TEC and MAPK Kinase Signalling Pathways in T helper (T\textsubscript{H}) cell Development, T\textsubscript{H}2 Differentiation and Allergic Asthma

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Abstract

Significant advances in our understanding of the signalling events during T cell development and differentiation have been made in the past few decades. It is clear that ligation of the T cell receptor (TCR) triggers a series of proximal signalling cascades regulated by an array of protein kinases. These orchestrated and highly regulated series of events, with differential requirements of particular kinases, highlight the disparities between αβ\textsuperscript{+}CD4\textsuperscript{+} T cells. Throughout this review we summarise both new and old studies, highlighting the role of Tec and MAPK in T cell development and differentiation with particular focus on T helper 2 (T\textsubscript{H}2) cells. Finally, as the allergic epidemic continues, we feature the role played by T\textsubscript{H}2 cells in the development of allergy and provide a brief update on promising kinase inhibitors that have been tested in vitro, in pre-clinical disease models in vivo and into clinical studies.

Introduction

Peripheral αβ\textsuperscript{+}CD4\textsuperscript{+} T cell differentiation

Antigen-restricted effector and effector-memory αβ\textsuperscript{+}CD4\textsuperscript{+} T cells are a central component of adaptive immunity. Following successful development and activation in the periphery, effector αβ\textsuperscript{+}CD4\textsuperscript{+} T cells function to rally innate cells, provide help to B cells for antigen-specific immunoglobulin production and stimulate local tissue responses; while regulatory αβ\textsuperscript{+}CD4\textsuperscript{+} T cells control the proliferation of effector αβ\textsuperscript{+}CD4\textsuperscript{+} T cells, suppress innate cell activation and prevent autoimmune reactions. These divergent functions are tightly regulated through cell-intrinsic and extrinsic mechanisms. When these regulatory checkpoints fail, effector αβ\textsuperscript{+}CD4\textsuperscript{+} T cells can cause lethal lymphomas or hyper-inflammatory conditions such as autoimmunity, allergy and leukaemia. Conversely, if effector αβ\textsuperscript{+}CD4\textsuperscript{+} T cells fail to develop or mature, individuals can be left with insufficient immunological protection with equally catastrophic outcomes, such as life-threatening severe immunodeficiency. Similarly, failure of regulatory αβ\textsuperscript{+}CD4\textsuperscript{+} T cell development can allow the activation of auto-reactive T cells and uncontrolled inflammation [1]. Thus, throughout the development, differentiation, activation, effector/regulatory function and long-term survival, multiple feedback loops are in place regulating αβ\textsuperscript{+}CD4\textsuperscript{+} T cell responses.

Once in the periphery, αβ\textsuperscript{+}CD4\textsuperscript{+} T cells can reversibly differentiate into a variety of helper (T\textsubscript{H}) / effector (T\textsubscript{H}1, T\textsubscript{H}2, T\textsubscript{H}17) T follicular helper (T\textsubscript{FH}) and regulatory (T\textsubscript{REG}) populations, often characterized by their cytokine expression profile and up-stream transcription factors (reviewed elsewhere [2-5]). With occasional exceptions, the molecular programs involved in the differentiation of T\textsubscript{H}1, T\textsubscript{H}2 or T\textsubscript{H}17 cells are mostly well defined. For example, IFNγ and IL-12 stimulate T\textsubscript{H}1 differentiation through STAT-1 and STAT-4 for T\textsubscript{H}1 transcription and IL-4 and IL-2 induce GATA-3 / STAT-6 and STAT-5 for T\textsubscript{H}2 differentiation. Similarly, IL-6 and TGFβ promote RORyt and STAT-3 for T\textsubscript{H}17 differentiation and IL-4 in combination with TGFβ induces PU-1 for T\textsubscript{H}9 differentiation (thoroughly reviewed [6,7]). While, the precise signals required for T\textsubscript{H}1 cell differentiation are unclear, BCL6 has been demonstrated to orchestrate part of the T\textsubscript{H}1 cell developmental program [8,9]. Finally, IL-2 and TGFβ induce STAT-5 and Foxp3, which prescribe natural T\textsubscript{REG} (nT\textsubscript{REG}) development in the thymus or inducible T\textsubscript{REG} (iT\textsubscript{REG}) development in the periphery [10]. Foxp3, a transcription factor restricted to T\textsubscript{REG} cells is essential for T\textsubscript{REG} development, maintenance and function [11-14]. Despite their importance in specifying T\textsubscript{H} cell lineage commitment, many of these transcription factors are not self sufficient in coordinating complete transcriptional programs; for example, Bcl6 and PU-1 for T\textsubscript{H}1 and T\textsubscript{H}9 cell differentiation respectively [7,8]. This suggests a role for multiple transcriptional regulators functioning together in T\textsubscript{H} cell differentiation. Although differentiated αβ\textsuperscript{+}CD4\textsuperscript{+} T cells can adopt different effector/regulatory characteristics, there is significant flexibility between their phenotypes [15-18]. In addition to being phenotypically flexible, different αβ\textsuperscript{+}CD4\textsuperscript{+} phenotypes share a common activation step via the T cell receptor (TCR).

T cell receptor (TCR) complex and proximal signalling events

The αβ-TCR functions as a biological bottlenecks, translating peptide-loaded MHCIIE-delivered messages into cellular responses via signalling modules and a series of inter-dependent signalling cascades. Signals transmitted via these pathways influence T cell fate decisions in the thymus, differentiation and proliferation in the periphery and antigen-induced cell death. The α and β subunits of the TCR, similar to the γ and δ subunits, undergo a series of selection processes during T cell ontogeny in the thymus. Pairing of β subunits with a chain occurs during the double negative 3 (DN3) stage with the emergence of CD4\textsuperscript{+}CD8\textsuperscript{+} (double positive, DP) thymocytes. At this stage, αβ\textsuperscript{+}CD4\textsuperscript{+} T cells are selected in the thymus by their ability to respond, or not, to the TCR.

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cell death by positive selection. Thymocytes that respond weakly to the antigen undergo further selection into CD4^+ or CD8^+ single positive cells that mature further to contribute to the peripheral T lymphocyte pool (a detailed review of this process can be found at [19]).

The α and β chains of the TCR encode short cytoplasmic tails and do not signal. Instead, they transduce TCR signals through the non-covalently associated CD3 proteins that exist as a series of hetero (CD3ζ and CD3ε) and homodimers (CD3ζ) along with the αβ chains [20,21]. The interaction between the αβ chains and CD3 is facilitated by positively charged amino acids in the αβ transmembrane domain and the negatively charged residues in the transmembrane regions of the CD3 complex [22]. Successful selection of a mature T lymphocyte involves the expression of all the components of the TCR, with unassociated protein components ubiquitinated and proteolytically degraded by the endoplasmic reticulum [23]. The cytoplasmic domain of CD3 encode immunoreceptor tyrosine-based activation motif (ITAM) that play a crucial role in initiating signalling downstream of the TCR.

