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New perspectives on the initiation of allergic immune responses at barrier sites

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Although allergies exert a devastating global impact and often lack effective treatment strategies, our knowledge on the mechanisms that initiate and propagate type-2 immune responses remain enigmatic. Recent advances have highlighted additional roles for epithelial cells (e.g. tuft cells) and sensory neurons as initiators and amplifiers of type-2 immune responses. In response to protease activity of allergens, Toll-like receptor stimulation or cellular damage, these type-2 sentinels can release cytokines, alarmins or neuropeptides capable of (i) activating and expanding innate immune cells, (ii) polarizing T helper type-2 cells and (iii) promoting allergic inflammation. Overexpression of these type-2 immune mediators has been associated with allergic disorders and together with their disease promoting role in experimental model systems have paved the way for the generation of new biologics. The aim of this review is to provide a concise view on recent developments in the field and to discuss these findings in the context of allergic inflammation.

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Introduction

Type-2 immune responses have evolved to provide immunity against macroparasites, to protect from non-microbial noxious compounds or venoms, to maintain metabolic homeostasis and to regulate tissue repair [1–3]. However, excessive and chronic activation of these defence mechanisms can also mediate pathologic conditions such as fibrosis or allergic disease [4,5]. Despite their importance in health and disease, how type-2 immune responses are initiated and promote effector T helper type-2 (Th2) responses remains an active area of research. Studies of helminth infection have significantly contributed to a better understanding of cellular and molecular pathways orchestrating type-2 cell mediated immunity [6]. These pathways are often shared and operative in allergic conditions and thus provide potential targets for the treatment of allergies.

Non-hematopoietic cells such as epithelial cells or neurons are primary sentinels of type-2 immune agonists that can be recognized by pattern recognition receptors (PRRs) or danger-associated molecular patterns (DAMPs) [7]. Upon activation, these cells actively communicate with the innate and adaptive immune system by releasing chemokines, cytokines or neuropeptides. Among these, TSLP, IL-25, IL-33, GM-CSF or neuromedin U have gained a lot of attention as these factors significantly contribute to the initiation and maintenance of downstream inflammatory Th2 effector responses. The scope of this review is to discuss recent developments in the field that contribute to a better understanding of epithelial cells and neurons as sensors and initiators of type-2 immune responses, provide new conceptual advances as to their role in the initiation of allergic inflammation and to discuss current use and future prospects of biologics that target allergic mediators upstream of the canonical type-2 cytokines.

Epithelial cells: sensors of type-2 immune agonists

By contrast to type-1 immune sensing, our understanding of the mechanisms that can sense a bewildering set of stimuli that induce type-2 immune responses is very limited. Emerging insights suggest that alternative pathways such as enzymatic activity of allergens or recognition of tissue damage caused by allergens may provoke type-2 immune responses beyond the classical PRR-dendritic cell paradigm [7]. Epithelial cells (ECs) are among the first to encounter allergens. Besides providing a physical barrier, there is accumulating evidence that ECs, by sensing the environment, are central players in the initiation and regulation of allergic inflammation [5,8,9]. Natural allergens are complex mixtures of various constituents and enzymes. Sensing of allergen-associated enzymatic activities by protease-activated receptors (PARs) expressed on ECs or tissue damage sensed by DAMPs may act as an adjuvant for the initiation of type-2 allergic responses. Recent studies revealed that PAR-2 is highly expressed on keratinocytes in patients with atopic dermatitis. PAR-2 activation promotes epidermal barrier impairment of atopic skin by compromising tight junction integrity and composition [10]. Work by Kale *et al.* further demonstrates that the serine protease activity of Per a 10,

a major cockroach allergen, impairs epithelial barrier integrity, induces the secretion of the pro-allergic cytokines IL-33 and TSLP and promotes ATP and uric acid release from activated ECs, suggesting that the proteolytic activity of cockroach allergens can play a significant role in the initiation of allergic inflammation [11]. Further, proteolytic allergens have the capacity to directly alter the binding and structure of polypeptides expressed on ECs. House dust mite (HDM) allergens through cysteine protease activity cleave fractalkine (CX3CL1) from the apical epithelial surface to yield an immunereactive protein that has been associated with the recruitment of innate immune cell populations and allergic airway inflammation [12]. Other studies established a critical role for airway epithelial expressed NADPH oxidase dual oxidase 1 (DUOX1) as mediator of allergic airway inflammation in responses to common airborne allergens [13,14]. Together, ECs can sense allergens or tissue damage to orchestrate a type-2 immune signalling circuit (discussed below) that may have evolved to mount appropriate defence mechanisms against invading parasites, environmental toxins or allergens to restore barrier integrity and tissue homeostasis [1]. However, in the context of excessive or chronic stimulation EC-orchestrated type-2 immune responses can promote pathologic conditions associated with allergic inflammation.

