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Innate and adaptive immunity: ILC2 and Th2 cells in upper and lower airway allergic diseases.

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Abstract

Advances in our understanding of the immune system, with the recent discovery of a parallel set of innate T lymphocytes, the ILCs, have led to a reassessment of the pathogenesis of allergic and eosinophilic airway disorders, including allergic rhinitis, asthma and chronic rhinosinusitis with nasal polyps. We review current understanding of both elements of type-2 inflammatory responses and their relative influence in these common conditions and consider possible impacts of this on treatment selection.

Introduction

A current dilemma facing chest physicians, ENTs and allergists is the choice of therapy for severe eosinophilic asthma and/or rapidly recurrent eosinophilic nasal polyps. Licensed monoclonal antibodies targeting IgE, Th2 cytokines or their receptors are costly, so significant experience is limited to specialized centres. Newer drugs target upstream mediators, including TSLP, which may have crucial roles linking innate and adaptive immunity. Improved knowledge of the workings of the immune system has been key to identifying new drug targets. Identifying biomarkers indicating which drugs are most suitable for which patients is an on-going process. Is it valuable to decide which arm of the immune system is primarily driving inflammation when selecting therapy?

Innate and adaptive Immunity

“Evolution is a tinkerer, not an engineer”, opined Nobel Prize winner Francois Jacob (1). This certainly applies to the multi-layered immune system, with its innate and acquired arms.

Innate or 'natural' immunity is present at birth and provides the initial line of defence against pathogens (Table 1). Its mechanisms are inbuilt and specific for common microbial structures (pattern recognition receptors, PRRs) on different microorganisms (bacteria, viruses, parasites), but are incapable of fine distinction. PRR binding activates basic disposal mechanisms, such as phagocytosis. Similar mechanisms are responsible for reactions to tissue damage, resulting in inflammation. Lack of an innate immune function, such as deficiencies in the complement cascade, can lead to overwhelming infection and sepsis.

Adaptive or acquired immunity, which involves T and B lymphocytes and antibodies, is built onto innate immunity and develops over time as exposure to microorganisms occurs. It has both specificity (the ability to distinguish between different pathogens) and memory (the ability to respond more vigorously to repeated exposure to the same organism). Pathogen-derived peptides are recognized by T lymphocytes in the context of self-MHC antigens. In the right milieu, this may lead to formation of antibodies against pathogen surface molecules (antigens) and/or T cell activation and orchestration of inflammatory and/or cytotoxic responses. T cells have varying functions. Cytotoxic CD8 T-cells attack and lyse virally-infected cells, whereas helper CD4 T-cells support B cell antibody production and increase chemotaxis and activation of innate immune cells, including neutrophils, macrophages and eosinophils. Vaccination is the art of inducing acquired immunity without the organism having to suffer full infection. Allergen-specific immunotherapy (AIT) is a modified vaccine approach leading to protective/anti-inflammatory, allergen-specific responses through generation of allergen-specific IgG4 antibodies, regulatory T and B cells, and deletion/anergy of allergen-specific Th2 cells (2).

Innate mechanisms, such as ciliary beating, are present in primitive organisms like the amoeba. Adaptive immune processes are more recently evolved, being first evident in vertebrate fish (3). They can function alone against certain antigens, but usually their effects are exerted by interactions: of antibody with innate components such as complement and phagocytic cells, and of T cells with macrophages, frequently provoking inflammation. This can be acute (ending when the stimulus is removed) or chronic (if the stimulus persists or the reaction becomes self-propagating). If problematic and harmful to the organism, such inflammation is known as hypersensitivity.

More recently, a parallel universe of innate T cells, the innate lymphoid cells (ILCs), has been discovered. These also derive from common lymphoid progenitors (CLPs). They

contribute to immunity via the secretion of signalling molecules and the regulation of both innate and adaptive immune cells, in response to alarmin signals from the epithelium, such as IL-33 and TSLP (4). ILCs reside in peripheral, rather than lymphoid, tissues and are abundant at barrier surfaces. They are early responders to tissue perturbation, producing cytokines within hours of activation, in contrast to the days required in priming, differentiation, expansion and chemotaxis of adaptive lymphocytes. Other innate and innate-like lymphocytes such as mucosal associated invariant T cells (MAITs), $\gamma\delta$ T cells, intra-epithelial lymphocytes (IELs) and natural killer (NKT) cells share features with ILCs.

