients diagnosed with Wilms tumor (42). Immunohistochemical analysis of IFN-γ expression showed that glomeruli and tubules in HSP patients had significantly higher IFN-γ expression than those in control patients. This suggests that IFN-γ may contribute to HSP in children and provides indirect evidence that Th1 cells may be involved in the pathogenesis of HSP. Another study suggesting Th1 predominance in HSP studied the transcriptional factor T-bet, which regulates the differentiation of Th lymphocytes into the Th1 subset (43). The relative expression of T-bet was significantly higher in the urinary sediment from patients with HSP than in healthy controls. Moreover, a significant increase in T-bet expression was observed in glomeruli biopsy specimens from all patients studied. When the patients received immunosuppressive therapy, expression of T-bet was reduced (43), suggesting a predominant role for Th1 cells in the development of HSP. However, other studies have found no evidence that Th1 is involved in the pathogenesis of HSP (44, 45).

4.2. Th2 cells

Th2 cells are the host immunity effectors against extracellular parasites, including helminths. They are triggered by IL-4 and their effector cytokines are IL-4, IL-5, IL-9, IL-10 and IL-13. The key Th2 transcription factors are STAT6 and GATA3 (46). IL-4 is the positive feedback cytokine for Th2 cell differentiation, and overactivation of Th2 in response to autoantigen causes Type1 IgE-mediated allergy and hypersensitivity. Allergic rhinitis, atopic dermatitis and asthma belong to this category of autoimmunity (39).

The transcriptional factor GATA-3, which regulates the differentiation of Th lymphocytes into the Th2 subset, was examined in HSP patients (43). The relative expression of GATA-3 was significantly lower in the urinary sediment of patients than in control subjects. When the patients received immunosuppressive therapy, the expression of GATA-3 remained static (43), which suggested that Th2 cells were not be involved in the pathogenesis of HSP. In another study, histone modification patterns in peripheral blood mononuclear cells (PBMCs) from HSP patients were analyzed and the expression of inflammatory cytokines (IFN-γ, IL-2, IL-4, IL-6 and IL-13), transcription factors (T-bet, GATA-3 and TIM-1) and chemokines (CXCL4 and CXCL10) were investigated (47). Results showed that histone H3 acetylation and methylation were significantly enhanced in PBMCs from HSP patients. In particular, there were marked increases in histone H3 acetylation and H3 lysine 4 trimethylation at the IL-4 locus in these patients. In addition, the expression levels of IL-4, IL-6, IL-13, GATA-3, TIM-1 and CXCL4 were increased, indicating that abnormal histone modifications may have led to the Th1/Th2 cytokine imbalance in HSP, and hence that Th2 cells may contribute to the pathogenesis of HSP. The same conclusion can be drawn from another study which showed that toll-like receptor 2 (TLR2) and TLR4 overactivation induced HSP-related renal impairment, and further indicated that activated TLR2 and TLR4 may mediate the pathogenesis of HSP by upregulating a Th2-type immune response (45). Finally, a study of 42 children with acute HSP and 30 healthy children showed that the plasma levels of IL-4, IFN-γ and IL-17 were significantly higher in the

HSP group compared to the controls. And the TLR6 protein expression levels in the monocytes of the HSP group significantly positively correlated with the serum IL-4 and IL-17 levels, but not with the serum levels of IFN-γ. Thus, the activation of TLR6 may be involved in the immunopathogenesis of HSP by upregulating the immune responses of Th2 and Th17 cells (48). However, further studies will be required to confirm Th2 cell involvement in the pathology of HSP.

4.3. Th17 cells

Th17 cells are a subset of Th cells, and are developmentally distinct from Th1 and Th2 lineages in that they produce IL-17. They are related to Treg cells because the signals that cause Th17 to differentiate inhibit Treg differentiation (49). Transforming growth factor beta (TGF-β), IL-6, IL-21 and IL-23 contribute to Th17 formation in mice and humans. Key factors involved in the differentiation of Th17 cells are STAT3 and retinoic acid receptor-related orphan receptor gamma (RORγ) and alpha (RORα) (50). Th17 cells can alter their differentiation program, ultimately giving rise to either protective or pro-inflammatory pathogenic cells.

