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T cells and their function in the immune response to viruses

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Summary. – The development of $CD4^+$ T helper cells is determined by the set of transcription factors and the genes these transcription factors transcribe. In this review, we describe the basic nature of Th1, Th2, Th9, Th17, T-follicular helper (Tfh), gamma delta (γδ) T cells, and T-regulatory (Treg) cells subsets, their master regulator transcription factors and their corresponding signature cytokine production profiles. Cellular immunity plays important role during virus infection. Optimal immune response to viral infections require a gentle balance of effector responses to clear the infected cells and regulatory mechanism to prevent immunopathology. The behavior of the helper cells differs with each virus – while in some cases, the response is beneficial; in other cases, it is harmful. We discuss the protective and pathological role of T cell immunity against influenza A virus (IAV), respiratory syncytial virus (RSV), immunodeficiency virus type 1 (HIV-1), and hepatitis B virus (HBV) infection.

Keywords: T cell; cytokine; influenza virus; respiratory syncytial virus; hepatitis B virus; human immunodeficiency virus type 1

Introduction

The immune response elicited by virus infection is one of the main factors contributing to the pathogenesis of the disease. Both innate and acquired immune responses are essential for an effective viral clearance.

T cells exert diverse functions in defense and antibody response against intracellular as well as extracellular pathogens. Naïve T cells originate from hematopoietic stem cells in bone marrow, and then undergo the positive and negative processes of central selection in the thymus. Differentiation into specific subsets of T-cell depends on the presenting stimulus and the immunological environment. Naïve T cells are precursors for effector and memory subsets of T cells. $CD4^+$ effector T cells, also called helper (Th) cells play pivotal roles in the humoral and cellular adaptive immune response. The helper T cells are divided into several distinct subsets (e.g. Th1, Th2, Th9, Th17, T-follicular helper (Tfh) and T-regulatory (Treg) cells), differentiated by their corresponding signature cytokine production profiles. These cells function in host defense against different types of infectious pathogens. They are also involved in different types of tissue damage and play important role in antibody responses. Every subset develops by producing its unique cytokines, master regulator, potential transcription factors and binding sites. T cell differentiation to cellular subsets is an intricate process subtly controlled by the master regulator and many regulatory signals and molecules. The balance among different subsets of T cell sets the stage for the acquired immunological response and play a significant role in pathogenesis.

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Abbreviations: BATF = B-cell activating transcription factor; Bcl-6 = B-cell lymphoma 6 transcription factor; BTLA = B- and T-lymphocyte attenuator; FOXP3 = forkhead box P3; HBV = hepatitis B virus; HIV-1 = human immunodeficiency virus type 1; IAV = influenza A virus; IFNs = interferons; IL = interleukine; RA = rheumatoid arthritis; RORC2 = retinoic acid receptor-related orphan receptor C2; RORγt = retinoic acid receptor-related orphan nuclear receptor gamma t; RSV = respiratory syncytial virus; STAT = signal transducer and activator of transcription; Tfh = T-follicular helper cells; Th = helper T-cells; Treg = T-regulatory cells

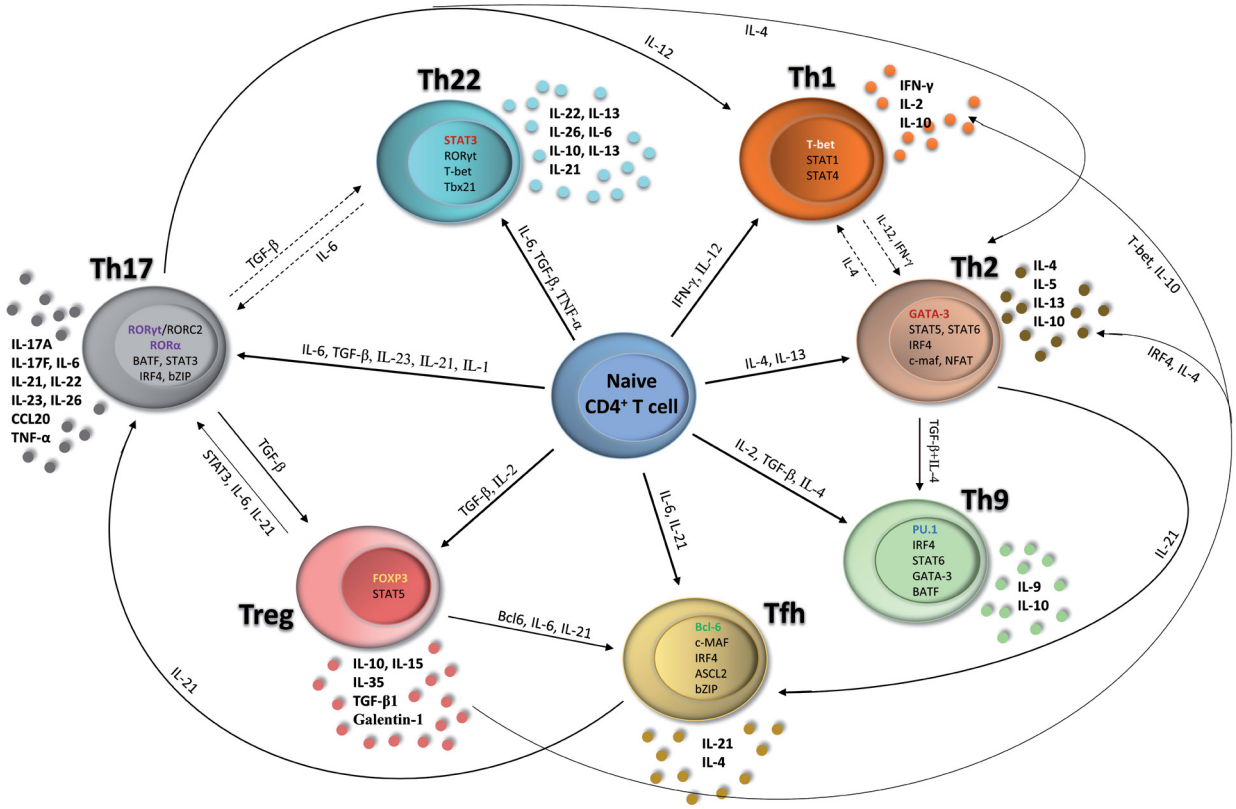

Fig. 1

Differentiation of the Th subsets
Full arrow-stimulation; dashed arrow-inhibition.