ILCs, in contrast to B and T lymphocytes, lack antigen-specific receptors and do not undergo genomic receptor rearrangements or clonal selection. They react with standardized functions ordained during development. Their functional diversity, however, mirrors that of adaptive T cells – three subsets of helper ILCs: ILC1, ILC2, and ILC3 correspond to T helper-1 (Th1), Th2, and Th17 T cell subsets (5); NK cells are an innate counterpart to cytotoxic CD8⁺ T cells. ILCs respond rapidly to intracellular pathogens, extracellular bacteria or yeasts, helminth worms and allergens. They play complementary roles to their T cell analogues in inflammatory responses (6, 7). There is also a subpopulation of IL-10-producing ILCs, with possible regulatory function, mirroring the role of adaptive T regulatory cells (8).

Cytokines IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) activate ILC2s (9). Classical Th2-associated mediators, including lipids such as cysteinyl leukotrienes and prostaglandin D2 (CysLTs and PGD2), and TNF-like ligand 1A (TL1A), are also capable of activating ILC2s (10, 11, 12), while PGI2 and lipoxin A4 (LXA4), derived from arachidonic acid, are inhibitory (13, 14). In mice ILC2 activation can be triggered by house dust mite (HDM), *Alternaria spp.*, and papain, as well as viruses: influenza, rhinovirus (RV) and respiratory syncytial virus (RSV) (15, 16). Similar findings are emerging in man. *Alternaria* sensitization is associated with both allergic fungal sinusitis and severe asthma. It promotes rapid IL-33 release and subsequent ILC2 responses, independent of the adaptive IgE response (17). *Alternaria* administered to mice during an adaptive response to rye grass augmented eosinophilia, AHR, and ILC2 activation (18). The augmenting effect of ILCs is also shown in HDM-challenged mice where ILC2 cells from bronchoalveolar lavage produced more type 2 cytokines than CD4⁺ T cells during repetitive HDM challenges (19). ILC2 deficient mice, still possessing CD4 cells, had reduced levels of IgE and of Th2 cytokines post-HDM challenge (20).

Papain, like *Alternaria*, induces eosinophilic lung inflammation in the absence of T and B cells in murine models. ILC2s must be involved since their depletion abrogates this response (20, 21). This mechanism may be operative in human papain-induced occupational asthma (23).

Respiratory viral infection in mice stimulates release of IL-33 and IL-25, leading to ILC2 activation, airway hyperreactivity and/or tissue repair (24, 25, 26). Rhinovirus (RV) challenges in human asthmatics and controls found elevation of IL-5, IL-13 and IL-33 levels in the broncho-alveolar lavage and nasal fluid of asthmatics compared to baseline and non-asthmatics (27). Supernatants from RV-infected epithelium added to purified ILC2s led to IL-33-dependent cytokine production (28). RV may utilize the IL-33/ILC2 pathway to induce asthma exacerbations.

Once activated, ILC2s produce and secrete Th2 cytokines IL-5 and IL-13. IL-5 is important for eosinophil growth, differentiation, recruitment and survival. IL-13 affects epithelial and airway smooth-muscle cells to cause bronchial hyper-reactivity and promotes mucus production and fibrosis (27). ILC2s may produce IL-4, promoting CD4⁺ Th2 cell differentiation and IgE class switching (28). ILC2s also secrete IL-9, promoting mast cell accumulation, mucus secretion, and production of amphiregulin (AREG), the epidermal growth factor receptor (EGFR) ligand, which promotes lung tissue repair post viral infections (29-31). Thus, ILC2s have restorative functions as well as initiating inflammation and linking innate and adaptive responses.

Neural-mediated regulation of ILC2s occurs. Mucosal neurons, sensitive to parasitic worms and alarmins, exist next to ILC2s in mice, conferring initial defence via neuro-immune responses (32). Catecholamines negatively regulate ILC2 activity and proliferation via β -2 adrenergic receptors (33).

During fetal development, ILCs become established in niches, with further expansion in tissue pools at and after birth. Their effector phenotypes develop under environmental control: tissue, diet and microbes. If ILC2s are overrepresented in infancy, perhaps by insufficient microbial stimulation, this might, hypothetically, lead to atopy or asthma. Conversely, if the fetal ILC niche favours type 3 responses (ILC3s) this might contribute to inflammatory conditions such as psoriasis, arthritis and inflammatory bowel disease (34).

