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Chapter

Immune-Mediated Inflammation: Human T CD4 Helper Lymphocyte Diversity and Plasticity in Health and Disease

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Abstract

The CD4+ T helper (Th) cells have a critical role in organizing the adaptive immune response. The emerging cells of the differentiation after the immune synapse produce helper T cell subpopulations that activate, suppress, or regulate the immune response upon interaction with varying immune cells. There are two main Th cell functional categories: the "effector cells" and the "regulatory T cells." Classic T helper lymphocytes can also be distinguished by their lineage according to the developmental microenvironment, the expression of cell adhesion-homing receptors, the profile of cytokines they are exposed to, and the involved transcription factors. Traditionally, the CD4+ and CD8+ phenotypes have been considered as helper and cytotoxic/suppressor T lymphocytes, respectively. Currently, the distinction is little rigorous. The immune response is exceedingly complex beyond the classic Th1 and Th2 effector cells' involvement, and other populations of helper T lymphocytes like the Th17, Tfh, Th22, and Th9 lymphocytes have been phenotypically characterized. These lymphocytes also participate in the pathogenesis of several immune-mediated inflammatory disorders. Here, we revisit and discuss the essential aspects of the state of the art regarding phenotypic diversity and plasticity of TCD4 cells in the T lymphocyte repertoire frame and their potential implication in human inflammatory diseases.

Keywords: CD4+ subsets, inflammation, health, disease, plasticity, diversity, CD4+, Th17

1. Introduction

The CD4+ T cells play a key role in triggering various immunological effector and regulatory functions, promoting or attenuating inflammation.

Such a diverse repertoire includes the early activation during immune synapses in the ganglion, activation of cytotoxic T cells, full activation of macrophages effector functions, maturation of B cells into plasma cells and memory B cells, antibody

production by B cells, immunoglobulin isotype switching, recruitment of PMNs, and eosinophil and basophil inflammation [1]. The Th cells promote the amplification of inflammatory leukocytes effector activity in a broad spectrum of scenarios which under physiological conditions determinate protective and tolerogenic immune response. Failure in T effector and/or dysregulated regulatory functions could aid immune disorders, including immunodeficiency, autoimmunity, and cancer [2–5].

Helper T cells assist in B cells' differentiation into antibodies-producing plasma B cells in a concerted cellular-humoral immune response. This process is triggered by specific cytokines and ligand-receptor interactions [6].

The effector T cell phenotype is driven by a specific transcriptional factor, a distinctive array of cell surface molecules, and a specific profile of cytokines, which along with microenvironmental specific conditions enable T cell subset within an arm of the immune system [7].

The Jak/Stat (Janus kinase/signal transducer and activator of transcription) pathways [8] and a specific Stat associated with one of the four main transcriptional "signature" factors, T-bet (T-box transcription factor), GATA-3, RORγt (retinoic acid receptor-related orphan receptor gamma), and Foxp3 (forkhead-box/winged-helix transcription factor P3), are essential for Th differentiation [9].

Each differentiation pathway requires specific transcription factors: T-bet and STAT-4 for Th1 and GATA 3 and STAT 6 for Th2 cells and RORyt for TH17 and Foxp3 cells for regulatory T cells (Treg) [10–13].

The T lymphocytes present a remarkable phenotypic, functional, and anatomical diversity. The T cell lineages are extraordinarily diverse and present a very broad functional repertoire (**Table 1**) bearing innate [14] and adaptive immunogenic or tolerogenic immune properties [15, 16]. According to the greater complexity and heterogeneity of subsets of T cells, reconsidering the pathogenicity of inflammatory diseases beyond the "classical Th1/Th2 paradigm", Th17 effector cells and T-regulatory lymphocytes (Treg) would be appropriate. Relative increases in the number of Th9 lymphocytes, follicular helper T cells (Tfh), and Th22 subsets have been described, and even NK and NKT cells contribute to the pathogenesis of immune-mediated inflammatory diseases [17]. These helper T-cell subtypes trigger specific responses upon different tissue environments by expressing a unique set of cytokines and chemokine receptors (**Figure 1**).

The T cells, like the CD1d-restricted natural killer T cells (iNKT) and gamma delta T cells, and other "unconventional" T cell subsets with invariant TCRs (T-cell receptors) exhibit several characteristics that place them at the border between the innate immune system and the adaptive immune system, influencing subsequent challenges by the same antigen. Although "unconventional" T cells provide rapidly available protection and contribute to the adaptive immune system, they have no ordinary helper properties [18].