The cytokine environment activates differentiation program usually via phosphorylation of STAT proteins. This program involves the induction of transcription factors that maintain subset identity and genes involved in cell migration and cytokine production. Such signaling is essential for the ability of the Th subset to regulate immune responses (Jabeen *et al.*, 2013). The activation of the differentiation program requires the coordinated function of a network of transcription factors.

Th1 and Th2 subsets are relatively stable, but under certain cytokine stimulation, Treg and Th17 cells switch to other T helper subsets. This conversion of terminally differentiated lineage committed subset to other terminally differentiated lineage committed subset is called "plasticity" (Yang *et al.*, 2015). The defining characteristics of each subset of T cells are the cytokines they produce, the transcription factors they express and epigenetic changes in their specific cytokine gene loci (Fig. 1).

Properties of Th1 subset

The signature cytokines produced by the Th1 subset is interferon (IFN)-γ, IL-2, and IL-10. Th1 cells express high level of the chemokine receptors CXCR3 and CCR5 (Sallusto *et al.*, 1998). These receptors bind chemokines, which elaborate in tissue during innate immune responses and therefore Th1 cells are abundant in sites of infection. Th1 cells also express high level of ligands for E-selectin and P-selectin, which regulate migration of immune cells to the site of severe inflammation. The master regulator of Th1 cells is considered T-bet, signal transducer and activator of transcription (STAT) 1 and STAT4. T-bet initiates the development of the Th1 lineage from naïve T-helper lymphocyte cells (Thp) by both, activating Th1 genetic programs and repressing the opposing Th2 programs. Th1 cell specific expression of IFN-γ is associated with selective expression of T-bet (Szabo *et al.*, 2000). T-bet represses Th2 lineage commitment through tyrosine kinase-mediated interaction between the two transcription factors (T-bet and GATA-3) that interferes with the binding of GATA-3 to its target DNA (Hwang *et al.*, 2005). Moreover, IL-2 and IFN-γ secreted by Th1 cells suppress Th2 (Mosmann *et al.*, 1986). STAT factors are required for the optimal induction of the master switch determinant. Although STAT-independent T-bet induction, has been described, it seems to be incapable to achieve a necessary

effector function without STAT1 and STAT4 (Kaplan *et al.*, 1998; Szabo *et al.*, 2000). The IFN-γ – STAT1-T-bet pathway plays an important role in Th1 differentiation *in vitro* (Grogan *et al.*, 2001; Afkarian *et al.*, 2002). IL-12 activates STAT4, which is critical for Th1 responses *in vitro* and *in vivo* (Kaplan *et al.*, 1998; Cai *et al.*, 2000). STAT4 is also expressed in Th2 cells, although expression level is higher in Th1 cells (Usui *et al.*, 2003).

Properties of Th2 subset

The signature cytokines produced by the Th2 subset include interleukins – IL-4, IL-5 and IL-13. Th2 cells express the chemokine receptors CCR3, CCR4, and CCR8 (Sallusto *et al.*, 1998). These receptors recognize chemokines that are highly produced during helminthic infection or allergic reactions, especially in mucosal tissues, where Th2 cells tend to infiltrate. STAT5, STAT6, c-Maf, GATA-3, and NFAT transcription factors are major regulators of Th2 development and function (Paul and Zhu, 2010; Lambrecht and Hammad, 2012). Induced GATA-3 activates STAT6 and facilitates chromatin remodeling of the IL4-IL5-IL13 locus during Th2 cell differentiation (Kurata *et al.*, 1999; Lee *et al.*, 2000; Ouyang *et al.*, 2000; Fields *et al.*, 2002; Avni *et al.*, 2002; Takemoto *et al.*, 2002; Yamashita *et al.*, 2002). Cytokines IL-4 and IL-13 are expressed in a copy number-dependent manner at high level only in Th2 cells. IL-5 is not expressed in a copy number-dependent manner (Lee *et al.*, 2003). Interferon regulatory factor IRF4 is essential for the development of Th2 cells, which secrete IL-4 and IL-10 cytokines inhibiting Th1 responses (Mosmann *et al.*, 1986; Staudt *et al.*, 2010).

Properties of Th9 subset

Naïve $CD4^+$ T cells and Th2 cells differentiate into Th9 cells at presence of TGF-β (Zhou *et al.*, 2009) The signature cytokines produced by the Th9 subset are IL-9 and IL-10 (Dardalhon *et al.*, 2008; Veldhoen *et al.*, 2008). Secretion of IL-9 dependent on IL-2, is synergistically enhanced by a balanced combination of TGF-β and IL-4, and is inhibited by IFN-γ (Schmitt *et al.*, 1994). B cell-activating transcription factor-like (BATF) has been shown to be required for the development of Th9, Th17 cells, T follicular helper cells, and possibly Th2 cells (Bettz *et al.*, 2010; Schraml *et al.*, 2009; Ise *et al.*, 2011). TGF-β in conjunction with IL-4 reprograms Th2 cell differentiation and results in the development of Th9 cells. The switching factor between Th2 and Th9 subsets is PU.1, which belongs to an ETS transcription factor family. The PU.1 specifically promotes the development of IL-9-secreting cells and restricts the Th2 genetic program (Chang *et al.*, 2005, 2009; Goswami *et al.*, 2012a). Differentiation of Th9 is also promoted by IL-4 and several transcription factors including STAT6, GATA-3, and IRF4, which are also required for development of Th2 cells (Veldhoen *et al.*, 2008; Staudt *et al.*, 2010). The IFN-γ and IFN-γ promoting cytokines such as IL-12, IL-18, and IL-23 as well as Th1-associated transcription factor T-bet inhibit the induction of Th9 cells (Goswami *et al.*, 2012b).

Th9 cells lack suppressive function and promote tissue inflammation. IL-9 is critically involved in the resistance to parasites (*Trichuris muris*) and plays a detrimental role concerning the pathogenesis of asthma (Khan *et al.*, 2003; Temann *et al.*, 1998; Staudt *et al.*, 2010). Due to the pleiotropic function of IL-9, Th9 cells might be involved in pathogen immunity and immune-mediated disease.