In adults, local ILC renewal occurs, plus a small contribution from circulating precursors, increased by stress. Adaptive lymphocytes gradually replace ILCs in adulthood, probably with similar imprinting, so Th2 lymphocytes replace ILC2 cells. With advancing age, local cell populations wane and immune senescence occurs. Hence fetal, birth and early life conditions could, via ILC niche distribution, affect health for the whole of life. This could be the mode of action of the hygiene hypothesis, with early life microbiome (and deficiencies therein) determining the level of ILC2 tissue occupancy in gut, skin and airways. It could also explain the phenomenon of local IgE production in CRSwNP and non-allergic asthma if ILC2s later attracted adaptive Th2 cells to their established niche while they remained hidden from the systemic circulation.

Adaptive immunity appears to be a *sine qua non* in coping with microbial infections: lack of functional T and B cells in severe combined immunodeficiency (SCID) leads to death in infancy. ILCs seem neither necessary nor sufficient for survival from infection in man, based on studies in SCID and hematopoietic stem cell (HSC) transplants (35). However natural genetic deletions of these pathways in humans remain undescribed. ILC2s and the IL-13-mediated pathway may be needed in homeostatic mechanisms, such as lung repair following influenza virus infection (36).

Eosinophilia is rapidly induced by Type 2 cytokines, preceding tissue remodelling. Eosinophil involvement, together with IgE, occurs in the immune response to metazoan worms. IgE-coated worms attract eosinophils which then secrete highly toxic damaging molecules (eosinophil cationic protein, ECP; eosinophil derived neurotoxin, EDN), at the same time stimulating gut peristalsis to cause evacuation. This amplification, which allows killing of organisms significantly larger than phagocytic cells, is now known to involve ILC2 cells as well (37). In asthma this reaction is misapplied, resulting in airways inflammation, hyperreactivity and remodelling. In allergic rhinitis, also involving IgE and eosinophilia, remodelling is not seen, even with repeated allergen exposure (38), perhaps related to the different embryological origins of upper and lower airways.

Allergy

Allergy is a form of hypersensitivity, initially defined as “altered responsiveness” by von Pirquet in 1906. It involves the acquired immune system forming IgE antibodies to commonly encountered environmental proteins. ILC2s may be implicated in propagation of these inflammatory diseases by non-allergic mechanisms, such as viral infections, pollutants and cigarette smoke, independent of specific allergen exposure, and also as a result of intrinsic protease activity, such as with HDM.

Figure 1 shows the interaction of the innate and adaptive immune systems in allergic diseases.

The prevalence of atopic (literally, *out of place*) diseases such as allergic rhinitis, asthma, food allergy, atopic eczema and anaphylaxis increased markedly over the last century. The reasons for this remain incompletely understood, but from the timing it must be largely environmental and possibly relates to relevant bacterial exposure, or lack of it, in early life. However, rising levels of exposure of epithelial surfaces to chemicals and pollutants, possibly activating TSLP, IL-33, IL-25 and hence involving ILCs, may also be relevant in generating allergic inflammation (38).

Allergic Rhinitis

Allergic rhinitis (AR) is considered the archetypal Th2 acquired immune reaction, involving T lymphocyte recognition of allergen and interleukin 4, 5 and 13 production. Subsequent B cell class switch to IgE occurs. IgE arming of mast cells and basophils enables degranulation and mediator release in response to subsequent allergen contact. Eosinophil ingress also occurs as part of the late phase reaction (3,39). The efficacy of allergen-specific immunotherapy, particularly for pollen allergens, is consistent with this Th2, acquired immunity dominant role.

Yet ILC2s may also be involved, possibly depending on the allergen. For example, they are increased in the blood of HDM-sensitive AR patients, but not in mugwort sensitivity, compared to healthy controls. In HDM-AR patients’ symptom scores and IL-13 levels were positively associated with ILC2 levels (40). Stimulation of AR PBMCs by epithelial cytokines induced IL-5 and IL-13 production (41), possibly secondary to direct enzymatic damage by mite proteins. ILC2s also increase during the grass pollen season in AR subjects

compared to controls, a finding apparently abrogated by subcutaneous grass pollen immunotherapy (42). Numbers of circulating blood ILC2s also increase following cat allergen challenge (43). So, whilst AR remains the archetypal Th2 disease, a contribution from ILC2s appears likely, perhaps more relevant in HDM-AR than pollen-AR.