The natural killer NK (large granular lymphocytes) and NKT (T cells) cells contribute to the pathogenesis of immune-mediated inflammatory diseases (IMIDs). A

CD4 T cell	Th1, Th2, Th3 (iTreg), Th9, Th17, Th22, ThF, nTreg, and Tr1
CD8 T cell	Tc1, Tc2, Tc9, and Tc17
Gamma delta T cell	Tγδ1 and Tγδ2
Natural killer T cell	NKT and NK cells

*h, helper; c, cytotoxic; reg, regulatory; n, natural; i, induced*

Table 1.
Representative T cell types.

large increase in these infiltrating innate immune cells has been observed in IMIDs lesions and also in blood as reported for moderate to severe skin psoriasis. In addition, NKT cells might display different cytokine profiles [19, 20].

Gamma delta T cells express a distinctive surface TCR which, unlike TCRαβ, is made up of one γ (gamma) chain and one δ (delta) chain. These cells are abundant in the mucosa and do not require antigen processing and major histocompatibility complex (MHC) presentation of peptide epitopes [21].

Gamma delta T cells, often tissue-specific, are abundant in the epithelia, orchestrating immune responses in inflammation, tumor surveillance, infectious disease, and autoimmunity.

Gamma delta 1 (Tγδ1) and gamma delta 2 (Tγδ2) cells were defined as a CD3+ cell subtype expressing γδ TCR [22]. Phenotypic analysis of gated CD3+ Tγδ1-positive cells has revealed that nearly 75% of them are CD4⁻ CD8⁻ (glycoprotein cluster of differentiation). Gamma delta T cells may be regarded as a rapidly available response to pathogens triggering the innate and adaptive immune system and a memory phenotype. Besides,
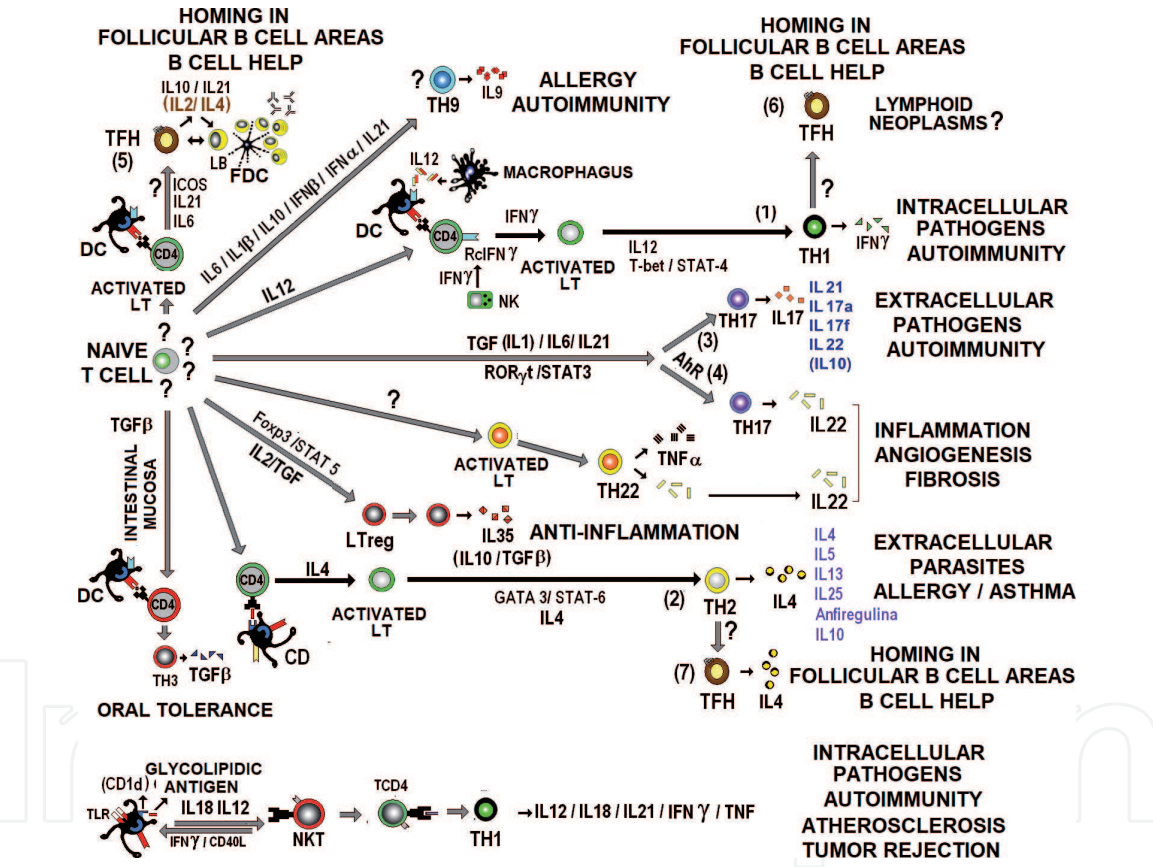
Figure 1.
