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Review Article

Delineating the Transcriptional Mechanisms in Immunity behind Allergy and Asthma: Milestones and Challenges Ahead

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Abstract

Allergy and asthma have roots in imbalances in immune cell homeostasis, namely a shift towards T-helper 2 (T_h2)-driven increases of Immunoglobulin E (IgE) immunity. Here, we describe the transcriptional processes that lead to the emergence of the immunological actors of allergy and asthma, i.e. T_h2, type 2 Innate Lymphoid Cells (ILC2), mast, IgE plasma and regulatory T-cells (T_{reg}), as well as to the advent of imbalances towards T_h2 responses in pathological cases. We review in detail the latest advances in terms of genome-wide characterisation of the transcriptional landscapes of the protagonists of allergy and asthma, both in normal and pathological contexts if available, as well as a summary of current clinical approaches and discuss the requirement for further functional-based genome-wide characterisation of mechanisms that can lead to the attenuation of these conditions.

Introduction

The immune system is an amazingly adaptive piece of machinery that safeguards the integrity of the organism from attacks by pathogens. It is however not entirely error-proof; even if failsafe mechanisms exist to suppress abnormal immune reactions, mismanagement of the various factors involved in immune responses does occasionally give rise to immune disorders. While several of these conditions have been extensively characterised and thus make up the bulk of research in immunity due to their severity (e.g. auto-immune diseases, leukaemia and lymphoma), a number of disorders, such as allergic diseases and asthma generally affect a much higher proportion of the population, even if mortality rates are far lower for those [1.2]. Historically, following the discovery of histamine [3], its release during allergic responses was identified to occur via degranulation by mast cells [4], the most obvious mechanism underlying these pathologies. There is no single protagonist of allergy and asthma but multiple ones, which has resulted in the detailed study of the following cell types: classically mast cells, Immunoglobulin E (IgE)-secreting B-cells, T_h2 cells [5], with the recent addition of type 2 Innate Lymphoid Cells (ILC2s) [6,7], whose function is related to T_h2 cells [8]. Mast cells express the high-affinity receptor to IgE antibodies (fragment crystallisable epsilon receptor 1, FcεR1) [5], causing de granulation upon IgE Fc binding [9]. Patients suffering from asthma and/or allergy present elevated serum IgE levels [10,11], thus increasing sensitivity towards the degranulation process. B-cell class-switch towards the IgE isotype is in turn positively affected by T-helper 2 (T_h2) cytokines [12, 13]. Thus, allergy and asthma mostly result from imbalanced cross-talk within the T_h2 response. In fact, allergy and asthma are generally regarded as early-acquired immune bias towards T_h2 responses [14], whereby attempts have been made to restore the balance between T_h1 and T_h2 responses [15,16]. Further, while tolerance to antigens can normally be regulated by regulatory T-cells (T_{reg}), however there has recently been increasing evidence that T_{reg} fail to elicit adequate immune suppression in certain allergies [17]. It thus becomes quickly apparent not only a comprehensive understanding of the how the interplay within the T_h2 response becomes biased, but also to understand the origin of imbalances in the differentiation, proliferation and maintenance of its protagonists is key to develop treatments against al-

lergic and asthmatic reactions. The emergence of the haemopoietic system and its actors is a tightly-controlled process whereby the timing and nature of epigenetic and transcriptional regulation is critical [18,19]. Thus, to fully understand how allergies and asthma arise, i.e. via imbalance towards the T_h2 response, the origin and specification of the cell types involved must be fully understood. Here, we review the transcriptional mechanisms that lead to the emergence of the main actors involved in allergy and asthma, i.e. T_h2 cells, ILC2s, mast cells, IgE B-cells and T_{reg}, as well as within the framework of modern transcriptional regulation. We also describe current treatment approaches and further discuss possible challenges and research directions, notably using inhibitor treatments coupled with genome-wide characterisation of transcriptional landscapes of the actors of allergy and asthma.

