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# A role for Th1-like Th17 cells in the pathogenesis of inflammatory and autoimmune disorders

Ali N. Kamali[a,1], Seyedeh Masoomeh Noorbakhsh[b,1], Haleh Hamedifar[a], Farhad Jadidi-Niaragh[c,d], Reza Yazdani[e], José M. Bautista[f,g], Gholamreza Azizi[h,i,*]

[a] CinnaGen Medical Biotechnology Research Center, Alborz University of Medical Sciences, Karaj, Iran
[b] Department of Immunology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[c] Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[d] Department of Immunology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[e] Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[f] Department of Biochemistry and Molecular Biology, Complutense University of Madrid, Faculty of Veterinary Sciences, 28040, Madrid, Spain
[g] Research Institute Hospital 12 de Octubre, Madrid, 28041, Spain
[h] Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran
[i] Department of Immunology, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran

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ABSTRACT

The T helper 17 (Th17) cells contain a dynamic subset of CD4+ T-cells that are able to develop into other different lineage subsets, including the Th1-like Th17 cells. These cells co-express retinoic acid-related orphan receptor gamma t (RORγt) and transcription factor T-box-expressed-in-T-cells (T-bet) and produce both interleukin (IL)-17 and interferon (IFN)-γ. Recent reports have shown that Th1-like Th17 cells play crucial roles in the pathogenesis of autoimmune diseases such as inflammatory bowel disease, multiple sclerosis and rheumatoid arthritis, as well as, some primary immunodeficiency with autoimmune features. Here, the actual mechanisms for Th17 cells plasticity to Th1-like Th17 cells are discussed and reviewed in association to the role that Th1-like Th17 cells have on inflammatory and autoimmune disorders.

## 1. Introduction

The T helper (Th) cells are a diverse group of CD4+ T cell that play crucial role in the immune system predominantly in the mechanisms involved with adaptive immunity (Uchiyama et al., 2017). In the adaptive immunity, Th cells are crucial, since they provide help to B cells and cytotoxic T cells and additionally by releasing various types of cytokines in tissues to mediate and enhance protectiveness of T cells against a broad range of pathogenic microorganisms (Takeuchi and Saito, 2017; Sallusto, 2016). Based on the specificity of cytokines production and expression of transcriptional factors, these cells have been categorized into various lineages (Bending et al., 2011). Besides the classical Th1 and Th2 cells, further consecutive studies identified other subsets of Th cells including Th3, Th9, Th17, Th22 and follicular helper T (TFH) (Table 1) (Annunziato and Romagnani, 2009; Zhou et al., 2009).

Th1 cell is most frequent subset of effector memory T cells; its development involves signals delivered from antigen-presenting cells and those from cytokines secreted in response to pathogens, with interferon (IFN)-γ itself, interleukin (IL)-12, and IL-18 that each subsequently enhances specific pathways (Ma and Phan, 2017). Th2 cells orchestrate protective type 2 immune responses and produces detectable amounts of IL-4, IL-5, and perhaps IL-6 (Mosmann and Coffman, 1989). Th9 cell is a new member in the Th cell family. Although IL-9 has been recognized as a classical Th2-related cytokine, the signature cytokine for Th9 cells is IL-9 (Li et al., 2017). These cells are involved in the pathogenesis of allergic and autoimmune diseases (Li et al., 2017; Deng et al., 2017; Licona-Limon et al., 2017). Additionally, newly described Th22 and its secreted cytokine IL-22 have recently been reported to be involved in the pathogenesis of autoimmune and inflammatory skin diseases (Fard et al., 2016; Perusina Lanfranca et al., 2016). TFH cells are a different type of CD4+ T cell specialized in providing B-cell help for the induction of antigen-specific antibody production at the germinal centre (GC) reaction. During chronic infections a consistent TFH promotion is acknowledged (Greczmiel and Oxenius, 2018; Greczmiel et al., 2017), as well as that a physiopathological balance should be

* Corresponding author at: Non-Communicable Diseases Research Center, Vice Chancellor for Research, Alborz University of Medical Sciences, Karaj, Iran.
*E-mail address:* azizi@abzums.ac.ir (G. Azizi).
[1] These authors contributed equally to this work.

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**Table 1**
The different types of CD4+ T cells.

