Mucosal immunity relies on the delicate balance between antigen responsiveness and tolerance. The polarization of T helper cells plays a key role in maintaining or disrupting this equilibrium.

The role of Th1/Th2 polarization in mucosal immunity

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Mucosal surfaces such as exist in the airways or the gut have pleiotropic tasks that include absorption, macromolecule transport, barrier and secretory functions. However, large mucosal surfaces (for example, greater than 300 m^2 in human gut) are continuously exposed to millions of potentially harmful antigens from the environment, food and bacteria. To meet this task, mucosal surfaces possess a unique immune system that tightly controls the balance between responsiveness and non-responsiveness (tolerance). It consists of an integrated network of tissues, lymphoid and non-lymphoid cells, and effector molecules such as antibodies, chemokines and cytokines for host protection. Recent data suggest that antigen-presenting cells (APCs; such as macrophages and dendritic cells (DCs)), T lymphocytes and their cytokines play a key role in orchestrating a specific mucosal immune response[1–8]. In particular, the signature cytokines of distinct T-cell subsets and the transcriptional regulation of T-cell differentiation appear to be of fundamental importance in mucosal immunity. However, uncontrolled mucosal T-cell responses may lead to immunologic diseases such as allergy, hypersensitivity and inflammation. Thus, a more detailed understanding of T-cell differentiation and cytokine signaling is essential for greater insight into mucosal immune responses in health and disease.

A key component of the mucosal immune defense against pathogens is mediated by $CD4^+$ T lymphocytes that can differentiate into functionally distinct subsets. Whereas T-helper 1 (Th1) cells secrete the cytokines interferon-γ (IFN-γ) and tumor necrosis factor-β (TNF-β), Th2 cells secrete interleukin-4 (IL-4), IL-5, IL-9 and IL-13. In addition, Th3 and regulatory $CD25^+CD4^+$ T (T_R) cells exist that produce transforming growth factor-β (TGF-β) and IL-10, respectively[9,10]. Here we review the molecular and immunologic principles underlying Th1/Th2-cell polarization in the mucosal immune system. For in-depth reviews of T_R and Th3 cells and their role in suppression of mucosal immune responses and oral tolerance, we refer readers to other sources[3,5,9]. We will focus on recent data regarding Th1/Th2 polarization with particular reference to the mucosal immune system of the gut and the lung. These data provide novel insights into pathogenic mucosal T-cell responses and have important implications for the design of novel therapeutic strategies in allergic responses and in chronic intestinal inflammation.

Structure and function of the mucosal immune system

The mucosal immune system is structurally and functionally divided into sites for antigen uptake and processing at inductive sites on one hand, and effector sites engaging lymphocytes, granulocytes and mast cells on the other hand[11]. Organized secondary lymphoid tissues (for example, Peyer's patches and tonsils) in the gastrointestinal and upper respiratory tracts have been shown to represent key inductive sites for mucosal immunity. The two prototypes of this mucosa-associated lymphoreticular tissue (MALT) are the gut-associated lymphoreticular tissue (GALT) and the nasal-associated lymphoreticular tissue (NALT), which both possess APCs, T lymphocytes and immunoglobulin A (IgA)-committed B cells (Fig. 1). There are two different important outcomes of immune responses generated by organized lymphoid structures in the MALT (Fig. 1). One result is the development of B cells capable of producing antigen-specific immunoglobulins that can reach the draining lymph nodes and other mucosal tissues where they differentiate into plasma cells. A second major outcome of the entry of antigen and antigen presentation by DCs is the activation and differentiation of T cells that subsequently can migrate out of the MALT and reach mucosal as well as peripheral nonmucosal tissues. Such T cells can secrete cytokines that are essential for the induction of suppressive T-cell responses and oral tolerance (for example, IL-10 and TGF-β)[5,9,11]. Alternatively, mucosal Th1 and Th2 cells can produce pro-inflammatory cytokines (Fig. 2).

Due to the high antigen load of mucosal surfaces the mucosal immune system exhibits immunologic 'hyporesponsiveness' or unresponsiveness to most antigens. On the other hand the mucosal immune system must also be capable of inducing effective cell-mediated and antibody-mediated immune responses towards selected antigens[11]. Given the complex and highly interactive nature of the MALT and its diverse tasks, it is clear that this system may be highly sensitive to disturbances caused by bacterial antigens and other pathogens; in particular in situations where a genetic predisposition exists. In fact, there is growing evidence that chronic inflammatory diseases in the mucosa such as inflammatory bowel disease (IBD) and allergic asthma are due to a dysregulation of the mucosal immune system and pathological T-cell responses in a genetically susceptible host[12–15].