Properties of Th17 subset

The signature cytokines produced by the Th17 subset are interleukins: IL-17A, IL-17F, IL-6, IL-21, IL-22, IL-23, IL-26, CCL20 and tumor necrosis factor alpha (TNF-α) (Korn *et al.*, 2009). Th17 cells express CCR4 and CCR6. The CCR6 receptor binds the chemokine CCL20, which is produced by macrophages and various tissue cells after bacterial and fungal infections. In addition to CCR6, CXCR3, CXCR6 and CCR5 receptors are also expressed on the Th17 cells. Th17 cells control the immune response to extracellular pathogens such as *Klebsiella* or *Candida*, and play a key role in autoimmune diseases such as rheumatoid arthritis. Th17 cells directly or via proinflammatory cytokines modulate anti-tumor immune responses. Th17 cells are generated from naïve T cells by IL-6, IL-1, IL-21, with or without TGF-β. They further expand and stabilize with IL-23. Retinoic acid receptor-related orphan nuclear receptor gamma t (RORγt)/ retinoic acid receptor-related orphan receptor C2 (RORC2) induces IL-6 expression, which is regulated by STAT3 (Laurence *et al.*, 2007; Yang *et al.*, 2007). The master switch factors for Th17 cells are the transcription factor RORγt/RORC2 (mice/human), RORα, basic leucine zipper transcription factor, ATF-like (BATF), and IRF4 (Ivanov *et al.*, 2006; Unutmaz, 2009). RORγt and RORα control the key Th17 genes including IL-17A, IL-17F, IL-23R, CCL20 and CCR6 (Castro *et al.*, 2017). The development of the Th17 phenotype is regulated by RORC2, STAT3 factors and BATF, which are part of a BATF/Jun/IRF4 pathway (Ciofani *et al.*, 2012; Li *et al.*, 2012). Th17 differentiation is connected with a low concentration of TGF-β (Zhou *et al.*, 2008). Th17 cells can be converted after IL-12 stimulation into IFN-γ producing Th1 cells or after stimulation with IL-4 into Th2 cells producing IL-4 (Zhou *et al.*, 2009).

Properties of Th22 subset

Th22 cells have been identified as a novel $CD4^+$ T cells present in the skin. They primarily secrete various interleukins including IL-22, IL-6, IL-10, IL-13, IL-21, IL-26 and IL-1β (Eyerich *et al*., 2009). The signature cytokines produced by Th22 cells are IL-22, IL-26, and IL-33. CCR4, CCR6, and CCR10 expressed on the surface of Th22 cells are associated with cutaneous T cell homing (Duhen *et al*., 2009; Nograles *et al*., 2009).

Th22 subset is induced from $CD4^+$ T cells in the presence of IL-6 and TNF-α. The Th22 subgroup expresses the ligand-activated master switching transcription factor, the aryl hydrocarbon receptor (AhR). By engaging this receptor and activating STAT3, Th22 cells produce a number of cytokines such as IL-22, IL-26, and IL-13 and one of the most important functional cytokine, IL-22 (Duhen *et al*., 2009; Ramirez *et al*., 2010; Akdis *et al*., 2012; Jabeen and Kaplan, 2012; Kaplan, 2013). The transcriptional signature of Th22 differentiation includes pronounced expression of *Tbx21*, cell death-inducing granzymes (particularly *Gzmb*), and *IL-13*. RORγt and T-bet transcription factors act as positive and negative regulators of Th22 cells differentiation, respectively (Plank *et al*., 2017). IL-22 production in Th22 cells is stimulated by many factors, including IL-1β, IL-6, IL-21, and IL-23 (Yeste *et al*., 2014; Plank *et al*., 2017).

Th22 cells play important role in promoting repair of damaged epithelial barriers as well as enhancing immune responses against some pathogens (Eyerich *et al*., 2009). Th22 cells can also express granzyme B and IL-13, factors associated with host defense and tissue remodeling (Plank *et al*., 2017). Elevated level of IL-22 produced by Th22 lymphocytes are associated with various disorders, such as infections, autoimmune diseases, hepatitis, pancreatitis, rheumatoid arthritis (RA), and tumors.

Properties of regulatory T (Treg) subset

Treg cells are divided into two groups: thymus-derived Treg cells (tTreg, or nTreg – natural Treg) and induced regulatory T cells (iTreg) (Sakaguchi *et al*., 2008). Tregs can also be classified into three new subsets: central Tregs, effector Tregs, and tissue-resident Tregs (Liston and Gray, 2014). Central Tregs (also naïve Tregs, or resting Tregs) and effector (memory) Tregs comprise the majority of all Tregs, while they are minor population of circulating and secondary lymphoid organ Tregs, respectively. Tissue-resident Tregs have a long-term residence in non-lymphoid tissues such as skin/ lung, gut, germinal center, and adipose tissue and are distinguishable from classical lymphoid-organ Treg cells in phenotype and function (Burzyn *et al*., 2013).

The signature cytokines produced by the Treg subset are secreted factors: IL-10, IL-15, IL-35, TGF-β1, and Galentin-1 (Han *et al*., 2012). The CD3, CD4, CD25, and CD127 are surface markers that define human Treg cells (Santegoets *et al*., 2015). The master switch factors for Treg cells are forkhead box P3 (FOXP3) and STAT5 (Hori *et al*., 2003; Zhou *et al*., 2009). Low TGF-β concentrations promote Th17 cell development, while high concentrations induce FOXP3 expression and Treg cell development (Zhou *et al*., 2008). TGF-β1 and IL-2 are responsible for Tregs expansion. IL-2-induced STAT5 plays an important role in promoting FOXP3 expression (Zhou *et al*., 2009). Treg cells are predominantly activated downstream of STAT5 rather than MAPK and PI3K pathways partly due to the high expression of the phosphatase PTEN (Malek and Castro, 2010; Walsh *et al*., 2006). IL-2–STAT5 signaling also depends upon serine-threonine kinases Mst1 and Mst2 (Shi *et al*., 2018).