T_h2 Cells: The Substrate for Allergy and Asthma

T_h2 cells represent the cornerstone of humoral immune responses. Once naïve $CD4^+$ T-cells (T_h0) are activated via antigen presentation via the Major Histocompatibility II Complex (MHCII) on the T-cell receptor and CD3, T-cells can differentiate towards the following T-helper types: T_h1, involved in cell-mediated responses;T_h17, related to T_h1 but involved in the control of inflammation, extracellular pathogens and pathogen clearance; T_h2, involved in humoral-mediated responses; T_h9, related to T_h2, involved in defence against helminths; T_{reg} or memory T-cells [20]. Importantly, T_h2s secrete interleukin 4 (IL-4), IL-5, IL-6, IL-13 and recruit IgE B-cells, mast cells and eosinophils [12] (Figure 1). This feature makes T_h2 cells critical players in allergic and asthmatic reactions. As there is evidence for a bias favouring T_h2 responses over T_h1 in allergy and asthma [14], attempts have been made at restoring Th1 responses [15,16]. Differentiation towards T_h2 is driven via IL-4, while IL-12 drives T_h1 differentiation [21]. IL-4 is known to down regulate T_h1 differentiation [22]. As a result, Th2 cytokines as well as chemokines are higher in allergy and asthma patients [12,23] with T_h2 cell counts reportedly higher [24]. On the other hand, interferon gamma, which is secreted by T_h1 cells, down regulates T_h2 responses [25]. IL-4 and IL-5 also specifically prime mast cells for different profiles of IgE-dependent cytokine production [26]. Importantly, ILC2s also express the IL-33 receptor, which drives the production of T_h2 cytokines [27].

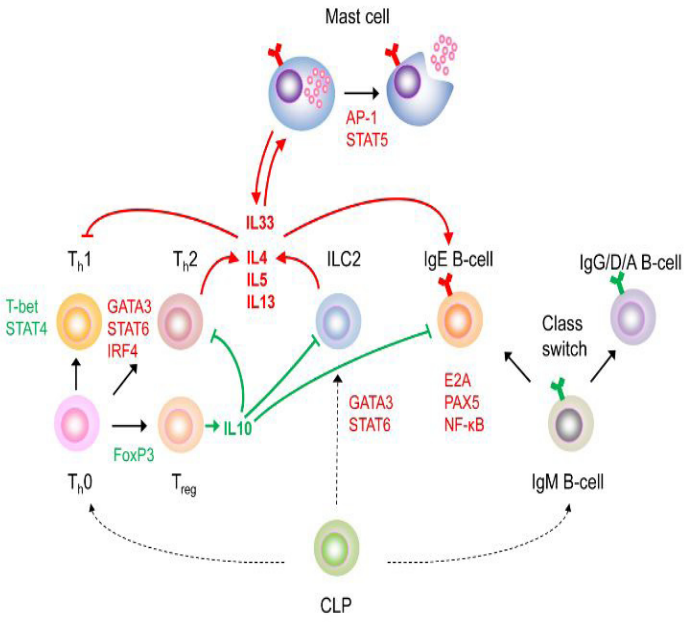

Figure 1: Summary of transcriptional actors involved in the differentiation of effectors of allergy and asthma, and main interactions between immune cell types via secretion of cytokines (shown in bold). Interactions favouring allergy or asthma are shown in red; those inhibiting it are shown in green. Arrows and blunt edges originating from cytokines indicate activation and inhibition; respectively. CLP: Common Lymphoid Progenitor; ILC2: Innate Lymphoid Cell; T_h: T-helper; Ig: Immunoglobulin.