IL-17 and Th17 cells are known to be involved in many autoimmune diseases, and studies have shown that IL-17 and Th17 cells may be involved in the pathogenesis of childhood HSP. For example, it has been shown that children with acute HSP have significantly higher serum levels of IL-17, IL-6 and TGF-β than healthy controls (44, 51). These patients also had more Th17 cells but not Th1 cells in peripheral blood, indicating that Th17 cells and serum IL-17 may each contribute in part to HSP and that upregulation of Th17 cells may perpetuate the inflammatory response in HSP. Immunohistochemical analysis of renal biopsy specimens from children with HSP demonstrated significantly higher IL-17 expression (42). Another study of 42 children with acute HSP and 30 healthy children also showed that plasma levels of IL-17 were significantly higher in patients than in healthy controls (48). Thus, the activation of TLR6 may be involved in the immunopathogenesis of HSP by upregulating the immune responses of Th2 and Th17 cells. Taken together, these studies suggest a role for Th17 cells in HSP.

4.4. Treg cells

Tregs are a subpopulation of T cells that modulate the immune system, maintain tolerance to self-antigens and prevent autoimmune disease. Tregs come in many forms, with the well-understood being those that express CD4, CD25 and forkhead box P3 (FOXP3). Tregs are immunosuppressive and generally suppress or downregulate induction and proliferation of effector T cells (52). The cytokine TGF-β has been found to be essential for Treg differentiation from naive $CD4^+$ T cells and for the maintenance of Treg homeostasis (53, 54). The immunosuppressive cytokines TGF-β and IL-10 have also been implicated in Treg function.

Treg cells have been implicated in a wide range of autoimmune disorders, such as rheumatoid arthritis, autoimmune liver disease, systemic lupus and immune-mediated diabetes (53, 55, 56). A study of 63 children with HSP showed that both FoxP3 and TGF-β1 mRNA expression was significantly lower than in healthy controls, indicating lowered Treg activity (57). Another study reported a lower frequency of Treg cells and reduced IL-10 concentration in HSP patients compared to healthy controls (51). However, further studies will be required to fully elucidate the role of Treg cells in HSP.

4.5. Tfh cells

Tfh cells are found in the periphery of B cell follicles and are identified by their constitutive expression of the B cell follicle-homing receptor, CXC chemokine receptor 5 (CXCR5) (58). They are critical for the activation of B cells, antibody class switching and GC formation (59). The inducible T-cell co-stimulator ICOS or CD278 was shown to provide a particularly critical signal for Tfh cells (60). It has been reported that ICOS induces the secretion of IL-21 by activated $CD4^+$ T cells and that IL-21 plays a crucial role in the development of Tfh cells and GCs (61–63). B-cell lymphoma-6 (Bcl-6) and programmed death 1 (PD-1) have also been identified as transcription factors in Tfh cells. Thus, Tfh cells are characterized by the expression of CXCR5, ICOS, PD-1, Bcl-6 and IL-21 (59). However, different studies define blood Tfh cells in different ways. Although some studies have defined circulating human Tfh cells as the total population of $CXCR5^+$ $CD4^+$ T cells, other studies have investigated subsets of these cells, such as $CXCR5^+$ $ICOS^+$, $CXCR5^+$ ICOShi, $CXCR5^+$ $PD1^+$, $CXCR5^+$ PD1hi, $CXCR5^+$ $ICOS^+$ $PD1^+$, $CXCR5^+$ $CD57^+$ and $CXCR5^+$ $IL\text{-}21^+$ cells (64–73).

Tfh cells play crucial roles in regulating immune responses. Studies have shown that the frequency of circulating $CXCR5^+$ $CD4^+$ Tfh cells co-expressing ICOS was significantly higher in children with acute HSP than in healthy controls, whereas the frequency of $CXCR5^+$ $CD4^+$ Tfh cells expressing PD-1 was not increased in these patients (74, 75). Moreover, serum levels of IL-21, IL-6, IgA and C3 were also significantly higher in HSP children than in healthy controls. A positive correlation was observed between the frequency of circulating $ICOS^+$ $CXCR5^+$ $CD4^+$ Tfh cells and the serum levels of IL-21 or IgA (74). Additionally, mRNA expression levels of IL-21, IL-6 and Bcl-6 were also significantly increased

in peripheral blood from children with acute HSP compared to healthy controls (74). Following treatment, the numbers of $CD4^+$ $CXCR5^+$, $CD4^+$ $CXCR5^+$ $PD\text{-}1^+$ and $CD4^+$ $CXCR5^+$ $ICOS^+$ Tfh cells, as well as serum levels of IL-21 were significantly reduced (75). Taken together, these findings suggest that Tfh cells and their associated molecules may play critical roles in the pathogenesis of HSP, and thus can be considered as possible therapeutic targets.