Tregs play a pivotal role in the preservation of self-tolerance and prevention of autoimmunity (Sakaguchi *et al*., 2010). In addition, Treg cells can also directly inhibit differentiation, proliferation, and function of conventional T cells, including $CD4^+$ and $CD8^+$ T cells, by direct cell-cell contact and by down-modulation of antigen presenting cells (APCs) function, especially dendritic cells (DCs) (Park *et al*., 2011; Maeda *et al*., 2014).

iTregs possess extensive plasticity and can be switched to Th1, Th2, Tfh, and Th17 cells. In the presence of B cells and CD40-CD40L interaction signaled by B-cell lymphoma/leukemia 6 (Bcl-6) transcription factor, iTregs can be switched to follicular T helper cells. IRF4 transcription factor mediates the switch of iTregs to Th2 cells and T-bet mediates the switch to Th1 cells. The conversion of iTreg to Th17 cells is regulated by STAT3 transcription factor, which is stimulated by IL-6 and IL-21 (Coomes *et al*., 2013).

Properties of follicular helper (Tfh) cells

Tfh cells provide a helper function to B cells and are one of the most numerous and important subsets of effector T cells in lymphoid tissues. The signature cytokine produced by the Tfh is IL-21. Tfh can also produce IL-4 (Jandl *et al*., 2017). Tfh cells express various receptors and proteins on their surface, including CXCR5 receptor, the inducible co-stimulatory receptor ICOS, the programmed cell death protein-1 (PD-1) and B and T lymphocyte attenuator (BTLA) (Akiba *et al*., 2005; Haynes *et al*., 2007; King *et al*., 2008). The master switch factor for Tfh cells is Bcl-6. However, the other transcription factors such as c-Maf, Achaete-scute complex homolog 2 (ASCL2), basic leucine zipper (bZIP) transcription factor, and IRF4 are also crucial. Bcl-6 expression, associated with the downregulation

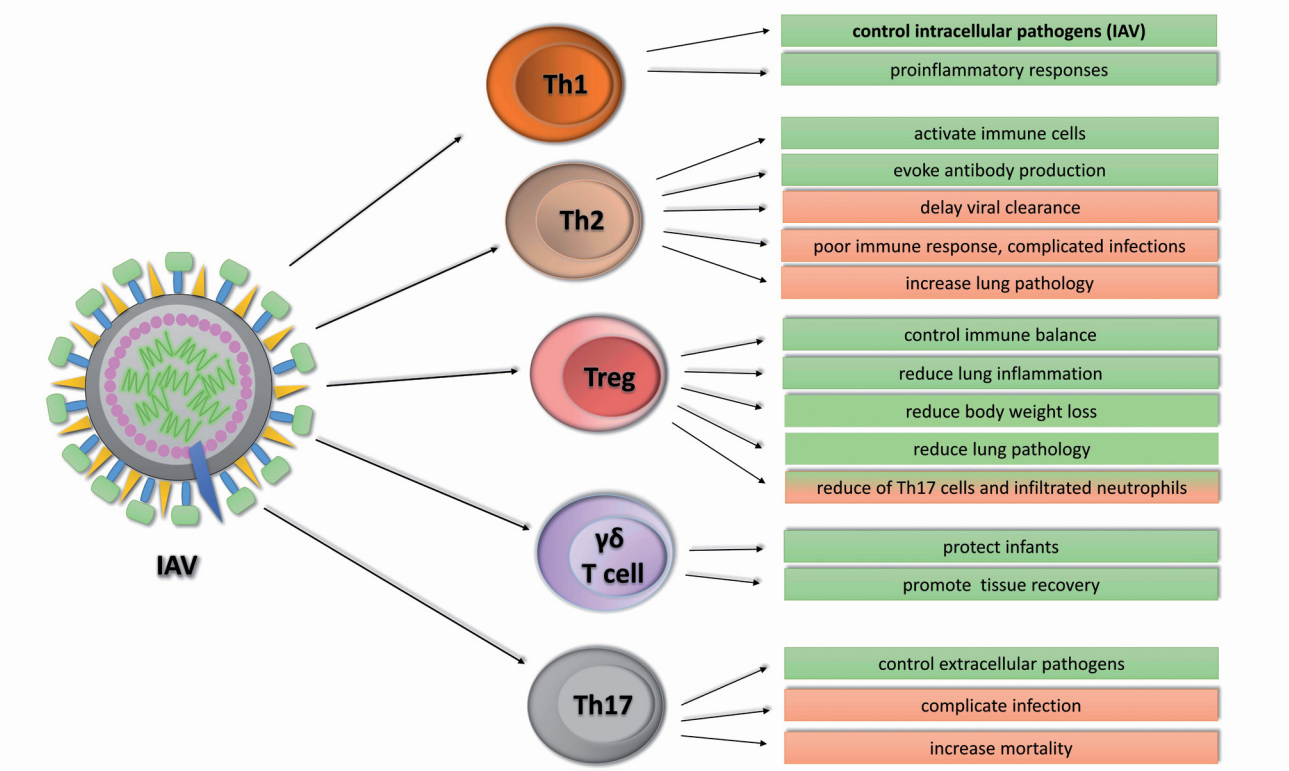

Fig. 2

A schematic representation of the Th cells subsets involved in immune response to influenza A infection
The positive role of individual subset is displayed in green panel and negative role is displayed in red panels.

of its antagonist Blimp-1, leads to the inhibition of the other transcription factors specific for other T helper cell lineages (T-bet, GATA3, and RORγt especially) (Gensous *et al.*, 2018). Tfh cells are the specialized B cell providers that help to produce antibody against foreign pathogens.

Properties of gamma delta (γδ) T cells

γδ T cells are scarce in lymphoid tissues and abundant at mucosal sites such as skin, tongue, intestine and reproductive organs (Itohara *et al.*, 1990). γδ T cells, depending on the types of signals presented in the tissue microenvironment, produce pro-inflammatory cytokines such as IFN-γ, TNF-α and IL-17, as well as anti-inflammatory cytokines like TGF-β, IL-4 and IL-10, (Rochman *et al.* 2009; Rei *et al.*, 2014). They also express several co-stimulatory and regulatory molecules such as CD27, CD28, CD30, B- and T-lymphocyte attenuator (BTLA), natural-killer group 2, member D (NKG2D), natural-killer group 2, member A (NKG2A), Toll-like receptors (TLRs) and CD39 (Ribot *et al.*, 2009; Sun *et al.*, 2013; Bekiaris *et al.*, 2013; Nedellec *et al.*, 2010; Wang *et al.*, 2012; Otsuka *et al.*, 2013). Signaling from these receptors dictates the cytokine production and γδ T cells effector functions. γδ T cells can also act as professional antigen-presenting cells and help in shaping the Th1 and cytotoxic $CD8^+$ T cells response (Brandes *et al.*, 2005).