Role of T cells in chronic mucosal inflammatory disease

A key role for T lymphocytes in pathogenic immune responses at mucosal effector sites has been clearly established in recent years. In particular, an essential role for T lymphocytes has been demonstrated in animal models of allergic asthma and experimental colitis (Fig. 3)[8,16–19]. Although chronic asthma in patients is thought to be mainly mediated by Th2 cells, both Th1 and Th2 cells have been shown to induce pulmonary inflammation and airway hyperresponsiveness in animal models and antigen-specific Th1 cells (in contrast to Th3 cells) cannot counteract Th2-induced lung inflammation in an adoptive transfer model[20]. Conversely, both Th1 and Th2 cells induce chronic intestinal inflammation *in vivo*[18,21–25] and the action of these cells may be suppressed by cytokines produced by T_R and Th3 cells[26,27]. Interestingly, most Th1 models of chronic intestinal inflammation exhibit a transmural inflammation as seen in patients with Crohn disease, an inflammatory bowel disease thought to be mediated by Th1 cells. In contrast, at least some of the Th2 models are characterized by a more superficial colonic inflammation and epithelial hyperplasia as seen in pa-

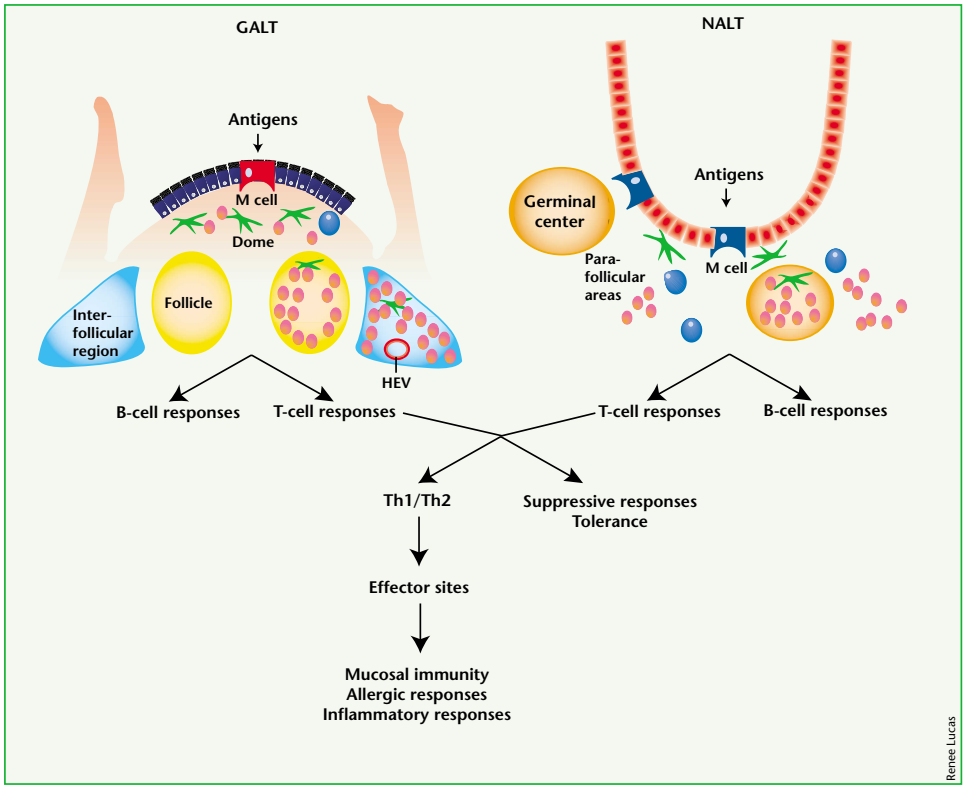

Fig. 1 Inductive sites of the MALT: Whereas the NALT appears to be the major inductive site for mucosal immunity to inhaled antigens, the GALT (for example, Peyer's patches in the small bowel and colonic follicles in the large bowel) is the major inductive site for the gastrointestinal tract. The Peyer's patches of the GALT consist of a follicle-associated epithelium with specialized epithelial cells known as M cells, a subepithelial dome overlying B-cell follicles, and interfollicular regions enriched in T cells[11]. Following ingestion, antigens and microorganisms are transported from the gut lumen to the dome region through specialized M cells. Here they encounter APCs such as DCs leading to cognate interactions between APCs and T cells. DCs can also migrate to the interfollicular regions (enriched with T cells and containing high endothelial venules (HEV) and efferent lymphatics) to initiate immune responses upon antigen uptake. The generation of mucosal immune responses in the NALT seems to follow similar principles. In fact, the organized lymphoid structures in the NALT share some structural features with the Peyer's patches such as M cells and are composed of loose networks in which lymphocytes (B-cell follicles, parafollicular areas with T cells), DCs and macrophages are embedded. Following induction in the MALT, mature lymphocytes leave the inductive sites and migrate to the effector sites such as the lamina propria and the lung where they can induce pro-inflammatory as well as suppressive immune responses. Among the pro-inflammatory signals cytokines produced by mucosal Th1 and Th2 effector cells have a central regulatory role.

tients with ulcerative colitis, an IBD thought to be mediated by T cells producing IL-5 rather than IFN-γ (ref. 28).