| Subset | Differentiation factors | Transcription factors | Main cytokines | Function | Immunopathogenesis |
|---|---|---|---|---|---|
| Th1 | INF-γ, IL-12 | T-bet | IFN-γ, TNF-α, IL-2, IL12, LT | React to distinct types of intracellular pathogens, help B cells to produce antibody | Autoimmune diseases (Jager et al., 2009; Umetsu and DeKruyff, 1997), Immunodeficiencies (Cecchinato et al., 2008), Failed pregnancy (Hill and Choi, 2000), and Graft rejection (Umetsu and DeKruyff, 1997). |
| Th2 | IL-4, IL-2 | GATA3, STAT6 | IL-4, IL-5, IL-6, IL-13 | Orchestrate protective immune responses, such as those that target helminths and facilitate tissue repair | Lead to chronic inflammatory diseases, such as asthma and allergy (Walker and McKenzie, 2018). |
| Th9 | TGF-β, IL-4 | GATA3, STAT6, IRF4 | IL-9 | Preserve against parasitic helminth infections and boost IgG and IgE production by B cell | Autoimmune diseases, and Allergies (atopic dermatitis, SLE, psoriasis, RA, IBD), Cancer, Immunodeficiency (Yazdani et al., 2018). |
| Th17 | IL-6, TGF-β, IL-23, IL-1β | RORα, RORγτ, STAT3, RUNX1 | IL-17A, IL-17F, IL-21, IL-22, TNFα, IFNγ, GM-CSF | Important mediators of immune responses against extracellular and intracellular bacteria (protective immunity to Mycobacterium tuberculosis and chlamydia trachomatis), fungi, viruses and critical regulatory roles in protect mucosal homeostasis, Enhance neutrophil response | Involved in inflammation, several autoimmune diseases such as RA and tumour (van Hamburg and Tas, 2018; Asadzadeh et al., 2017; Chen and O'Shea, 2008; Dong, 2008; Basu et al., 2015; Nalbant and Eskier, 2016; Azizi et al., 2013; Li et al., 2018a,b). |
| Th22 | TNF-α, IL-6 | AHR | IL-22, IL13, TNF-α | Preserve against virus infection, intercede interactions of the immune system with stromal cells, protecting intestinal mucosa against inflammation, modulate wound repair and healing | Involved in various autoimmune diseases such as RA, SLE, type 1 and 2 diabetes, ITP and chronic inflammatory disease like Crohn's disease (CD) (Fang et al., 2018). Inflammatory skin disorders such as psoriasis and atopic dermatitis (Kagami et al., 2010; Tamasauskiene and Sitkauskiene, 2018; Azizi et al., 2015b; Mirshafiey et al., 2015). |
| Th1-like Th17 | IL12 | RORγt, T-bet, RUNX1 | IL-17, IFN-γ | Capability to help B cells | Autoimmune and inflammation diseases (Cohen et al., 2011; Schmolka et al., 2018). |
| Treg | TGF-β, IL-12 | Foxp3, RUNX1/3 | IL-10, TGF-β | An important role in the induction and maintenance of immunological tolerance by direct cytotoxic effect, anti-inflammatory cytokines, metabolic disruption, maintenance of intestinal homeostasis and modulation of the dendritic cells function. | Cancer, inflammatory, colitis and autoimmune diseases (Fard et al., 2016; Duggleby et al., 2018; Wang et al., 2018). |
| Tr1 | IL-27, IL 21 | T-bet, | IL-10, TGF-β | Controlling T cell responses | Autoimmunity and infection, suppression of immune and autoimmune responses (Artis et al., 2004; Kemper et al., 2003; Pot et al., 2009; Spolski et al., 2009). |
| Th3 | TGF-β, IL-4, IL-10 | FOXp3 (Controversial) | TGF-β, low amounts of IL-4 and IL-10 | Main mediators of peripheral immune tolerance both by direct effects and indirectly by the induction of Foxp3+ Tregs | Peripheral immune tolerance, suppressive features for both Th1 and Th2 cells (Wan and Flavell, 2008; Carrier et al., 2007; Chen et al., 1994). |
| TFH | IL-21, IL6, IL-12, and negatively regulated with IL-7, IL2 | T-bet, miR-17–92, FOXO1 | IL-21, IL-4 | Activation of B cells, antibody class switching, germinal center (GC) formation. | Involvement to autoimmune diseases and virus replication (Jandl et al., 2017; Jogdand et al., 2016). |

Th: T helper, Tr1: type 1 regulatory T cells, TFH: follicular helper T cells, IL: interleukin, IFN: interferon, TNF: tumor necrosis factor, ROR: RAR-related orphan receptor, AHR: aryl hydrocarbon receptor, STAT: signal transducer and activator of transcription, IRF: interferon regulatory factor, Foxp3: fork head box P3, Runx: runt-related transcription factor, T bet: T-box transcription factor, TGF: transforming growth factor, LT: Lymphotoxin, GM-CSF: Granulocyte-macrophage colony-stimulating factor, Ig: Immunoglobulin., GC: germinal center.

fine-tuned since extreme production of TFH cells can lead to autoimmunity and low levels can result in insufficient protection from infection (Ma and Phan, 2017; Webb and Linterman, 2017). The Th17 lineage is another recently discovered subset of effector memory T cells which play a critical role in the induction of the tissue inflammation that is hallmarks of many autoimmune and inflammatory diseases (Fouser et al., 2008; Eisenstein and Williams, 2009; Gaffen, 2008). In inflammatory conditions, Th17 cells demonstrate potential for transdifferentiation into Th1, Th2, or anti-inflammatory Tr1 cells (Krebs and Steinmetz, 2016). Some Th17 cells extinguish IL-17 expression and acquire expression of IFN-γ, giving rise to "Th1-like" cells. Th1-like Th17 cells producing both IL-17 and IFN-γ are functional in humans and mice and associated to potential pathogenicity (Gartlan et al., 2017). These Th1-like Th17 cells that additionally co-express RORγt and T-bet are reviewed elsewhere (Brucklacher-Waldert et al., 2016).