Briefly, in response to TCR engagement by antigen, clustering of the TCR and the co-receptors induces protein tyrosine kinases (PTKs) such as Lck, a member of the Src family of tyrosine kinases, to phosphorylate the tyrosine residues in the ITAMs in the cytoplasmic tails of CD3. These phosphorylated ITAMs serve as docking sites for the Src homology 2 (SH2) domain containing tyrosine kinase ZAP-70. ZAP-70 phosphorylates adaptor proteins such as LAT and SLP-76, which brings about downstream activation of different signalling pathways like the PI3-kinase pathway, Ras-MAPK pathway, Ca^2+-mediated signalling and Vav-1 mediated signalling leading to actin-cytoskeletal reorganization (Figure 1).

The kinase kingdom

Over 500 kinases regulate many aspects of a cell function. By the addition of phosphate groups to substrate proteins, kinases coordinate protein movement, localisation and activity. With regard to T lymphocytes, three PTK families namely, the Src family kinases (Lck, Fyn), the Syk family kinases (Syk, Zap-70) and the Tec family kinases (Tec, Itk, Btk and Rlk), are essential for peripheral T cell development. Spontaneous mutations in any of these kinase families, or genetic ablation in murine models, results in dramatically dysregulated T cell development [24-30]. In addition to regulating the function of these protein kinases, the T cell kinome also regulates processes ranging from metabolism, actin re-organisation, anergy/ tolerance and cytokine secretion [31-36].

Kinases are subdivided into eight conventional groups and four atypical groups based on sequence similarity, accessory domains and known modes of regulation (Table 1) [37]. The different kinase families share divergent roles in T lymphocyte development, differentiation of T^+ cells and their effector functions. Although other kinase families serve important functions in T cells, reviewed elsewhere [38-40]. Tec kinase and MAPK (ERK, p38 and JNK) signalling pathways have been intensively studied in qβ-CD4^+ T cells and are the main focus of this review. We have highlighted the unique features of these kinases in T^+ cells in the context of allergic diseases, and provide an update on current therapeutic strategies using inhibitors to interfere with these signalling pathways in allergic diseases.

Involvement of Kinases in qβ-CD4^+ T helper cell Development and Differentiation

Tec-family Kinases

The Tec family of non receptor tyrosine kinases came into focus when Btk (Bruton’s tyrosine kinase), one of the members of the family was identified in severe B cell immunodeficiency, X-linked agammaglobulinemia (XLA) and X-linked immunodeficiency in humans and mice, respectively [64-67]. These reports provided the first evidence of how mutations in tyrosine kinases affect lymphocyte signaling and hence could be linked to primary immunodeficiencies. The first family of kinases, of which Tec (tyrosine kinase expressed in hematopoietic cells) was the first to be identified, also consists of: Btk, Itk (interleukin-2 (IL-2)-inducible T-cell kinase; also known as Tsk or Emt), Rlk (resting lymphocyte kinase; also known as Tskk) and Bmx (bone-marrow tyrosine kinase gene on chromosome X; also known as Etk) [68]. These proteins expressed primarily in hematopoietic cells are characterized by a common domain organization (Figure 2A). With the exception of Rlk, these proteins encode a pleckstrin homology (PH) domain that binds to phosphatidylinositol 3, 4, 5- triphosphate (PtdIns(3,4,5)P_3) on their amino-terminal end [68]. Rlk is an atypical Tec kinase that has a palmitoylated string of cysteine residues at its amino-terminal end [69,70]. This is followed by one or two proline rich regions (PRRs), a SRC-homology 3 (SH3), SH2 and a kinase domain at the carboxy terminal end [68]. The presence of the PH domain allows for these proteins to be regulated by phosphatidylinositol 3- kinase (PI3K) mediated signalling, while the cysteine string in Rlk allows for its constitutive association with the plasma membrane independent of PI3K signalling [71-73].

Typically, recruitment of Tec kinases to the plasma membrane through interaction with PtdIns(3,4,5)P_3 (generated upon PI3K action on phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P_2)), is followed by the phosphorylation of a tyrosine residue in the kinase domain by Src-family kinases, which brings about conformational changes that allow for the recruitment of these proteins into antigen-receptor signalling complexes [68,74]. Downstream phosphorylation
Table 1: Kinase families and their functions.

| Family | Description | Reference |
|--------|-------------|-----------|
| AGC | Named after Protein Kinase A, G and C families, consisting of 60 members across 16 families of cytoplasmic serine/threonine kinases, regulated by secondary messengers. E.g.: PKC and PKA. Mutation and dysregulation linked to many conditions such as diabetes and cancer. | [41,42] |
| CALM | Named after Calfcaldin/Calcium regulated kinases, the CALM group consists of both calcium and non-calcium regulated kinases. E.g.: CALM I, CALM II and CALM IV. CALM II is essential for NF-κB activation following TCR ligation. | [43,44] |
| C1 | Named after Casein kinase 1 (CK1), these monomeric serine/threonine selective kinases are evolutionary conserved within eukaryotes. CK1 kinases regulate diverse functions form circadian rhythm, Wnt signalling, DNA replication and RNA metabolism. | [45] |
| CMGC | The CMGC group includes the evolutionarily conserved, cyclin-dependent kinases (CDKs), mitogen-activated protein kinases (MAPKs), glycogen synthase kinases (GSKs) and CDK-like kinases (CLKs). Their roles include, cell cycle regulation, immune signalling mediated downstream gene expression, regulating cell proliferation and apoptosis. | [32,46-49] |
| RIO | The right open reading frame (RGO) kinases synthesize cyclic GMP from GTP. RGCs are membrane bound and are activated by calcium or the binding of atrial naturetic peptide or related peptides. E.g.: GC-A and GC-G. | [50,51] |
| STE | Serine threonine kinases (STE) are subdivided into 3 main families Ste7, Ste11 and Ste20, which sequentially activate each other and MAPK members. Ste20 kinases (MAP4K) act on Ste11 kinases (MAP5K), which activate Ste7 kinases (MAP2K, MEK, MKK). These families have distinct roles in T lymphocyte activation. | [32,52] |
| TK | Tyrosine kinases (TK) evolutionarily conserved in mammals, phosphorylate tyrosine residues. The TK are divided into receptor and non-receptor (cytoplasmic) tyrosine kinases (CTK). The receptor tyrosine kinases are activated by extracellular signals such as growth factors at the cell surface. The CTK include, Src kinases such as Tec and Janus kinases (JAK). | [53,54] |
| TKL | The Tyrosine kinases-like (TKL) group has close sequence similarity to the TKs. These diverse, serine/threonine kinases, are subdivided into 7 major families, including the RAF, IRAK and RIPK. The TKLs are involved in a wide range of immune cell processes including cell growth, Toll like receptor (TLR) and IL-1 signalling and cell death. | [55-57] |
| Alpha | α-Kinases have low sequence homology with other conventional kinases and have known functions in protein translation, intracellular transport, cell migration and proliferation. E.g.: elongation factor 2 kinase and Dictyostelium myosin heavy chain kinases | [58] |
| PIKK | The phosphoinositide 3-kinase-related kinases (PIKK), required for oxidative metabolism mediate the phosphorylation of pyruvate dehydrogenase. There are four known mammalian isoforms; PDHK1-4, and these regulate the balance between glycolysis and lipid metabolism. | [33,59] |
| PDK | The mitochondrial pyruvate dehydrogenase kinases (PDKs), required for oxidative metabolism mediate the phosphorylation of pyruvate dehydrogenase. | [60,61] |
| RIO | The right open reading frame (RIO) kinases are expressed in archea to humans. Their functions include, ribosome biogenesis and chromosome maintenance, although the precise substrate of the RIO kinases is unknown. RIO kinases from the ruminant nematode, Haemonchus contortus have been targeted for nematocidal drugs. | [62,63] |

Figure 2: Tec kinases structure and their differential roles.