Taken together, increasing numbers of Th1, Th2 and Tfh cells, together with decreasing Treg cell numbers may contribute in part to the pathogenesis of HSP. Further research into the differentiation of Th cells can be expected to provide more information regarding the pathogenesis of HSP and to identify novel targets for disease control and prevention.

5. KEY FACTORS AFFECTING $CD4^+$ T CELL DIFFERENTIATION AS THERAPEUTIC TARGETS

The various functions of mature $CD4^+$ T cells are achieved through the differentiation of naive $CD4^+$ T cells following stimulation by their cognate antigens presented by competent antigen-presenting cells. This results in the formation of subsets of effector and/or memory cells with specialized phenotypes. Our knowledge of Th cells has expanded greatly. T cell heterogeneity and plasticity open new opportunities for targeting or redirecting specific subsets of cells in autoimmune and allergic diseases. These targets may become clinically feasible when we more fully understand the regulation of Th cell subsets and their relationship to one another.

Cytokines play critical roles in determining Th cell differentiation. The distinctive differentiated states of the various CD4 effector/regulatory subpopulations are determined largely by the set of transcription factors they express and the genes they transcribe. The induction of distinctive patterns of gene expression may be achieved in several ways, but *in vitro*, the major determinants of the differentiated state of the cell are the set of cytokines present during the TCR-mediated activation process. A combination of cytokines is required for the differentiation of each lineage: IL-12 and IFN-γ for Th1; IL-4 and IL-2/IL-7/thymic stromal lymphopoietin for Th2; TGF-β and IL-6/IL-21/IL-23 for Th17; TGF-β and IL-2 for Treg; and IL-6 and IL-21 for Tfh cells (Figure 1). One of the effector cytokines produced by each subset of Th cells further promotes the differentiation process, providing a powerful positive amplification loop. The IL-1 family of cytokines may also participate in inducing TCR-independent effector-cytokine production by Th cells, including IL-18 for Th1, IL-33 for Th2 and IL-1 for Th17 cells.

Master transcription factors and STAT proteins are indispensable for Th cell fate determination and cytokine production. GATA3, the Th2 master regulator, was the first master regulator to be identified (76, 77). GATA3 expression is upregulated or downregulated during Th2 or Th1 differentiation, respectively (77–79). Deleting *Gata3* from fully differentiated Th2 cells by the introduction of retrovirally-encoded Cre has only a modest effect on IL-4 production but completely blocks the production of IL-5 and IL-13, consistent with GATA3 binding directly to the IL-5 (80) and IL-13 (81, 82) promoters, but only binding IL-4 enhancers (83). T-bet is a major factor for inducing IFN-γ production and Th1 cell differentiation (84). T-bet induces IFN-γ partly through remodeling the *Ifng* gene and by upregulating IL-12Rβ2 expression, thus promoting both IFN-γ expression and selective Th1 cell expansion in response to IL-12 (85, 86). The differential requirement for T-bet in IFN-γ production by CD4 and CD8 T cells may be explained by the heightened expression of another T-box family member, Eomesodemin (Eomes), in CD8 T cells (87). IL-21 inhibition of Th1 cell IFN-γ production may be mediated by suppression of Eomes but not by suppression of T-bet (88), suggesting that Eomes is also upregulated during Th1 differentiation and is involved in optimal IFN-γ production by CD4 T cells. Foxp3 has been reported to be the master transcriptional regulator for Tregs (89, 90). Continuous expression of Foxp3 in Tregs is required to maintain the suppressive activity of these cells (91). Limiting Foxp3 expression appears to divert cells that would have differentiated into Tregs into becoming Th2-like cells, implying a close relationship between the Th2 and Treg lineages (92). Th17 cells do not express GATA3 or T-bet. Instead, they express high levels of RORγ (50, 93, 94). RORγt is the master regulator of Th17 cells, and RORγt-deficient mice are partially resistant to experimental autoimmune encephalomyelitis (95). Bcl-6 is a transcriptional repressor. It is frequently translocated and hypermutated in diffuse large B cell lymphoma and is critical for GC B cell differentiation and thus GC formation (96). Bcl-6 is also expressed in Tfh cells and is critical for Tfh cell differentiation. It is necessary and sufficient to induce Tfh-related molecules, including CXCR5, PD-1, IL-6R and IL-21R (97–99). Bcl-6 also suppresses the expression of Th1, Th2 and Th17 cytokines.