Regulatory FOXP3 + T cells (Tregs) are CD4 + T cells that constitute 5%–10% of the total peripheral CD4 + T cell population in naïve mice, while in humans Tregs with intense suppressive activity are limited to 1–2 % of the CD4 + T cells that show high expression levels of CD25 (van Hamburg and Tas, 2018; Nedoszytko et al., 2017; Lee and Lee, 2018; Schmidt et al., 2017). Type 1 regulatory T (Tr1) cells play important role in inhibition of autoimmunity and inflammation with secretion of IL-10 and transforming growth factor beta (TGF-β) (Sanjabi et al., 2017; Pot et al., 2011). Generation of Tr1 cells promotes with secretion of IL-27 through suppression of effector Th17 cells in which two transcription factors, aryl hydrocarbon receptor (AHR) and musculoaponeurotic fibrosarcoma oncogene (MAF/c-MAF) are actively involved (Pot et al., 2011). In predominant IL-6 microenvironment Th17 cell differentiation upregulates while elevated level of TGF-β advocates Tr1 cells differentiation (Pot et al., 2011). Other Treg subset that is able to differentiate from CD4 + T cells known as Th3 cells. Differentiation of these cells occur mainly after ingestion of exogenous antigens via oral route of administration (Wan and Flavell, 2008). Low and high doses administration of antigens lead to active suppression and clonal anergy or deletion, respectively (Fukaura et al., 1996). Th3 cells help secretion of IgA by releasing TGF-β and show suppressive properties for both Th1 and Th2 cells.

The concept of imbalanced Th subsets has been associated with a variety of chronic inflammatory and autoimmune diseases (Mosmann and Coffman, 1989; Wong et al., 2015; Berenson et al., 2004; Tau and Rothman, 1999). In this review, we aim to discuss evidences for Th17 plasticity, especially of Th1-like Th17 cells, and its active contribution to the pathogenesis of inflammatory and autoimmune disorders (Table 2).

## 2. Th17 plasticity

Despite that Th1 and Th2 cells have lineage stability, Th17 cells are not a “fixed” subset, since they are capable to be converted into different other lineage subsets influenced by the microenvironment (Fig. 1) (Verstappen et al., 2018). Thus, Th17 cells can transdifferentiate into other effector cell types including Th1, Th2, Treg and TFH cells enabling them with diverse functionality and qualitatively distinct response (Guery and Hugues, 2015). Th17 cell plasticity, both in humans and mice leads to the protective immunity, but also to autoimmunity (Carr et al., 2017). There is a complex relationship between the Th1 and Th17 lineages plasticity. Th17 cells play a role in autoimmunity, cancer, and infections through its development towards Th1 cells (Wacleche et al., 2017; Asadzadeh et al., 2017). The pathogenic Th17 cells engender the IL-17 + IFN-γ + double-positive T cells subset (also termed Th1-like Th17, Th17/Th1 or Th17-1 cells) (Uchiyama et al., 2017). Th1-like Th17 cell clones express IL-23R, C-C motif chemokine receptor 6 (CCR6), and the transcription factors T-bet and RORγt (Annunziato et al., 2007). These cells with low cytotoxicity and limited sensitivity to autologous regulatory T cells, while still capable to help B cells (Annunziato et al., 2007), are involved in inflammatory responses and have active role in the development of autoimmune disorders like insulin-dependent diabetes mellitus (IDDM), experimental autoimmune uveitis (EAU), autoimmune arthritis and inflammatory colitis (Harbour et al., 2015).

IL-17 and IFN-γ, both secreted by co-expression of CXCR3 and CCR6 from Th1-like Th17 cells, contribute mainly in the pathogenesis of autoimmune disorders (Verstappen et al., 2018; Guery and Hugues, 2015; Zenewicz et al., 2009). Thus, according to these evidences, the targeting of either Th1 or Th17 cells could be considered a rationale alternative for the treatment of patients with autoimmune disorders (Guery and Hugues, 2015; Stadhouders et al., 2018; Damsker et al., 2010). Importantly, the pathogenic role of Th17 cells in various autoimmune disorders by acquisition of pathogenicity through IL-23R, granulocyte-macrophage colony-stimulating factor (GM-CSF), T-bet along with runt-related transcription factor (RUNX) and anti-inflammatory cytokine IL-10 signals should not be neglected (Sonderegger et al., 2008; Schmitt et al., 2018; Wang et al., 2014). In organ-related autoimmunity GM-CSF promotes IL-23 production and consequently can increase Th17 cells pathogenicity (Sonderegger et al., 2008). In addition secretion of IL-6 that is promoted by GM-CSF enhances Th17 cells survival rate by controlling RORγt expression that finally facilitates Th17 cells polarization (Sonderegger et al., 2008). Interestingly recently studies indicate IL-10$^{+}$ Th17 cells that produce mainly IL-17A accelerate progression of endometriosis particularly in advanced stages (Chang et al., 2017). Hence besides Th1 phenotype of Th17 pivotal role in autoimmunity, cancer and infections, the Th17 cells acquisition of pathogenicity through aforementioned conditions should not be over looked.

Th17 cells can transdifferentiate into Tr1 cells that produces IL10. Adversely, down-regulation of Th17 cells via IL 10 receptor (IL- 10R) signaling in regulatory T cells has been reported, even though the underlying mechanism has not been completely uncovered (Diefenhardt et al., 2018). Although plasticity between Treg and Th17 cells has been described in mice and in humans extensively (Guery and Hugues, 2015), more recently, modulation of the Treg/Th17 balance has been reported in the improvement of acute colitis with probiotics (Park et al.,

**Table 2**
Increased frequency of reports associating Th1-like Th17 cells with autoimmune diseases.

| Year | Diseases examined | Th1-like Th17 cells changes | Reference |
|---|---|---|---|
| 2010 | Multiple Sclerosis | Increased | Domingues et al. (2010) |
| 2010 | Multiple sclerosis | Increased | Fletcher et al. (2010) |
| 2014 | Experimental autoimmune encephalomyelitis | Increased | Wang et al. (2014) |
| 2015 | Inflammatory bowel disease | Increased | Ueno et al. (2015) |
| 2017 | Primary Sjogren's syndrome | Increased | Verstappen et al. (2018) |
| 2017 | Bacterial infection | Increased | Uchiyama et al. (2017) |
| 2018 | Rheumatoid Arthritis | Increased | Bazzazi et al. (2018) and Hickman-Brecks et al. (2011) |
| 2018 | Common variable immunodeficiency | Unchanged | Azizi et al. (2018b) |
| 2018 | LRBA deficiency | Increased | Azizi et al. (2018a) |
| 2018 | Multiple sclerosis | Increased | van Langelaar et al. (2018) |