The different members of the Tec kinase family are shown in a schematic. The proteins typically encode a N terminal pleckstrin homology domain (PH), followed by a Btk homology domain (BH), a proline rich region (PRR), a Src homology 3 (SH3) domain, a SH2 domain and a carboxy terminal kinase domain. Rlk, unlike the other members, encodes a palmitoylated string of cysteine residues on its amino terminal domain. Itk is expressed maximally in and is important for T cell differentiation, while Rlk has a significant role in regulating Tc1 cells. The role of Itk in Tc1 cells is unclear, while Rlk may compensate for Itk function in Itk-/- cells. BMS-509744 is a pharmacological inhibitor of Itk.

of adaptor molecules, LAT and SLAP-76 brings about the recruitment of the protein tyrosine kinase Itk. Itk in turn phosphorylates and activates PLC-γ, which catalyzes inositol-1,4,5-triphosphate (Ins(1,4,5)P3) and diacylglycerol (DAG). This activates DAG binding proteins like protein kinase C (PKC) and Ras guanyl releasing proteins (RasGRP), which activate the MAPK family leading to downstream effector responses (Figure 1). Increases in the intracellular Ca2+ levels due to Ins(1,4,5)P3 signalling also activates the nuclear factor of activated T cells (NFAT) family of transcription factors, which bring about changes in the gene expression levels.

In addition to being primarily activated in response to TCR signalling, Tec kinases are also involved in chemokine, cytokine, growth factor and co-stimulatory signalling pathways [74]. For example, Itk and Tec interact with the T cell co-stimulatory receptor CD28, where they become phosphorylated and mediate downstream signalling [75-77]. Itk is involved in CD2, CXCR4 and the chemokine, stromal cell derived factor 1a (SDF-1a)/(CXCL12) mediated signalling [78-81]. Tec regulates signalling downstream of cytokine receptors, IL-3, IL-5, prolactin, erythropoietin, GCSF, c-kit and the IL-6 family, while Rlk is involved in CXCL12 and MIP3-β mediated signalling [74,81].

Tec kinases and T lymphocytes

T lymphocytes express Itk, Rlk and Tec differentially; suggesting their importance in different sub-populations of T lymphocytes, with Itk maximally expressed in naïve T cells [68,74]. T cell activation further increases the expression of Itk, with higher expression of the protein in Tc1 cells compared to Tc2 cells. In this regard, Itk has been implicated in the development of Tc1 responses [82]. In addition to T cell activation, IL-2R signalling can also induce Itk expression [82,83]. Rlk, akin to Itk, is also expressed in thymocytes and mature naïve T lymphocytes. Of the Tec kinases, Rlk is thought to be the most important for Tc1 differentiation.
lymphocytes, though its expression levels are 3-10 fold lower in naive T lymphocytes compared to Itk [84]. Unlike Itk, Rlk is preferentially expressed in T\(_{\text{H}1}\) cells implicating its importance in T\(_{\text{H}1}\) responses [85,86]. Tec has relatively low expression in T lymphocytes compared to Itk and Rlk with 100-fold lower expression than Itk. Tec is increased upon stimulation and, similar to Itk, is expressed higher in T\(_{\text{H}2}\) cells than in T\(_{\text{H}1}\) cells [84,87]. These observations suggest that Tec kinases play an important role in regulating effector T cell differentiation.

**Function of Tec kinases in T lymphocytes**

In accordance with their roles in TCR activation, mice deficient in Tec kinases demonstrate defective PLC-\(\gamma\) phosphorylation and activation. Consequently, this leads to defective production of Ins(1,4,5)P\(_3\), reduced Ca\(^{2+}\) influx and activation of downstream transcription factors. Impaired activation of MAPKs like extracellular signal regulated kinase (ERK), JUN N-terminal kinase (JNK) and activated protein-1 (AP-1) is also observed in these cells [68]. Mutations affecting Tec kinases lead to impaired TCR stimulation, proliferation and IL-2 production [27,88,89]. Itk was first demonstrated to be important for the development of conventional T lymphocytes [27]. This was followed by studies demonstrating the role of Itk in Tec in positive selection and negative selection in response to both MHC class I and class II restricted transgenes [27,28,90]. These roles of Itk and Rlk were attributed to decreased ERK activation and defects in cellular adhesion in the kinase deficient cells [28,91,92]. Among other important roles, Tec kinases have been implicated in the development and differentiation of T lymphocytes. Specifically, Itk deficiency led to impaired recruitment of Vav-1, a guanine nucleotide exchange factor, at the TCR, resulting in disruptions in the nucleation of actin polymerization [68]. Itk also regulates integrin expression and adhesion, following TCR engagement, with Itk deficiency resulting in reduced TCR activation [93]. Collectively both Itk and Rlk regulate the strength of signal originating from the TCR during T cell development. It is also important to note that beyond \(\alpha\beta\) T cells, Itk is also required for the development and function of INK7 cells and \(\gamma\delta\) T cells (reviewed in [94]).

Itk and Rlk have been analysed for their roles in cytokine production, immunity to infection and inflammatory diseases, such as allergy and autoimmunity. These studies have established clear roles for Itk in the differentiation of T\(_{\text{H}2}\) cells (Figure 2B), with CD4\(^+\) T cells from Itk\(^{-/-}\) mice impaired in their ability to produce T\(_{\text{H}2}\) cytokines in vitro [82,83,95,96]. Concordant with this, Itk\(^{-/-}\) mice failed to mount T\(_{\text{H}2}\) responses following infection with *Leishmania major*, *Nippostrongylus brasiliensis*, *Schistosoma mansoni*, or allergen-induced airway inflammation [82,83,95]. In contrast, Itk\(^{-/-}\) mice were capable of generating effective T\(_{\text{H}1}\) responses in these settings. Consistent with its role in regulating T\(_{\text{H}2}\) responses, enhanced Itk expression was observed in patients with atopic dermatitis, a T\(_{\text{H}2}\)-associated inflammatory disease of the skin [97]. These defects have been attributed to impaired recruitment of Vav-1 and PKC-\(\delta\) following TCR activation, with reduced NFAT activation, as well as the requirement of Itk to support the maintenance and amplification of the T\(_{\text{H}1}\) effector responses [98].

