Review Article

T Helper Subsets, Peripheral Plasticity, and the Acute Phase Protein, \( \alpha 1 \)-Antitrypsin

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The traditional model of T helper differentiation describes the naïve T cell as choosing one of several subsets upon stimulation and an added reciprocal inhibition aimed at maintaining the chosen subset. However, to date, evidence is mounting to support the presence of subset plasticity. This is, presumably, aimed at fine-tuning adaptive immune responses according to local signals. Reprograming of cell phenotype is made possible by changes in activation of master transcription factors, employing epigenetic modifications that preserve a flexible mode, permitting a shift between activation and silencing of genes. The acute phase response represents an example of peripheral changes that are critical in modulating T cell responses. \( \alpha 1 \)-antitrypsin (AAT) belongs to the acute phase responses and has recently surfaced as a tolerogenic agent in the context of adaptive immune responses. Nonetheless, AAT does not inhibit T cell responses, nor does it shutdown inflammation per se; rather, it appears that AAT targets non-T cell immunocytes towards changing the cytokine environment of T cells, thus promoting a regulatory T cell profile. The present review focuses on this intriguing two-way communication between innate and adaptive entities, a crosstalk that holds important implications on potential therapies for a multitude of immune disorders.

1. Introduction

The necessity to defend against a diverse world of pathogens, toxins, or transformed cells requires different types of immune responses in order to overcome a pathological entity while maintaining tolerance towards self-tissues. During evolution, vertebrates developed lymphocytes that bare combinatorial T cell receptors (TCR) and B cell receptors (BCR) in order to overcome the enormous and evolving variety of antigenic events. An accurate adaptive response must accommodate the type of pathogen, its mechanism of intrusion, and the tissue that is affected. The response must be tightly regulated as undesirable collateral damage from autoreactive T cells and antibodies can result in autoimmune disorders and hypersensitivity responses, some as common as allergies. Allograft transplantation is another platform in which the activity of the adaptive immune response is the target of therapeutic manipulation. A rigid determination of the type of immune response, without retaining flexibility or regulation of an activated T cell and an appreciation of the changing environment along the adaptive immune response, can result, on the one hand, in an often lethal organ failure associated with the site of infection, or, on the other hand, promotion of autoimmunity that follows an infection.

Endowing the immune system with local communication capacity through a diverse array of cytokines represents an important mechanism for an environment to control T cell responses. T helper cells initially differentiate according to local cytokine composition, resulting in different subsets of CD4\(^+\) T helper cells. The composition of cytokines is so influential that even a subtle change in one of the components, such as IL-6 in a TGF\(\beta\)-rich environment, can facilitate the differentiation of a T helper (TH) subset from a regulatory T cell to an aggressive TH17 effector cell. On top of this apparent complexity, one should note that, to date, the number of established TH subsets is rising; different helper cells appear to conduct a variety of events, such as regulation or enhancement of inflammation, activation of phagocytes,
induction of specific cell migration, stimulation of antibody production, or promotion of class switching in activated B cells.

With such a myriad of TH subsets, it becomes more tangible to appreciate the possibility that each TH subset does not necessarily represent its own final differentiation state and that some plasticity exists based on the immediate environment in which activated TH cells roam. As such, we chose the acute phase response to signify a profound environmental change during an adaptive immune response. Within this state of elevated systemic inflammation, it appears that some proteins exert immunomodulatory activities of which a few are indicative of peripheral TH cell plasticity, switching between subsets of TH cell according to the changing environment. One of these proteins, α1-antitrypsin (AAT), has recently been recognized as a tolerogenic agent, changing the course of hazardous adaptive processes (e.g., type I autoimmune diabetes) towards active antigen-specific immune tolerance.

In this review, we discuss the various CD4+ T helper subsets known to date and the signals required for their development. In addition, innovative reports of reprogramming of already differentiated T helper cells towards different helper subsets, and the mechanism allowing the plasticity of helper cells, are presented.

2. A Plethora of Helper T Cell Subsets

2.1. Traditional Helper T Cell Subset Classification: TH1/TH2. Distinguishing between TH1 and TH2 subtypes was made possible in the late 70s based on two major cell properties: the property of adhering to nylon wool columns and the ability to help B cells produce antibodies, respectively [1]. Mosmann et al later expanded on the classic TH1/TH2 model [2] and in 1986 introduced several pivotal cell responses to better represent the molecular polarization of helper T cell subtypes: TH1 cells were described as helper T cells that produce interferon-γ (IFNγ) and interleukin-2 (IL-2), while TH2 cells were described as helper T cells that secrete B cell stimulating factor 1 (BSFI), later termed IL-4 and identified as the factor responsible for driving B cells to produce IgG1 and IgE.

The behaviors of TH1 and TH2 in the larger framework of adaptive immune responses were further studied, allowing a more context-dependent classification, that is, the identification of TH1 cells as predominating in the immune response towards intracellular pathogens, in which the helper T cell will promote other local T cell responses by secreting IL-2 and activate local macrophages by releasing IFNγ, and the identification of TH2 cells as predominating in the immune response towards extracellular pathogens, such as helminths, by using a particular set of B cell-activating cytokines and promoting the production of clonal antibodies, such that the antibodies will target the pathogens and either neutralize them, dock the complement system onto them, or mediate local degranulation of mast cells and eosinophils. In this regard, unlike cytotoxic T cells, helper T cells never directly kill a target but rather activate local destructive macrophages, drive B cell processes towards an effector humoral response, and fuel neighboring cytotoxic T cells with IL-2 once both these cells become locally attracted to an antigen-rich site (illustrated in Figure 1).

Polarization of TH0 towards TH1/TH2 cells occurs following the exposure of TH0 cell to distinct sets of cytokines in its immediate environment. These cytokines originate primarily from professional antigen presenting cells (pAPCs). pAPCs that encounter a pathogen and engulf related antigens stimulate T cells by forming a TCR-MHC class II complex, with the provision that costimulatory signals are also satisfied; then, particular sets of cytokines may be produced so as to divert the course of T cell differentiation towards either TH1 or TH2.

The major factor that promotes differentiation of TH0 towards TH1 is the dimeric cytokine, IL-12. A lack in the subunit IL-12p40 results in impaired TH1 responses and in an increased susceptibility to intracellular pathogens, such as Leishmania major [3, 4]. In contrast, the major cytokine for the differentiation of TH0 into TH2 is IL-4, which will induce the release of IL-5 and IL-13, as well as additional IL-4 [5]. These TH2 cytokines stimulate B lymphocytes towards further maturation, antibody isotype switching and production, somatic hypermutation, and a memory phenotype. In addition, the cytokines will initiate intracellular signals that will induce transcription of genes, which will execute and maintain the consequential T helper subset programming [6]. A transcription factor that is activated downstream to the TCR signal nuclear factor of activated T cells (NFAT) has the ability to bind to either infg or il4 promoters, committing the cell to either TH1 or TH2 phenotype [7]. Additional intracellular signaling pathways activate one of two master transcription factors, either T-bet or GATA-3, which will further consolidate the T helper fate towards being either TH1 or TH2, respectively.

How are these signaling pathway distinctions made? Two signal pathways activate the TH1 transcription factor, T-bet. Following activation of the IL-12 receptor (IL-12R), STAT4 is activated and T-bet is upregulated [8, 9]. T-bet, in turn, activates the transcription of IL-12Rβ2 and IFNγ,
which then activate STAT1 that also upregulates the transcription of T-bet. This sequence of events enhances additional IFNγ transcription, completing a TH1 differentiation positive feedback loop [10]. T-bet acts in synergy with RUNX3 in order to activate IFNγ production but at the same time inhibits IL-4 transcription; reciprocity between TH1 and TH2 phenotypes is thus achieved [11]. In contrast, for the differentiation of TH0 into TH2, IL-4R signaling activates STAT6, which upregulates the transcription of GATA-3 [12–13]; IL-4 production requires the activation of c-Maf [15], GATA-3 then activates the transcription of IL-5 and IL-13; IL-4 production requires the activation of c-Maf [15], which is activated either by GATA-3 or by the TCR signal itself. Thus, GATA-3, in TH2, and T-bet, in TH1, achieve an obligatory reciprocal effect, which is strengthened both by auto-positive-feedback loops and by reciprocal inhibition of the opposing components [3, 9, 14, 16].

2.2. A Third Type of Helper T Cell Emerges: TH17. Initially, TH17 cells were termed “IL-23-derived autoreactive CD4 T cells” [17]; subsequently, they were identified as “IL-17-producing T helper cells” [18] and then, finally, TH17 cells [19]. The definition of TH17 lineage had followed the discovery of the cytokine family, IL-17, initially coined CTLA-8 family of cytokines [20, 21]. To date, IL-17 is a common name used to describe the IL-17 family of cytokines, of which the most studied ones are IL-17A and IL-17F; these two share the highest homology amongst the family members and can form a homo- or heterodimer that binds to a single IL-17 receptor (IL-17R) [22]. While the levels of IL-17 and IL-17R correlate with enhanced antimicrobial responses, as observed primarily in mucosal tissues (where IL-17 was found to be secreted from γδT cells [23]), the involvement of IL-17 was also exemplified in several autoimmune disorders [24]. In fact, in as far as autoimmune disorders are regarded, TH17 cells were shown to be involved in some pathologies that were, until then, considered as TH1-related. Examples include EAE, rheumatoid arthritis, and lupus, colitis, in addition to other unwanted immune responses such as acute allograft rejection [17, 25–27].