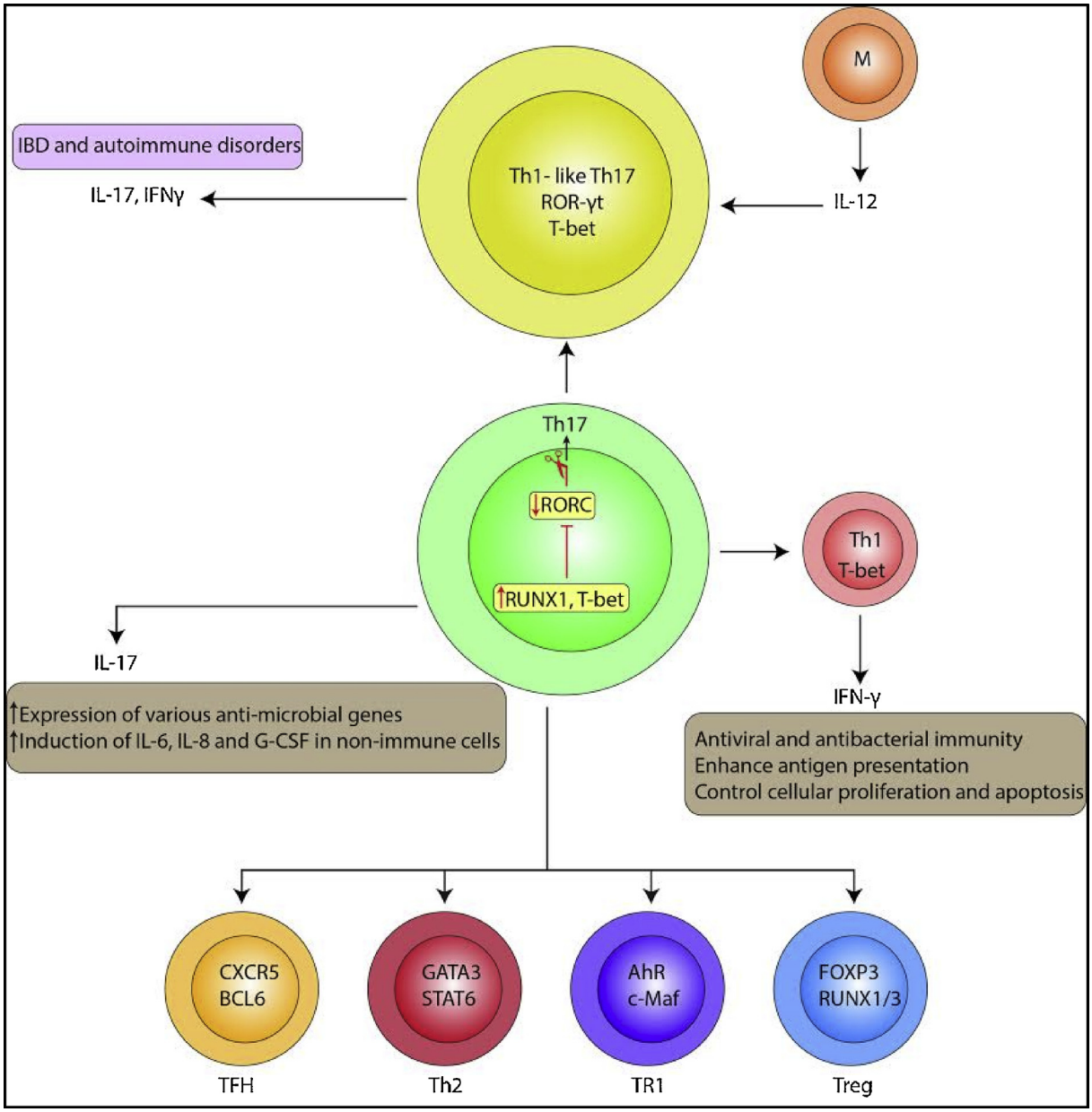


**Fig. 1.** Th1-like Th17 plasticity and its relevance to autoimmune disorders.

2018). Moreover, several studies confirm that IL-17 produced by Treg cells are associated with Foxp3 reduction and subsequently with the increase of RORγt expression, which shows Th17 cell subset alteration *ex vivo* and in vivo (Zou et al., 2018). Transdifferentiation of Th17 to Tr1 has been confirmed during resolution of inflammation by following the transcriptional profiling of TGF-β, downstream SMAD3 signaling and subsequent levels of AHR (Gagliani et al., 2015). Therefore, Treg/Th17 plasticity might be sensible targets to restore immune balance in the immunogenicity of cancer or towards tolerance in autoimmune diseases (Guery and Hugues, 2015; Stadhouders et al., 2018; Fernandez et al., 2016).