T cells and respiratory viruses

It has been thought that T-helper cells exist as two major subsets, Th1 and Th2 cells. This Th1/Th2 paradigm was based on the mechanisms involving elimination of microbial pathogens. Th1 cells are critical for the clearance of many intracellular pathogens, such as *Leishmania major* and viruses while Th2 cells are important for the elimination of helminthic parasites, such as *Nippostrongylus brasiliensis* and *Schistosoma mansoni* (Reiner and Locksley, 1995; Pulendran and Artis, 2012). An optimal immune response to viral infections requires delicate balance of effector responses to clear infected cells and regulatory mechanisms to prevent immunopathology (Duan and Thomas, 2016). Initial targets for respiratory viruses are lung epithelial cells and alveolar macrophages.

The helper cells behavior differs for each respiratory virus – in some cases, the response is beneficial; in other cases, it is harmful. In many cases, Treg cells inhibit excessive virus specific T cell responses that may contribute to viral pathogenicity.

T cells and influenza A virus (IAV)

IAV is a major respiratory pathogen that causes annual epidemics with serious health consequences. IAV belongs to the family *Orthomyxoviridae*. The genome contains eight segments of negative-sense, single-stranded RNA. Each segment contains a viral RNA-dependent RNA polymerase and is embedded into ribonucleoproteins. The approximately 13 kb genome encodes up to 18 proteins. An important host innate immune mechanism is the production of interferons (IFNs), which can establish an antiviral state by up-regulating interferon stimulated genes that interfere with various steps in the virus life cycle (Švančarová *et al*., 2015a,b; Škorvanová *et al*., 2015; Lachová *et al*., 2017). The neutralizing antibody is considered to be the main immune mechanism against influenza virus. CD4+ T cells also play an important role in the strong Th1-based immune response to IAV infection (Fig. 2). Tfh cells are required for highly specific and memory humoral responses (Miyauchi, 2017). Oh and Eichelberger (2000) have showed that DC infected with influenza virus A/PR/8/34 (PR8) stimulate T cells which produce different types of cytokines in a dose-dependent manner. The mixed Th1/Th2 response was influenced by NA activity. It has recently been shown, that increased pathogenicity of NS1-truncated virus (NS80) does not influence Th1/Th2 balance (Turianová *et al*., 2020). Th2 cytokines such as IL-4, IL-5, IL-6, IL-10 and IL-13, are associated with the development of the influenza virus encephalopathy and increased pathology (Betáková *et al*., 2017). Lethal influenza virus infection induces cytokine profiles corresponding to the mixed Th1/Th2 response in mice (Turianová *et al*., 2019). Th2-controlled immune responses to influenza virus infection exacerbate lung tissue damage and delay viral clearance (Graham *et al*., 1994; Turianová *et al*., 2019). A dysregulated Th1/Th2 cytokine profile was detected in pregnant ferrets, resulted in a poor immune response against IAV infection (Yoon *et al*., 2018). During severe infection with pandemic influenza A (H1N1), the imbalance between pro-inflammatory and anti-inflammatory molecules, such as Th1 and Th17 cytokines, is associated with complicated infections and mortality (Sarda *et al*., 2019).

Infants suffer from relatively high hospitalization rates, severe clinical complications, and influenza related mortality. Exaggerated type 2 responses that are characteristic of the IL-33 mediated infant immune system pathway may function to prevent tissue damage due to excessive inflammation (de Kleer *et al*., 2016; Saluzzo *et al*., 2017). γδ T cells are the first T cells to appear in the thymus during fetal development and have the ability to recognize a wide range of antigens and respond rapidly to infections. For example, it is known that these cells play an important role in protecting infants from viral infection (Chien *et al*., 2014; Vantourout and Hayday, 2013). These cells have some important roles in regulating the production of IL-17A and IL-33, in promoting tissue recovery after infection (Guo *et al*., 2018).

Tregs can control immune balance during viral infection and prevent tissue damage (Moser *et al*., 2014). The presence of Treg cells in lungs of IAV infected mice resulted in decrease of Th17 cells, infiltrated neutrophils, and lung inflammation (Egarnes and Gosselin, 2018). mTregs persist in host long time after primary IAV infection. They have a competitive advantage in migrating to the IAV-infected lungs. Adoptively transformed mTregs are able to significantly reduce body weight loss, lung pathology and infiltration of immune cells into infected lungs (Lu *et al*., 2019).

T cells and respiratory syncytial virus (RSV)

RSV is common respiratory virus that causes viral bronchiolitis and pneumonia in the children worldwide. In addition, it causes considerable morbidity and mortality in infants, in the immunocompromised, and the elderly. Seventy percent of children are infected with RSV in their first year of life (Bueno *et al*., 2008). RSV as a member of the *Paramyxoviridae* family, is an enveloped RNA virus and its RNA encodes 11 proteins. Both innate and acquired immune responses are essential for effective viral clearance. Since an antibody hampers infection and an effective B-cell response with efficient neutralizing antibodies is absent, the clearance of RSV infection is predominantly dependent on T cells response (Fig. 3) (Gonzáles *et al*., 2012). Th1 and Treg cells play an important role in virus clearing. Moreover, γδ T cells are critical in protecting infants from RSV infection (Vantourout *et al*., 2014).