As mentioned above, the major signaling pathway triggered by cytokines is the activation of the STAT family of proteins. STATs play critical roles in the differentiation and expansion of Th cells. Activation of STAT1 by IFN-γ is important for the induction of T-bet during *in vitro* Th1 differentiation (100, 101). The existence of a positive feedback loop—in which IFN-γ, acting through T-bet, induces more IFN-γ—indicates that STAT1 serves as a critical mediator for the amplification of *in vitro* Th1 responses. STAT2 forms

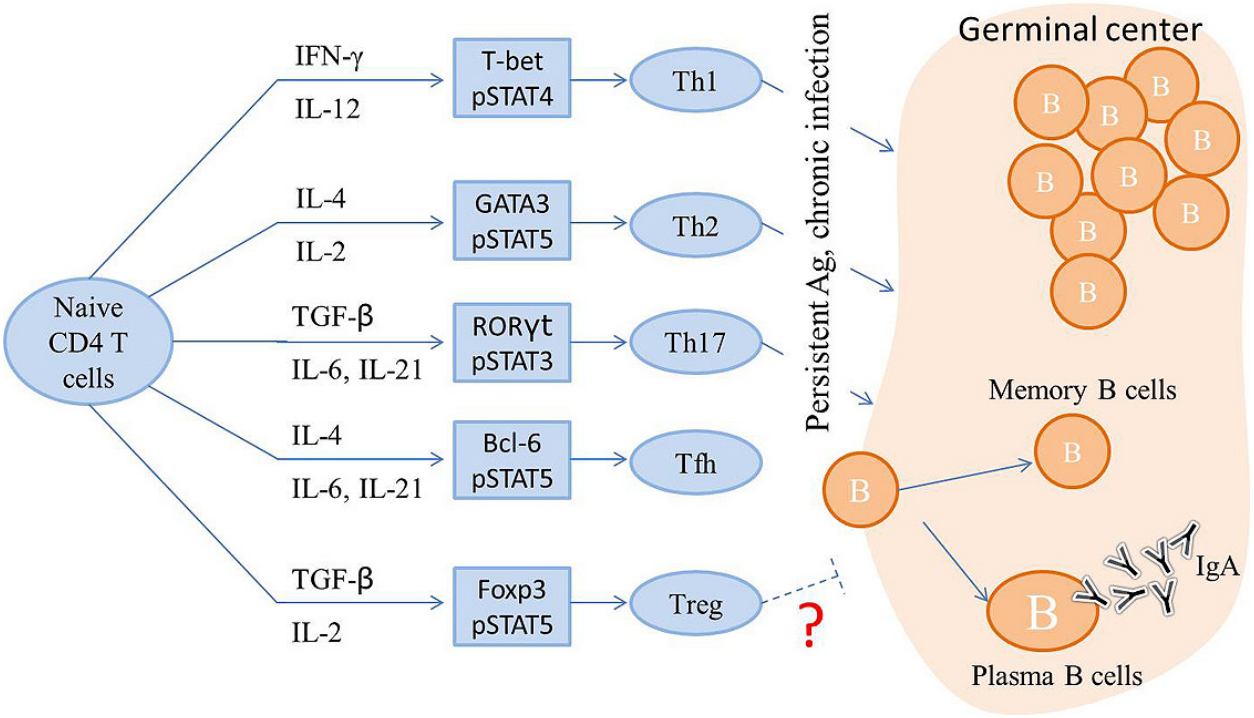

Figure 1. Differentiation of Th cells and their role in B cell function. Upon TCR activation triggered by antigen-presenting cells, naive CD4 T cells differentiate into distinct Th lineages in the context of combinations of cytokines. The differentiation processes involve upregulation of master transcriptional regulators and activation of STAT proteins. With the help of different Th cells, B cell is activated and migrates into the germinal center and proliferates, followed by differentiation further to memory B cells or antibody secreting plasma cells. Plasma B cells then secret IgA which mediates HSP.