It has been revealed that Th17 cells can shift to Th2 cells (Cosmi et al., 2014). Th17/Th2 cells are reported to circulate in blood of patients with asthma triggered by inflammation and with different clinically outcomes (Guery and Hugues, 2015; Cosmi et al., 2011). These cells display properties of both Th17 and Th2 subsets, by expressing transcription factors GATA binding protein 3 (GATA3) and RORγt as well as the secretion of the cytokines IL-22, IL-5, IL-13, IL-4 and IL-17, with the two later associated to disease phenotypes variation (Guery and Hugues, 2015; Cosmi et al., 2011).

Recently, common early stage differentiations for human Th17 and TFH have been reported (Raymond et al., 2011). Conversion of Th17 cells towards a TFH phenotype has been intensively explored in aggregated lymphoid nodules with increased expression of B-cell lymphoma 6 protein (BCL6), C-X-C chemokine receptor type 5 (CXCR5), programmed cell death-1 (PD1), and IL-21 along with elevated level of IgA-secreting GC B cells (Hirota et al., 2013). Moreover, it was reported that dysregulation in the function of TFH cell, along with irregularities in expression of TFH cells regulators such as inducible costimulator (ICOS) or IL-21, may cause various autoimmune disorders or immunodeficiencies (King et al., 2008).

## 3. Th17 cells transdifferentiation into Th1-like Th17 cells

AS mentioned earlier, the mechanisms involved in the Th17 plasticity includes those of cytokine pathways, transcription factors and epigenetic regulation. It has described that cytokines IL-12 (Ueno et al., 2015), IL-23, IL-1β, low level of TGF-β (Guery and Hugues, 2015), TNF-