During the RSV infection, Tregs are maintained in the immunological environment with a focus on virus clearance. During the second infection, the Tregs' response is decreased. Secondary RSV infection leads to an increased Th17 response, where a defective Tregs' response leads to Th2-mediated airway inflammation. Initially, the severity of RSV infection is associated with the induction of Th2 cells rather than Th1 cells (Becker, 2006; Durant *et al*., 2013). However, the Th17 and Treg subsets have been

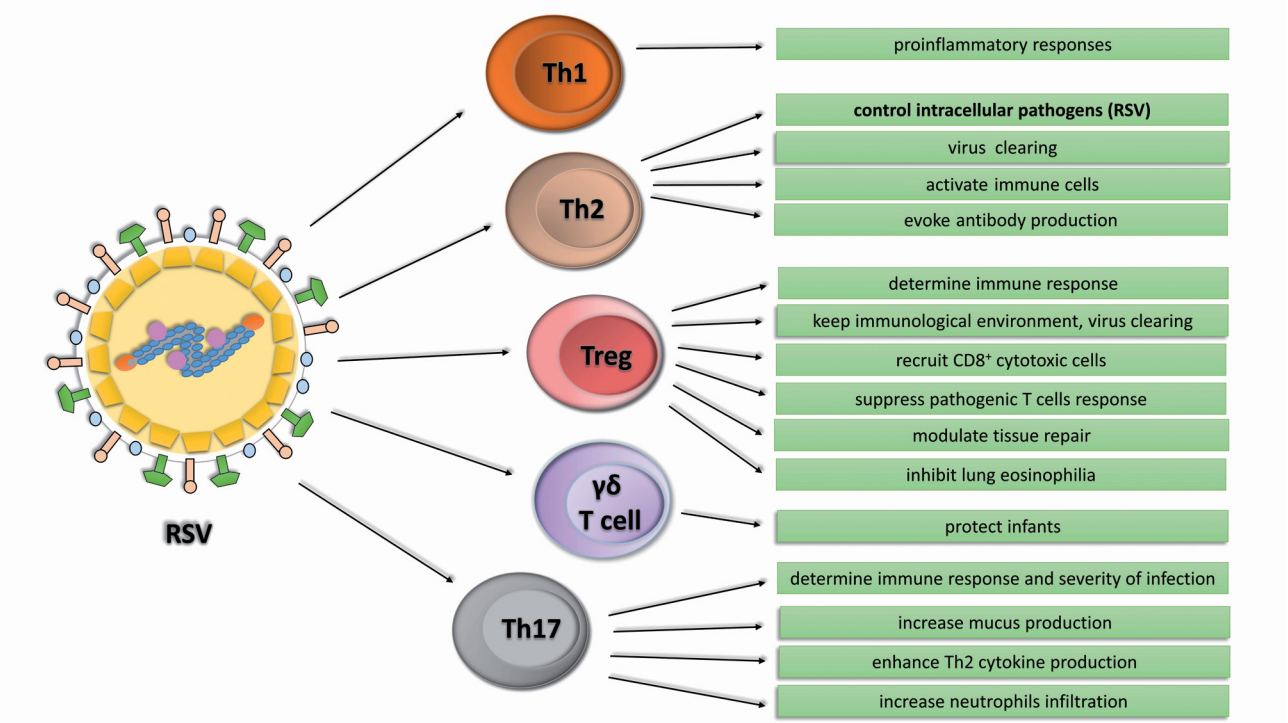

Fig. 3

A schematic representation of the Th cells subsets involved in immune response to respiratory syncytial virus
The positive role of individual subset is displayed in green panel.

shown to determine the nature of the immunological response and the severity of RSV infection. During RSV infection, Treg cells are responsible for early recruitment of activated CD8⁺ cytotoxic cells into the lungs in order to regulate/facilitate RSV viral clearance (Ruckwardt *et al.*, 2009; Fulton *et al.*, 2010). In Treg-depleted mice, the abundant presence of CD8+ T cells producing TNF-α and IFN-γ lead to tissue pathology and increased disease severity (Fulton *et al.*, 2010; Durant *et al.*, 2013). Treg cells perform vital anti-inflammatory functions, suppressing pathogenic T cell responses and inhibiting lung eosinophilia (Durant *et al.*, 2013).

Treg response is different during primary and secondary RSV infection. During primary Th17 response, the concomitant reaction is Th2 response (Mukherjee *et al.*, 2011; Bystrom *et al.*, 2013). The Th17 response is induced by activated complement factor C3 and tachykinins (Bera *et al.*, 2011). IL-17 causes exaggerated mucus production, increases Th2 cytokine production, it is associated with increased neutrophils infiltration in the lungs, and diminishes viral clearance by negative regulation of T-bet and Eomes transcription factors (Mukherjee *et al.*, 2011; Bystrom *et al.*, 2013).

T cells and human immunodeficiency virus type 1 (HIV-1)

HIV-1 belongs to the *Retroviridae* family, the subfamily *Orthoretrovirinae* and it is grouped into the genus *Lentivirus*. The development of infection has several phases. First, the eclipse phase is a period between 1- and 2-weeks post infection, during which the virus replicates and spreads from the site of infection into various tissues and organs (Coffin and Swanstrom, 2013). The second phase is referred as an acute phase of infection characteristic of a rapid increase in viremia and a concomitant decrease in the CD4⁺ T cells population (particularly in gut lymphoid tissue, GALT). During the third phase, clinical latency develops after activation of host-specific cellular immunity, the level of viremia is usually low and this stage may last up to 20 years. During this phase, some virus replication may occur and cause a decrease in the number of CD4⁺ T-cell via immune activation. Phase fourth is characterized by a loss of control of the immune system, leading to opportunistic infections, malignancies, and death of untreated individuals. HIV-1 infection causes hyperactivation of the immune system and constant depletion of helper CD4⁺ T cells (Catalfamo *et al.*, 2012).