Interestingly, the distinction between TH1 and TH17 systems was initially made possible by the more in-depth characterization of IL-23 and IL-12. Both these cytokine share the same IL-12p40 subunit. This subunit was targeted, appropriately at the time, in order to study TH1 responses; however, when the individual unique adjoining subunits of IL-12 and IL-23 (IL-12p35 and IL-23p19, resp.) were deleted in mouse genomes, the distinct involvement of TH1 and TH17 cells in autoimmune disorders was unearthed [17, 26]. Nonetheless, it later became apparent that IL-23 alone is not sufficient in order to induce differentiation of TH0 cells towards TH17 cells. It appears that the combination of IL-6 or IL-21, together with TGFβ, is required in order to advance a TH17 phenotype. In addition, IL-1β and TNFα exert an amplifying effect on the TH17 cell population, while IL-23 was found to be primarily required for the survival of the already differentiated TH17 subset [28, 29].

Differentiation into TH17 cells requires a master transcription factor, the orphan nuclear receptor, RORγT (RORC, in humans), or RORα, which also drives the cells toward a TH17 phenotype [30]. While transcription of RORγT was shown to be dependent on STAT3, which is activated by IL-23 [31], the mechanism by which RORγT and RORα induce TH17-related genes has yet to be determined.

2.3. Regulatory Helper T Cells. In order to regulate the effector arm of T cells, for example, so as to avoid collateral damage or discourage an autoimmune response, two major mechanisms had evolved: central tolerance, in which putative T cell clones that recognize self-antigens undergo apoptosis in the thymus before reaching secondary lymphoid organs, and peripheral tolerance, in which an effector T cell response is counteracted at the time and location of its activation, based on local factors.

For central tolerance, naturally occurring regulatory T cells (nTreg) develop in the thymus, and their specific depletion results in autoimmune syndromes [32]. Indeed, this subtype was discovered based on the observation that neonatal thymectomy results in autoimmune disorders [33, 34], and reconstitution of CD4+ T cells cancels that phenomenon [35, 36]. These cells are characterized by the expression of surface CD4 and, without an apparent need for activation, surface IL-2Rα (CD25). The source of IL-2, required for Tregs, is the activated effector T cell. Therefore, counter regulation of excessive T cell activities actually increases with T cell activation and clonal expansion, as IL-2 levels rise [37]. The dependence of immune regulation on an intact thymus implies that there exists a development of two different CD4+ T cell entities in the thymus: effector CD4+ T cells, among which might persist some autoreactive clones that had escaped central tolerance negative selection, and CD4+ regulatory T cells, capable of inhibiting the effector CD4+ T cells in the periphery.

Controlling the regulatory profile of Tregs, foxp3 was shown to be the major transcription factor of these CD4+CD25+ T cells. Foxp3 was initially identified as essential for prevention of autoimmune diseases. Indeed, in mice, mutated foxp3 is associated with unregulated T cell activities, and, in humans, mutations in foxp3 correlate with an X-linked syndrome comprised of immunodeficiency polyendocrinopathy and enteropathy (IPEX) [24, 38]. Up to the time of these observations, foxp3 was considered unique to nTreg cells; however, ectopic expression of foxp3 was found to be able to drive non-Treg CD4+ cells toward a Treg phenotype [39], and extrathymic elevated levels of TGFβ or retinoic acid were found to induce foxp3+ T cells. Thus, such T cells were termed inducible Tregs (iTregs). Importantly, TGFβ has been shown to require that the rest of the local cytokine milieu does not contain excessive amounts of IL-1β or IL-6.

Among the mechanisms in which Tregs can suppress T effector cells are the regulation of APC stimulatory molecules, for example, by expressing CTLA4 that will compromise CD28 signaling, by induction of T cell apoptosis, by deprivation of IL-2, and by secretion of inhibitory cytokines, such as IL-10 and TGFβ, which in turn stimulate foxp3 expression in T cells [40].
Unlike Tregs, which display the classical CD4+CD25+foxp3+ phenotype, other types of immunosuppressive T cells were described. Two such cell types can have immunoregulatory functions comparable to those mediated by Tregs and are termed TH3 and regulatory T-1 (Tr1) cells. TH3 cells were suggested to induce tolerance following oral administration of antigens to mice. These cells mediate suppression by releasing large amounts of TGFβ, which in turn can promote regulation by promoting the expansion of iTregs [41]. Tr1 cells, on the other hand, were described as IL-10 producing T cells and, much like foxp3-positive Tregs, they suppress effector T cell proliferation [42]. Differentiation of Tr1 is mediated by IL-10, and the expansion of the population requires IL-27 [43]. The significance of being able to produce IL-10 as a component of T cell suppression was clarified by patients with severe combined immunodeficiency, which exhibited high levels of IL-10-producing donor-derived T cell clones that had mediated tolerance and prevented graft versus host disease (GVHD), despite mismatched HLA and the presence of host-reactive T cells. This phenomenon indicates that peripheral tolerance may be maintained by these IL-10-producing T suppressor cells [44]. In addition, Tr1 cells can be antigen-specific, and reduction in the levels of Tr1 cells can result in autoimmune disorders, such as pemphigus vulgaris, type 1 autoimmune diabetes, rheumatoid arthritis, and autoimmune hemolytic anemia [45]. Moreover, adoptive transfer of Tr1 cells has been shown to promote tolerance in the context of autoimmune disorders and during islet allograft transplantation [46]. While much of the suppression exerted by Tr1 cells relates to IL-10 release [47], they can, like TH3, also secrete TGFβ. Therefore, Tr1 and TH3 were suggested to promote tolerance by manner of synergism with iTregs [45].

2.4. Non-TH2 Cells That Promote B Cells: Follicular T Helper Cells (TFH). According to the classic TH1/TH2 classification, TH1 is primarily restricted to cellular responses and TH2 to humoral responses. However, in TH1 responses, IFNγ can also induce B cell class switching towards IgG2a antibodies, and TH1-related antibodies facilitate anti-intracellular pathogen responses by opsonization of infected cells. Moreover, mice deficient in TH2 development, as obtained using STAT6 knockout mice that are essentially lacking IL-4, were unable to produce IgE, which is critical for the immune response against helminthes; nonetheless, these mice did respond to infections by producing IgG1, IgM, and IgG2a [48]. Thus, there are helper cells that are distinct from TH2 cells and can help promote B cell responses.

In order to ascertain that TFH are distinct from TH1/TH2, mice that lack the major genes encoding T helper subsets TH1, TH2, and TH17 were studied, confirming that TFH are indeed a unique subset [49], which express unique phenotype markers. Interestingly, these markers help to understand some of the mechanisms by which TFH facilitate B cell responses in lymph nodes. Indeed, these cells were termed follicular T helper cells because of their location in the lymph node follicle [50, 51]. They can be identified by high expression levels of ICOS, CXC5, and the CXC5-inducer, BCL-6 [52, 53]. Expression of this particular set of genes further downregulates non-TFH gene transcription [54]. TFH require IL-6 for their differentiation, as well as IL-21, which is necessary for expression of BCL-6 [53, 55, 56]. While circulating activated helper T cells have but transient CXC5 expression, TFH express CXC5 in a sustained manner.

While T cells normally express CCR7 and are thus guided to the T zone in lymph nodes, B cells localize to B cell follicles via CXC5 and its cognate chemokine CXCL13, which is released from germinal center stromal cells. Interestingly, TFH-like ICOS+ extrafollicular CD4+ cells were observed immediately outside germinal centers and had correlated with autoreactive antibody production [57, 58]. Indeed, pre-TFH may encounter B cells due to their upregulation of CXC5 (following antigen presentation by dendritic cells (DC)), while activated B cells increase CCR7 expression, therefore enabling migration toward each other and facilitating an encounter between B cells and pre-TFH in the B-T cell border. There, B cells present the internalized and processed BCR-specific antigen to T helper cells. Since the TFH are already activated by DC with the same antigen and are activated in a CD80/86-CD28-dependent manner [49, 59], they may serve as a second validation step before mounting potentially hazardous antibody production. By this, the foreign origin of the antigen is further verified, as CD40L and ICOS are presented to the cognate B cell, which is dependent on these signals for optimal activation, isotype switching, and survival.

TFH in the germinal center can thus facilitate class switching from IgM to IgG1, IgG2a, or IgA, based primarily on cytokine secretion. There, B cells are further positively selected by TFH according to their affinity to antigens during somatic hypermutation [60, 61]. In addition, TFH also increase survival of B cells by secreting IL-21, which in turn upregulates BCL-6 in both the B cell and the TFH. Failure to regulate antibody production by TFH can result in systemic autoimmunity, since antibodies can be produced against self-antigens. In a study that examined a mouse model of systemic lupus erythematosus (SLE), autoantibody production correlated with the presence of TFH; accordingly, anti-dsDNA antibodies were mounted [61]. Under these settings, suppression of TFH cell differentiation by mouse strain crossing with either BCL-6+/− or SAP−/− had reduced the emergence of SLE-like features but resulted in germinal center formation defects and immunodeficiency disorders [61]. In addition, adoptive transfer of TFH resulted in increased level of germinal center formation and also correlated with an SLE-like phenotype in immunized naïve wild-type mice [62].

2.5. TH22: Mediators with Epithelial Barriers. IL-22 is a member of the IL-10 cytokine family, originally identified in activated T cells and considered a TH1-related cytokine. Soon after the description of TH17 cells, IL-22 was reported to be expressed by IL-17-producing RORγT-expressing cells and was accordingly associated with TH17 cells [63, 64]. Its receptor, IL-22R, consists of two chains, one is the IL-22 receptor 1, and the other is the IL-10 receptor 2, which is also...
a component of IL-10 receptor. However, IL-22 is not a ligand for IL-10 receptor.