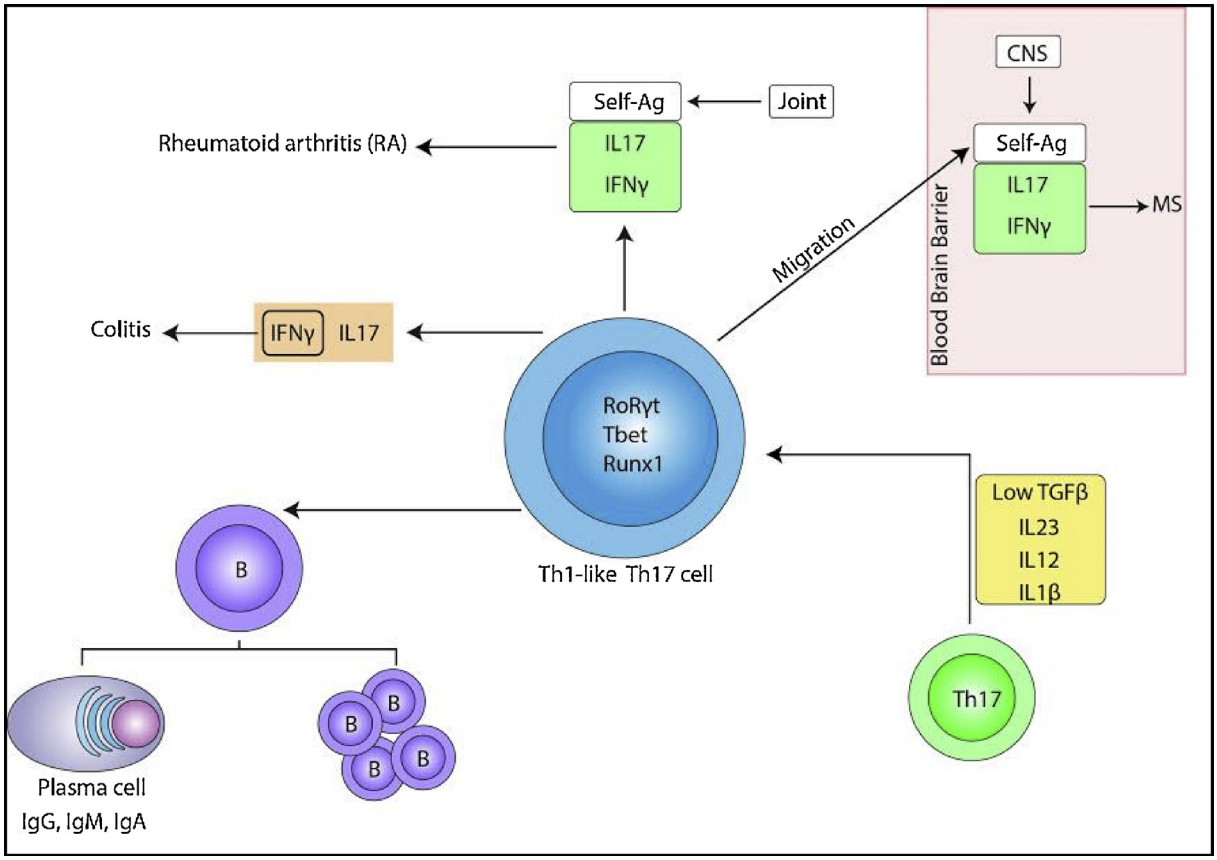


**Fig. 2.** The plasticity of Th1-like Th17 cells in the pathogenesis of autoimmune and inflammatory disorders.

α and PGE2 (van Hamburg and Tas, 2018), play active role in the plasticity of Th17 to Th1-like Th17 cells. The combined role of cytokines during differentiation pathways for Th17 cells further deserves attention. IL-23 and IL-1β have been found as potential inducer to promote Th17 differentiation in human (Annunziato et al., 2010). TGF-β and IL-6 act as Th17- promoting cytokines and induce differentiation of naïve $CD4^+$ to Th17 cells via conventional pathway. Additionally differentiation of naïve $CD4^+$ cells to either Th1 or Th17 cells in response to combined IL-1β, IL-6 and IL-23 cytokines should not be neglected (Geginat et al., 2016). Th17 cells can transdifferentiate to Th1-like Th17 cells with ability to express T-bet and producing IFN-γ, which have found to be highly pathogenic in various immune mediated diseases. Th1-like Th17 cells also could be directly generated from naïve precursor upon stimulation with combined pro-inflammatory cytokines such as IL-1β, IL-23 and IL-6 (Geginat et al., 2016). In the alternative pathway of Th17-cell generation, Th1-like Th17 cells can be transdifferentiated from Th1 cells in the presence of TGF-β, IL-6, IL-1β and IL-23. In this context, the high plasticity of Th1 cells facilitates upregulation of RORγt and IL-17 production with TGF-β and IL-6 stimulation prior to final transdifferentiation (Geginat et al., 2016). T-bet, RORγ and run-related transcription factors such as RUNX1 and RUNX3 are other factors that are involved in the differentiation of Th1-like Th17 cells under inflammatory conditions in mouse and human (Wang et al., 2014). Moreover, although these transcriptional factors are pivotal for the progression of pathogenic Th1-like Th17 cells (Wang et al., 2014), T-bet is capable to suppress the ontogeny of Th17 cells via silencing the *Rorc* locus and inhibiting subsequent transcriptional regulation (Mukasa et al., 2010). Interestingly, interaction of T-bet with RUNX1 is able to block RUNX1-mediated transactivation of RORC (Lazarevic and Glimcher, 2011). Our previous study (Azizi et al., 2018a), have shown that the increased frequency of Th1-like Th17 cells involves a high expression of T-bet and RUNX1, concomitantly with low levels of RORC in CD4+ T cells of patients with LPS responsive beige-like anchor protein (LRBA) deficiency, a condition that is compatible with the polarization of Th17 to Th1-like Th17 phenotype. Last but not least, expression of RORγ is rather unstable and influenced mostly by environmental signals, a condition allowing Th17 heterogeneity and plasticity (Stadhouders et al., 2018). The plastic properties of Th17 cells further can be explained by the epigenetic regulation of the *IFNG* locus. Interestingly Th17 cells exhibit an *IFNG* chromatin landscape that is similar to that of Th1 cells (Stadhouders et al., 2018). In fact, in patient with autoimmune disorders the broad epigenetic priming in *IFNG* locus of Th17 cells contribute actively to plasticity of Th17 cells towards Th1-like Th17 phenotype. Understanding epigenetic priming with associated functional properties could further be expanded by 3D genome topography study, nevertheless the structural mechanisms have not been systematically explored. For instance it can be speculated similar to Th1 cells, in Th17 cells the dimensional proximity of *IFNG* promoter with enhancer would hamper demand for local topological reshaping in Th17 cells particularly when exposed to Th1-boosting signals (Jhunjhunwala et al., 2008). All together in vivo molecular mechanism involved with Th17 cell plasticity also remains an interesting part that needs to be unveiled (Stadhouders et al., 2018). In Th17 cells approximately 600 super-enhancer elements with diverse single nucleotide polymorphism (SNPs) are strongly associated with broad range of autoimmune disorders and importantly their hypersensitivity to various epigenetic inhibitors further can be applied as potential therapeutic targets (Simeonov et al., 2017; Consortium, 2012).

## 4. Th1-like Th17 cell and autoimmunity

Th1-like Th17 cells selectively express IL-23R, CCR6, and the transcription factor RORγt and T-bet (Annunziato et al., 2007). Reported features of these cells include competence to help antibody

secretion (IgM, IgG, and IgA, but not of IgE) by B cells with minimal cytotoxicity, and low susceptibility to control by autologous regulatory T cells (Annunziato et al., 2007). The granzyme A expression by Th1-like Th17 cells is lower than in Th1 subsets, and consequently, its cytotoxic potential is significantly decreased. Furthermore, the capacity assay of Th1-like Th17 cells subsets to proliferate in response to allogeneic stimulation in the existence of an autologous Treg cell clone has shown that its clones exhibit low susceptibility to the suppressive activity of an autologous Treg cell clone (Annunziato et al., 2007; Shibata et al., 2018; Hu et al., 2017). Hence, all together suggest that the Th1-like Th17 cells actively participate in the pathogenesis of autoimmune diseases (Fig. 2) (Annunziato et al., 2007; Shibata et al., 2018).

Regarding therapeutic targets in autoimmunity, ex-Th17 cells known as non-classical Th1 cells with ability to produce less IL-17 but able to produce IFN-γ are also important mostly at sites of autoimmunity. Basdeo et al. in vitro study has shown although ex-Th17 cells losing the majority of IL-17 secretion, they actively produce IFN-γ, TNF, GM-CSF and IL-2 cytokines. This study additionally shows ex-Th17 cells are resistant to Treg-mediated suppression with actually unknown mechanism that further support contribution of these cells in pathogenicity of autoimmune disorders (Basdeo et al., 2017). These data suggest ex-Th17 cells are also pivotal therapeutic targets in the context of Th17 cells plasticity to combat with autoimmunity disorders like inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) especially where anti-IL-17 therapy has failed to be effective (Maggi et al., 2013; Basdeo et al., 2015; Patel et al., 2013; Hueber et al., 2012).