Th1/Th2 polarization and the role of DCs

After differentiation and migration to the peripheral immune organs, $CD4^+$ T cells are termed naive T precursor cells and are functionally immature[29–31]. The activation and differentiation of these cells requires at least two separate signals. The first signal is delivered by the T-cell receptor/CD3 complex after its interaction with antigen/major histocompatibility complex on APCs. The second signal is produced by a number of costimulatory or accessory molecules on the APC that interact with their ligands on T cells (for example, CD28/B7-1, CD28/B7-2, OX40/OX40L, ICOS/B7H). This signal is also important for the pathogenesis of T cell–mediated mucosal inflammation, as blockade of the CD28/B7, OX40/OX40L and ICOS/B7H systems has been shown to profoundly suppress mucosal diseases such as experimental allergic airway inflammation and/or chronic intestinal inflammation in mice[32–35].

The cytokines themselves play the most critical role in T-helper cell polarization[29,30,36]. Two pivotal cytokines that control Th1 and Th2 differentiation are IL-12 (p35–p40) and IL-4, respectively. These two cytokines induce the generation of their own T-helper subset, and simultaneously inhibit the production of the opposing subset[29]. Whereas mice lacking IL-12 p40 or the IL-12 receptor β2 chain have defective Th1 responses, mice that lack IL-4 or its receptor fail to develop Th2 cells in response to various stimuli. The cytokine IL-18 also modulates Th1 development. And although IL-18 alone can not induce Th1 cell differentiation, it strongly augments IL-12-dependent Th1-cell development and effector functions, probably due to IL-18-induced upregulation of IL-12Rβ2 chain expression on T cells and AP-1-(c-fos/c-jun) dependent trans-activation of the IFN-γ promoter[37,38]. The importance of this observation is underlined by the finding that mice lacking IL-18 exhibit defective Th1 responses *in vivo*[39]. Another cytokine, IL-13, appears to play an important role in Th2 development. While its function is partially overlapping with IL-4, IL-13 can drive Th2 development and IgE synthesis in an IL-4-independent fashion in certain situations[40].

Although the cytokines that regulate T-helper cell polarization are known, the original sources of these cytokines *in vivo* have been a matter of debate[41]. Recent evidence suggests a key role for DCs in orchestrating the lineage commitment of naive T helper cells[31,42]. In mice, two subsets of $CD11c^+$ DCs ($CD8\alpha^+$ and $CD8\alpha^-$ DCs) have been identified that induce distinct classes of antigen-specific T-cell responses *in vivo*[31]. Whereas splenic $CD8\alpha^+$ DCs elicit Th1 responses, $CD8\alpha^-$ DCs favor Th2 responses and similar data have been obtained using CD8α-sorted DCs from the Peyer's patches in the mucosal immune system[41] (Fig. 2). Although both DC subsets can be found in the murine Peyer's patches, antigen-pulsed DCs from the Peyer's patches have been shown to induce Th2-type rather than Th1-type T-cell responses[42]. The latter bias is also true for DCs from the respiratory tract, which preferentially induce Th2 cytokine responses[43]. The DC molecules that induce Th2 responses are unknown, however $CD8\alpha^+$ DCs can be induced by bacterial antigens and IFN-γ to produce large amounts of IL-12/p35–p40 heterodimer, which seems essential for their potential to induce Th1 differentiation[31]. Similar to the murine system,

monocyte-derived myeloid CD11c⁺ DCs have been shown to induce IL-12-dependent Th1 responses in humans, whereas plasmacytoid CD1a⁻ DCs derived from CD11c⁻ pre-DCs favor Th2 responses[41].

Whereas many key aspects of Th3 and T_R development remain unresolved, much progress has recently been made in understanding the key principles of Th1/Th2 polarization at the transcriptional level. T lymphocytes transit through sequential stages of cytokine activation, commitment, silencing and physical stabilization during polarization into differentiated effector Th1 and Th2 cells, a process tightly controlled by regulatory transcription factors[44–47]. The implications of recent studies on the transcriptional regulation of T-helper cell differentiation for mucosal immunity with specific emphasis on IBD and allergic asthma are discussed below.