IL-22R is absent from immune cells. It is expressed mainly by epithelial barriers such as skin, kidney, respiratory tract, and gastrointestinal tract [65]. On the other hand, only hematopoietic cells express IL-22; it is expressed by activated T cells and, to a lesser extent, by NK cells [66], CD8 T cells [67], and γδ T cells [68]. Therefore, IL-22 appears to take part in the crosstalk between immune cells and nonimmune cells, particularly at important sites of mucosal immune barriers.

IL-22 was depicted both as an immune-regulatory mediator, as well as a pathogenic cytokine, as it displayed a correlation with severity of chronic inflammation and with skin autoimmune disorders [69, 70]. IL-22 is involved in airway inflammation [71], as well as protection from liver inflammation [72], activation of fibroblasts, and wound repair [73]; IL-22 is also involved in rheumatoid arthritis [74] and systemic sclerosis [75]. Human CCR6 CCR4 CXCR3 CCR10 memory T cells, considered as TH17-enriched cells, have a subpopulation of cells that express IL-22 and IL-13, but not IL-17, IFNγ, or IL-4; thus, TH22 are distinct from TH1, TH2, and TH17 subpopulations. However, similar to TH17 cells, RORC and aryl hydrocarbon receptor (AHR) signaling both appear to be essential for TH22 accumulation [76]. Nonetheless, although the main source of IL-22 is indeed TH22 cells, it can be also found expressed in TH1 and TH17 cells together with IFNγ or IL-17, respectively [77].

The cutaneous association of TH22 cells is quite prominent. CD11c+ dendritic cells help polarize CD4+ cells into TH22 by secreting TNFa and IL-6, but it appears that, preferentially, cutaneous DCs, rather than monocyte-derived DCs, will induce TH22 differentiation (62) [77]. TH22 cells were also found to present a skin-homing molecule, cutaneous lymphocyte-associated antigen (CLA), in addition to the CCR6, CCR4, and CCR10 receptors [69, 77]. In vitro, TH22 cells promote wound healing processes in keratinocytes [78], and, in the skin of patients with inflammatory disorders, such as psoriasis, atopic eczema, and allergic contact dermatitis, TH22 were found to infiltrate into the epidermis and affect wound healing and tissue repair processes by secreting fibroblast growth factor (FGF).

2.6. TH9. Up until recently, IL-9 was defined as TH2 cytokine, secreted from mast cells and T cells, correlating with levels of IL-3, IL-4, and IL-5, and associated with antiparasitic responses [79]. IL-9 was found to correlate with disorders such as autoimmunity, allergy, viral and intracellular infections, cancer, and transplantations [79–81]. Later studies showed that IL-9 can also be found produced by Tregs, TH1, and TH17 cells [79]. Finally, a unique subset of cells specialized in IL-9 production has been identified, TH9 cells [82].

TGFβ, which is practically sufficient to drive CD4+ toward iTreg differentiation (at low IL-6 conditions) or TH17 differentiation (at high IL-6 conditions), is also the cytokine that determines TH9 maturation. The major TH2 cytokine, IL-4, that was initially reported to synergize with TGFβ in order to induce IL-9 in CD4+ cells [83] appears to be but a second signal for the generation of TH9 [82]. Indeed, it was found that while IL-4 is able to inhibit TGFβ-induced of foxp3 expression IL-4-derived GATA-3 is not inhibited by TGFβ [84]. In another study, TH9 was shown to be induced by IL-10 in an IL-4-independent manner [85]. The IL-4-inducible factor, interferon regulatory factor 4 (IRF4) initially identified with TH2 cells and then as a TH17 transcription factor, was shown to have a significant role in the differentiation of TH9 cells [81]; IRF4 represses T-bet and foxp3 in T cells [86].

IL-17E, also known as IL-25, is another important cytokine for the development of TH9 cells and for IL-9 production. In vivo, IL-25 was found to correlate with severity of an IL-9-related disease model, that is, mouse allergic lung inflammation [87]. Accordingly, TGFβ and IL-4-derived TH9 cells upregulate the receptor for IL-25, IL-17RB, and IL-25 signaling inducing IL-9 expression in a TGFβ-dependent IL-4-independent manner; by this, it is suggested that IL-25 may serve as an alternative synergic signal to TGFβ towards TH9 development.

Other cytokines that augment TH9 differentiation include type I interferons, IL-1, and IL-33. Both IFNγ and IFNγ enhance TH9 differentiation through the induction of IL-21, which also promotes TH17 and TH1, while IFNγ, the prototypical TH1 cytokine, suppresses IL-9 production [29, 49, 83, 84]. IL-1 and IL-33 were shown to induce IL-9 production [88, 89], while IL-23 has an inhibitory effect on IL-9 levels [90].

Like TH1, TH2, TH17, and Treg cells, it became necessary to identify a master regulator gene for the TH9 subset; indeed, none of the major T helper transcription factors, that is, T-bet, GATA-3, foxp3, or RORγT, are expressed by TH9 cells. Moreover, a unique transcription factor, PU.1, was found to induce differentiation towards TH9 cells. Accordingly, overexpression of PU.1 promotes IL-9 transcription and is a prerequisite for TH9 differentiation both during in vitro stimulation and during the in vivo course of the allergic pulmonary inflammation model [91].

A summary of major helper T cell subsets and the cytokines that promote their development is presented in Figure 2.

3. Plasticity and Reprogramming of T Helper Phenotypes

In recent years, evidence is mounting to suggest that particular cytokine combinations may affect not only the differentiation of naïve TH0 cells but also that of differentiated T cells towards various helper subsets. This phenomenon is termed “T cells plasticity” and is quite significant considering that the adaptive response may switch from one type to another. To counter such plasticity, helper T cells secrete cytokines that maintain their subset phenotype. Thus, termination of an existing response and initiation of a new type of response are practically restricted due to this positive feedback loop.

Survival of a host is dependent upon an optimized and appropriate choice of strategy within adaptive immunity. This is most evident, for example, in the case of the response chosen towards intracellular and extracellular pathogens.
Thus, the ability of differentiated T helpers to alter their phenotype when opposing signals develop is detrimental, and in situ effector cells require turning the subset master gene off while turning the transcription of a new master gene on.

Such plasticity is observed in the case of iTregs, as they turn into TH17: both types of cells depend on TGFβ, either alone (for iTreg), or with IL-6 (for TH17). Thus, in a TGFβ-rich environment, naïve T cells can differentiate into either one of the subsets according to the level of the acute phase cytokine, IL-6. This dichotomy in differentiation into either a pathogenic TH17 or a tissue protective Treg was demonstrated by Bettelli and colleagues, in an EAE mouse model [92]. Retinoic acid (RA) also possess the capacity to alter the fate of a naïve T cell towards a helper T cell subset, as it preferentially promotes Tregs instead of TH17 cells; this is executed in an IL-2-dependent manner [93].

However, these two functionally antagonistic subsets are capable of switching phenotypes on-the-go: in a study by Xu et al., Treg cells not only contributed to the development of TH17 cells by secreting TGFβ but had also themselves re-differentiated into TH17 in an IL-6-rich environment [94]. Yang et al. showed that iTreg and nTreg cells are able to re-differentiate into TH17 cells [95]. In another study using a foxp3 reporter mouse, it was demonstrated that ex-foxp3 positive cells are capable to re-differentiation towards IFNγ- or IL-17-producing T effector cells [96]. The group also evaluated re-differentiation of Tregs into effector cells carrying a TCR which recognizes islet β cell antigens in nonobese diabetic (NOD) mice and in BDC2.5-derived cells and concluded that Treg reprogramming is obtained also in autoimmune environment and may participate in pancreatic islet destruction. Another study used isolated TH17 from BDC2.5 mice, which were already known to exacerbated diabetes similar to TH1 cells in NOD/SCID mice [97].

Oral infection by Toxoplasma gondii (T. gondii) results in increased TH1 effector population, together with decreased numbers of Treg cells. This effect is possible both by the reduction in IL-2 levels, required for the survival of Tregs, and also due to the re-differentiation of Tregs into TH1 effector cells, which resulted in exacerbated gut pathogenesis [98].

Unlike other T helper cell subsets, TFH are suggested to have greater plasticity. TFH were shown to migrate within the germinal center, where they serve as helpers for B cells following adoptive transfer [60], and to display some relationship with TH17 subsets. For example, activation of TFH by ICOS, which in turn activates the transcription factor c-Maf, assists in maintaining TH17 clonal survival, most probably by the secretion of IL-21 [99]. IL-6, on the other hand, is required for the development of both TH17 and TFH [49].

Re-differentiation of Treg cells towards TFH was also demonstrated. Using foxp3-GFP reporter mice, transfer of foxp3+ cells into CD3ε−/− mice was shown to create novel germinal centers within the Peyer's patches, although, inexplicably, not in the spleen or LN; in these germinal centers, foxp3+ cells remained in the T zone, while cells which lost their foxp3 were localized in the B cell follicle [100]. These cells were found to have TFH phenotype.

Interestingly, plasticity between TH17 and TH1, two major effector subsets, was demonstrated to occur in the absence of TGFβ: activation with IL-12 and IL-23 allowed for a switch from TH17 to IFNγ-expressing TH1 cells; these ex-TH17 TH1 phenotype was dependent on active STAT4 and T-bet [101].

TH2 cells appear to maintain the potential to re-differentiate into TH9 cells [82]. Veldhoen et al. cultured CD4+ cells with conditioned media from TH1, TH2, TH17, iTreg, and TH9 cells and observed that TH9 conditions did not differentiate naïve cells towards any subset other than TH9, and vice versa. Upon culturing IL-4-expressing TH2 cells, however, re-differentiation into TH9 was observed, at the expense of their TH2 characteristics, most probably due to stimulation with TGFβ. These outcomes depict a capacity to reprogram TH9 and TH2 subtypes, both, incidentally, highly important in the immune response against helminths.