### 4.1. Inflammatory bowel disease

IBD is a chronic inflammation of digestive tract and can be categorized into 2 types with distinct clinically phenomena: Crohn's disease (CD) and ulcerative colitis (UC) (Lee et al., 2018; Ueno et al., 2013). Generally, Th17 cells are known as a principally critical factor in the pathogenicity of IBD. In patients with CD, Th1-like Th17 cells are induced chronic inflammation. In fact Th1-like Th17 cells could be characterized by the expression of CD161, a signature marker of Th17 cells progenitors with ability to produce both IL-17 and IFN-γ. It should be noted that in the absence of TGF, downregulation of RORγt and upregulation of T-bet with both IL-23 and IL-12 may suppress IL-17 while promoting IFN-γ secretion (Galvez, 2014). A mouse model of colitis have shown that Th17 cells play a role as precursors of IFN-γ secreting Th1 cells, involving the Th17/Th1 plasticity in the pathogenesis of UC (Harbour et al., 2015). The Th17-promoting cytokine IL-23 enact intestinal inflammation as pre-clinically probed in a induced murine colitis model where immunizing mice against IL-23 successfully improved clinical signs with intestinal inflammation reduction (Guan et al., 2018). In addition, IL-23 accompanies with IL-12 signaling boosts IFN-γ secretion from Th17 in intestine, tending to Th17/Th1 plasticity (Verstappen et al., 2018; Ueno et al., 2015; Lee et al., 2018).

### 4.2. Multiple sclerosis (MS)

MS is an autoimmune disease characterized by demyelinating of the central nervous system (CNS) with self-immune reaction to myelin antigens. Studies that have been performed in various animal models for MS revealed that Th1 cells play main role in the induction of this autoimmune and inflammation disease (Bowles et al., 2018). Expression of IL-17 and IFN-γ by T cells has been found in MS brain tissue, suggesting that Th1-like Th17 cells may participate in the pathology of the disease (Fletcher et al., 2010). Moreover, recent research has demonstrated active pathogenic role for Th17, and Th22 cells in MS (Qureshi et al., 2018). Th22 and its signature cytokine IL-22 increase in different autoimmune disorders. Previously, several studies have shown significant alteration in the frequency and functionality of Th22 in MS (Fard et al., 2016). In MS patients the Th1-like Th17 cells vigorously respond against self-antigens. Although the mechanisms that arouse this plasticity has not been clarified in humans, but an experimental autoimmune encephalomyelitis (EAE) animal model of MS have revealed an stimulating plasticity of Th17 cells (Verstappen et al., 2018). In this model, alteration of Th17 cells to both IFN-γ-single producing Th1 cells and IFN-γ/IL-17 double producing Th1-like Th17 cells is the main pathological mechanism (Verstappen et al., 2018). It is further specified that human memory B cells are potentially broadened into a Th17 phenotype, with a subpopulation of cells concurrently able to express IFN-γ and IL-17 (Kebir et al., 2009). It is noted that lymphocytes taken from the blood of relapsing MS patients possess an increased tendency to broaden into IFN-γ-producing Th17 cells, while the double producing cells are found in brain tissue of MS patients (Kebir et al., 2009). It has been shown that Th1-like Th17 cells (expressing both RORγt and T-bet) are capable of crossing the human blood-brain barrier and accumulation of these cells in the CNS of mice have been also observed all along the effector phase of EAE (Kebir et al., 2009). In a recent study, Th1-like Th17 cells also found to be able to sustain CD161 expression resembling for ex-Th17 phenotype (van Langelaar et al., 2018). Additional data has emphasized the involvement of Th1-like Th17 cells in the etiopathology of MS and EAE and their eminent enrolment into the CNS during stages of inflammation (Verstappen et al., 2018; Domingues et al., 2010). By analysing CCR6/CXCR3, IFN-γ/GM-CSF and VLA-4 expression, Th1-like Th17 cells have found to be related with $CD4^+$ Tcells during the early stage of disease. Th1-like Th17 cells and in particular Th17.1 subpopulation ($IFN\text{-}\gamma^{high}$ $GM\text{-}CSF^{high}$ $IL\text{-}17^{low}$) have been prominently associated with multiple sclerosis with actually increasing hope for more specific T-cell targeted therapies (van Langelaar et al., 2018). However it should be taken into account that a single lineage of Th cells cannot be pledged for immunopathology and diverse Th cell lineages or immune cell types may be beneficial for disease-modifying therapies.

### 4.3. Rheumatoid arthritis

RA is a chronic and intrinsic inflammatory abnormality identified with inflammation in synovia of diarthrodial joints. Various types of immune cells, remarkably Treg cells and three subsets of Th cells including Th1, Th17 and Th22 cells are responsible for the pathogenesis of RA (Srivastava et al., 2018). It has newly reported that Th22 cells and IL-22 critically control the pathogenesis of RA (Zhong et al., 2017; Wen et al., 2018), hence, addressing IL-22 and/or Th22 as potential therapeutic targets are pivotal (Azizi et al., 2015a). As mentioned above, the inequality between Tregs and Th17 cells also considers critical in RA and further supported by the effectiveness of an N-3 polyunsaturated fatty acid to balance them which in turn is successful for the treatment of RA (Kim et al., 2018). A feature of this pathogenic Th17 cell phenotype is the abundant production of GM-CSF and TNF-α as well as the co-expression of Th1 cell markers, such as T-bet and IFN-γ (van Hamburg and Tas, 2018). Consequently, in agreement with such significant switch, the plasticity of Th17 to Th1 and the high frequency of Th1-like Th17 cells are considered a major pathogenic driver of RA. Thus, it has been reported that the Th1/Th17 ratio in RA patients is significantly distinct from healthy individual and is negatively related with disease progression (Bazzazi et al., 2018). Reduction of the Th1/Th17 ratio in RA implies a new prototype of autoimmune disease since inequality or plasticity between these subsets can substantially modify progression, diagnosis and treatment of the disease (van Hamburg and Tas, 2018; Bazzazi et al., 2018; Kobak and Bes, 2018). Recently, distinguishing Th1, Th17 and ex-Th17 cells based on some CD161 features such as their expression of IL-17 or IFN-γ, or chemokine receptors CXCR3, CCR, and CCR4 has drawn attention to investigate the outcome of Th17 plasticity in inflamed RA joints (Maggi et al., 2012; Sallusto et al., 2012). Basdeo et al. have found Th17 cells are highly plastic toward an ex-Th17 phenotype especially at inflamed sites. In other set of experiments ex-Th17 cells have shown to produce high level of GM-CSF and TNF comparing with either Th17 or Th1 cells (Basdeo et al.,