Schematic representation of T lymphocyte differentiation. The T lymphocyte differentiation progresses upon the presence of IL12, IFNγ, and other signals provided by the antigen-presenting cells. Each differentiation pathway requires specific transcription factors, e.g., T-bet and STAT-4 for Th1 and GATA 3 and STAT 6 for Th2 cells, retinoid-related retinoid receptor orphan receptor (ROR t) for TH17, and FOXP3 cells for regulatory T cells (Treg). The production of IL12 and IL18 by the immune system cells triggers the early release of IFNγ, which influences the natural and adaptive immune response. According to the current differentiation model, a new subpopulation known as Th17 or Th IL17, which originates from virgin T helper cells might comprise a separate lineage from Th1/Th2. The differentiation of Th17 requires the presence of several factors in humans. The IL-23 might be an essential requirement for the development of effector cells. The IL21 might amplify the differentiation to Th17. The effector cells may eventually differentiate upon the participation of the aryl hydrocarbon receptor AhR, a cytoplasmic receptor that translocates to the nucleus. Although RORγt and AhR are highly expressed in the cells, it is unknown whether the AhR is preferentially found in Th17 cells producing IL22. The relationship between the Th17 cells producing IL22 and the recently identified Th22 effectors is not clear. The Th22 subpopulation typically secretes IL22 and TNFα but not IFNγ, IL4, or IL17. The secretion profile includes growth factors and chemokines involved in angiogenesis and fibrosis. TFH, follicular helper T lymphocyte; DC, dendritic cell.