Rlk, distinct from Itk, is not only expressed in high levels in T\(_{\text{H}1}\) cells but also bound to the Ifng promoter and was required for the production of IFN-\(\gamma\) [86] (Figure 2B). Despite this preferential regulation in T\(_{\text{H}1}\) cells, Rlk\(^{-/-}\) mice show only minor defects in response to infection by *Toxoplasma gondii*, a T\(_{\text{H}1}\) inducing pathogen [83,89]. Though this observation is yet to be completely understood, it is currently thought that the existence of compensatory mechanisms in these mice could contribute to this effect [68].

Despite the distinct roles of Itk and Rlk in T\(_{\text{H}1}\) cell differentiation, further examination of Itk/Rlk double knockout mice under different T\(_{\text{H}2}\) regulatory conditions suggests that this dichotomy might be an oversimplified model. Itk/Rlk double knockout (DKO) mice upon initial characterization demonstrated severely impaired T\(_{\text{H}1}\) responses following *T. gondii* infection [89]. In contrast, Itk/Rlk DKO mice mounted an effective T\(_{\text{H}2}\) response following *S. mansoni* infection, despite impaired NFAT activation [83]. These differences have lead to many different ideas about the roles of the individual Tec kinases in T\(_{\text{H}1}\) cells [68].

The models put forth to explain these differences in the Itk\(^{-/-}\), Rlk\(^{-/-}\) and the Itk/Rlk DKO mice include, the idea of “differential expression of Tec kinases in T\(_{\text{H}1}\) cells regulate their distinct functions”. This idea is supportive of the individual roles of Itk and Rlk in T\(_{\text{H}1}\) and T\(_{\text{H}2}\) cells respectively, and the compensatory roles of Itk and Rlk, as the expression of an Rlk transgene in the Itk\(^{-/-}\) mice rescues the impaired T\(_{\text{H}2}\) response upon challenge with T\(_{\text{H}2}\)-inducing *Schistosoma egg* antigen (SEA) or in a mouse model of allergic asthma [99].

Another model draws its basis from, “the TCR signal strength dictates TH-cell development”. This model was put forth to explain the T\(_{\text{H}2}\) biased nature of Itk/Rlk DKO mice upon *S. mansoni* infection. This notion would explain how weak signals, such as low antigen doses or altered peptide ligands, promotes a T\(_{\text{H}2}\) biased response [100], as activated cells down regulate GATA-3 and differentiate into other lineages [83]. Concordant with this, Itk/Rlk DKO mice were severely compromised in signalling downstream of their TCR and T cells from these mice were defective in their ability to repress the expression of GATA-3 [83]. This suggests, that regulation of GATA-3 expression by TCR signalling in Itk/Rlk wild type cells is precedent to the differentiation of the T\(_{\text{H}1}\) cells to the T\(_{\text{H}2}\) lineage.

Defective activation of the NFAT family members in Itk/Rlk DKO mice might also be responsible for the intact T\(_{\text{H}2}\) responses [83,89]. Inadequate NFAT activation, due to a lack of, or impaired activation of, NFATc2 and NFATc3, members of the NFAT family, is also associated with increased development and activation of T\(_{\text{H}2}\) cells [101,102]. Additionally, the potency of the TCR signal contributes to the differential expression of NFATc1, another NFAT family member, which enhances T\(_{\text{H}2}\), polarization, and transcription of *ift* [103]. Despite these observations, the differential expression of NFAT proteins in Itk/Rlk DKO mice is debated [68,83]. Since impaired Ca\(^{2+}\) flux is associated with the development of a T\(_{\text{H}2}\) phenotype and tyrosine mutant LAT is associated with impaired Ca\(^{2+}\) flux and a T\(_{\text{H}2}\) bias, the possibility of a similar LAT mutant in Itk/Rlk DKO mice is a plausible hypothesis worth evaluation [104]. Moreover, the role of T cell intrinsic mechanisms such as contributions from Natural killer (NK) cells, Mast cells, Basophils and Eosinophils’s in Itk/Rlk DKO mice is another aspect yet to be explored [68].

Although the precise roles of Itk and Rlk in modulating T\(_{\text{H}2}\) development with contributions from the above-mentioned models is yet to be confirmed, the role of Itk in modulating T\(_{\text{H}2}\) responses remains undisputed. These observations have prompted several studies targeting Itk as a potential therapeutic target for asthma and other inflammatory disorders, described in more detail below [105-107].

Itk also regulates T\(_{\text{H}17}\)-associated cytokines [108]. CD4\(^+\) T lymphocytes from Itk\(^{-/-}\) mice expressed very low levels of IL-17A when
Mitogen Activated Protein Kinases (MAPKs)

MAPKs are one of the most ancient and evolutionarily conserved families of kinases. These proteins are activated in response to cytokines, growth factors, and environmental stresses and are involved in cell proliferation, differentiation and death. The MAPK family includes three major groups in mammalian cells: the extracellular signal regulated kinases (ERKs), the p38 MAPK family and the c-Jun N-terminal kinases (JNK) (Figure 3) [109-111]. Each family of MAPK is activated by dual phosphorylation of threonine and tyrosine residues in their activation loop (Thr-X-Tyr) by evolutionarily conserved upstream kinases. MAPK kinases (MAPKKs) and MAP kinase kinases (MAP3Ks). The MAPKKs are serine/threonine kinases that are typically activated by RAS superfamily GTPases or signalling intermediates in response to cytokines and growth factors. This brings about the phosphorylation of the downstream MAPK, which activate the MAPKs by dual phosphorylation of the threonine and tyrosine residues in the activation loop. Once activated, the MAPKs phosphorylate their substrates such as transcription factors, phospholipases, cytoskeletal proteins, as well as several additional protein kinase families such as the ribosomal S6 kinases, mitogen and stress activated kinases and MAPK-interacting kinases [49].

The role of MAPKs, specifically the MEK-ERK pathway, in early polarized under T<sub>h</sub>17 conditions in vitro. This effect was even more dramatic in T lymphocytes from Itk/Rlk DKO mice, supporting the functional redundancy between the Tec kinases. This role of Itk was once again coupled to its ability to activate NFAT in response to TCR signalling, suggesting activated NFAT binds to the IκBα promoter in wild type cells but not in Itk<sup>−/−</sup> cells [108]. Collectively, Tec kinases regulate distinct T lymphocyte development and functions at multiple levels and provide an ‘Achilles heel’ to target T cell-mediated diseases.