In T_h2 cells, at the transcriptional level, the hallmark T_h2 Transcription Factor (TF) GATA binding protein 3 (GATA3) outcompetes T-box protein expressed in T cells (T-bet), the defining T_h1 TF [28]. Other hallmark TFs for T_h2 cells are Signal Transducer and Activator of Transcription 6 (STAT6) and Interferon Regulatory Factor 4 (IRF4), while STAT4 expression characterises T_h1 cells [21,29]. However, there are signs that priming towards either cell-type already exists in freshly activated T-cells [30]. Since T_h2 cells have been long described and due to their abundant cell counts, T_h2 differentiation has been comprehensively characterised at the transcriptional level, more recently using high-throughput sequencing: characterisation of binding patterns of hallmark TFs (T-bet; GATA3; IRF4; basic leucine zipper transcription factor ATF-like,

BATF) has been performed via Chromatin Immune Precipitation Sequencing (ChIP-Seq) in during the last decade [31,34]. Gene expression profiling using RNA Sequencing (RNA-Seq) has also shed light on the full extent of genes characterising T_h2 signatures [35,36], notably at the single-cell level [37,38]. More recently, a RNA-Seq study performed on T_h2 cells involved in allergic airway inflammation demonstrated that T_h2 activity and survival is regulated by IL-10 [39], further pointing as an important role for T_{reg} in these pathologies. Further, chromatin accessibility profiling was also performed in T_h2 cells using DNase I hypersensitive site Sequencing (DNAse-Seq) and Assay for Transposase-Accessible Chromatin Sequencing (ATAC-Seq) [34,40]. Single cell assays studying T_h0 to T_h1 and T_h2 transitions have also been performed [37,38]. Certain histone modification ChIP-Seq assays performed in T_h2 cells from asthmatic and healthy also revealed regulatory elements linked with asthma susceptibility [41].

ILC2s: The New Allergy and Asthma Players in Town

ILC2s represent a relatively newly-described type of innate immune cells: their discovery resulted into a new class of innate lymphocytes, ILCs, now encompassing Natural Killer (NK) cells. Lacking Recombination-Activating Gene (Rag) 1 and 2 expression, they do not rearrange or express the T-cell receptor. If an analogy can be made, ILCs are the innate equivalent of cytotoxic and helper T-cells, except that their function is antigen-independent. The analogy also extends to T_h cells, with ILC1s displaying features similar to T_h1, notably T-bet expression, while GATA3 was shown to be essential for ILC2 function [42,43], conferring ILC2s a function related to T_h2 [8]. As for T_h2, ILC2s express and require STAT6 and T-Cell Factor 1 (Tcf1) [44,45]. The typical ILC2 markers are CD25, CD117, Inducible T-cell Co-Stimulator (ICOS), CD161, prostaglandin D2 receptor 2 (CRTH2), and GATA3 [46]. ICOS activation was recently shown to be required for type 2 innate lymphoid cell function, homeostasis, and induction of airway hyper reactivity [47]**.** ILC2s also express the IL-7 receptor and their survival and proliferation may require STAT5 function [47]. Importantly, ILC2s also express the IL-33 receptor [27]. Thus, as for T_h2, they are equally as important for the onset of allergy and asthma as they secrete IL-4,5,9,13 (Figure 1). In fact, they were shown to be critical for the initiation of adaptive $T_h2$cell-mediated allergic lung inflammation [48]. In Rag2-deficient mice, ILC2s can induce allergy alone [49], reviewed in [50], being able to produce very high amounts of IL-5 and IL-13 [51].

Understanding the transcriptional regulation events that lead to ILC2 should thus be at the centre of current efforts, especially given that they can produce copious amounts of IL-5 and IL-13. A question remains as to whether attempts to down regulate T_h2 responses in favour of T_h1 ones also affect ILC2s. Recently, genome-wide screens have been performed: mapping of chromatin accessibility revealed convergent regulomes between ILC2s and T_h2 cells [34]. Other efforts, including genome-wide mapping of GATA3 in ILC2s and ILC3s, showed that while this TF is essential for ILC2 function, ILC3s also continuously require GATA3 expression after commitment, albeit at low levels [43]. Further, single-cell RNA-Seq assays have demonstrated the heterogeneity that exists in the transcriptomes of ILCs, including ILC2s [52,53].