they show potent antigen-presenting properties upon translocation to the ganglion. However, the various subsets may also be considered part of the innate immunity where a restricted TCR may be used as a pattern recognition receptor, indicating the importance of these lymphocytes in immunity and tissue monitoring of pathogens [21].

In particular situations, T CD8 cells can exert helper functions and vice versa, regardless of the existing heterogeneity of CD4 and CD8 T cells. Two functionally distinctive T lymphocytes subpopulations having effector or regulatory properties were considered [23]. Currently, the traditional distinction between the CD4 phenotype as a T helper and the CD8 phenotype as a cytotoxic/suppressor T lymphocyte is relative. Both CD4+ lymphocytes with cytotoxic properties and CD8+ lymphocytes presenting a secretory profile of cytokines have been identified [24], both unable to recognize the antigen in its soluble form.

Like CD4 (+) T cells, under particular conditions, also CD8 (+) T cells express different types of interleukins or gain suppressive activity [2]. Certainly, neither the heterogeneity of T cells nor the relative cytotoxic capacity of CD8 and CD4 cells is limited to the mentioned phenotypes. Regarding CD8+ T cells, the proliferative response prevails over its cytotoxic potential against cells infected by viruses, tumors, and allogeneic cells in different situations.

Recent studies have shown differences in the effector function of memory cells depending on their localization. While memory cells in the secondary lymphoid organs are generally non-cytotoxic, the cells in peripheral tissues show intense cytolytic activity. These observations follow the concept developed by Sallusto et al. [25], stating that centrally located memory cells expressing CCR7 occupy secondary lymphoid organs, whereas effector cells lacking CCR7 remain peripheral.
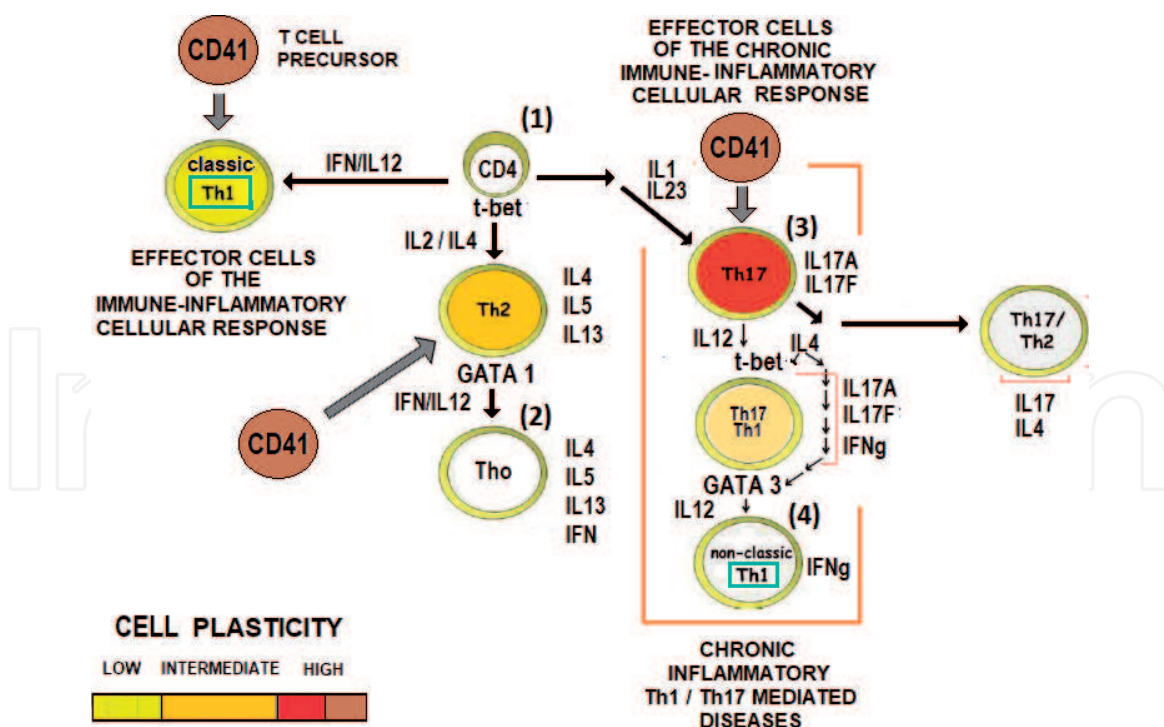
Figure 2.
T helper cell plasticity in inflammation. (1) Human Th1 cells originating from virgin CD41 cells in response to the coordinated activity of IFN and IL-12 induce stable expression of the transcription factor T-bet. (2) Human Th2 cells also originate from naive CD41 cells in response to the combined activity of IL-2 and IL-4, which induce stable expression of the GATA3 transcription factor. In the presence of IL-12, T-bet is upregulated in Th2 cells, which change to produce IFN (Tho). Human Th17 cells originate from a small subset of native CD41 cells present in the newborn thymus with receptors IL-23R, IL-1RI, and CCR6 and differentiate into mature Th17 cells in response to the combined activity of IL-1b and IL-23 in vitro. (3) In the presence of IL-12, the expression of T-bet is upregulated in Th17 cells, which change to the production of IFNγ. (4) In the presence of IL-4, GATA3 expression is upregulated in Th17/Th1 cells, which progress to nonclassical Th1 cells producing IFNγ.

4

No doubt that the immediate availability of effector memory cells upon infection in peripheral tissue is critical to the rapid control of pathogens. Centrally located memory cells represent a precursor T population with the ability to acquire effector properties after antigen-directed expansion.

Virgin T cells are the most homogeneous subpopulation of T lymphocytes. After activation in immunological synapses, lymphocytes differentiate into effector and memory cells with a broad phenotypic repertoire. Their properties may obey to different maturation programs, localization, and particularities in the antigenic presentation. Likewise, CD4 T cells of different lineage show phenotypic plasticity [26], eventually shifting into another T cell subset (**Figure 2**).