TH1 and TH2 are well known for their reciprocal inhibition of differentiation. Nonetheless, a study of T cell responses towards the well-known TH1 inductive virus, lymphocytic choriomeningitis virus (LCMV), challenges this dogma. The study shows that TH2-committed cells can alter their TH2 phenotype following the trigger of their TCR by LCMV, after induction with IL-12 and type I/II interferons [102]; experiments using adoptive transfer of TH2 cells into infected mice demonstrated clear TH2-to-TH1 reprogramming. These TH2 cells upregulated TH1-associated genes, however, with persisting TH2 genes.

**Figure 2: T helper (TH) cells differentiation and reprogramming.** TH0 cell can differentiate into specific TH subsets (gray arrows) under the influence of cytokines, which on the one hand can promote differentiation into a specific subset (green arrows) and on the other hand block differentiation towards a functionally-opposing subset (red blocked arrows). In addition, differentiated TH cells may be reprogrammed to acquire a different TH phenotype (black arrows).
4. Epigenetic Regulation of T Helper Subset Genes

How does a T helper cell decide between maintaining its phenotype or rather allowing changes in its profile? Some studies describe the presence of epigenetic gene regulation that can override a programmed subtype.

One of the many mechanisms of transcription control involves changes in chromatin accessibility without modifying the primary genetic code. This can be obtained by methylation of the DNA molecule on the cytosine of a CpG segment within the DNA sequence. A methylated CpG will silence genes that require silencing in a particular cell or tissue. Methylation pattern is inherited; thus, it is maintained in the differentiated phenotype of cells.

Another mechanism of transcription control involves compacting or releasing the nucleosomal structure at a regulatory site in a gene, profoundly affecting chromatin accessibility. Modifications of the histone tails can result in either heterochromatin (for repression) or euchromatin (for activation) of transcription. The “histone code” of cells is more flexible than DNA methylation and can be changed in order to reopen or shutdown transcription of genes based on relevant signals.

Polarization of stimulated T cells with activated NFAT1 is maintained by altering the accessibility of NFAT1 to the chromatin of infg or il4 promoter in TH1 and TH2 cells, respectively [7]. Analysis of the infg gene shows that TH1 cells have H3k4me2-enriched histone modifications and increased CpG demethylation, thus allowing transcription of IFNγ; this is in contrast to TH2 cells, which display increased H3k27me3 (as opposed to H3k4me2) and excessive CpG methylation, counteracting the TH1 phenotype [103].

Global mapping of similar and other modifications, including H3k4me3 and H3k27me3, from T helpers of the TH1, TH2, TH17, nTreg, and iTreg subsets depicted some flexibility between subset-specific genes [104]. As expected, major cytokine promoters in each subset were indeed accessible to transcription in each appropriate cell type; for example, TH1, TH2, and TH17 were associated with H3K4me3 in infg, il4, il17, and il21, respectively. However, when examining transcription repression by H3k27me3, the situation appears to have become more complicated; while infg was rich in H3k27me3 in TH2 and TH17, this was not the case in nTregs. On the other hand, il4 promoter was associated with H3k27me3 in TH1 cells, rather than in TH17 and Tregs. TH17 gene products, namely, IL-17 and IL-21, were more conclusive in as far as all other T helpers exhibited reduction in their transcription via H3k27me3.

Interestingly, at least one aspect of the mechanism behind maintaining plasticity of T helper subsets was elucidated by analysis of the epigenetic modifications of T helper master transcription factors. For example, H3k27me3 modification in TH1 and TH2 cells silences foxp3 but is less abundant in TH17 cells. In contrast, the gene for RORC did not contain H3K27me3 in iTregs, unlike in other subsets, and nTregs had both H3K4me3 and H3K27me3, indicating some plasticity in the distinction between TH17 and Tregs. Dnase I hypersensitivity (HS), an indicator of permissive chromatin obtained by H3K4me, is associated with infg loci or il17a and il17f in TH1 and TH17, respectively. However, TH17 cells stimulated with IL-12 exhibited higher levels of H3K4me in the infg loci, in addition to H3K27me3 repression of il17a and il17f loci. These histone-remodeling modifications are dependent on repression of RORC by H3K27me3 in the rorc locus, as mediated by T-bet and STAT4 [105].

TH1 and TH2 main transcription factor genes, tbx21 and Gata3, were associated, as expected, with increased levels of H3K4me3 in the TH1 and TH2 accordingly. However, both had H3K4me3 and K3K27me3 in the opposite gene; this most probably allows the maintaining of a potential for a helper cell to establish a new phenotype. By reducing the abundance of K3K27me3, the promoter, now with only H3K4me3, may allow for a helper re-differentiation. This kind of epigenetic switch is known mainly to occur in multipotent stem cells that require the maintaining of genes in a repressed mode but poised for future activation [106].

5. The Implications of Elevated Acute Phase Protein, α1-Antitrypsin (AAT), on T Helper Cells

5.1. AAT Targets Non-T Cell Immune Cells and Modifies the Inflammatory Environment. AAT is a 52-kDa protein whose levels rise in the circulation during acute phase responses. It is primarily an anti-inflammatory agent, executing most of its activities by inhibition of inflammatory serine-proteases as reviewed in [107]. For example, neutrophils have been shown to be strongly affected by excess concentrations of AAT, as they rely on membrane neutrophil-elastase for extravasation and on degranulated elastase, cathepsin G, and proteinase-3 for further processing and activation of pivotal inflammatory molecules. Nonetheless, at high proximity, activated neutrophils will counter these activities of AAT by the release of oxidative radicals; these will readily neutralize the inhibitory capacity of AAT [108]. Indeed, oxidation of AAT by neutrophil-derived myeloperoxidase (MPO) leads to formation of IgA-AAT complexes, further reducing AAT activity to inhibit elastase [109]. In addition to oxidation by neutrophils, AAT may be oxidized by cigarette smoke. Although unable to inhibit elastase, oxidized AAT may gain inflammatory properties, leading to release of MCP-1, IL-6, IL-8, and TNFα, further allowing neutrophils and macrophages to spearhead towards their target tissues [110, III]. Indeed, oxidized AAT was detected in Alzheimer’s disease, heart failure, and premature rupture of the fetal membrane [112–114]. Despite reports attributing proinflammatory properties to oxidized AAT, Churg et al. have reported that oxidized AAT exerts anti-inflammatory activities, as it was able to reduce TNFα plasma levels in smoke-induced emphysema mouse model [115].

The oxidation of AAT may be reversible in the presence of reducing agents [116]. This may allow AAT to continue to protect tissues from excessive inflammation when it distances from the epicenter of a neutrophilic attack. Indeed, in the rare condition of genetic AAT deficiency, lung tissues of affected individuals exhibit an excessive number of neutrophils and
subsequently the enzymatic degradation of alveolar walls, resulting in emphysema [117].

Similar to neutrophils, macrophages have been shown to be functionally altered by locally elevated levels of AAT. The predominant motif, again, is a change towards an anti-inflammatory environment: a sharp rise in inducible production of IL-10, a dramatic reduction in stimulated levels of IL-6, and, under some conditions, elevated release of TGFβ [118–121]. Indeed, it has been postulated that AAT fits well in timing and spectrum of activities to act in the resolution phase of an inflammatory flare, a point in the immune response whereby the wound-healing aspects of innate immune cells reign. Yet, upon examining responses of DCs to elevated levels of AAT, the anti-inflammatory pretense of AAT changes; in its presence, DCs do not shut off all inflammatory responding genes. While they do express more IL-10 and less IL-6, they appear to display a semimature midrange costimulatory molecule profile and, most strikingly, a maintained expression of inflammation-stimulated CCR7 [122]. Accordingly, AAT-treated DCs migrate towards draining lymph nodes in a hastened manner, the outcome of which is an expansion of foxp3+ T helper cells, and the surfacing of a proposed immunological mechanism for the large number of reports on improved allograft survival during AAT treatment: beneficial changes in an EAE model [120], amelioration of disease markers in experimental RA [123], and profound reversal of the course of GVHD [124], ulcerative colitis [125], and type 1 autoimmune diabetes [126, 127]. Yet the most perplexing element within these attractive attributes of AAT is quite pivotal: AAT does not directly influence T cell responses.

The presence of any particular effect of AAT on T cells was examined in several studies. For example, human PBMCs were stimulated with various concentrations of IL-2 in the presence of AAT; then, IFNγ levels and cell proliferation were determined [128]. In this setup, AAT did not impair T cell proliferation nor did it alter IFNγ release. Similarly, mouse splenocytes were pretreated with AAT and stimulated with ConA. Again, proliferation and IFNγ release were unaffected by AAT. In contrast to lymphocytes, peritoneal macrophages that were stimulated with IFNγ and treated with AAT displayed reduction in nitric oxide release [129]. These setups combine innate and adaptive cells, limiting the ability to deduce the direct effect of AAT on T cell responses. Koulmanda et al. further examined the effects of AAT on T cells using CFSE labeled enriched T cells treated with anti-CD3 and anti-CD28 antibodies [126]. Again, AAT did not impair T cell proliferation or had any influence on acquisition of an activated phenotype. In as far as IL-2 levels are regarded, AAT was found not only to allow IL-2 release but also to enhance the levels of IL-2, as established in a coculture of OVA-stimulated DCs and OVA-responsive T cells [122]. Thus, it is by now assumed that the outcomes of AAT treatment, in which T cell subsets are altered in any way, is the result of changes experienced by innate cells that indirectly dictate to the T cells their preferential phenotype.