Asthma

Early phenotyping of asthma with respect to response to therapy was undertaken by Harry Morrow Brown. He showed that only eosinophilic asthma was responsive to corticosteroids, both oral and inhaled (44), preventing the suggested abandonment of both therapies after previous unsuccessful trials in non-phenotyped patients. The eosinophils were assumed to be present as a result of the classical allergic reaction, hence this was later referred to as Th2 asthma, because of the involvement of helper T cells producing IL-4, IL-5 and IL-13 and promoting IgE production from B cells.

ILC2s are found in asthmatic sputum and produce IL-5 and IL-13 on stimulation with TSLP and IL-33 (45). Overall frequencies of ILC2s in peripheral blood were higher in asthmatics than healthy controls, though absolute numbers were low. IL-13-expressing ILC2 levels were higher in uncontrolled than in partially-controlled asthmatics, with both groups being higher than controlled asthmatics where proportions were equal to those in healthy individuals. Effective asthma treatment reduced IL-13+ILC2 levels, although *in vitro* ILC2s were more glucocorticoid-resistant than Th2 cells (46). The prevalence of ILC2s in blood was greater in the allergic asthma group than in the AR group or the healthy control group in another study (47). In both asthma and AR, ILC2 numbers were increased by specific allergen challenge (43).

Thus, the derivation of the tissue and sputum eosinophilia in asthma (and AR) cannot with any certainty be ascribed solely to Th2 lymphocytes but could also result from their ILC2 counterparts. As a result, eosinophilic asthma is now designated T2 asthma rather than Th2 asthma. The same is true of eosinophilia in other allergic diseases such as atopic dermatitis and nasal polyposis (48).

Asthma with childhood onset differs from that starting later. As noted previously (49), a gene for sphingolipids (which protect epithelial surfaces against environmental factors with a stable, chemically resistant outer lipid bilayer of the plasma membrane) is the most frequent locus (*ORMDL3/GSDMB* on chromosome 17q21) identified in genome wide association studies (GWAS) of paediatric asthma (50). This is independent of atopic or immunoglobulin E-mediated pathways (51) but could relate to ILC2s which interact directly with epithelial-derived factors. Children with severe, therapy-resistant asthma have higher numbers of ILC2s, Th2 cells and eosinophils than those with milder asthma; IL-17⁺ cell numbers are similar. ILC2s are sensitive to systemic steroids whereas IL-17⁺ cells remain unaltered (52).

In recent years it has been appreciated that, like rhinitis, asthma is not one single disease, either in children (53) or adults (54). So-called intrinsic asthma could be a misnomer: some such patients do possess allergen-specific IgE, not in the circulation, but locally in the airways. Similarly, in the upper airway, local allergen-specific IgE, in the absence of systemic specific IgE, has been identified in both local allergic rhinitis and in some patients with nasal polyposis (55-58).

Overall, it would be easier to make a case for a greater contribution of ILC2s in asthma than in AR, though to some extent this is simply the result of less data being available for AR. They may be particularly important in virally-induced asthma exacerbations, as discussed earlier. Moreover, they appear to be a plausible candidate in the pathology of adult-onset, non-atopic asthma, where classic allergen-induced Th2 pathways do not appear to play a major role.

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

As with asthma, phenotyping provides an important guide to therapy in chronic rhinosinusitis (59). ILC2s are present in sinus and nasal polyp tissue (CRSwNP) (60), particularly in eosinophilic compared with non-eosinophilic endotypes (61). Nasal polyp tissue responds to epithelial IL-33 and TSLP by induction of IL-13 production by ILC2s (62). Systemic corticosteroids reduced nasal polyp ILC2s numbers, with steroid resistance mediated through

TSLP (63). In CRSwNP patients with NSAID exacerbated respiratory disease (N-ERD), ILC2s were significantly increased in the nasal mucosa and decreased in blood following challenge with aspirin. The magnitude of this change positively correlated with the severity of the clinical reaction (64). As with adult-onset, non-atopic asthma then, ILC2s may well play the major role in orchestrating the pathogenesis of CRSwNP.

Therapeutic considerations

Does the innate or acquired derivation of inflammation matter? Does it differ between patients, between allergens, is it of consequence for therapy?

Allergen specific immunotherapy (AIT)

Results in AIT trials for pollen allergy show a decrease of around 30-40% in symptom-medication scores beyond that seen in placebo-treated subjects. Occasionally complete disease remission occurs. The effect size is less in HDM-AIT trials where 20% reduction over placebo is the norm. There are many possible reasons for this, including the greater difficulty of identifying the major driving allergen in individuals with perennial symptoms. However, the fact that HDM can act directly on mucosal surfaces, not via specific IgE, may also be relevant. The ILC2:ILC1 ratio in AIT responders was similar to healthy controls, whereas non-responders had higher ratios of ILC2s to ILC1s, suggesting the ratio might be a response biomarker (65). Moreover, the fact that ILC2s may impair AIT responsiveness means that HDM avoidance plus nasal douching should always accompany HDM AIT.