2. T-helper cell subtypes 1 and 2

The Th1 and Th2 are the most studied subtypes of helper T cells [27]. They can be distinguished by their characteristic cytokine secretion profile, Th1 classically producing IFNγ and Th2 producing IL4 and IL5, among other cytokines. Following CD4 lymphocyte characterization, different studies have found similitudes for the CD8 subpopulations called Tc1 (or type I) and Tc2 (or type II) [28]. At first sight, IL12 and IL4 appear critically involved in the differentiation to type I and II cells of the CD4 and CD8 subtypes, though the scenario is not that simple. Whereas IL21 suppresses type I differentiation and promotes type II differentiation, IL18 blocks IL4-mediated suppression of type II differentiation and promotes IL12 receptor expression and type I differentiation. Collectively, different experimental outcomes seem to support the existence of factors that stabilize, retard, or reverse Th1/Th2 polarization [27]. Likewise, as variations in the secretion profile of cytokines do not respond to the prototypical type I and II dichotomy, some authors have postulated that Th1/Th2 polarization is artefactual and may not resemble the in vivo situation [29].

Recently, transcription factors associated with lymphocyte differentiation like T-bet associated with the induction of Th1 differentiation have been characterized [30]. Certainly, TCD4 cells lacking T-bet are unable to produce IFNg but release large amounts of Th2 cytokines IL4 and IL5. Transcription factor T-bet induces the expression of the IL12 receptor and transactivates the IFNg gene. The IL12 derived from dendritic cells and macrophages triggers the release of IL12, which induces STAT 4 activation in developing Th1 cells by increasing IFNg level and IL18 receptor expression [31].

Dendritic cells are also involved in Th2 differentiation. Histamine acting on H1 and H2 receptors in dendritic cells downregulates IL12 expression and stimulates IL10 release, which with the participation of specific transcription factors (GATA-3 and STAT-6) promotes Th2 differentiation [32].

3. Follicular helper T lymphocyte

Described over a decade ago, T helper lymphocytes with follicle-positive tropism (ThF) differ from the classic Th1 and Th2 lymphocytes by expressing an array of factors essential to interact with follicular B lymphocytes [33]. The differentia-tion markers include CXCR5, CD25, CD69, CD95, CD57 (only in humans), OX40 (CD134), and CD40L (CD154). The homing pattern and functional characteristics of ThF have been the subject of intense investigation. The ThF interacts with B lymphocytes and modify the type of humoral response inducing long-lived memory B cells that release high-affinity antibodies [34].

Curiously, ThF cells dysfunction may induce systemic autoimmunity. The ThF cells comprise a TCD4+ subpopulation restricted to the B areas of the lymphatic organs, critically involved in the events following the interaction of dendritic cells with the virgin T lymphocytes in the secondary lymphatic organ T zone [35]. The development of follicular homing capacity by activated T cell helper is the first event in the generation of ThF cells. Virgin T cells expressing CD62L and CCR7 enter the secondary lymphatic organs in the T paracortical lymphoid region, and T-lymphocyte activation induces sub-sensitivity to lymphoid chemokines along with an increase in follicular chemokines CXCL13 (also known as B cell-attracting chemokine BCA-1 or B lymphocyte chemoattractant BLC) [36].

Activated ThF and lymphoblast B lymphocytes express the CXCR5 receptor, which confers follicle-positive tropism, and the stroma and dendritic follicular cells express the ligand CXCL13. Follicular dendritic cells supply proliferative, antiapoptotic signals, and ThF lymphocytes undergo changes increasing antigenic specificity and promote the differentiation of lymphoblasts into plasma cells or B lymphocytes with memory. The antigen-dependent T-B interaction is critical in triggering the humoral immune response [37]. The T-B collaboration is essential to generating short-lived plasma cells and inducing the germinal center where they trigger isotype change and somatic hypermutation, yielding high-affinity long-lived plasma cells and memory cells [38].

Regarding ThF relationship with Th1, Th2, and Th17 subpopulations, some authors mention that ThF cells produce IL4, IFNγ, and IL17, respectively, associated with them [39].

4. T helper subtype 9 (Th9) cells

Certain inflammatory conditions give rise to the T helper subtype 9 (Th9) cells of unknown functional contribution to the immune response [40, 41]. The in vitro development of effector cells specific to constituents of oligodendrocytes (myelin oligodendrocyte glycoprotein) Th17, Th1, Th2, and Th9 allowed evaluating the encephalitogenic activity in adoptive transfer. All Th1, Th17, and Th9 subpopulations but not Th2 successfully induced experimental allergic encephalitis [23]. The Th9 cells might express varied chemokine patterns involved in different immune responses. Their effector function balanced by regulatory T cells induces regulatory activity restoring homeostasis. This recently described Th9 subset of helper lymphocytes may escalate chronic inflammation under certain conditions independently from Th1, Th2, Th17, and regulatory T cells [42].