a heterodimeric complex with STAT1 in response to type I IFNs. IL-6, IL-21 and IL-23 cytokines that are involved in Th17 cell differentiation, amplification and maintenance also induce TCR-independent, cyclosporine A-independent IL-17A production through the activation of STAT3 (102–105). STAT3 binds to *IL17* (106) and *IL21* (107) and is responsible for the induction of RORγt and IL-23R (103, 108, 109). STAT4 expression is higher in Th1 compared to Th2 cells (117). Activated STAT4 can directly induce IFN-γ production and the expression of IL-12Rβ2 and T-bet during Th1 differentiation (54, 117). Low levels of STAT5 activation are sufficient for cell proliferation and survival; however, strong STAT5 signaling is required for Th2 differentiation (110, 111). STAT5 activation by IL-2 is also critical for Treg development (112–114). STAT5 may contribute to Foxp3 induction by binding to its promoter (114, 115). STAT5 activation also regulates the activity of the Bcl6 promoter in B cells (116). In view of the expression of Bcl-6 in Tfh cells, this regulation raises the possibility that such an effect may be important for Tfh cell differentiation. STAT6 is the major signal transducer in IL-4-mediated Th2 differentiation and expansion (117–119). *In vitro*, STAT6 activation is necessary and sufficient for inducing high levels of expression of the Th2 master regulator gene, GATA3 (120, 121).

In summary, a collaboration exists between the master regulators and STAT family members in T cell differentiation and expansion: T-bet and STAT4 for Th1; GATA3 and STAT5 for Th2; RORγt and STAT3 for Th17; Foxp3 and STAT5 for Treg; and Bcl-6 and STAT5 for Tfh (Figure 1). Other transcription factors are either secondary to master regulators and STAT proteins or are responsible for the induction of master regulators; these include Runx family members (Runx1, Runx2, and Runx3) (122–125), IFN regulatory factor family members (IRF4 and IRF1) (126, 127), Gfi-1 (128, 129), Ikaros family members (Ikaros, Helios, Aiolos, Eos, and Pegasus) (130), c-Maf (131), and others like Hlx (a transcription factor induced by T-bet) (85), Ets-1 (a cofactor for T-bet during Th1 differentiation) (132, 133) and Blimp-1 (an important transcription factor induced in Th2 cells) (134, 135).

6. CONCLUSIONS

Like most human illnesses, HSP is an etiologically-complex disease. Although the prognosis is generally good, the failure to find effective treatment strategies for HSP remains a key problem. The immune system is believed to play a role in targeting the blood vessels involved. In recent years, the role of T cells in the pathogenesis of HSP has become a

focus of research, but information regarding Th cell involvement in HSP is still incomplete. Many signaling molecules and transcription factors shown to be critical for Th cell differentiation in mouse models are also defective in human diseases related to abnormal Th cell differentiation. Linking animal models with clinical studies should provide greater insight into the details of Th cell differentiation. As abnormalities in Th cell differentiation are present in HSP, it is important to elucidate pathologies in Th cell differentiation to fully understand this disease.

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Abbreviations: HSP, Henoch-Schonlein purpura; HSPN, Henoch-Schonlein purpura nephritis; Th, T helper; Treg cells, regulatory T cells; Tfh, t follicular helper; C3, complement component 3; GN, glomerulonephritis; IFN-γ, interferon-gamma; TGF-β, transforming growth factor beta; PBMCs, peripheral blood mononuclear cells; RORγ, retinoic acid receptor-related orphan receptors gamma; GC, germinal center; PD-1, programmed death-1; STAT, signaling transducer and activator of transcription.

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