Mast Cells: The Main Effector of Allergy and Asthma

Mast cells are the main effector cell type of allergy and asthma. They are myeloid cells derived from Common Myeloid Progenitors (CMP) or Granulocyte-Macrophage Progenitors (GMP), evolving into Basophil/Mast Cell Progenitor (BMCP) and ultimately mast cells. Beside the high-affinity IgE receptor that causing degranulation upon IgE Fc binding [5,9] (Figure 1), mast cells also express receptors to cysteinyl leukotrienes [54]. Generally, the transcriptional activators needed for mast cell differentiation have been well characterised, mostly using single locus assays [55]. Mast cell differentiation is dose-dependent on correct Purine-Rich 1 (PU.1) and CCAAT-Enhancer-Binding Protein Alpha (C/EBPα) levels and requires for expression [56,57], a general trait of normal myeloid differentiation [58]. Activator Protein 1 (AP-1) is also required for the degranulation process [59]. Upstream Transcription Factor 2, c-Fos interacting (USF2) was also showed to play a critical role in driving mast cell differentiation [60]. Gata1 deletion impairs mast cell differentiation [61], although this process can be rescued [62], except in skin and the stomach [63]. E74-like ETS Transcription Factor 1(ELF1) and GATA1 were also shown to bind to tissue-specific enhancers elements of human high-affinity IgE receptor alpha-chain gene [64]. STAT3 and Melanogenesis Associated Transcription Factor (MITF) cooperation was also to be critical in mast cell development [65]. Importantly, IL-33 is produced by mast cells and regulates IgE-dependent inflammation [66]. Further, besides the high-affinity FcεRI receptor [5], low-affinity IgG receptors can also induce IgE-mediated degranulation in mast cells [67]. STAT5 expression is required for IgE-mediated mast cell function including degranulation [68]. STAT6, a mediator of T_h2 immunity, is also expressed in mast cells [44]. From a pathological standpoint, asthmatic patients present enhanced degranulation of mast cells [69], and furthermore T_h2 cytokines such as IL-5 are critical for the mobilisation of mast cells in airways [70]. Importantly, mast cells express IL-33 as well as its receptor [27]. IL-33 appears to be critical for the development of asthma at a young age, as it was shown to promote type 2 immunity in the developing lung, with local accumulation of T_h2 cells [71].

At the genome-wide level however, characterisation of transcriptional regulation in mast cells remains scarce, even though one study comprehensively mapped binding of key mast TFs such as ETS-Related gene (Erg), Finkel-Biskis-Jinkins murine osteogenic sarcoma virus transforming gene (Fos), MITF, transcription factor E2-Alpha (E2A), Stem-Cell Leukaemia (Scl), GATA2, Friend Leukaemia Integration 1 (Fli1), LIM domain only 2 (Lmo2), Runt-Related Transcription Factor 1 (Runx1) and myeloid ecotropic vi-

ral integration site 1 homolog (Meis1) [57]. Importantly, within the framework of allergy and asthma, early gene expression microarray assays identified mast cells as a source of IL-11 [72], as well as upregulation of chemokine genes [73]. A more recent study using RNA-Seq carried out in human mast cells stimulated by IgE or FcεRI-aggregation pointed to a complex network of genes involved in inflammatory responses [74]. More recent studies using Cap Analysis Gene Expression Sequencing (CAGE-Seq) have also increased the resolution of our knowledge of mast cell gene expression patterns [75].

IgE B-Cells: Which Factors Drive Proliferation?

IgE B-cell, like all mature B-cells, are derived from IgM-expressing immature B-cells that have undergone Class-Switch Recombination (CSR) in the germinal centre, following initial VDJ recombination of the heavy chain starting in pro B-cells and completing by the pre-B-cell stage (Figure 1). For IgE isotypes, CSR results in the excision of chains up to the ε chain. CSR to the IgE isotype also requires germline transcription from the promoter [76]. Polymorphism of these isotypes is enhanced by Activation-Induced Cytidine Deaminase (AID)-induced Somatic Hypermutations (SHM), a process which generates mutations of C-G pairs via deamination at the DNA level. AID is also essential for CSR. There is controversy whether Inhibitor of DNA binding 2 (Id2) inhibition of CSR and SHM [77] is involved in the down regulation of IgE isotope generation [78,79] as Id2-deficient mice exhibit enhanced CSR to IgE [80], which points to the importance of this inhibitor in allergy and asthma. However, in normal conditions, E (IgE) isotype antibodies are normally present at low levels in the plasma and are mainly produced by plasma cells in the mucosal-associated lymphoid tissue [76]. As a result, these isotypes are the least abundant in healthy individuals [81]. While even in allergic and asthmatic conditions, serum IgE remains low, as opposed to the rare hyper-IgE syndrome [82], there is evidence of elevated IgE production local to the nasal mucosa in asthma patients [83]. There is however indication that while serum IgE levels remain low, they are increased in allergic patients [12]. In mechanistic terms, IgE CSR is directly influenced by T_h2 cytokines [12,13,84]. IL-4/IL-13 and CD40 ligation are needed for IgE CSR [12,85]. B-cells also express the low-affinity FcεRII IgE receptors (CD23) [5]. Further, it was shown that CD23 negatively regulates IgE CSR [86].