5. T helper subtype 22 cells

Another LT helper subpopulation, the Th22, has been recently identified in epidermic infiltrates in a variety of inflammatory skin disorders, including psoriasis [43]. They secrete IL22 and TNFα but not IFNg, IL4, or IL17, and their clones derived from psoriatic patients are stable in culture, exhibiting a distinctive transcription profile compared with the already mentioned subpopulations. Secretion profile includes fibroblast growth factors and chemokines potentially involved in angiogenesis and fibrosis [44].

6. T helper subtype 17 cells

Differentiation of Th17 cells, like Th1 and Th2 cells, requires the co-participation of CD28 and ICOS after the initial stimulus derived from antigenic recognition via

the TCR complex (TCR, CD3, ζ chains) for differentiation from virgin CD4+ T cells [45]. Ivanov and colleagues suggested that the nuclear receptor ROR gamma T is the key transcriptional factor [46] in the differentiation of the Th17 lineage. The Th17 cells producing IL17 induce inflammatory responses [47].

Differentiation to Th17 requires IL6, TGFβ, and IL23 [48], whereas IL1 and TNFα might be involved in Th17 maturation. According to this model, IL27, another member of the IL12 family, programs the TCD4+ cells to differentiate to Th1 inducing the expression of IL12Rβ2. The IL12 is required for the differentiation of the programmed cells into Th1 cells producing IFNγ. In turn, IL23, a member of the IL12 family [49], triggers the proliferation of Th1 cells from memory cells and induces the development of inflammatory Th17 cells [50]. Conversely, IL27 inhibits differentiation to Th17 cells by an unknown mechanism suppressing inflammation. The relative amount of IL6 and TGFβ in the cellular microenvironment is crucial to the severity of inflammation [51].

The proinflammatory cytokine IL-17, originally named IL-17A, has been the subject of intense research since its discovery in 1993 [52]. Interest in this cytokine increased considerably when its production by a specific subset of CD4 + T cells, the so-called Th17 cells [53], was reported. Nevertheless, Th17 lymphocytes can change their phenotype to Th1 or Th2 cells depending on the dominant cytokines [2, 54]. **Figure 2** illustrates how this plasticity can influence arthritis and cardiovascular risk.

Other immune cells subsets can also synthesize and express IL-17, including CD8 + T cells (CD8 + IL17 T-cell, or Tc17). Differentiation of CD8 (+) T cells depend on the antigen, co-stimulatory molecules, cytokines, and transcription factors inducing them to progress to Tc1, Tc2, Tc9, Tc17, or TCD8 [55].

Since Th17 hyperactivation is responsible for the Th17/Treg imbalance in certain pathologies, IL-17A might be considered a potential therapeutic target in modulating Th1 activity enhancing the regulatory response [56].
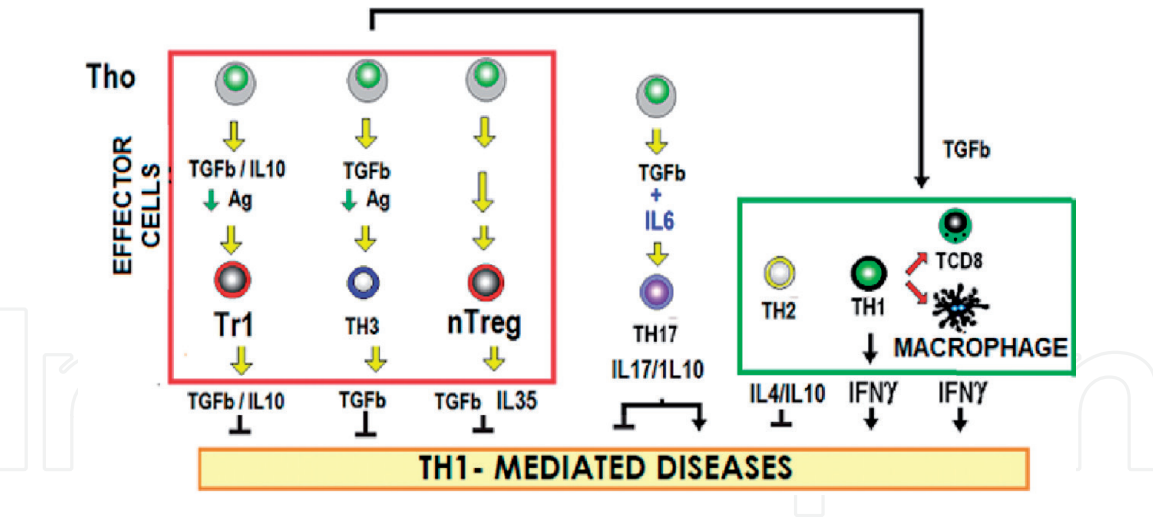
7. Regulatory T cells