5.2. AAT and foxp3+ Regulatory T Helper Cells. The most notable indirect effect of AAT on T cells is the facilitation of foxp3+ Treg expansion. This attribute of AAT has been shown to persist across multiple immunological settings in which the progression of a given pathology is primarily antigen-driven. Treg expansion requires a particular cytokine milieu, that is, low levels of IL-1β [130], low levels of IL-6, and high levels of TGFβ [92]. These trends in cytokine levels are afforded by AAT in a highly consistent manner both in vitro and in vivo. Moreover, another inflammation-inducible molecule that remains highly expressed in the presence of AAT is IL-1Ra, which is only elevated by AAT in cells exposed to an inflammatory signal [131]. Thus, by adding a layer of active inhibition on the IL-1 pathway, AAT breaks the vicious cycle of the IL-1-perpetuated inflammatory flare which, at least in part, was responsible for downplaying immune tolerance.

Koulmanda et al. have shown that AAT-treated NOD mice exhibit a reduction in T-bet and RORγt transcription factors and that their expression of foxp3 was increased [126]. Accordingly, it was established that the autoimmune arm of pathology in the NOD mouse has been addressed by AAT as spontaneous diabetes was markedly diminished in treated NOD mouse cohorts, and the heightened response towards self-grafted autoreactive NOD islets was abrogated by preconditioning of the mice with AAT. Indeed, this latter outcome favors the possibility that a tolerant profile had been imprinted upon reactive T cell clones, perhaps so much as to suggest a tolerogenic antigen-specific memory profile.

5.3. The Significance of an Uninterrupted Stimulatory Expression of CCR7. AAT has been shown to promote semimature DCs [122]. Upon introduction of AAT to stimulated DCs, the cells display a reduction in costimulatory markers and an elevation in IL-10 production, while maintaining inducible inflammation-dependent membrane CCR7 levels. The latter indicates that AAT-induced semimature DCs can migrate towards the CCL19/21-releasing draining lymph node T zones. Indeed, the concept of a readily migrating semimature DC was important enough to challenge, as the current dogma of DC-directed T cell differentiation does require that the DC engages with a T cell in the lymph node. That an anti-inflammatory agent allows an array of inflammation-driven molecules to persist presents simultaneously as an indication and also as an enormous challenge in as far as the mechanism of action of AAT is regarded.

5.4. AAT Modifies T Helper-Related B Cell Responses. Treg population expansion may be also promoted by IL-10-producing AAT-derived B cells [132]. As reported by Mizrahi et al., LPS-stimulated B cells that were treated with AAT displayed a reduction in CD40, MHC class II, and CD86 surface levels, while at the same time they produced more IL-10 than untreated LPS-stimulated B cells. A similar trend was observed when, instead, B cells were stimulated with recombinant CD40L and IL-4. Interestingly, AAT was shown to increase Treg cell population in a B cell-dependent manner, as demonstrated in B cell-knockout mice; as described in the study, these mice were unable to mount an AAT-driven Treg expansion.
5.5. The T Helper-Predominant Xenoimmune Response and the Role of AAT-Modified Non-T Cells. An unexpected indirect effect of AAT on T cells came from combination studies. Based on the positive outcomes of islet allograft transplantation models using AAT therapy, Ashkenazi et al. examined the ability of AAT to prolong islet xenograft transplant survival [133]. Unfortunately, treatment with AAT alone failed to prolong xenograft survival even upon extending pre-treatment duration and increasing its dose to the upper limit. Nonetheless, molecular profiles appeared to have changed for the better within explanted grafts, demonstrating more insulin transcripts and less inflammatory genes and important chemokines; thus, a combination therapy approach had followed.

When combining AAT treatment with a suboptimal dose of costimulatory blockade antibodies, an approach proven by itself to benefit xenograft survival, there appears to have been no significant change in outcomes; AAT plus costimulation blockade could not remove the immunological barrier that prevented an islet xenograft from being accepted by a diabetic host. However, when AAT was combined with temporal T cell depletion, yet another approach that holds an established background in literature and more importantly is already incorporated in clinical practice, xenografts exhibited significantly extended survival rates. Alone, removal of T cells by anti-CD3 or anti-CD4/CD8 depleting antibodies resulted in a significant prolongation of xenograft survival. Once T cell depletion was complete, however, xenograft survival was significantly reduced compared to those of lymphocytes cultured in the presence of control cells.

5.6. Evidence for the Utilization of Peripheral T Cell Plasticity by AAT. In order to depict whether AAT levels are required to be elevated in the circulation for its beneficial effects on islet β cell survival, a β cell line was generated that stably expresses human AAT (NIT-hAAT) [134]. Tested for its impact on lymphocytes, a mixed lymphocyte reaction (MLR) study was performed. According to study results, compared to control NIT-1 and NIT-vector cells, NIT-hAAT primed lymphocytes and lymphocytes cocultured with NIT-hAAT cells displayed a significant reduction in IFNγ production and produced more IL-4, in effect skewing the TH1 response towards a TH2 response. In addition, lymphocyte proliferation rates when cocultured with NIT-hAAT cells were significantly reduced compared to those of lymphocytes cultured in the presence of control cells.

This intriguing system was then challenged in a transplantation model [134]. Mice that were grafted with NIT-hAAT cells displayed reduction in TH17 cell population size in the days following transplantation. These findings agree with the observed systemic effects of AAT, whereby human AAT expressing mice exhibit reduced IL-17 levels and an expanded Foxp3+ Tregs population in an EAE model [120]. Selected examples of the effects of AAT on TH subset differentiation are displayed in Figure 3.

6. Conclusion

Once one appreciates the large diversity and plasticity within the helper T cell arm of the immune system and the tight relation to local cytokines and the functions of local non-T cells, the possibility that a molecule alters practically every immune entity but T cells becomes less of a provocation. The fact that our liver generates 4–6-fold greater amounts of AAT during acute phase responses, at a time in which T cell activities must conquer pathogenic threats but in which their overenthusiasm might prove lethal to the host, fits the recent appreciation of the possibility that AAT acts by modifying responses as basic as inflammation, without interfering with the antigenic threat, the T cell axis. For this, the plethora of helper T cell subtypes appear to be superb partners for, based on local inflammatory cues, executing fine changes in the mounting of an untainted adaptive immune response.

There are vast aspects of helper T cell responses and their modification by AAT-conditioned environments that have yet to be studied. Beside the charting of the cytokine
profile exerted by AAT under various conditions and its implication on the profile of helper T cells, there are many more interfaces to consider whereby AAT may alter the function of a T cell. Clinical studies that examine the prospect of AAT therapy for individuals who are not genetically deficient in AAT incorporate major findings recently established with regard to AAT and T cells, namely, recent onset type 1 autoimmune diabetes (NIH clinical trial registries NCT01183455, NCT01319331, NCT01183468, NCT02005848, NCT01304357, and NCT01661192) and treatment-resistant GVHD (NCT01523821).

Understanding in detail this novel niche between innate and adaptive immunity may allow for some novel and more precise designs of clinical trials for the optimal utilization of the readily available and safe for use molecule, AAT, without compromising T cell functionality.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

**References**

[1] T. Tada, T. Takemori, K. Okumura, M. Nonaka, and T. Tokuhisa, "Two distinct types of helper T cells involved in the secondary antibody response: independent and synergistic effects of Ia- and Ia+ helper T cells," *Journal of Experimental Medicine*, vol. 147, no. 2, pp. 446–458, 1978.

[2] T. R. Mosmann, H. Cherwinski, M. W. Bond, M. A. Giedlin, and R. L. Coffman, "Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins," *The Journal of Immunology*, vol. 136, no. 7, pp. 2348–2357, 1986.

[3] J. Magram, S. E. Connaughton, R. R. Warrier et al., "IL-12-deficient mice are defective in IFNγ production and type 1 cytokine responses," *Immunity*, vol. 4, no. 5, pp. 471–481, 1996.

[4] F. Mattner, J. Magram, J. Ferrante et al., "Genetically resistant mice lacking interleukin-12 are susceptible to infection with Leishmania major and mount a polarized Th2 cell response," *European Journal of Immunology*, vol. 26, no. 7, pp. 1553–1559, 1996.

[5] T. Sornasse, P. V. Larenas, K. A. Davis, J. E. de Vries, and H. Yssel, "Differentiation and stability of T helper 1 and 2 cells derived from naïve human neonatal CD4+ T cells, analyzed at the single-cell level," *The Journal of Experimental Medicine*, vol. 184, no. 2, pp. 473–483, 1996.

[6] M. Moser and K. M. Murphy, "Dendritic cell regulation of TH1-TH2 development," *Nature Immunology*, vol. 1, no. 3, pp. 199–205, 2000.

[7] S. Agarwal, O. Avni, and A. Rao, "Cell-type-restricted binding of the transcription factor NFAT to a distal IL-4 enhancer in vivo," *Immunity*, vol. 12, no. 6, pp. 643–652, 2000.

[8] N. G. Jacobson, S. J. Szabo, R. M. Weber-Nordt et al., "Interleukin 12 signaling in T helper type 1 (Th1) cells involves tyrosine phosphorylation of signal transducer and activator of transcription (Stat)3 and Stat4," *Journal of Experimental Medicine*, vol. 181, no. 5, pp. 1755–1762, 1995.

[9] S. J. Szabo, N. G. Jacobson, A. S. Dighe, U. Gubler, and K. M. Murphy, "Developmental commitment to the Th2 lineage by extinction of IL-12 signaling," *Immunity*, vol. 2, no. 6, pp. 665–675, 1995.

[10] M. Afkarian, J. R. Sedy, J. Yang et al., "T-bet is a STAT1-induced regulator for IL-12R expression in naïve CD4+ T cells," *Nature Immunology*, vol. 3, no. 6, pp. 549–557, 2002.

[11] I. M. Djuretic, D. Levanon, V. Negreanu, Y. Groner, A. Rao, and K. M. Ansel, "Transcription factors T-bet and Runx3 cooperate to activate Ifng and silence Il4 in T helper type 1 cells," *Nature Immunology*, vol. 8, no. 2, pp. 145–153, 2007.