Transcriptional activation of the I^{ϵ} promoter is achieved by binding of STAT6 and nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB), which are induced by IL-4 and CD40 in this case, respectively, as well as PU.1, E2A, paired box protein 5 (PAX5) and CEBP [76]. STAT5b also appears to influence IgE CSR, as Stat5b-deficient patients show increased serum IgE levels, as well as decreased $CD8^+$ T cell number, and severe eczema [87,88]. The IgH locus also features two Matrix Attachment Regions (MARs) around the Eμ enhancer [89]. MARs confer permissive transcriptional conformations [89,90] and are bound by special AT-rich Sequence-Binding Protein (Satb) proteins, which, in T-cells, are required for the correct expression of the rearranged TCR chains [91,92]. In antibody-secreting B-cells, Satb1 is expressed, at least at the mRNA level [93]. Satb proteins might thus also represent the focus of transcriptional research in B-cells and more particularly in IgE-producing cells, coupled with chromosome capture conformation assays. It might be, as for other the initial recombination in other Igs, that each CSR towards the various isotypes, including IgE, requires a distinct, specialised chromatin structure [94]. However, while histone modification patterns have been described in the IgE switch region in IgE cells using extensive ChIP-qPCR characterisation [95], to date, no wider-reaching endeavour has been attempted in these cells, neither using TF ChIP-Seq. Thus, the transcriptional landscape of IgE cells remains largely uncharacterised, even a recent study extensively characterised the transcriptional landscape of class-switching germinal centre B-cells, using ChIP-Seq, ATAC-Seq and RNA-Seq [96].

At the gene expression level, several characterisations have already been performed within the framework of allergy and asthma, at first using microarray technology, which uncovered extensive numbers of novel key genes involved in these pathologies, such as Bcl2 and IL-33 itself [97,100]. More recently, RNA-Seq from circulating $CD19^+$ B-cells from allergic asthma patients also evidenced up regulation of the IL-4 receptor [101]. Importantly, IgE repertoire sequencing also highlighted more apparent changes in IgE repertoires in patients with allergic rhinitis [102]. B-cell single-cell RNA-Seq was also recently performed in the model lymphoblastoid cell line GM12878 [103].

T_{reg}: Cells that Can (Suppress Allergy and Asthma)

T_{reg} have recently come at the centre of focus of research in allergy and asthma. These cells are derived from activated T_h0 cells, and are characterised by intermediary CD25 expression as well as high fork head Box P3 (FoxP3) expression [104]. Their main function consists of suppressing auto reactive T-cells, which is achieved by IL-10 and Transforming Growth Factor Beta (TGF-β) secretion (Figure 1). Recently, an allergen-suppressing T_{reg} subtype has been uncovered, suggesting that the maintenance of these cells is important in combatting allergy and asthma via IL-10-mediated suppression of allergenic T_h2 and IgE cells [39,105,106]. Importantly, T_{reg} can also suppress ILC2 cells [107]. However, there are also hints of a defective T_{reg} response in allergy and asthma [108]. Further, in those pathological conditions, the balance between T_h2/T_{reg} populations is shifted towards T_h2 cells, resulting in less T_{reg} cells [109,110]. Artificially skewing the T_h2/T_{reg} ratio towards a T_h2 cell-like lineage via reprogramming of T_{reg} was also shown to impair oral tolerance and to promote food allergy [17]. The converse, which entailed reprogramming T_h2 cells into T_{reg} by exposure to TGF-β, all-trans retinoic acid and rapamycin, resulted in fully functional T_{reg} able to suppress T_h2-mediated airway hyperreactivity and allergen-dependent IgE secretion in allergic asthma [111].