Th1 differentiation and IBD

Inflammatory bowel diseases such as Crohn disease are defined as chronic inflammations of the gastrointestinal tract not due to specific pathogens. Crohn disease is characterized by a discontinuous, transmural inflammation that can occur anywhere in the gastrointestinal tract, whereas ulcerative colitis is characterized by a more superficial, continuous colonic inflamation that affects the mucosa and submucosa[12]. Interestingly, recent evidence suggests that IL-12 driven Th1 T cells play an important pathogenic role in Crohn disease.

The IL-12/p35–p40 heterodimer produced by CD8α⁺ DCs or macrophages is a critical cytokine that induces Th1 T-cell differentiation, a function that requires activation and phosphorylation of the transcription factor STAT4 (signal transducer and activator of transcription 4) in T cells[31,48,49] (Fig. 4). The roles of IL-12 and STAT4 activation for Th1-mediated intestinal inflammation are well documented. In particular, it has been shown that Crohn disease in humans and Th1-mediated animal models of IBD are associated with increased IL-12 production (Fig. 3) and neutralizing antibodies to IL-12 suppress Th1-mediated chronic intestinal inflammation, presumably by the prevention of Th1 T-cell development and the induction of Fas-mediated T-cell apoptosis[24,50–52]. Conversely, STAT4-deficient T cells failed to induce Th1-mediated colitis in an adoptive transfer system, whereas STAT4 transgenic mice develop Th1-mediated colitis[21,24]. However, it is not clear whether the effects of STAT4 *in vivo* can be entirely attributed to IL-12, since IL-23 (p19–p40) has been recently shown to activate STAT4 in T cells, and p19 transgenic mice develop multi-organ inflammation including gut inflammation[53,54]. IL-18 is also important for mucosal Th1 responses and activates the transcription factors AP-1 (c-fos/c-jun) and nuclear factor-κB (NF-κB) in T cells. The functional importance of IL-18 is underscored by recent studies that demonstrate suppression of Th1-mediated intestinal inflammation upon blockade of IL-18 expression or function[55–58]. Collectively these data have important implications for Crohn disease, an IBD of unknown origin, that is thought to be mediated by IL-12- and IL-18-driven mucosal Th1 cells and genetically linked to mutations in the NOD2/CARD15 gene that presumably controls immune responses against bacterial infections in the gut[3,13,14,59,60]. In fact, novel therapeutic methods for this disease that are currently being tested in clinical trials include neutralizing IL-12 antibodies, and methods to decrease IL-18 in this disease may be anticipated in the near future.

Although the transcription factors STAT4 and STAT1 have been implicated in Th1 differentiation and IFN-γ regulation (Fig. 4), STAT proteins are expressed in both Th1 and Th2 subsets and may not have a unique role in directly regulating the transcription of the IFN-γ gene. Indeed, some IFN-γ production is retained by STAT4- and STAT1-deficient T cells[61,62]. Thus, it appears that alternative regulatory pathways exist to control IFN-γ gene expression. Further insight elucidating Th1 lineage commitment and IFN-γ expression has recently been provided by the cloning of a novel transcription factor of the T-box family, denoted T-bet[63]. T-bet has been found to be expressed by IFN-γ-producing Th1 but not Th2 cells and increased transcripts for T-bet have been reported to occur within 72 hours after stimulation of T cells under Th1-inducing conditions[45,63]. The functional role of T-bet in regulating IFN-γ production in Th1 cells is supported by recent studies showing profound suppression of IFN-γ production in CD4⁺ but not CD8⁺ T cells from T-bet-deficient mice[64]. Retroviral transduction of primary de-