[12] F. W. Quelle, K. Shimoda, W. Thierfelder et al., "Cloning of murine Stat6 and human Stat6, Stat proteins that are tyrosine phosphorylated in responses to IL-4 and IL-3 but are not required for mitogenesis," *Molecular and Cellular Biology*, vol. 15, no. 6, pp. 3336–3343, 1995.

[13] M. Kubo, J. Ransom, D. Webb, Y. Hashimoto, T. Tada, and T. Nakayama, "T-cell subset-specific expression of the IL-4 gene is regulated by a silencer element and STAT6," *The EMBO Journal*, vol. 16, no. 13, pp. 4007–4020, 1997.

[14] W. Ouyang, S. H. Ranganath, K. Weindel et al., "Inhibition of Th1 development mediated by GATA-3 through an IL-4-independent mechanism," *Immunity*, vol. 9, no. 5, pp. 745–755, 1998.

[15] J. I. Kim, I.-C. Ho, M. J. Grusby, and L. H. Glimcher, "The transcription factor c-Maf controls the production of interleukin-4 but not other Th2 cytokines," *Immunity*, vol. 10, no. 6, pp. 745–751, 1999.

[16] K. M. Murphy, W. Ouyang, J. D. Farrar et al., "Interleukin-17 drives a pathogenic T cell population that induces autoimmune inflammation," *Journal of Experimental Medicine*, vol. 201, no. 2, pp. 233–240, 2005.

[17] H. Park, Z. Li, X. O. Yang et al., "A distinct lineage of CD4+ T cells regulates tissue inflammation by producing interleukin 17," *Nature Immunology*, vol. 6, no. 11, pp. 1133–1141, 2005.

[18] L. E. Harrington, R. D. Hatton, P. R. Mangan et al., "Interleukin-17-producing CD4+ effector T cells develop via a lineage distinct from the Th1 and Th2 lineages," *Nature Immunology*, vol. 6, no. 11, pp. 1123–1132, 2005.

[19] E. Rouvier, M.-F. Luciani, M.-G. Mattei, F. Denizot, and R. L. Coffman, "CTLA-8, cloned from an activated T cell, bearing AU-rich messenger RNA instability sequences, and homologous to a herpesvirus Saimiri gene," *The Journal of Immunology*, vol. 150, no. 12, pp. 5445–5456, 1993.

[20] Z. Yao, S. L. Painter, W. C. Fanslow et al., "Human IL-17: a novel cytokine derived from T cells," *Journal of Immunology*, vol. 155, no. 12, pp. 5483–5486, 1995.

[21] R. Pappu, V. Ramirez-Carrozzi, N. Ota, W. Ouyang, and Y. Hu, "The IL-17 family cytokines in immunity and disease," *Journal of Clinical Immunology*, vol. 30, no. 2, pp. 185–195, 2010.

[22] E. Lockhart, A. M. Green, and J. L. Flynn, "IL-17 production is dominated by Th6 T cells rather than CD4+ T cells during Mycobacterium tuberculosis infection," *Journal of Immunology*, vol. 177, no. 7, pp. 4662–4669, 2006.

[23] M. Chabaud, P. Garnero, J.-M. Dayer, P.-A. Guerne, F. Bossiez, and P. Miossec, "Contribution of interleukin 17 to synovium matrix destruction in rheumatoid arthritis," *Cytokine*, vol. 12, no. 7, pp. 1092–1099, 2000.

[24] S. Fujino, A. Andoh, S. Bamba et al., "Increased expression of interleukin 17 in inflammatory bowel disease," *Gut*, vol. 52, no. 1, pp. 65–70, 2003.
[26] D. J. Cua, J. Sherlock, Y. Chen et al., “Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain,” Nature, vol. 421, no. 6924, pp. 744–748, 2003.

[27] V. Gorbatheva, R. Fan, X. Li, and A. Valujskikh, “Interleukin-17 promotes early allograft inflammation,” American Journal of Pathology, vol. 177, no. 3, pp. 1265–1273, 2010.

[28] M. Veldhoen, R. J. Hocking, C. J. Atkins, R. M. Locksley, and B. Stockinger, “TGFβ in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells,” Immunity, vol. 24, no. 2, pp. 179–189, 2006.

[29] T. Korn, E. Bettelli, W. Gao et al., “IL-21 initiates an alternative pathway to induce proinflammatory Th17 cells,” Nature, vol. 448, no. 7152, pp. 484–487, 2007.

[30] X. O. Yang, B. P. Pappu, R. Nurieva et al., “T helper 17 lineage differentiation is programmed by orphan nuclear receptors RORα and RORγt,” Immunity, vol. 28, no. 1, pp. 29–39, 2008.

[31] A. N. Mathur, H.-C. Chang, D. G. Zisoulis et al., “Stat3 and Stat4 direct development of IL-17-secreting Th cells,” The Journal of Immunology, vol. 178, no. 1, pp. 179–185, 2007.

[32] W. J. Penhale, A. Farmer, R. P. McKenna, and W. J. Irvine, “Spontaneous thyroiditis in thymectomized and irradiated Wis-tar rats,” Clinical and Experimental Immunology, vol. 15, no. 2, pp. 225–236, 1993.

[33] A. Kojima and R. T. Prehn, “Genetic susceptibility to post-thymectomy autoimmune diseases in mice,” Immunogenetics, vol. 14, no. 1-2, pp. 15–27, 1981.

[34] W. J. Penhale, W. J. Irvine, J. R. Inglis, and A. Farmer, “Thyroiditis in T cell-depleted rats: suppression of the autoallergic response by reconstitution with normal lymphoid cells,” Clinical and Experimental Immunology, vol. 25, no. 1, pp. 6–16, 1976.

[35] S. Sakaguchi, T. Takahashi, and Y. Nishizuka, “Study on cellular events in post-thymectomy autoimmune oophoritis in mice. II. Requirements of Lyt-1 cells in normal female mice for the prevention of oophoritis,” Journal of Experimental Medicine, vol. 156, no. 6, pp. 1577–1586, 1982.

[36] R. Setoguchi, S. Hori, T. Takahashi, and S. Sakaguchi, “Homeostatic maintenance of natural Foxp3+ CD25+ CD4+ regulatory T cells by interleukin (IL)-2 and induction of autoimmune disease by IL-2 neutralization,” Journal of Experimental Medicine, vol. 201, no. 5, pp. 723–735, 2005.

[37] M. E. Brunke, E. W. Jeffery, K. A. Hjerrild et al., “Disruption of a new forkhead/winged-helix protein, scurfyn, results in the fatal lymphoproliferative disorder of the scurfy mouse,” Nature Genetics, vol. 27, no. 1, pp. 68–73, 2001.

[38] S. Hori, T. Nomura, and S. Sakaguchi, “Control of regulatory T cell development by the transcription factor Foxp3,” Science, vol. 299, no. 5609, pp. 1057–1061, 2003.

[39] S. Sakaguchi, M. Miyara, C. M. Costantino, and D. A. Hafler, “FOXP3+ regulatory T cells in the human immune system,” Nature Reviews Immunology, vol. 10, no. 7, pp. 490–500, 2010.

[40] Y. Carrier, J. Yuan, V. K. Kuchroo, and H. L. Weiner, “Th3 cells in peripheral tolerance. I. Induction of Foxp3-positive regulatory T cells by Th3 cells derived from TGF-β T cell-transgenic mice,” The Journal of Immunology, vol. 178, no. 1, pp. 179–185, 2007.

[41] P. L. Vieira, J. R. Christensen, S. Minaee et al., “IL-10-secreting regulatory T cells do not express Foxp3 but have comparable regulatory function to naturally occurring CD4−CD25+ regulatory T cells,” Journal of Immunology, vol. 172, no. 10, pp. 5986–5993, 2004.

[42] A. Awasthi, Y. Carrier, J. P. S. Peron et al., “A dominant function for interleukin 27 in generating interleukin 10-producing anti-inflammatory T cells,” Nature Immunology, vol. 8, no. 12, pp. 1380–1389, 2007.

[43] R. Bacchetta, M. Bigler, J.-L. Touraine et al., “High levels of interleukin 10 production in vivo are associated with tolerance in SCID patients transplanted with HLA mismatched hematopoietic stem cells,” The Journal of Experimental Medicine, vol. 179, no. 2, pp. 493–502, 1994.

[44] M. G. Roncarolo, S. Gregori, M. Battaglia, R. Bacchetta, K. Fleischhauer, and M. K. Levings, “Interleukin-10-secreting type 1 regulatory T cells in rodents and humans,” Immunological Reviews, vol. 212, no. 1, pp. 28–50, 2006.

[45] N. Gagliani, T. Jofra, A. Stabilini et al., “Antigen-specific dependence of Tr1-cell therapy in preclinical models of islet transplant,” Diabetes, vol. 59, no. 2, pp. 433–439, 2010.

[46] M. Battaglia, S. Gregori, R. Bacchetta, and M.-G. Roncarolo, “Tr1 cells: from discovery to their clinical application,” Seminars in Immunology, vol. 18, no. 2, pp. 120–127, 2006.

[47] M. H. Kaplan, U. Schindler, S. T. Smiley, and M. J. Grusby, “Stat6 is required for mediating responses to IL-4 and for the development of Th2 cells,” Immunity, vol. 4, no. 3, pp. 313–319, 1996.

[48] R. I. Nurieva, Y. Chung, D. Hwang et al., “Generation of T follicular helper cells is mediated by interleukin-21 but independent of T helper 1, 2, or 17 cell lineages,” Immunity, vol. 29, no. 1, pp. 138–149, 2008.