Following Th3 cell identification and characterization based on their functions in the intestinal mucosa, many studies investigated the phenotypic characteristics of conventional Treg cells in different tissues and pathological situations. The Th3 cells (CD4+ TGFβ +) and the Foxp3+ can be induced by oral tolerance, and the TGFβ released by iTreg prevents experimental colitis [57]. Though regarded as separate lineages, the induced Treg (iTreg) and Th3 cells are substantially superimposed.

Regulatory T cells and maintenance of self-tolerance rely on natural Treg cells, typically expressing CD4, CD25, and Foxp3. They develop in the thymus and recognize specific autoantigens [58].

The Treg-induced cells (iTreg), another subset of Treg cells, are also generated in the periphery during an active immune response. In fact, CD4 + CD25− cells in the periphery can be converted, in the presence of TGFβ and IL10 into CD25 + CD4 + Foxp3 + cells. The iTreg cells induced by IL-10 are called Tr1 cells and if induced by TGFβ are called Th3. One subpopulation of nTreg expresses activation markers suggesting that it comprises autoreactive Tregs continuously activated by tissue autoantigens.

Three suppression mechanisms, not fully elucidated, have been proposed to explain the inhibitory actions of Treg cells on activated T cells. These are the contact-dependent inhibition between Treg and effector cells, the consumption and limitation of growth factors like IL-2, and the inhibition of LT effectors by the production of soluble inhibitory cytokines (TGFβ, IL-10, and IL-35) and CTL4 ligands of the Treg which interacts with the CPA molecules [59].

Figure 3.
Modulation of T lymphocyte function by TGFβ factor and its importance in Th1-mediated diseases. TGFb released by different types of regulatory cells modulates the inflammatory activity of all effector cells, Th1 cells included.

The T-regulatory activity (Treg) is pathologically low in both psoriasis and atherosclerosis [60]. The activity of pathogenic T cells is regulated by Treg cells activity via IL-10 and TGFβ [61]. The TGFβ inhibits Th1, and Th2 differentiation favors Th1 and Th17 hyperactivity [62] in both pathologies [60]. The increase in TGFβ [63] was reported inversely correlated with cardiovascular and psoriatic severity.

The critical role of TGFβ and Treg cells was evidenced by the finding that TGFβ-deficient mice developed multiple inflammatory diseases [64–66].

Both nTreg cells and Tr1-induced cells are able to produce IL10. The relevance of IL10 was evidenced by the specific blocking experiments of lymphocyte IL-10 triggering protection against inflammatory processes. The Tr1 cells expressing IL-10 require the presence of TGFα [67]. Regarding Th2-mediated counterregulation, the Th2 produces anti-inflammatory IL-4, IL-5, and IL-13 which decrease Th1 cells activity. The proinflammatory, metabolic, and systemic mechanisms that operate in the pathogenesis of psoriatic disease may explain the accelerated atherosclerotic process in these patients (**Figure 3**). Serum level of proinflammatory cytokines can increase cell-mediated immunity, which upon decreased regulatory Th2 activity and Treg level promote endothelial infiltration of inflammatory cells and plaque formation [68].

8. Conclusions

The heterogeneity of the T cells in general and TCD4 helper, in particular, may reflect divergent pathways in response to epigenetic factors or different stages of a unique differentiation pathway. Adhesion molecules, e.g., LFA1 and ICAM, CCR and CXCR chemokine receptors, and activation molecules, among others of undetermined function, reflect the transition.

The heterogeneity may obey to a programmed developmental process or to microenvironmental stimulation. Immunosuppressive or stimulatory signals like cytokines seem crucially involved though both may participate. This information is expected to shed light on the possible pathogenic role of Th cells in human inflammatory diseases beyond the Th1/Th2 paradigm.

The relationships between the classic Th1/ Th2 and the more recently defined Th17/iTreg/ Tfh/Th9 cells and effector-regulatory cell interactions need clarification regarding their pathogenic role in human inflammatory diseases.

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