The transcriptional landscape of T_{reg} has been extensively characterised via high-throughput approaches hinging on factors critical T_{reg} development, on histone modification status and RNA-Seq [33,112,113]. Recent genome-wide studies pertaining to tissue-resident T_{reg}, also involved in allergy tolerance, showed that IRF4, BATF and, importantly, IL-33 are responsible for the development and maintenance of these cells [114]. These cells, which might fail to suppress allergenic T-cells, are thus also preserved in allergic pathologies, thereby contributing to their maintenance.

Current Clinical and Translational Approaches

Besides anti-histamine, anti-leukotriene, mast-cell stabiliser or bronchodilator -based approaches, several clinical approaches have been developed against allergy and asthma in the last 30 years, based on the increased physiological and transcriptional understanding of these pathologies. For example, anti-IgE monoclonal antibody treatments [115], reviewed in [116], have been used to treat allergic asthma for almost two decades, prompted by the discovery of elevated IgE levels in the nasal mucosa. Further, treatment with a CD23 transducing monoclonal antibody also reduces allergic pulmonary inflammation [117]. Importantly, the Phosphoinositide 3-Kinase (PI3K) pathway was also shown to be a negative regulator of IgE production [118], which may represent novel approaches. Against excessive T_h2-based immunity, interferon gamma was importantly described as a potent allergy suppressor [119]. For mast and T_h2 cells, IL-33 was shown to play a key role at a young age [71]. Type-2 immunity thus appears to be mostly IL-33-dependent and not T- or B- cell dependent, hinting at a critical role for this axis and pointing to early treatments aiming to reduce IL-33 levels. The so-called "Hygiene Hypothesis", whereby how excessive antiseptic sterility could potentially lead to reduced stimulation towards T_h1 development, favouring T_h2 development over T_h1 [76], has also led to original treatments, such as the use of farm dust and endotoxin to reduce lung epithelial cell allergy [120], indicating that, per se, the initial IL-33 boost in early age might not be an irreversible phenomenon. Current characterisation efforts of the IL-33 axis, notably at the transcriptional level, could thus give rise to further treatments aiming to reduce early-acquired T_h2 sensitisation. Further, aiming to restore the T_h2/T_{reg} balance [111] could also provide new treatment approaches, and thus warrant further characterisation of T_{reg} differentiation at the transcriptional level.

The Need for Further Integrative, Functional and Translational Studies as well as in Novel Cell Types Involved in Allergy and Asthma

In this review, we have described current advances in the transcriptional understanding underlying allergy and asthma and a summary of current treatment approaches. For each of the key players in allergy and asthma, i.e. T_h2 cells, ILC2 cells, mast cells, IgE B-cells and T_{reg}, single-cell assays carried out in pathological conditions would be of great interest to understand how part of these cells get primed towards an allergic/asthmatic phenotype. For IgE B-cells, further characterisation is required to comprehend the up regulation of CSR that leads to this isotype. While single-cell B-cell RNA-Seq has been performed [103], the field of allergy and asthma would greatly benefit from such assays from patient cells, notably from the nasal mucosa where IgE production can be elevated in allergic reactions [83]. This would enable identifying how the differentiation trajectories of B-cells get skewed towards the IgE isotype, coupled with transcriptional assays such as ChIP-Seq and ATAC-Seq. Further, functional assays, used with current anti-IgE monoclonal antibody treatments in combination with genome-wide approaches would also shed light on the full effects and possible compensation mechanisms of these therapies. Further, a subtype of allergenic memory B-cells was recently identified as long-lived IgE producing plasma cells, at higher levels in patients with rhinitis [121]. Finally, a class of regulatory B-cells, secreting IL-10 similarly to T_{reg}, was recently identified to modulate immunological tolerance by suppressing pro-inflammatory B- and T-cells [122]. These latest cell types could thus also represent the next focus of research at the transcriptional level in allergy and asthma. The germinal centre B-cell stage is also of particular importance, albeit limiting in cell numbers, as most studies on B-cell differentiation, e.g. Encyclopaedia of DNA Elements (ENCODE) genome-wide screens, were performed using immortalized cell lines often corresponding to later stages of differentiation using B-cells of isotypes other than IgE, and not plasma cell lines expressing IgE such as the U266 cell line [123], which could thus constitute a suitable model for such investigations to identify TFs involved in IgE CSR and SHM.