[49] D. Breitfeld, L. Ohl, E. Kremmer et al., “Follicular B helper T cells express CXCR chemokine receptor 5, localize to B cell follicles, and support immunoglobulin production,” Journal of Experimental Medicine, vol. 192, no. 11, pp. 1545–1551, 2000.

[50] P. Schaefer, R. Willmann, A. B. Lang, M. Lipp, P. Loetscher, and B. Moser, “CXCR chemokine receptor 5 expression defines follicular homing T cells with B cell helper function,” Journal of Experimental Medicine, vol. 192, no. 11, pp. 1553–1562, 2000.

[51] Y. S. Choi, R. Kageyama, D. Eto et al., “ICOS receptor instructs T follicular helper cell versus effector cell differentiation via induction of the transcriptional repressor Bcl6,” Immunity, vol. 34, no. 6, pp. 932–946, 2011.

[52] M. Pepper, A. J. Pagán, B. Z. Igyártó, J. J. Taylor, and M. K. Jenkins, “Opposing signals from the Bcl6 transcription factor and the interleukin-2 receptor generate Th helper 1 central and effector memory cells,” Immunity, vol. 35, no. 4, pp. 583–595, 2011.

[53] R. J. Johnston, A. C. Poholek, D. DiToro et al., “Bcl6 and Blimp-1 are reciprocal and antagonistic regulators of T follicular helper cell differentiation,” Science, vol. 325, no. 5943, pp. 1006–1010, 2009.

[54] R. I. Nurieva, Y. Chung, G. J. Martinez et al., “Bcl6 mediates the development of T follicular helper cells,” Science, vol. 325, no. 5943, pp. 1001–1005, 2009.

[55] Y. S. Choi, D. Eto, J. A. Yang, C. Lao, and S. Crotty, “Cutting edge: STAT1 is required for IL-6-mediated Bcl6 induction for early follicular helper cell differentiation,” Journal of Immunology, vol. 190, no. 7, pp. 3049–3053, 2013.

[56] J. M. Odegard, B. R. Marks, L. D. Diplacido et al., “ICOS-dependent extrafollicular helper T cells elicit IgG production
via IL-21 in systemic autoimmunity,” *Journal of Experimental Medicine*, vol. 205, no. 12, pp. 2873–2886, 2008.

[58] J. A. Bubier, T. J. Sproule, O. Foreman et al., “A critical role for IL-21 receptor signaling in the pathogenesis of systemic lupus erythematosus in BXXSB-Yaa mice,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 5, pp. 1518–1523, 2009.

[59] C. C. Goodnow, C. G. Vinuesa, K. L. Randall, F. MacKay, and R. Brink, “Control systems and decision making for antibody production,” *Nature Immunology*, vol. 11, no. 8, pp. 681–688, 2010.

[60] N. Fazilleau, L. Mark, L. J. McHeyzer-Williams, and M. G. McHeyzer-Williams, “Follicular helper T cells: lineage and location,” *Immunity*, vol. 30, no. 3, pp. 324–335, 2009.

[61] M. A. Linterman and C. G. Vinuesa, “Signals that influence T follicular helper cell differentiation and function,” *Seminars in Immunopathology*, vol. 32, no. 2, pp. 183–196, 2010.

[62] M. A. Linterman, R. J. Rigby, R. K. Wong et al., “Follicular helper T cells are required for systemic autoimmunity,” *Journal of Experimental Medicine*, vol. 206, no. 3, pp. 561–576, 2009.

[63] M.-H. Xie, S. Aggarwal, W.-H. Ho et al., “Interleukin (IL)-22, a novel human cytokine that signals through the interferon receptor-related proteins CRF2-4 and IL-22R,” *Journal of Biological Chemistry*, vol. 275, no. 40, pp. 31335–31339, 2000.

[64] S. C. Liang, Y. X. Tan, D. P. Luxenberg et al., “Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides,” *The Journal of Experimental Medicine*, vol. 203, pp. 2271–2279, 2006.

[65] K. Wolk and R. Sabat, “Interleukin-22: a novel T- and NK-cell derived cytokine that regulates the biology of tissue cells,” *Cytokine and Growth Factor Reviews*, vol. 17, no. 5, pp. 367–380, 2006.

[66] N. Satoh-Takayama, C. A. J. Vossenrehr, S. Lesjean-Pottier et al., “Microbial flora drives interleukin 22 production in intestinal NKP46+ cells that provide innate mucosal immune defense;” *Immunity*, vol. 29, no. 6, pp. 958–970, 2008.

[67] H. Hamada, M. D. L. Garcia-Hernandez, J. B. Reome et al., “IκB7, a unique subset of CD8 T cells that can protect against lethal influenza challenge,” *Journal of Immunology*, vol. 182, no. 6, pp. 3469–3481, 2009.

[68] B. Martin, K. Hirotta, D. J. Cua, B. Stockinger, and M. Veldhoen, “Interleukin-17-producing γδ T cells selectively expand in response to pathogen products and environmental signals,” *Immunity*, vol. 31, no. 2, pp. 321–330, 2009.

[69] H. Fujita, K. E. Nogreles, T. Kikuchi, J. Gonzalez, J. A. Carucci, and J. G. Krueger, “Human Langerhans cells induce distinct IL-22-producing CD4+ T cells lacking IL-17 production,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 51, pp. 21795–21800, 2009.

[70] K. Wolk, E. Witte, K. Witte, K. Warszawski, and R. Sabat, “Biology of interleukin-22,” *Seminars in Immunopathology*, vol. 32, no. 1, pp. 17–31, 2010.

[71] A.-G. Besnard, R. Sabat, L. Dumoutier et al., “Dual role of IL-22 in allergic airway inflammation and its cross-talk with IL-17A,” *American Journal of Respiratory and Critical Care Medicine*, vol. 183, no. 9, pp. 1153–1163, 2011.

[72] P. J. Chestovich, Y. Uchida, W. Chang et al., “Interleukin-22: implications for liver ischemia-reperfusion injury;” *Transplantation*, vol. 93, no. 5, pp. 485–492, 2012.

[73] H. M. McGee, B. A. Schmidt, C. J. Booth et al., “IL-22 promotes fibroblast-mediated wound repair in the skin,” *Journal of Investigative Dermatology*, vol. 133, no. 5, pp. 1321–1329, 2013.

[74] L. F. da Rocha Jr., A. L. B. P. Duarte, A. T. Dantas et al., “Increased serum interleukin 22 in patients with rheumatoid arthritis and correlation with disease activity,” *The Journal of Rheumatology*, vol. 39, no. 7, pp. 1320–1325, 2012.

[75] A. Mathian, C. Parizot, K. Dorgham et al., “Activated and resting regulatory T cell exhaustion concurs with high levels of interleukin-22 expression in systemic sclerosis lesions,” *Annals of the Rheumatic Diseases*, vol. 71, no. 7, pp. 1227–1234, 2012.

[76] S. Trifari, C. D. Kaplan, E. H. Tran, N. K. Crellin, and H. Spits, “Identification of a human helper T cell population that has abundant production of interleukin 22 and is distinct from Th1-17, Tc1,1 and Tc1,2 cells,” *Nature Immunology*, vol. 10, no. 8, pp. 864–871, 2009.

[77] T. Duhlen, R. Geiger, D. Jarrossay, A. Lanzavecchia, and F. Sallusto, “Production of interleukin 22 but not interleukin 17 by a subset of human skin-homing memory T cells,” *Nature Immunology*, vol. 10, no. 8, pp. 857–863, 2009.

[78] S. Eyerych, K. Eyerych, D. Pennino et al., “Th22 cells represent a distinct human T cell subset involved in epideral immunity and remodeling,” *The Journal of Clinical Investigation*, vol. 119, no. 12, pp. 3573–3585, 2009.

[79] H. Li and A. Rostami, “IL-9: Basic biology, signaling pathways in CD4+ T cells and implications for autoimmunity,” *Journal of Neuroimmune Pharmacology*, vol. 5, no. 2, pp. 198–209, 2010.

[80] E. C. Nowak and R. J. Noelle, “Interleukin-9 as a T helper type 1 cytokine,” *Immunology*, vol. 131, no. 2, pp. 169–173, 2010.

[81] V. Staudt, E. Bothur, M. Klein et al., “Interferon-regulatory factor 4 is essential for the developmental program of T helper 9 cells;” *Immunology*, vol. 33, no. 2, pp. 192–202, 2010.

[82] M. Veldhoen, C. Uyttenhove, J. van Snick et al., “Transforming growth factor-β ‘reprograms’ the differentiation of T helper 2 cells and promotes an interleukin 9-producing subset,” *Nature Immunology*, vol. 9, no. 12, pp. 1341–1346, 2008.

[83] E. Schmitt, T. Germann, S. Goedert et al., “IL-9 production of naive CD4+ T cells depends on IL-2-1, is synergistically enhanced by a combination of TGF-β and IL-4, and is inhibited by IFN-γ,” *The Journal of Immunology*, vol. 153, no. 9, pp. 3989–3996, 1994.

[84] M. T. Wong, J. J. Ye, M. N. Alonso et al., “Regulation of human Th9 differentiation by type I interferons and IL-21,” *Immunology and Cell Biology*, vol. 88, no. 6, pp. 624–631, 2010.

[85] P. Montyene, J.-C. Renauld, J. Van Broeck, D. W. Dunne, F. Brombacher, and J.-P. Coutelier, “IL-4-independent regulation of in vivo IL-9 expression;” *Journal of Immunology*, vol. 159, no. 6, pp. 2616–2623, 1997.

[86] R. Goswami, R. Jabeen, R. Yagi et al., “STAT6-dependent regulation of Th9 development,” *Journal of Immunology*, vol. 188, no. 3, pp. 968–975, 2012.