Epithelial cells as orchestrators of allergic immune responses

On exposure to allergens, activated or damaged ECs release allergic mediators such as TSLP, IL-25, IL-33 or GM-CSF that operate upstream of the classical canonical Th2 cytokines IL-4, IL-5 and IL-13. These cytokines promote the recruitment and activation of numerous innate immune cells (e.g. Group 2 innate lymphoid cells (ILC2), basophils, dendritic cells (DCs), mast cells, eosinophils) to create a tissue microenvironment that contributes to the differentiation of allergen-specific Th2 cells. While the role of EC-derived cytokines in the orchestration of allergic inflammation has been widely covered [5,15–18], we here discuss the most recent literature that further support their critical role as initiators and amplifiers of type-2 immune responses.

Advances in TSLP regulation

While TSLP has several homeostatic functions, aberrant expression at barrier sites such as the skin, the intestine or the airways has been linked to the pathogenesis of numerous Th2-related allergic disorders [15,19]. Recent studies have shed new light on the dichotomous role of this cytokine [20,21]. They find that TSLP exists in two isoforms, a short form that may function as antimicrobial peptide whose expression is constitutive and controlled by a separate promotor, and a long isoform barely detectable during homeostasis but that is upregulated during inflammation. Together, these studies demonstrate that posttranslational modifications of the TSLP gene have different biological properties and emphasize the importance for a separate analysis of the two isoforms in future studies. Other studies demonstrated that TSLP can be truncated in two fragments by furin-like and carboxypeptidase N proteases in inflamed tissues with the truncated forms having enhanced activity on type-2 innate immune cells such as mast cells or ILC2s [22]. Further, Ganti *et al.* characterized TSLP gene cis-acting regulatory elements in epidermal keratinocytes and intestinal ECs and identified that transcriptional regulation of TSLP can be fine-tuned by tissue-specific signalling pathways [23]. Together, these studies suggest that posttranslational modifications of the TSLP gene have different biological functions and that the transcriptional control of TSLP expression can be regulated by the local tissue environment.

Recent advances in IL-33 regulation

Genetic polymorphisms near the IL33 and IL1RL1 (ST2) loci have been strongly linked to allergic disease and increased levels of IL-33 and the soluble form of IL-33R, sST2, can be found in tissues and body fluids of allergic patients [24]. IL-33 is constitutively expressed in the nucleus of a variety of cell types including ECs [25]. Upon cellular damage or necrotic cell death, IL-33 is released in its full-length form, gets processed by proteases into highly active forms to alert the immune system of tissue damage [26]. A series of studies now demonstrate that the proteolytic activity of a variety of clinically relevant allergens can convert full length IL-33 ($IL\text{-}33_{FL}$) into mature forms of IL-33 that are potent inducers of allergic inflammation [27•]. Endogenous calpains released from damaged ECs can also process $IL\text{-}33_{FL}$ and potentiate its activity [28]. These findings suggest that $IL\text{-}33_{FL}$ functions as a protease sensor able to detect the proteolytic activity of environmental allergens to rapidly activate the immune system, a mechanism that may represent a universal upstream trigger of type-2 immune responses. Oxidative stress occurring as a result from environmental exposure to air pollution or allergens represents another checkpoint for IL-33 release by ECs. The oxidative stress response is critical for the initiation of a series of biochemical events such as ATP release and Ca^{2+} increases that promote extracellular release of IL-33 [29].

Advances in IL-25 biology — tuft cells in the spotlight

Three independent studies have recently identified tuft cells, rare chemosensory intestinal ECs, as the sole source of constitutive IL-25 expression [30••,31,32,33]. Tuft cells expand in response to intestinal dwelling nematodes to kick-start type-2 immune responses by a signalling circuit in which tuft cell-derived IL-25 induces IL-13 production in ILC2s. In a positive feed-back loop, IL-13 can signal to the pluripotent intestinal stem cell niche to induce tuft cell proliferation and goblet cell hyperplasia from undifferentiated epithelial progenitors to promote parasite expulsion.