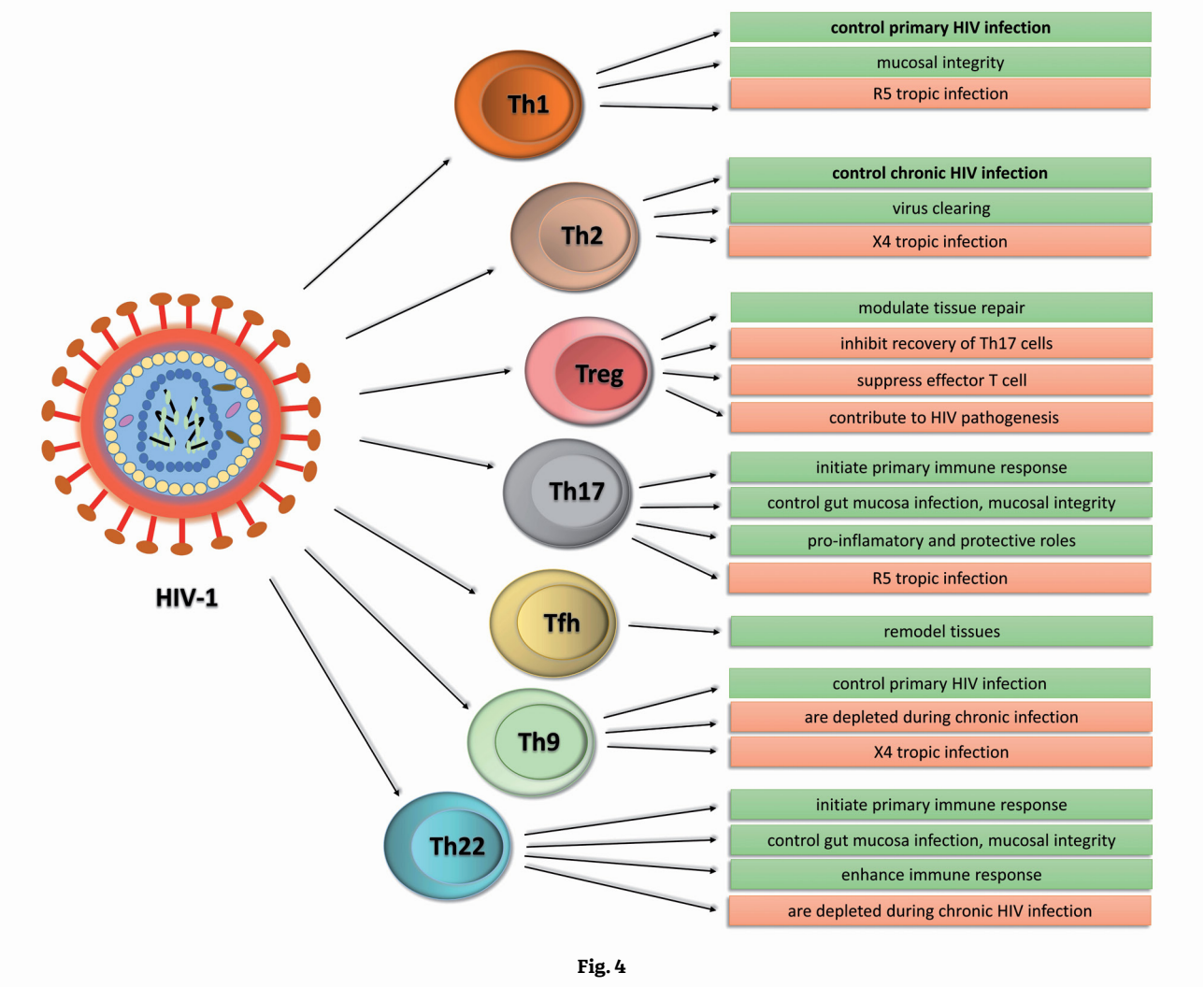

Fig. 4

A schematic representation of the Th cells subsets involved in immune response to human immunodeficiency virus type 1
The positive role of individual subset is displayed in green panel and negative role is displayed in red panels.

During pathogenesis of HIV, effector functions of CD4⁺ T cells depend on cytokine immunity and CD4⁺ T cells differentiate into Th1, Th2, Th9, Th17, Th22 as well as Treg and Tfh cell populations (Fig. 4) (Reuter *et al.*, 2012; Gorenec *et al.*, 2016). Th1, Th17, and Th22 cells are critically important for initiating primary immune responses and for maintenance of mucosal integrity. Infection and dysregulation of Tfh and other key CD4+ T cell results in hyperactive, yet non-protective immune responses that supports active viral replication and evolution, and thus persistence in host tissue reservoirs (Veazey, 2019). Chronic HIV infection is characterized by Th1 and Th2 production (Gorenec *et al.*, 2016). The number of Th17 cells is depleted in the gut mucosa, where they play a key role in a host defense against bacteria (Shirazi and Pitha, 1992). Th17 cell regeneration is inhibited by Tregs (Favre *et al.*, 2010). However, HIV recovery was shown to be lower when γδ T cells were present (James *et al.*, 2020). Tregs play both a positive but also negative role in the pathogenesis during HIV infection. Strong Treg responses may contribute to the pathogenesis of HIV by suppressing HIV-specific immune responses, particularly effector T cells (Kinter *et al.*, 2007). Tfh cells are located in a tissue that undergoes significant remodeling during HIV infection (Estes *et al.*, 2007). Chronic HIV infection leads also to depletion of Th9 and Th22 cell subsets (Kim *et al.*, 2012; Gorenec *et al.*, 2016). Reduced IL-22 production and Th22 depletion in the gut mucosa are important factors in HIV mucosal immunopathogenesis (Kim *et al.*, 2012). The development of T cell response depends on the HIV virus tropism. Th9 cells and, to a lesser extent, Th2 cells express higher surface levels of CXCR4, and are more