Fungal direct activation of the innate immune system, including ILC2s, may reduce fungal AIT efficacy. Only one extract, of *Alternaria alternata*, showed some AIT effectiveness, mostly in children (66).

AIT timing could be vital: preferably undertaken before susceptible Th2 cells colonize the ILC2 niches and become less available to systemic influences. Age response stratification has not been critically examined in AIT, nor has disease duration. Data collection on effectiveness and longevity of response is important.

Monoclonal antibody drugs

Current anti-IL-5 biologics (mepolizumab, benralizumab, reslizumab) counteract IL-5 generated by both Th2 and ILC2 cells, but are administered systemically, which might mean

that local ILC2-generated cytokine production is less affected. Early anti-IL5 molecules reduced blood and sputum eosinophilia without changing the late asthmatic response (67) or improving peak flow, symptoms or quality of life (68). Airway eosinophils were only partially depleted, suggesting that local, probably ILC2-induced cells, were vital (69).

Anti-IL-5 biologics give greatest benefit in patients with severe eosinophilic asthma. It is unclear which drug is the most efficacious, though a recent indirect treatment comparison of licensed doses suggests that mepolizumab gave greater improvements in exacerbations and asthma control compared with reslizumab or benralizumab in patients with similar blood eosinophil counts (70).

Dupilumab, directed against the common cytokine receptor subunit IL-4R α , blocks both IL-4 and IL-13 signalling. Notably, the therapeutic response appears greater in asthmatic subjects with higher FeNO and eosinophil counts (71). Also noteworthy is the impressive effect of this drug in CRSwNP. Both these observations imply an interaction between IL-4 and/or IL-13 pathways and IL-5-driven eosinophilic inflammation and might imply a major role for classical Th2 inflammation, even in CRSwNP. However, whilst Th2 cells are major producers of IL-4, other sources include basophils and NKT cells, as well as ILC2s themselves, so the efficacy of dupilumab might still be explained in part by an effect on ILC2-directed inflammation.

Although all these monoclonals reduce asthma exacerbations, there were different effects on lung function and on symptoms, possibly related to their ability to reach cytokines from airway ILC2s. Direct comparative studies are unlikely to occur because of high costs. Real world studies and meta-analyses have yet to provide convincing answers. If threshold values of blood eosinophils and FeNO were set at 150 cells/ml and 25 ppb, respectively, some 25% of severe asthmatic patients in one study had indications for all biologics, including omalizumab, mepolizumab, benralizumab and dupilumab (72). Figure 2 gives a theoretical approach to what each molecule is likely to cover, however in practice this is not necessarily observed.

Omalizumab (anti-IgE), clearly an anti-Th2/acquired immune system agent, is used in severe asthmatics with evidence of perennial allergen sensitization and total IgE levels within a specified dosing range (73). However anti-IgE also works in non-atopic subjects (74, 75). This may relate to the phenomenon of local IgE found in some intrinsic asthmatics, as well as

in some eosinophilic nasal polyps (76). Whether mucosal ILC2s have any role in promoting local IgE synthesis by B cells, or whether this is solely due to local Th2 cells, remains unknown. Newer biologics with more upstream targets, such as anti-TSLP or anti-IL-33, could reduce ILC2 activation and may prove more effective than those blocking downstream cytokines but may also have greater propensity for adverse effects, such as immune deficiency/propensity to infection (77).

Perhaps further phenotyping and endotyping will prove of benefit? NSAID-exacerbated respiratory disease (N-ERD) is a syndrome of highly eosinophilic asthma, often severe, eosinophilic chronic rhinosinusitis with rapidly recurrent nasal polyp (CRSwNP) formation, and intolerance to aspirin and other nonselective cyclooxygenase 1 (COX-1) inhibitors (78). Such drugs can trigger systemic reactions and even death from asthma in the most severely affected patients. Dupilumab, the first monoclonal approved to treat CRSwNP, shows its greatest benefit in N-ERD subjects (79).