2017). However, trafficking of ex-Th cells from peripheral blood into sites of inflammation cannot be ruled out due to existence of them in periphery, these results highlight that ex-Th17 cells may importantly produce these cytokines at inflamed tissues. Interestingly, regarding pathogenic roles of TNF and GM-CSF, these finding are also consistent with current anti-GM-CSF trials in inflammatory diseases (Wicks and Roberts, 2016).

### 4.4. Other autoimmune diseases

The plasticity of Th17 cells in to Th1-like Th17 cells, (co-expressing IL-17 and IFN-γ as well as CCR6 and CXCR3) may actively be involved in chronic inflammation and B cell activation in Sjogren's syndrome (pSS) patients (Verstappen et al., 2018). Noteworthy, in salivary gland tissue of pSS patients, the abundant IL-7 may stimulate the plasticity of Th17 cells to IFN-γ single or double producing Th1-like Th17 cells. Additionally, plasticity of Th17 cells and other effector T cell subsets actively participate in the pathobiology of patients recognized with pSS syndrome (Verstappen et al., 2018).

It is worth mentioning that Th17 cells and Th1-like Th17 population are further important factors in dry eye disease, which is a common ocular dysfunction. In this disease, elevated level of IFN-γ, IL-12 and IL-23 are involved in the pathogenesis of the disease (Subbarayal et al., 2016); in fact, it has been demonstrated that Th1-like Th17 cells play a key role in ocular surface autoimmunity through both IL-17A and IFN-γ (Chen et al., 2017).

Recently, the frequency of Th1, Th2, Th17, Th1-like Th17 and Th22 cells and their balance with Tregs has been studied in detail in patients with common variable immunodeficiency (CVID) (Azizi et al., 2018b,c) and LRBA deficiency (Azizi et al., 2018a,c). Thus, although the subsets of Th1, Th1-like Th17 and Th22 cells are normal in CVID associated with low clinical complications, other diverse outcomes are seen in patients with LRBA deficiency, characterized by high episode incidence of autoimmunity and enteropathy. Thus, in patients with LRBA deficiency, a significant high level of frequent Th1, Th1-like Th17 and Th22 cells are seen along with the expression of *TBET* and *RUNX1*. Moreover, high levels of IFN-γ and IL-22 production in LRBA-deficient CD4+ T cells are observed upon stimulation of CD4+ T cells, particularly in patients with enteropathy. However, Tregs significantly decrease in LRBA-deficient patients, principally in those with autoimmunity (Azizi et al., 2018d,e, 2017). Additionally, an unfavourable association between the frequencies of Treg cells and Th1-like Th17 cells in patients with LRBA-deficiency has been observed (Azizi et al., 2018b). In patients with enteropathy, lower frequency of Th17 cells is detected, while high levels of Th1-like Th17 cells are recognized. Thus, inequality in Th subsets (mainly in Th1-like Th17 and Treg cells and their corresponding mediators) in LRBA deficiency contribute as potential factors in the immunopathogenesis of autoimmunity and enteropathy (Azizi et al., 2018f).

## 5. Conclusion and future perspective

As mentioned Th17 cells are heterogeneous due to environmental, inflammatory and genetic factors, and able to adopt pathogenic and non-pathogenic phenotypes following plasticity to Th1-like Th17 or Tr1 cells. Recently, the plasticity of Th17 cells to Th1-like Th17 cells considered as a new mechanism commonly present in the aetiology of autoimmune and inflammatory conditions. The understanding of this plasticity using new emerging techniques such as single-cell RNA sequencing as well as new culture models and crystallized structures of the receptors may allow for design of novel therapeutic approaches for the treatment of these immune-mediated disorders. Currently, T cell-targeted therapy by manipulation of involved molecules in determining the balance between homeostatic and pathogenic Th17 cell responses is in processing. Based on this plasticity, future therapeutic targets including various pro-inflammatory mediators and their downstream signalling molecules, transcriptional regulators and non-coding RNA molecules might be of interest. Treatment strategies with JAK inhibition along with silencing and promoting receptor interacting protein 2 (RIP2) expressions may be beneficial. RIP2 is critical in determining the balance between homeostatic and pathogenic Th17 cell responses by suppresses pathogenic Th17 cell and supports conventional Th17 cell polarization. Moreover, induction of transcriptional activation or silencing using 'epigenetic drugs' which interfere with DNA methylation and histone modifications that could potentially alter disease-related gene expression may also need to be investigated precisely. Meanwhile, pharmacological interfering of metabolic pathways or restoring altered gut microbiota may be supplementary therapeutic approaches for future studies.

## Conflict of interest

The authors declare that they have no conflict of interest.

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