ERK family, the first family of mammalian MAPK to be identified, encodes two classical members, ERK1 and ERK2. These kinases are dual phosphorylated at the activation loop Thr-Glu-Tyr and are classically activated in response to mitogens or insulin resulting in the activation of the proto-oncogene, Ras. Ras recruits and activates the Raf family of MAP3Ks. Raf in turn phosphorylates the MAP2K members, MEK1 and MEK2 which activates the downstream ERK family of kinases [112]. The ERK family of kinases are also activated in response to pro-inflammatory cytokines, such as TNFa, IL-1β and pathogen associated molecular patterns (PAMPs) like lipopolysaccharide (LPS) [49]. The ribosomal S6 kinases (RSks), mitogen and stress activated kinase family members (MSks), MSK1 and MSK2 and the MAPK-interacting kinase (MNKs) MNK1 and MNK2 are selective substrates for the ERK family [113-117]. ERK can also regulate the activation of Elk1, member of the ternary complex factor (TCF) family, which is an important regulator of the AP-1 family of transcription factors [118].

The p38 family, another group of proteins in the MAPK family, has 4 members; p38α, p38β, p38γ and p38δ. These are activated in response to environmental stresses like ionizing radiation and osmotic shock, inflammatory cytokines and PAMPs. Upon activation, the MAP3Ks phosphorylate the MAP2Ks, MKK3/MKK4/MKK6, which in turn phosphorylate the p38 family members in their activation loop, Thr-Gly-Tyr. The p38 family in addition to regulating the MAPK-interacting kinases (MNK1/2) and the mitogen and stress activated protein kinases (MSK1/2) also regulate the MAPK-activated protein kinases (MK2) [119-122]. The p38 family members also regulate the activation of the transcription factors, C/EBP homologous protein (CHOP/GADD), myocyte enhancer factor 2 (MEF2) family members MEF2A/C and ATF2 of the AP-1 family [123-125]. The p38s also phosphorylate Sap-1α, a member of the TCF family, which together with serum response factor (SRF) binds to the serum response element (SRE) on the c-fos promoter and mediates c-fos induction [126,127].

The last group of the MAPK family, the JNK family, has 3 main members in eukaryotic cells; JNK1, JNK2 and JNK3 [111]. The JNK family, in addition to being activated by cytokines and growth factors, is also activated by environmental stresses, genotoxins, mechanical stress, pro-inflammatory cytokines, PAMPs and danger associated molecular patterns (DAMPs). The JNK family members are subject to differential pre-mRNA splicing thus giving rise to 12 different JNK polypeptides. While the functional significance of these isoforms remains unclear, it has been reported some of these isoforms (α and β JNK) differ in their affinities for their substrate [128-130]. A typical signalling cascade brings about the phosphorylation of the MAP2Ks, MKK4 and MKK7 by MAP3Ks. This in turn phosphorylates the JNK family at the activation loop Thr-Pro-Tyr to activate downstream signalling. A major group of JNK substrates are the AP-1 family of transcription factors including, c-Jun, JunD and ATF2 [128,131,132]. JNKs also phosphorylate Elk-1 at the carboxy terminus, contributing to the regulation of c-fos [133], NFAT4 and NFAT2 [134,135]. Since NFAT2 activity is important for the polarization of T<sub>h</sub>2 cells to T<sub>h</sub>2 cells, JNK mediated inhibition of NFAT2 has been shown to negatively regulate T<sub>h</sub>2 differentiation [136,137].

MAPKs in T cell Development, Differentiation and Function

ERK and T lymphocytes

The role of MAPKs, specifically the MEK-ERK pathway, in early
thymocyte development was initially established in fetal thymic organ cultures (FTOC) exhibiting compromised differentiation of immature CD25+CD44+ thymocytes to the pre-TCR expressing thymocytes [138]. Further support for the functional role of ERK in pre-TCR development came from studies that demonstrated that transfection with a TCR-β chain in Rag2-/- FTOC resulted in ERK activation. Furthermore, constitutive activation of ERK using a mutant form of c-Raf-1 induced maturation and expansion of CD25-CD44- thymocytes from Rag2-/- mice [139,140].

The importance of the Ras-ERK pathway in late thymocyte development was also demonstrated when Erk1-/- mice had reduced percentages of mature CD4+CD8+ thymocytes [141]. The role of the Ras-ERK pathway in positive selection was substantiated when Delgado and colleagues reported the inability of Clβ-/- DP thymocytes to undergo positive selection [142]. This report held important implications for the role of ERK in thymocyte maturation and TCR signalling, as the positive selection defect was coupled to impaired ERK activation, due to defective tyrosine phosphorylation of the upstream adaptor LAT and the CD3, chain upon engagement of the TCR. This suggested that activation of the LAT-Ras-ERK pathway was important for positive selection. ERK function in TCR signalling was also validated by studies linking the adaptor proteins, SLP76 and Grb2 to the downstream activation of the SOS-Ras-MEK-ERK pathway [143-145]. Simultaneously, studies demonstrated the functional significance of clonal anergy linked to incomplete Ras and ERK activation [146,147].

In addition to TCR signalling, the Ras-ERK pathway also regulates T0,2 differentiation. ERK activation, mediated by MEK, induced phosphorylation of STAT-6 and IL-4Rα in response to IL-4 [148]. Furthermore, TCR activation of the Ras-ERK pathway stabilized the T0,2 specific transcription factor GATA-3 through inhibition of its degradation by the ubiquitin proteasome pathway [149]. ERK activation has also been linked to IL-4 expression during TCR induced T0,1 differentiation [150,151]. The mechanism mediating this regulation was governed by the level of ERK activation, which in turn, was governed by the strength of signal originating from the TCR. Mechanistically, low strength TCR activation induced IL-4 production by naïve CD4+ T cells through activation of ERK weakly and transiently. Intense and sustained ERK activation in response to strong TCR signals inhibited the expression of early IL-4 from CD4+ T cells and led to T0,1 differentiation [100,150,152].

In addition to the direct reports of ERK regulation in T lymphocytes, the MAP3K, tumour progression locus-2 (TPL-2), has also been linked to T cell differentiation. TPL-2, initially identified as an oncprotein kinase, is an important regulator of ERK activation in macrophages [153-157]. Deficiency of pfl2 led to impaired IFN-γ production by T0,1 cells, with compromised control of T0,2 gondii [158]. The impaired T0,1 responses in T. gondii infected T0,2-/- mice was suggested to be T cell intrinsic. Furthermore, T0,2-/- mice develop an enhanced inflammatory T0,2 phenotype upon OVA challenge [159]. This exaggerated T0,2 response was linked to the intrinsic inability of the T lymphocytes to differentiate to IFN-γ producing T1,1 cells in vitro, as a consequence of poor induction of T-bet and STAT-4 [158,159]. This functional role of TPL-2 in influencing T0,1 polarization was further attributed to TPL-2 dependent ERK activation. Contrastingly in a separate study, T0,2-/- mice develop skewed T0,1 responses upon L. major infection and OVA immunization, suggesting TPL-2 functions as a negative regulator of T0,1 responses by inhibiting IL-12 production in innate cells [160]. These studies conflicting observations on the role of TPL-2 in T cell differentiation and function may be complicated further as TPL-2 regulates the proteolytic degradation of the NFκB inhibitory protein, p105, which functions to retain the NFκB subunits inactive in the cytosol [161]. Thus, defects in TPL-2 signalling pathway would also encode defects in NFκB signalling.