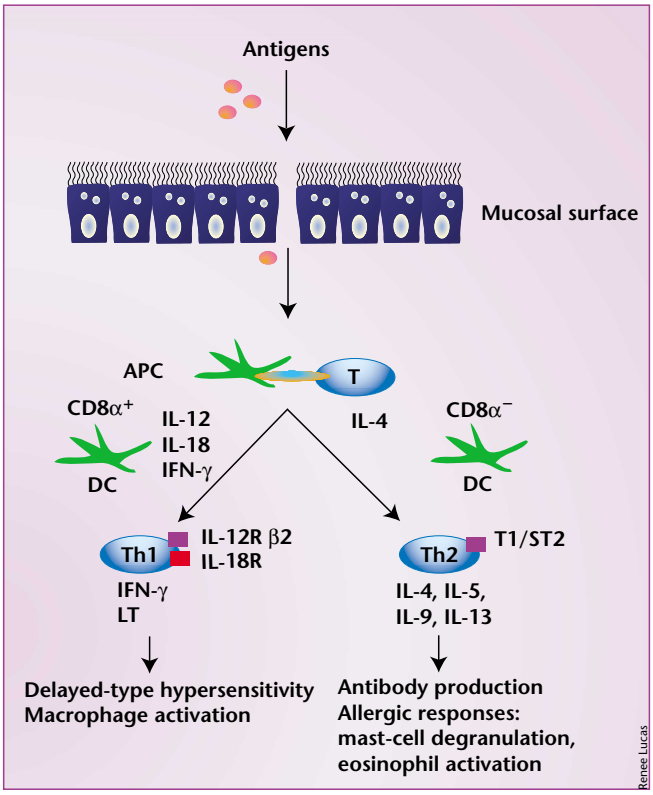

Fig. 2 Cytokine production by mucosal T-helper cells in response to antigens. Antigens can be presented by APCs such as DCs to T cells. In the normal gut immune system, immature DCs seem to preferentially induce T_R and Th3 T-cell responses. However, in the presence of cytokines such as IL-12 and IFN-γ produced by CD8α⁺ DCs, T cells can differentiate into Th1 effector cells, whereas IL-4 can induce Th2 T-cell differentiation[31,41]. Whereas Th1 cells express the IL-12 receptor β2 chain and the IL-18 receptor, Th2 cells express an IL-1-like molecule, denoted T1/ST2, that appears to regulate Th2 effector functions both in the peripheral and the mucosal immune systems[94,95]. Th2 T cells produce large amounts of cytokines such as IL-4, IL-5, IL-9 and IL-13 that regulate antibody production and allergic responses. In contrast, Th1 cells produce high levels of IFN-γ and induce delayed-type hypersensitivity reactions and macrophage activation. Although most of our knowledge of these DC- and cytokine-driven pathways of T-cell differentiation has been derived from experiments using peripheral T lymphocytes, it appears that similar principles exist for mucosal T cells.

veloping T cells or even fully polarized Th2 cells with T-bet induces high levels of IFN-γ production and simultaneously represses production of IL-4 and IL-5 (ref. 63). T-bet thus appears to be an important factor for Th1 development and the regulation of T-cell effector function by simultaneously suppressing Th2 cytokine production and inducing Th1 cytokine gene transcription[63,64]. This finding is also relevant for the mucosal immune system, as T-bet-deficient T cells fail to induce Th1-mediated experimental colitis[65]. This observation may not be attributed to the effects of T-bet on IFN-γ, since T cells from IFN-γ-knockout mice are capable of inducing Th1-mediated colitis in an adoptive transfer system[24], and points potentially towards a more general role of T-bet in Th1 T-cell differentiation, perhaps via induction of IL-12 receptor β2 chain expression and chromatin remodeling[66].

Th2 differentiation and implications for allergic asthma

Th2 development and IL-4 production are known to be regulated by ubiquitous as well as Th2-specific factors[29,47,67]. Various transcription factors such as c-maf, GATA-3, NFATc1, NIP45, JunB and STAT6 have been shown to induce or augment Th2 cytokine production, although only c-maf and GATA-3 are expressed selectively in Th2 cells[29,68–74]. In particular, GATA-3 has been shown to promote expression of several Th2 cytokines, including IL-4, IL-5 and IL-13[47,70,75–77].

GATA-3 is a pleiotropic transcription factor of the C4 zinc-finger family expressed in T-cells, mast cells, eosinophils, basophils, embryonic brain and kidney that binds to a DNA sequence characterized by a 5′-GATA-3′ core element. GATA-3 was found to be selectively expressed in Th2 but not in Th1 cells and to have an important role in chromatin remodeling and cytokine gene expression in T cells[29,70]. In particular, GATA-3 is important for the expression of IL-5 in T cells by trans-activation of the IL-5 promoter. Although GATA-3 only weakly trans-activates the IL-4 promoter directly, adjacent GATA-3 binding sites in the IL-4 locus can strongly enhance transactivation of the IL-4 promoter by GATA-3 in T cells[77]. The functions of GATA-3 on Th2-cytokine gene promoters can be suppressed by repressor of GATA (ROG), a recently cloned lymphoid specific repressor of GATA-3 induced transactivation[78]. In addition, ectopic expression of GATA-3 in developing Th1 cells leads to upregulation of IL-4 and IL-5 and downregulation of IFN-γ. The latter effect appears to be partly due to downregulation of the IL-12 receptor β2 chain[44,70,76]. Finally, ectopic expression of GATA-3 is sufficient to at least modestly induce Th2-specific cytokine expression even in committed Th1 cells[79].