[87] P. Angkasekwinai, S. H. Chang, M. Thapa, H. Watarai, and A. Ramming, D. Druzd, J. Leipe, H. Schulze-Koops, and A. Skapenko, “Maturation-related histone modifications in the PU.1 promoter regulate Th9-cell development,” *Blood*, vol. 119, no. 20, pp. 4665–4674, 2012.

[88] L. Blom, B. C. Poulsen, B. M. Jensen, A. Hansen, and L. K. Poulsen, “IL-33 induces IL-9 production in human CD4+ T cells and basophils,” *PLoS ONE*, vol. 6, no. 7, Article ID e21695, 2011.

[89] A. Jæger, V. Dardalhon, R. A. Sobel, E. Betteli, and V. K. Kuchroo, “Th1, Th7, and Th9 effector cells induce experimental autoimmune encephalomyelitis with different pathological phenotypes,” *Journal of Immunology*, vol. 183, no. 11, pp. 7169–7177, 2009.
[91] H.-C. Chang, S. Sehra, R. Goswami et al., “The transcription factor PU.1 is required for the development of IL-9-producing T cells and allergic inflammation,” *Nature Immunology*, vol. 11, no. 6, pp. 527–534, 2010.

[92] E. Bettelli, Y. Carrier, W. Gao et al., “Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells,” *Nature*, vol. 441, no. 7090, pp. 235–238, 2006.

[93] D. Mucida, Y. Park, G. Kim et al., “Reciprocal TH17 and regulatory T cell differentiation mediated by retinoic acid,” *Science*, vol. 317, no. 5835, pp. 256–260, 2007.

[94] L. Xu, A. Kitani, I. Fuss, and W. Strober, “Cutting edge: stromal cell factor-1 induces the development of stromal cells,” *American Journal of Pathology*, vol. 169, no. 1, pp. 36–43, 2006.

[95] X. Zhou, S. L. Bailey-Bucktrout, L. T. Jekere et al., “Increased H3K4me3 binding to regulatory elements directing transcription of the gene encoding the α1-antitrypsin,” *Nature Immunology*, vol. 10, no. 9, pp. 1167–1175, 2009.

[96] M. Komatsu, N. Komatsu, S. Kawamoto et al., “Alpha1-antitrypsin binds to heat-shock protein 105 and protects from endogenous gp96-mediated injury in the mouse,” *Frontiers in Immunology*, vol. 4, no. 2, pp. 46–55, 2013.

[97] G. Oldenhove, N. Boulaudoux, E. A. Wohlfert et al., “Decrease of Foxp3 + Treg cell number and acquisition of effector cell phenotype during lethal infection,” *Immunity*, vol. 31, no. 5, pp. 772–786, 2009.

[98] A. N. Hegazy, M. Peine, C. Helmstetter et al., “Interferon-γ inhibits development of follicular helper T cells from Foxp3 T cells in gut Peyer’s patches,” *Science*, vol. 323, no. 5920, pp. 1488–1492, 2009.

[99] Y. K. Lee, H. Turner, C. L. Maynard et al., “Late developmental plasticity in the T helper 17 lineage,” *Immunity*, vol. 30, no. 1, pp. 92–107, 2009.

[100] A. N. Hegazy, M. Peine, C. Helmstetter et al., “Interferon-γ and Tbet define the T helper 17 cell lineage,” *Immunity*, vol. 32, no. 1, pp. 116–128, 2010.

[101] J. R. Schoenborn, M. O. Dorschner, M. Sekimata et al., “Interferon-γ and Tbet define the T helper 17 cell lineage,” *Immunity*, vol. 32, no. 1, pp. 116–128, 2010.

[102] G. Oldenhove, N. Boulaudoux, E. A. Wohlfert et al., “Decrease of Foxp3 + Treg cell number and acquisition of effector cell phenotype during lethal infection,” *Immunity*, vol. 31, no. 5, pp. 772–786, 2009.

[103] A. N. Hegazy, M. Peine, C. Helmstetter et al., “Interferon-γ and Tbet define the T helper 17 cell lineage,” *Immunity*, vol. 32, no. 1, pp. 116–128, 2010.

[104] J. R. Schoenborn, M. O. Dorschner, M. Sekimata et al., “Interferon-γ and Tbet define the T helper 17 cell lineage,” *Immunity*, vol. 32, no. 1, pp. 116–128, 2010.

[105] H. M. Morrison, D. Burnett, and R. A. Stockley, “The effect of catalase and methionine-S-oxide reductase on oxidised alpha 1-proteinase inhibitor,” *European Journal of Clinical Pharmacology*, vol. 29, no. 5, pp. 371–378, 1986.

[106] J. S. Parmar, R. Mahadeva, B. J. Reed et al., “Polymers of α1-antitrypsin are chemotactic for human neutrophils: a new paradigm for the pathogenesis of emphysema,” *American Journal of Respiratory and Critical Care Medicine*, vol. 168, no. 2, pp. 199–207, 2003.

[107] D. E. Ochayon, M. Mizrahi, G. Shahaf, B. M. Baranovski, and E. C. Lewis, “Human α1-antitrypsin binds to heat-shock protein gp96 and protects from endogenous gp96-mediated injury in vivo,” *Frontiers in Immunology*, vol. 4, article 320, 2013.

[108] G. B. Pott, K. S. Beard, C. L. Bryan, D. T. Merrick, and L. Shapiro, “Alpha-1-antitrypsin reduces severity of pseudomonas pneumonia in mice and inhibits epithelial barrier disruption and pseudomonas invasion of respiratory epithelial cells,” *Frontiers in Public Health*, vol. 1, article 9, 2013.

[109] S. Subramanian, G. Shahaf, E. Ozeri et al., “Sustained expression of circulating human alpha-1 antitrypsin reduces inflammation and Treg cell population and prevents signs of experimental autoimmune encephalomyelitis in mice,” *Metabolic Brain Disease*, vol. 26, no. 2, pp. 107–113, 2011.

[110] H. Tilg, E. Vannier, G. Vachino, C. A. Dinarello, and J. W. Mier, “Antinflammatory properties of hepatic acute phase proteins: preferential induction of interleukin 1 (IL-1) receptor antagonist...
over IL-1β synthesis by human peripheral blood mononuclear cells,” *The Journal of Experimental Medicine*, vol. 178, no. 5, pp. 1629–1636, 1993.

[122] E. Ozeri, M. Mizrahi, G. Shahaf, and E. C. Lewis, “α-1 antitrypsin promotes semimature, IL-10-producing and readily migrating tolerogenic dendritic cells,” *The Journal of Immunology*, vol. 189, no. 1, pp. 146–153, 2012.

[123] C. Grimstein, Y.-K. Choi, C. H. Wasserfall et al., “Alpha-1 antitrypsin protein and gene therapies decrease autoimmunity and delay arthritis development in mouse model,” *Journal of Translational Medicine*, vol. 9, article 21, 2011.

[124] A. M. Marcondes, X. Li, I. Tabellini et al., “Inhibition of IL-32 activation by α-1 antitrypsin suppresses alloreactivity and increases survival in an allogeneic murine marrow transplantation model,” *Blood*, vol. 118, no. 18, pp. 5031–5039, 2011.

[125] C. B. Collins, C. M. Aherne, S. F. Ehrentraut et al., “Alpha-1-antitrypsin monotherapy ameliorates acute colitis and chronic murine ileitis,” *Inflammatory Bowel Diseases*, vol. 19, no. 9, pp. 1964–1973, 2013.

[126] M. Koulmanda, M. Bhasin, L. Hoffman et al., “Curative and β cell regenerative effects of α1-antitrypsin treatment in autoimmune diabetic NOD mice,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 42, pp. 16242–16247, 2008.

[127] S. Song, K. Goudy, M. Campbell-Thompson et al., “Recombinant adeno-associated virus-mediated alpha-1 antitrypsin gene therapy prevents type I diabetes in NOD mice,” *Gene Therapy*, vol. 11, no. 2, pp. 181–186, 2004.

[128] E. C. Lewis, L. Shapiro, O. J. Bowers, and C. A. Dinarello, “α1-antitrypsin monotherapy prolongs islet allograft survival in mice,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 34, pp. 12153–12158, 2005.

[129] E. C. Lewis, M. Mizrahi, M. Toledano et al., “α1-Antitrypsin monotherapy induces immune tolerance during islet allograft transplantation in mice,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 42, pp. 16236–16241, 2008.

[130] B. J. O’Sullivan, H. E. Thomas, S. Pai et al., “IL-1β breaks tolerance through expansion of CD25+ effector T cells,” *The Journal of Immunology*, vol. 176, no. 12, pp. 7278–7287, 2006.

[131] A. Abecassis, R. Schuster, G. Shahaf et al., “α1-antitrypsin increases interleukin-1 receptor antagonist production during pancreatic islet graft transplantation,” *Cellular & Molecular Immunology*, vol. 11, no. 4, pp. 377–386, 2014.

[132] M. Rosenthal, P. Cal, M. Rosenthal et al., “Human α1-antitrypsin modifies B-lymphocyte responses during allograft transplantation,” *Immunology*, vol. 140, no. 3, pp. 362–373, 2013.

[133] E. Ashkenazi, B. M. Baranovski, G. Shahaf, and E. C. Lewis, “Pancreatic islet xenograft survival in mice is extended by a combination of alpha-1-antitrypsin and single-dose anti-CD4/CD8 therapy,” *PLoS ONE*, vol. 8, no. 5, Article ID e63625, 2013.

[134] Y. Wang, H.-J. Yan, S.-Y. Zhou et al., “The immunoregulation effect of alpha 1-antitrypsin prolong β-cell survival after transplantation,” *PLoS ONE*, vol. 9, no. 4, Article ID e94548, 2014.