In mast cells, systematic characterisation of their transcriptional landscape is also still quite limited to a few TFs, while several more might be involved in allergy and asthma. Functional assays with in mast cells, such as with Mitogen-Activated Protein Kinase (MAPK) inhibitors, since AP-1 involved in degranulation, would shed further light on the transcriptional consequences of e.g. mast cell stabilisers. The importance of early exposure to the IL-33 axis in allergy and asthma [71] also hints at further research into approaches aiming to reduce IL-33 secretion by mast cells, thus warranting detailed transcriptional understanding of this gene and of its downstream effectors.

For ILC2s, T_h2 and T_{reg} cells, we have shown that there already exists extensive knowledge of the transcriptional landscape of these cells. Further, computational modelling has been used to model the T_h0 to T_h1/T_h2/T_h17/T_{reg} differentiation in systems biology [124]. By modulating the expression of key genes in silico using allergic conditions, determining how to readjust the balance towards normal T_h1/T_h17/T_{reg} differentiation could also pave the way to new mechanistic approaches. These approaches, coupled with genome-wide approaches, might be needed to obtain a com-

prehensive understanding of the full-complement of cell- and system-wide effects of pathway inhibitors used in current treatments for e.g. allergic or eosinophilic asthma, such as of the IL-4, IL-5, IL-13 axes [125,126], with already several drugs readily available, reviewed in [127]. Additionally, the relatively novel T-cell subclass, T_h9, which express IL-9 and PU.1 [128], may also have a link to allergy and asthma, warranting further characterisation of these cells [129]. Further, for T_{reg}, single-cell genome-wide assays would help delineate the differentiation trajectories of T_{reg} subpopulations, including those especially involved in suppressing allergenic T_h2 cells, as well as those that fail to do so. Such assays could provide mechanistic insights that may develop into translational research in the long run. In ILC2 cells, carrying single-cell assays in pathological conditions should be of great benefit to the field to study the development of allergenic ILC2 cells. In addition, to date, ChIP-Seq assays involving TFs have yet to be performed using T_h2 cells from allergy or asthma patients. This would be highly desirable to characterise the players involved in misregulation, notably to identify druggable targets, as the observed epigenome is often a direct consequence of TF binding [130], even though chromatin accessibility and histone modification status can also have a direct effect on TF binding [131]. Further, while single cell assays carried out in T_h2 cells should allow giving insights into potential priming towards each cell fate [37,38], what would ideally need to be done is to perform such assays in an allergic/asthmatic context, i.e. from patient samples.

Finally, while there is evidence that some allergies can be B-cell driven, several variables can influence which cell type is key to triggering allergic responses [132]. This points towards the need for co-culture and system-wide approaches. A wider-looking view on the imbalances between cell types involved in allergy versus those that are not might be required, notably using simple concepts, e.g. the so-called “hygiene hypothesis”. Thus, mass-scale genome-wide gene screens including expression data, such as the 100,000 genomes project [133] would benefit the field if they were to include cell types involved in allergy and asthma, and, combined with Genome-Wide Association Studies (GWAS) and hygiene, pathogen exposure data worldwide would provide means of testing if e.g. the hygiene hypothesis holds true. In any case, the field would also greatly benefit from compendia such as the epigenome roadmap [134] or ENCODE [135].

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