**p38 family in T cell development and differentiation**

The p38 kinase is required for the early expansion of immature thymocytes [162]. High levels of p38 kinase activity measured by an *in vitro* kinase assay, are associated with CD4+CD8 double positive thymocytes, which are CD25+/CD44- and CD25-CD44+; and CD25-CD44+. However, low levels of p38 kinase activity are associated with the CD25-CD44- pre-TCR thymocytes and CD4+CD8 DP thymocytes [162]. While p38 MAPK regulates the early stages of thymocyte development, constitutive activation of p38 MAPK in a constitutively active mkk6 transgenic mouse, blocks the differentiation of immature thymocytes to the DP stage, and results in a lack of T lymphocytes in the peripheral immune system [162]. The role of p38 MAPK in positive and negative selection was initially addressed using FTOC assays and a pharmacological inhibitor of p38 MAPK. This initial study demonstrated that p38 was not required for positive selection. Instead, forced expression of a constitutively active p38 MAPK caused the deletion of DP thymocytes [163]. Meanwhile, a contrasting study documented an important regulatory role for the p38 family in positive selection, where inhibition of p38 kinase using the pharmacological inhibitor SB203850 prevented the differentiation of DP cells into single positive cells *in vitro* [164]. This observation was further supported by studies using transgenic mice with dominant negative mutations in mkk3 and mkk6 that suggested, complete inhibition of p38 kinase activity lead to impaired positive selection with a decrease in single positive CD4 or CD8 thymocytes [165]. This study provided a definitive role for p38 kinase in positive selection, unlike the previous observations with incomplete inhibition of p38 kinase activity- either due to an ineffective dominant negative mutation or due to compensatory mechanisms from alternative signalling pathways [162,166].

With regard to T cell differentiation, inhibition of p38 MAPK in CD4+ T cells from a transgenic mouse expressing a dominant negative p38, resulted in decreased IFN-γ production [167]. The regulatory role of p38 in IFN-γ production was further supported by the observation that CD4+ T cells from a mkk6 transgenic mouse with a constitutively active p38 kinase also produced increased levels of IFN-γ [167]. These observations, supported by other independent studies, suggest an important role for the p38 MAPK pathway in regulating TH1 responses both *in vitro* and *in vivo* [168-170]. Additionally, the role of p38 kinase, specifically its a isoform, p38α in TH1 responses was demonstrated to be cytokine dependent with p38α-/- CD4+ T1,1 cells defective in IFNγ secretion upon IL-12 and IL-18 stimulation compared to TCR induced IFNγ production [171]. This suggested that p38 kinase played an important role in maintaining T1,1 cytokine production. Contrasting observations were made with respect to T0,2 cells. While, the CD4+ T cells from the dominant negative p38 transgenic model showed no change in IL-4 production, CD4+ T cells from the mkk6 transgenic model demonstrated decreased IL-4 production [167]. In an independent study, inhibition of p38 MAPK kinase activity using the inhibitor SB203850, demonstrated a role for p38 MAPK in GATA-3 phosphorylation and positive regulation of T0,2 cytokines [172]. Exactly how this differential regulation by p38 MAPK occurs in TH1 and TH2 responses is not completely understood. Common upstream activators like Rac2 and GADD45γ (the stress inducible protein), whose expression is specific to, or higher in, TH1 cells than TH2 cells, have been suggested to potentially activate one pathway over the other [170]. In this regard,
expression of GADD45γ or GADD45β in the stress activated MAP3K, MEKK4 sufficient cells, mediates p38 activation and up regulates IFN-γ production in CD4+ T cells [173].

In addition to the canonical pathway of p38 activation by MAP2Ks and MAP3Ks, there exists a non-canonical pathway of p38 activation, which is mediated by phosphorylation of Y323 of the p38 MAPK, catalysed by the TCR signalling adaptor Zap70 [174]. This phosphorylation is followed by the auto phosphorylation at the activation loop T180/Y181 that brings about the activation of the p38 MAPK [174]. The non-canonical pathway has important implications in T cell differentiation as a mutant form of p38α in T cells, which is incapable of undergoing non-canonical activation due to a Y323F mutation, has been linked to reduced IFN-γ production [175]. All these studies indicate the p38 MAPK family has important regulatory functions in early thymocyte maturation and differentiation of CD4+ T cells into IFN-γ producing T_{Th}1 cells.

**JNK family in T cell development and differentiation**

Though there is no strong support for the role of JNKs in the development of CD4+ or CD8+ T cells, several studies have implicated the JNK pathway in the deletion of CD4/CD8 TpH2 dp thymocytes [176-178]. These studies demonstrated that the JNK pathway is activated in response to signals initiating negative selection in response to MKK7 activation. Experiments with a dominant negative jnk transgenic mouse demonstrated that inhibition of the JNK pathway resulted in the deletion of CD4/CD8 DP thymocytes [176]. Of the different isoforms of JNK, JNK2 was demonstrated to have a dominant effect on TCR induced thymocyte apoptosis, which was in turn related to its ability to modulate c-Jun and NFAT [179].

JNKs are very weakly expressed in peripheral lymphoid tissues and their activity is also very low [180]. This low level of activity is also supported by the low level of expression of their kinases MKK4 and MKK7 [170]. However, their activity is significantly upregulated upon TCR activation and peaks 36-60h post activation. Despite comparable expression of the JNK proteins in the effector phase of T_{Th}1 and T_{Th}2 cells, JNK kinase activity is dominant in T_{Th}1 cells rather than T_{Th}2 cells [181].

Several groups analysed the role of JNK1 and JNK2 in T cell activation and cytokine production [136,137,177,178,182]. JNK2 deficient T_{Th}1 cells produced significantly lower levels of IFN-γ and CD4+ T cells from these mice failed to differentiate into T_{Th}1 cells [182]. Reduced IFN-γ production in Jnk2−/− mice was due to reduced expression of the IL-12 receptor β chain (IL-12Rβ2) [182]. JNK1, unlike JNK2, seemed to have a more pronounced role in freshly activated T cells despite comparable protein expression of the two isoforms in these cells [136]. This suggested that total JNK kinase activity in T cells might not always be a result of the cumulative effects of the functional JNK1 and JNK2 isoforms. Indeed, in support of this observation kinase activity by JNK2 is more pronounced in T_{Th}1 effector cells [182]. The role of JNK1 and JNK2 in IL-2 expression was resolved by Dong and colleagues, who generated JNK1/JNK2 double knockout mice and analysed the effect of JNK1/JNK2 absence on TCR activation and IL-2 expression [137]. This study revealed JNK1 and JNK2 were not required for the activation of T cells and IL-2 expression but were important for T_{Th}1 cell, particularly T_{Th}1 differentiation and its corresponding effector cytokine production, beyond IL-2.