Studies in retrovirally infected T cells have shown that the activation of GATA-3 occurs upon stimulation of the IL-4/STAT6 signaling pathway[71] suggesting that the exposure of naive T cells to IL-4 may be an early event that induces GATA-3 activation and Th2-cell differentiation. However, GATA-3 can fully reconstitute Th2 development in STAT6-deficient T cells suggesting that it is a master switch both in STAT6-dependent and -independent Th2 development[75]. Finally, GATA-3 has been shown to exert STAT6-independent autoactivation, creating a feedback pathway stabilizing Th2 commitment[75].

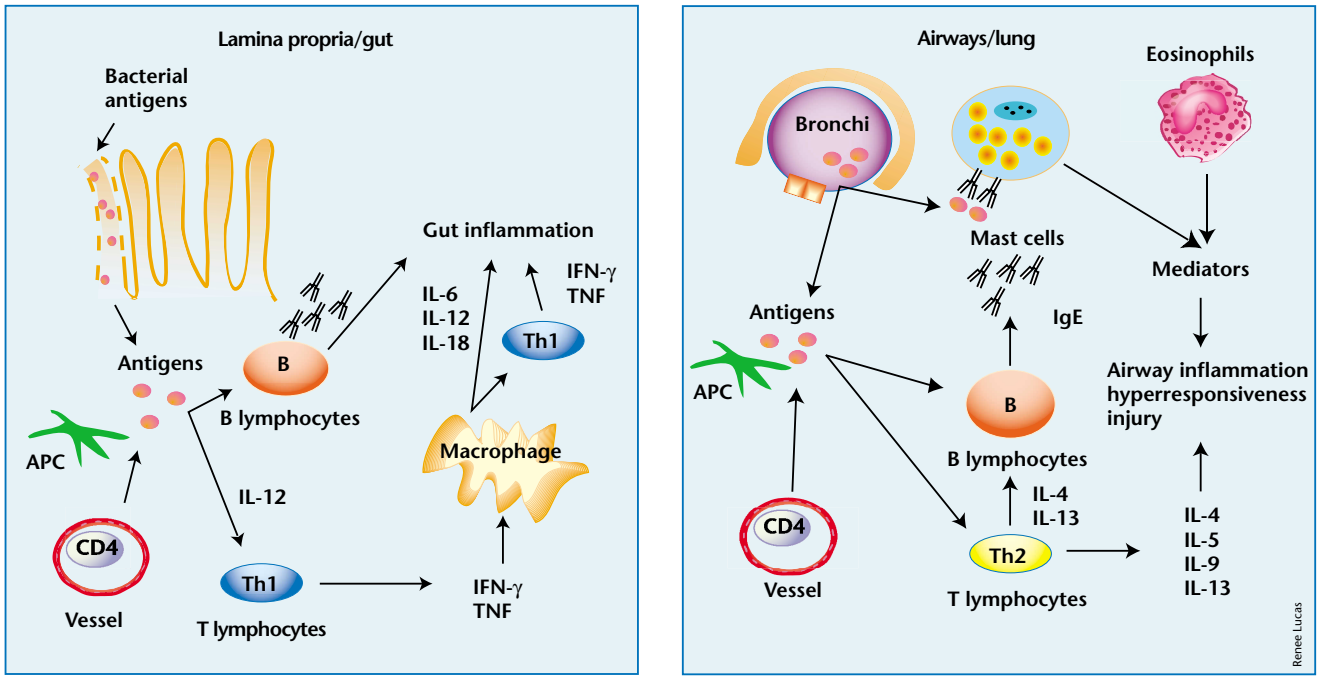

Fig. 3 Induction of pathogenic Th1 and Th2 immune responses at effector sites of the mucosal immune system using Th1-dependent chronic intestinal inflammation and Th2-dependent airway/lung inflammation as examples. In the former example (left), lymphocytes migrate to the lamina propria where they reencounter bacterial, luminal antigens. IL-12-driven Th1 effector cells then produce pro-inflammatory cytokines (IFN-γ and TNF) that activate macrophages to produce pro-inflammatory mediators (for example, IL-6, IL-12 and IL-18) that in turn activate T lymphocytes. The net balance of this scenario is a Th1-mediated inflammation of the gut; a situation similar to Crohn disease in humans[3,60]. In the latter example (right), lymphocytes migrate to the lung where they reencounter inhaled antigens. B lymphocytes produce antigen-specific immunoglobulins such as IgE that binds to its high-affinity receptor on mast cells (FcεRI). Furthermore, Th2 effector cells produce various pro-inflammatory cytokines (for example, IL-4 and IL-13) that cause local inflammation. Finally, IL5 produced by Th2 cells causes expansion of eosinophils that contribute to lung injury in asthma.The net balance of this scenario is a local Th2-mediated inflammation; a situation similar to allergic asthma in humans[40,96].