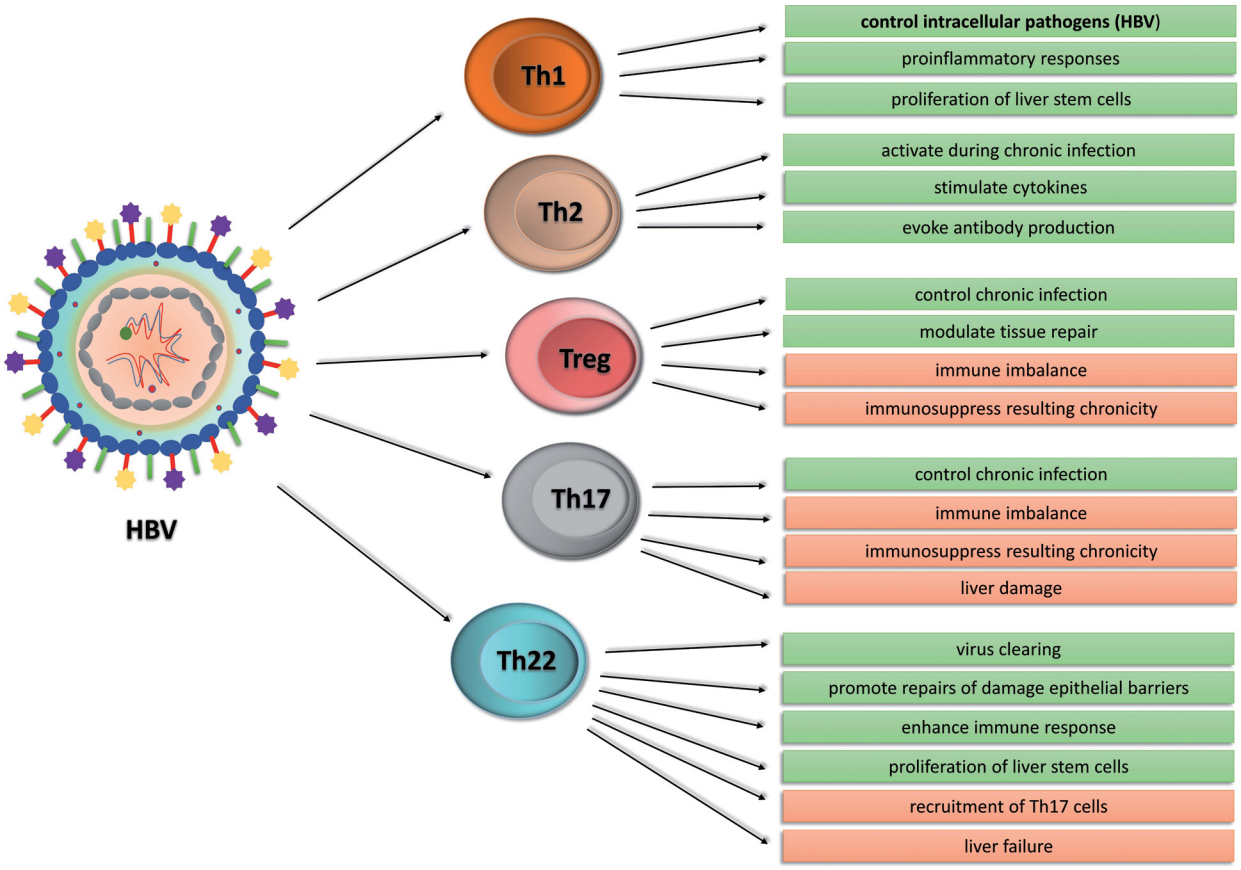

Fig. 5

A schematic representation of the Th cells subsets involved in immune response to hepatitis B infection
The positive role of individual subset is displayed in green panel and negative role is displayed in red panels.

permissive to X4-tropic infection *in vitro*. Th1 and Th17 cells exhibit stronger surface expression of CCR5, and are more susceptible to infection by R5-tropic viruses (Orlova-Fink *et al.*, 2017).

T cells and hepatitis B virus (HBV)

HBV, a member of the *Hepadnaviridae* family, is a small DNA virus, which replicates through an RNA intermediate and can integrate into a host genome. HBV infects more than 300 million people worldwide and it is a common cause of a wide range of liver diseases ranging from acute (including fulminant hepatic failure) to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Although, most adults infected with the virus recover, 5%–10% are unable to clear the virus and become chronically infected. Chronically infected persons usually suffer mild liver disease with little or no long-term morbidity or mortality. However, some individuals with a chronic HBV infection develop an active disease that can progress to cirrhosis and liver cancer.

HBV-associated liver damage is thought to be mediated by immunity (Fig. 5). It is believed that immune imbalance of Treg and Th17 exists in the chronic hepatitis B. Treg cells increase at the beginning of infection and then decrease with the virus clearance. However, changes of the Th17/Treg cells ratio could lead to immune suppression, resulting in the virus leakage to the immune system and chronic disease (Gao *et al.*, 2015). Th17 cells produce IL-17, a major effector cytokine that could recruit and activate immune cells into the liver and lead to tissue injury (Zhang *et al.*, 2010; Ge *et al.*, 2010). Moreover, IL-17 could exacerbate liver fibrosis by facilitating the activation of hepatic stellate cells to myofibroblasts via signal transducer and activator of STAT3 (Meng *et al.*, 2012). Transcriptional factor BATF regulates the Th17 differentiation and its over-expression might increase Th17 cell response, whereby the factor is related to disease progression in chronic HBV infection (Wang *et al.*, 2018). In contrast, Chen *et al.* (2019) have

shown that BATF interference significantly impedes proliferation of Th17 cells and secretion of IL-17 and IL-22, resulting in alleviated hepatic lesions.

Patients with acute hepatitis B displayed significantly elevated plasma level of IL-35 and the frequency of Th17 induced by circulating HBV peptides. IL-35 expression negatively correlated with the liver inflammation, contributing to immunosuppression in chronic hepatitis modulated by Th17 and Treg cells. IL-35 may be a novel mediator associated with hepatocyte damage and liver inflammation by regulating HBV peptides-induced Th17 cells during acute HBV infection (Teng *et al*., 2019).

Cytokine IL-22 can stimulate innate immune responses against pathogens and target particularly hepatocytes, keratinocytes, lung, and intestine cells (Thompson *et al*., 2010). IL-22 plays two leading roles in the body, pro-inflammatory and protective. In humans, IL-22 appears to be produced primarily by Th1 and Th22 T cell subsets and IL-22-producing cytotoxic T cells, as well as Th17 cells (Sonneberg *et al*., 2011). The direct antiviral effect of IL-22 is utterly insignificant, and cannot promote classical IFN-stimulated antiviral pathways and mediators (Wang *et al*., 2013). In the liver of mice and patients with chronic HBV infection, inflammatory cells produce IL-22, which promote proliferation of liver stem/progenitor cells by STAT3 (Feng *et al*., 2012). However, IL-22 plays a pathological role in exacerbating chronic liver inflammation and fibrosis by recruiting Th17 hepatic cells in HBV infected patients (Zhao *et al*., 2014). Persistently elevated circulating Th22 reversely correlates with the prognosis of acute-on-chronic liver failure, associated with hepatitis B virus (Mo *et al*., 2017).

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