The role of JNK1 in T_{Th}1 cell differentiation comes from studies using Jnk1−/− mice, which exhibit exaggerated T_{Th}2 responses in addition to impaired T_{Th}1 responses [136]. This was true even for CD4+ T cells cultured under T_{Th}1 conditions. The enhanced T_{Th}2 response observed in Jnk1−/− mice was consistent with their inability to heal skin lesions and ulcers upon infection with L. major [183]. Dong and colleagues examined the negative regulatory effect by JNK1 on T_{Th}2 differentiation and showed Jnk1−/− mice had elevated levels of NFATc, whose nuclear retention in wild type cells is regulated by JNK mediated phosphorylation [136]. JNK phosphorylation of NFATc prevents it from being dephosphorylated by calcineurin phosphatase that is responsible for the nuclear retention of NFATc [135]. In the absence of JNK signalling, NFATc susceptible to dephosphorylation by calcineurin phosphatase, accumulates in the nucleus and mediates exaggerated transcriptional activity by increasing the expression of T_{Th}2 cytokines.

Additionally, it has been demonstrated that JNK1 mediated suppression of T_{Th}2 effector cytokine production was dependent on the proteolytic turnover of the AP-1 family member, JunB [184-186]. JunB is post-translationally regulated by ubiquitination in CD4+ T cells [187]. This is mediated by the E3 ubiquitin ligase, Itch, which is activated following TCR co-stimulation by JNK1 phosphorylation [187,188]. These observations were corroborated by Enzler and colleagues who demonstrated that the stress induced MAP3K, MEKK1 upon TCR activation recruits Itch to its signalling complex and activates JNK1, thus regulating JunB mediated T_{Th}2 cytokine expression [189]. Itch induced ubiquitination of JunB, mediated by MEKK1-JNK1 signalling has also been shown to be involved in peripheral T_{Th}2 tolerance [190].

**The stress activated MAP3Ks and T lymphocytes**

The stress activated MAP3Ks consist of a family of five members, MEKK1-4 and the NF-kB-inducing kinase (NIK). This group of proteins can activate multiple members of the MAPK family. Of these family members, MEKK2 and MEKK3 are promiscuous activators as they are non-selective in their target substrates and equally activate ERK, JNK as well as the p38 MAPK family [49]. Their function in T cell activation and homeostasis has been demonstrated using biochemical and genetic studies, where they share the downstream activation of ERK, JNK and p38 MAPKs.

Both MEKK2 and MEKK3 are co-expressed in T cells suggesting they might have overlapping functions. Chang and colleagues generated MEKK2/MEKK3 DKO mice to investigate the role of MEKK2 and MEKK3 in T_{Th}1 cell differentiation [194]. These mice exhibited increased number of T_{Reg} as well as T_{Th}17 cells. This was due to a cell intrinsic phenomena as mixed bone marrow chimeras with equal ratios of wild type or MEKK2/MEKK3 DKO T cells in Rag2−/− mice maintained the phenotype correlates with decreased clearance of L. monocytogenes-OVA infection and is associated with reduced TCR mediated activation of ERK, JNK and p38 MAPKs.

This study also linked the enhanced sensitivity to TGF-β to defective activation of ERK1 and ERK2, which in turn brought about the hypo-phosphorylation of the SMAD2/3 proteins in their linker regions, which is important for suppression of TGF-β signalling [195-198].
Therapeutically Targeting Kinases in Allergy

Atopy and the manifestation of allergic asthma presents as a heterogeneous clinical disease, mediated in part by CD4+ Th2 cells, in addition to a dominant role played by Th17 cells [199]. Briefly, the development of IL-4-secreting allergen-specific Th2 cells, which promote the class-switching and clonal expansion of allergen-reactive B cells, leads to allergen-reactive IgE and an atopic or sensitized state. Following subsequent exposure to the same allergen, cross-linking of mast cell- and basophil-bound IgE molecules, trigger acute early phase reactions with histamine, prostaglandin and leukotriene release. Reactivation of allergen-specific T cells typify the late phase response, re-enforcing antibody class switching but also mobilizing, maturing and activating eosinophils and promoting goblet cell hyperplasia and mucus secretion, through the actions of IL-5 and IL-13. In chronic cases, resolution of repeated inflammatory events within the tissue can lead to excessive wound healing and the development of fibrotic plaques and smooth muscle thickening. Many cellular events contribute to this inflammatory disease, and therefore targeting of any particular kinase, or kinase family is fraught with complexities. Nevertheless, several kinase inhibitors have been proposed, tested or moved into pre-clinical and clinical trials to treat inflammatory diseases, including asthma. Below we summarize some of the many inhibitors being developed and refer to more focused reviews, where possible, for further reading.

Tec kinase inhibitors

PI3 kinase inhibitors: PI3Kδ, one member of the PI3K family, is predominantly expressed in hematopoietic cells including mast cells, B cells, T cells and neutrophils. Although not a Tec kinase, PI3Kδ converts the membrane phospholipid PtdIns(4,5)P2 into PtdIns(3,4,5)P3, allowing the recruitment of Tec family kinases. Concordant with its expression, PI3Kδ-dead knock-in mice have significant defects in B and T cell signalling, high affinity IgE receptor, FcεRI, signalling and neutrophil activation [200-202]. IC87114, an inhibitor of PI3Kδ (and to a lesser extent PI3Kγ and β), significantly inhibits the Th2-associated inflammatory cascade with diminished allergen-induced airway inflammation and hyper-reactiveness (AIR) in a mouse model [203]. Additionally, enhanced Th1 cell development has been reported in vitro upon PI3K δ interference, due to premature termination of TCR activation. Despite this observation, this effect does not fully translate in-vivo, as PI3Kδ-knock-in mice develop inflammatory bowel disease (IBD), a condition primarily due to a lack of intestinal Treg cells [200]. Hence, despite an array of PI3K inhibitors in development and phase 2 trials, few seem to have been applied to the allergy arena [204].

Btk inhibitors: Btk is crucial for B cell and IgE receptor (FcεRI) signalling but also appears to play important roles in myeloid cells [205-207]. Btk is neither expressed in T cells, nor capable of activating downstream pathways when over expressed in T cell lines [87]. Nevertheless, inhibiting Btk could disrupt the B cell / IgE / mast cell axis, which is responsible for allergen sensitisation. Indeed, inhibiting Btk with the selective irreversible inhibitor, PCI-32765, significantly blocked IgE-mediated basophil activation, cytokine secretion and degranulation [208]. Many Btk inhibitors (PCI-32765, terreic acid and LFM-A13, GDC-0834, RN486) have been tested in a variety of in vivo settings, with minimal toxicity and significant reduction in arthritis and leukaemia [209-213]. However, despite suitable B cell / IgE / mast cell-dependent models of allergic inflammation and an array of Btk inhibitors, there are no studies reporting the impact of Btk inhibitors in allergy models. Currently 27 Phase 1 and 2 clinical studies are investigating the use of Btk inhibitors in a variety of diseases.