Based on the above data, it was of particular interest to analyze the expression and functional role of STAT6 and GATA-3 in patients with atopic asthma; a disease thought to be mediated by mucosal Th2 cells and genetically linked to a cell-membrane protein (TIM1) at chromosome 5q that appears to regulate IL-4 and IL-13 production by T cells[67,80]. Allergic asthma is a chronic inflammatory disease characterized by airway inflammation and hyperresponsiveness that affects about 10% of the population in the United States[81]. Th2 T cells and their signature cytokines IL-4, IL-9 and IL-13 have key pathogenic roles in asthma[2,82]. For instance, transgenic overexpression of either IL-13 or IL-9 in the lung has been shown to result in AHR and airway inflammation in mice[83–85]. Furthermore, recent studies showed an increased expression of both STAT6 and GATA-3 in asthmatic airways suggesting that these factors may be involved in the regulation of Th2 cytokine responses in patients with asthma[86]. Additional studies in mice showed that STAT6-deficient mice were protected from Th2-mediated bronchial inflammation and airway hyperreactivity (AHR) in a mouse model of asthma[87] suggesting that STAT6 is an important factor for the development of AHR in asthma. Finally, in an adoptive transfer model of allergic asthma using *in vitro*-differentiated antigen-specific Th2 cells, injection of $STAT6^{+/+}$ Th2 cells into $STAT6^{-/-}$ mice failed to induce lung inflammation and AHR. In contrast, transfer of $STAT6^{+/+}$ Th2 cells into $STAT6^{+/+}$ mice induced lung inflammation and AHR suggesting that STAT6 is essential for both Th2-cell trafficking and effector function in asthma[88].

With regard to GATA-3 it was shown that transgenic expression of a dominant-negative form of GATA-3 in T cells prevents allergic airway inflammation in a mouse model of asthma, indicating that GATA-3 is an important factor in mediating allergic airway inflammation *in vivo*[89]. Furthermore, local targeting of GATA-3 expression in the lung using antisense phosphorothioate oligonucleotides led to suppression of established airway inflammation, AHR and IL-4 production in experimental asthma, suggesting that GATA-3 regulates both airway inflammation and AHR in chronic asthma[90]. NF-κB p50 seems to mediate overexpression of GATA-3 in allergic airway inflammation[91], as p50-deficient mice failed to show high GATA-3 expression and Th2 cytokine production in experimental asthma.

Finally, a recent observation suggests that mice deficient for the transcription factor T-bet display T cell–dependent AHR and bronchial inflammation[92]. This is consistent with the finding that lung T cells in patients with allergic asthma display reduced T-bet expression compared to controls[92] and supports a role for T-bet in controlling the hallmark features of allergic asthma. Indeed, increased amounts of Th2 type cytokines such as IL-4 and IL-13 were recovered from the lung of T-bet deficient mice consistent with the idea of a potentially Th2-mediated disease. These recent data establish T-bet as an important factor in controlling T cell–mediated mucosal immune responses. Taken together with the data on GATA-3, it thus appears that the mucosal balance between GATA-3 and T-bet strongly determines the T-cell fate at mucosal surfaces (Fig. 4) and that the regulation of this balance is a key factor in understanding T cell–mediated mucosal immune responses.