However, N-ERD has its own highly specific and inexpensive therapy: aspirin desensitization followed by long term aspirin therapy. This can be performed either orally or intranasally, improves both upper and lower airway symptoms and reduces asthma exacerbations (80). As with all these treatments, not everyone improves. Interestingly, in an audit of cases treated by one of the authors (GKS), it was those N-ERD subjects with positive skin prick tests, possibly more Th2 driven, who found greatest benefit (81), the same has recently been observed with respect to omalizumab therapy in N-ERD patients (82).

Conclusion

In allergic type airway diseases both innate and acquired immune systems are involved, to varying extents. There may be individual differences between patients in the relative influence of the two inflammatory systems even within a single condition, such as N-ERD. How should we proceed? The answer may lie, as with many complex quandaries, in artificial intelligence (83). If extensive data from many subjects with eosinophilic asthma and/or chronic rhinosinusitis with nasal polyps were amassed, plus their responses to therapy, then there is the possibility of deriving an algorithm to predict the best treatment for future affected individuals. This would demand a high level of co-operation from patients, clinicians and pharmaceutical companies, might provide financial winners and losers, but would likely

provide better health for many, which in the end is a big win for all. Further information is also likely to be derived from clinical studies investigating the role of ILC2s in pollutant-driven asthma, from clinical trials of treatments aimed at ILC2 targets, principally-TSLP, and shared targets, such as CRTH2, and, if ever feasible, head to head studies between monoclonal antibody drugs. In addition, more may be learned from studies which combine treatment approaches, such as the addition anti-TSLP or anti-IL-4 drugs to patients receiving allergen immunotherapy.

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Table 1

Innate Immunity
<i>Physical and chemical barriers, such as epithelia, including those with mucociliary clearance.</i>
<i>Chemicals with antimicrobial properties, such as interferons, produced at epithelial surfaces.</i>
<i>Gases such as nitric oxide, produced in the sinuses.</i>
<i>Phagocytic cells (neutrophils, macrophages), dendritic cells, natural killer (NK) cells and other innate lymphoid cells (ILCs)</i>
<i>Circulating proteins, including members of the complement system and other mediators of inflammation.</i>

Figure 1

Innate and acquired mechanisms in Type 2 diseases.

This simplified diagram shows the external factors which act upon the airway epithelium to promote T2 inflammation via both routes.

Key:

612 *DC= dendritic cell*

613 *IL-33= interleukin 33, an alarmin*

614 *IL-25- interleukin 25, an alarmin*

615 *BM- basement membrane*

616 *SM- smooth muscle*

617 *ECP- eosinophil cationic protein*

618 *EDN- eosinophil derived neurotoxin*

619 *MBP- major basic protein*

620 *Th2- helper T2 lymphocyte*

621 *ILC2- innate lymphocyte, producing similar cytokines*

622 *IL4 – interleukin 4*

623 *IL4 R alpha- receptor for IL4 and IL13*

624 *IL5/R- interleukin 5 / receptor*

625 *IL13- interleukin 13*

626 *IgE- immunoglobulin E*

627 *TSLP- thymic stromal lymphopoeitin*

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631 **Figure 2**

632 **Theoretical Effectiveness of therapy according to Immune Phenotype.** In theory therapy
633 directed against IgE-mediated mechanisms (anti-IgE, AIT) should have predominant
634 effectiveness in Th2-driven disease, whereas therapy targeting molecules common to both
635 innate and acquired arms (anti-IL5, anti-TSLP) should work across the inflammatory
636 spectrum. IL-4 is mainly produced by Th2 cells, so the IL4R α blocker, dupilimab, has been

placed towards the Th2 side, though its anti-IL13 activity should inhibit both innate and acquired arms.

The direct nature of ILC2 activation via epithelial insults means that maintaining a clean environment is important and simple avoidance measures, such as nasal douching, should be advised for all rhinitis/ rhinosinusitis sufferers. Niche locations of ILC2s need to be taken into consideration, as well as their later replacement by local Th2 cells. Drugs penetrating poorly into the tissues are unlikely to influence these. The age of the patient at disease onset and therapy onset needs to be considered. AIT should preferably be initiated early in the

Key:

Th2- helper T2 lymphocyte

ILC2- innate lymphocyte, producing similar cytokines

IL4 – interleukin 4

IL4 R alpha- receptor for IL4 and IL13

IL5/R- interleukin 5 / receptor

IL13- interleukin 13

IgE- immunoglobulin E

TSLP- thymic stromal lymphopoeitin

CRT_H2- Chemoattractant receptor-homologous molecule for prostaglandin D₂, expressed on T_H2 cells.