Itk inhibitors: Itk, as mentioned above, is significantly expressed in T cells and regulates Th2 cell development [27,83]. Itk also regulates mast cell cytokine secretion, but not degranulation [214,215]. In animal models, Itk-deficient mice and transgenic mice lacking Itk activity are protected from allergen-induced airway inflammation, supporting the case for therapeutic Itk inhibition [95,216-218]. A significant amount of work has been done optimizing inhibitors of Itk, however very few have made it through to pre-clinical trials, or at least been reported [106,107,219-222]. An Itk inhibitor, BMS-509744, was shown to inhibit airway eosinophilia in a murine model of ovalbumin-induced inflammation, however many of the other airway allergy-associated parameters were not reported in this study [223]. Many other pharmaceutical companies, including Boehringer Ingelheim, AstraZeneca and Sanofi-Aventis have products in the pipeline, but have not published their findings yet.

MAP Kinase inhibitors

The three-tier MAP kinases that phosphorylate serine/threonine MAP3Ks, which in turn phosphorylate MAP2Ks, that phosphorylate MAPKs, have been widely studied and interrogated at every level with small molecule inhibitors [224].

MEK/ERK inhibitors: Of the several MEK/ERK inhibitors, PD098059 and U0126 have received significant attention inhibiting MEK1 and MEK2 with a high degree of specificity [225,226]. Using in vitro guinea pig bronchial rings to test the contraction of airways as a model of airway contraction, PD098059 was shown to inhibit peptide-leukotriene’s from mast cells, allow a quicker recovery time post contraction and block IL-1β-induced prostaglandin D2 release from primary and immortalised airway epithelial cells [227-230]. In vivo, U0126 inhibited allergen-induced airway inflammation, although it also increased steroid resistance [231-233]. To date and to our knowledge, neither PD098059 nor U0126 have moved into clinical studies, but have remained invaluable tools for researchers to dissect molecular pathways. Eleven other MEK/ERK inhibitors, including PD184352, have proved promising in vitro and in vivo, and have been moved into phase 1 and 2 in various clinical trials in cancer patients [234-237]. Although cancer treatment has driven the development of PD184352 and other first and second-generation MEK/ERK inhibitors, their application to other inflammatory diseases, including allergy, will be of significant interest.

p38 inhibitors: p38 regulates many inflammatory pathways involved in respiratory diseases (reviewed by [238-240]). It has been extensively pursued, and unlike many MEK/ERK inhibitors to date, several p38 inhibitors have been tested in allergy models and allergic patients [241,242]. The p38 inhibitors, SD282, SB239063 and a respirable p38α antisense oligonucleotide have all been shown to inhibit experimental allergen-induced airway eosinophilia, IgE and airway hyper-responsiveness in mice [243-246]. Th2 cell-derived IL-5 mobilises eosinophils from the bone marrow, matures and activates them in the tissue [247]. In this context, the p38 inhibitor SB203580 inhibits IL-5, reduces IL-13 synthesis from human T cells and induces eosinophil apoptosis, thus suggesting that the IL-5/eosinophil axis is sensitive to p38 inhibition [231,248,249]. Additionally, it has been observed that many asthmatic patients are resistant, or insensitive, to...
inhaled corticosteroids (ICS) [250-252]. It appears that this insensitivity is mediated, in part, by p38 signalling, and that inhibition of p38 can restore steroid sensitivity [253-256]. Thus, p38 inhibitors hold great promise in interfering with allergen-induced inflammatory axis (IL-5/eosinophilia), and also in hard-to-treat allergic patients. There are currently 3 experimental clinical studies investigating the role of p38 in steroid sensitivity in severe asthmatics, with one phase 2 clinical trial testing the safety of the p38 inhibitor SB-681323.

**JNK inhibitors:** Several JNK inhibitors have been tested in a variety of *in vitro* and *in vivo* disease models (reviewed in [257]). In particular XG-102 and SP600125 have been successfully tested in pre-clinical *in vivo* models of IBD and have been shown to reduce TNFα expression and disease severity [258-260]. With respect to asthma, SP600125 has been tested in ozone and allergen-induced airway inflammation models in mice and rats, with both studies reporting positive outcomes [261-263]. In mice, 30 mg/kg of SP600125 reduced airway eosinophilia, goblet cell and mucus secretion and airway hyper responsiveness [263]. To date, several JNK inhibitors (CC-401, CNI-1493, AM-111, XG-102, CC359, CC930 and CEP-1347) have moved into phase 1 and phase 2 clinical trials, but are yet to be tested in allergic individuals [257].

**Concluding Comments**

In summary, TEC kinase-regulated pathways, which differentially control T<sub>H</sub>1, T<sub>H</sub>2, and T<sub>H</sub>17 responses through regulation of PLC-γ activation, Ca<sup>2+</sup> influx and transcription factor translocation are attractive therapeutic targets to disable T cell-mediated responses. Specifically in the allergy field, the TEC kinase Itk that is required for Th2 cells, may forestall atopy and Th2-reactivation. Similarly, the MAPKs, which integrate into proximal TCR signalling cascades, required for downstream transcription factor activation, including the phosphorylation of STAT6 and stabilisation of GATA3, are an attractive family of kinases to therapeutically target.

However, despite significant advances in our understanding of the signalling events in T cells, the complexities and abundance of kinase-regulated signalling pathways and a better grasp of the pathogenesis of allergic asthma, broad spectrum non-specific inhaled corticosteroids are still the mainstay of current treatment. This is due to many factors, including: the complexities of CD4 T cell development and differentiation, the apparent differential kinase requirements in different T cells and the emerging appreciation of T cell plasticity. For example, recent studies have identified that fully differentiated T cells maintain a degree of plasticity with the ability to change between different T<sub>H</sub> phenotypes and even between helper and regulatory cells [264]. If the kinase-regulated signalling pathways associated with the different T<sub>H</sub> phenotypes are also plastic, allowing for dynamic re-organisation, then this would pose a significant challenge for therapeutically targeting any specific T<sub>H</sub> population with inhibitors. Furthermore, allergic asthma is now viewed as a heterogeneous disease consisting of T<sub>H</sub>1-, T<sub>H</sub>2- and T<sub>H</sub>17-associated responses, with differential kinase requirements in different T<sub>H</sub> cells, as described above [228,245]. This poses an additional obstacle as it considerably expands both the number and expression of the potential targets. For example, targeting Itk, which is the most abundantly expressed TEC kinase and required for T<sub>H</sub>2 and T<sub>H</sub>17, but not T<sub>H</sub>1, cell development, may skew allergen-reactivity to T<sub>H</sub>1 cells that may be equally as damaging. The potential off-target effects of kinase inhibitors, whether in non-targeted cells or closely related pathways in the appropriate cell, pose another great difficulty which is yet to be overcome [265]. Thus, despite our current understanding of the substrates and phosphorylated residues involved in these signalling pathways, there are many unknown gaps in the chain, which need to be investigated and identified. Nevertheless, the requirement for kinase signalling pathways in various T<sub>H</sub> cells and at various stages is still an appealing therapeutic target. Finally, to tackle the complexities of allergic diseases and in a bid to move our efforts forward, a cross-disciplinary approach between chemists, biochemists, immunologists and *in-vivo* disease biologists may be more fruitful and greater than the sum of our individual parts.

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