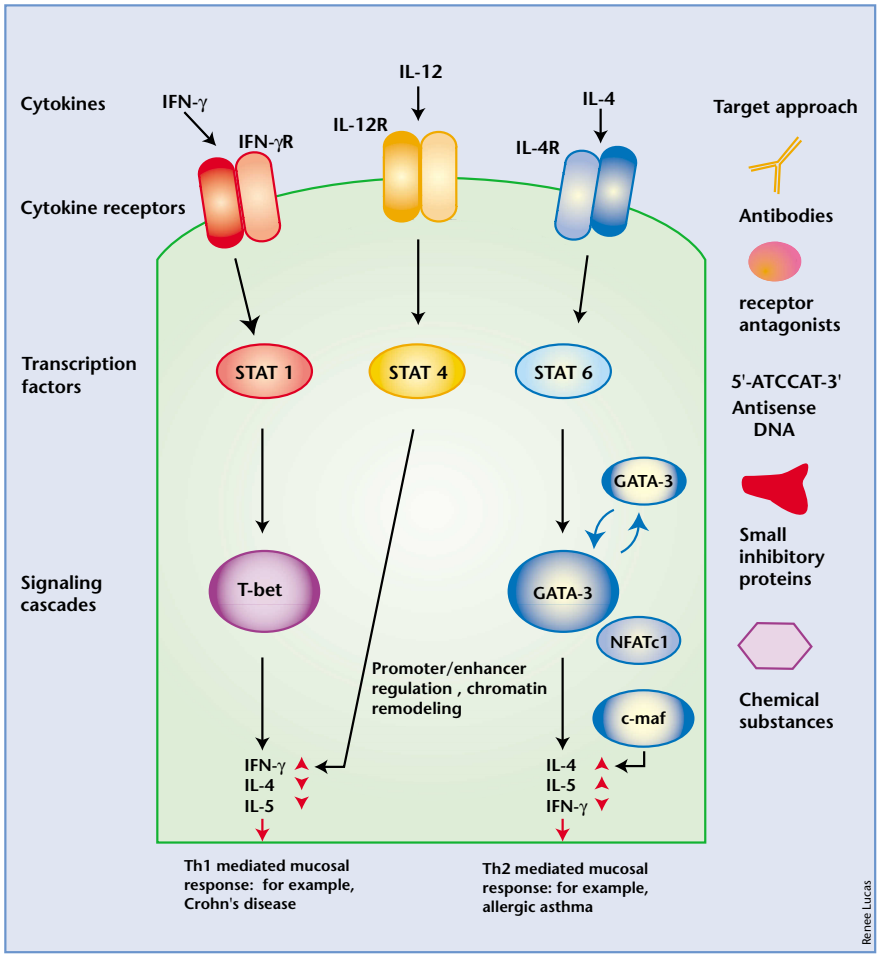

Fig. 4 Cytokine signaling in T lymphocytes via IFN-γ, IL-12 and IL-4. Upon binding to its receptor on the T-cell surface, IFN-γ induces activation of STAT1 and consecutively of T-bet[97]. T-bet is a master transcription factor for Th1 T cells that induces Th1 cytokine production as well as IL-12 receptor β2 chain expression while it simultaneously suppresses Th2 cytokine production[63]. IL-12 induces Th1 T-cell differentiation via activation of STAT4 and consecutive induction of IFN-γ production, but it does not induce T-bet activation directly[38,63,64]. In contrast, IL-4 induces Th2 cytokine production in mucosal T cells by activation of STAT6 followed by activation of the master transcription factor GATA-3 (refs. 70,75,76,89,90). GATA-3 has been shown to exert STAT6-independent autoactivation, creating a feedback pathway stabilizing Th2 commitment (blue arrows). In addition to GATA-3, c-maf and NFATc1 have been shown to regulate IL-4 production in T cells. In recent years, there is a growing interest in cytokine- or cytokine signaling-directed therapies for T cell-mediated mucosal diseases such as Crohn disease and allergic asthma using either recombinant cytokines or anti-cytokine strategies[96,98]. The latter strategies have proven more beneficial in clinical trials so far and include, for example, neutralizing antibodies (such as against IL-4 in asthma and against TNF in Crohn disease) and soluble receptor antagonists (for example, IL-4 receptor antagonists in asthma)[96,98,99,100].

Perspectives

In the last five years, tremendous progress has been made towards a molecular understanding of Th1/Th2 polarization. It is now becoming increasingly clear that these findings have major pathophysiological relevance for mucosal immunity. In particular, the balance between T-bet and STAT6/GATA-3 activation is of central importance for immune responses of mucosal T cells (Fig. 4). Overexpression of GATA-3 predisposes for Th2-mediated diseases such as allergic asthma, whereas activation of T-bet appears to be an essential step for Th1-mediated mucosal diseases such as Crohn disease. One important question will be whether patients with such diseases exhibit a genetic predisposition for overproduction or functional changes in these transcription factors. In fact, a recent study suggests a potential link between STAT6 variants on chromosome 12q and atopic asthma[93].

Recent findings on transcriptional polarization of T cells not only give valuable new insights into the immunopathogenesis of mucosal diseases, but also provide a rationale for selective targeting of transcription factors and signaling cascades in mucosal T cells in autoimmune and chronic inflammatory diseases. At least in animal models, targeting of GATA-3 is beneficial in experimental asthma[89,90], whereas suppression of T-bet inhibits Th1-mediated chronic intestinal inflammation. The obvious potential advantage of such approaches is that they target the expression and function of multiple pro-inflammatory cytokines simultaneously rather than of a single cytokine. For instance, suppression of GATA-3 expression in the lung would presumably suppress IL-4, IL-5 and IL-13 production concurrently. However, given the pleiotropic role of these transcription factors in the immune system, systemic targeting of these factors might cause various side effects suggesting that local targeting (for example, inhalation for the lung or intraluminal application for the gut) may be preferable. In any case, the predominance of T-bet or GATA-3 appears to determine the fate of mucosal precursor T cells. Uncovering the precise signals that induce and perpetuate T-bet and GATA-3 signals in mucosal T cells will likely provide another crucial advance in our understanding of mucosal immunity.

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