


EAACI POSITION PAPER



AllergoOncology: Danger signals in allergology and oncology: A European Academy of Allergy and Clinical Immunology (EAACI) Position Paper

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Abbreviations: AAMP, allergen-associated molecular pattern molecule; DAMP, damage-associated molecular pattern molecule; PAMP, pathogen-associated molecular pattern molecule.

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Abstract

The immune system interacts with many nominal 'danger' signals, endogenous danger-associated (DAMP), exogenous pathogen (PAMP) and allergen (AAMP)-associated molecular patterns. The immune context under which these are received can promote or prevent immune activating or inflammatory mechanisms and may orchestrate diverse immune responses in allergy and cancer. Each can act either by favouring a respective pathology or by supporting the immune response to confer protective effects, depending on acuity or chronicity. In this Position Paper under the collective term danger signals or DAMPs, PAMPs and AAMPs, we consider their diverse roles in allergy and cancer and the connection between these in AllergoOncology. We focus on their interactions with different immune cells of the innate and adaptive immune system and how these promote immune responses with juxtaposing clinical outcomes in allergy and cancer. While danger signals present potential targets to overcome inflammatory responses in allergy, these may be reconsidered in relation to a history of allergy, chronic inflammation and autoimmunity linked to the risk of developing cancer, and with regard to clinical responses to anti-cancer immune and targeted therapies. Cross-disciplinary insights in AllergoOncology derived from dissecting clinical phenotypes of common danger signal pathways may improve allergy and cancer clinical outcomes.

KEYWORDS

AAMP, allergy, ALR, cancer, DAMP, danger signals, immune response, immunotherapy, inflammation, NLR, PAMP, RLR, TLR, tolerance

1 | METHODS

This Position Paper is a product of the EAACI Working Group for AllergoOncology, an expert panel of clinical immunologists, allergists, biochemists and epidemiologists. The topic of the manuscript was identified at the WG workshop in May 2020, and a streamline of relevant subtopics was extensively revised and designated to individual WG members. After following workshops and using a circulation process, the manuscript was recirculated for review to the WG authors, compiled and again recirculated for complete consensus on text, tables and figures. The final manuscript was read and approved by all authors and represents an expert consensus position, with recommendations summarized in the 'Highlights box'.

2 | DATA SOURCES, SEARCH STRATEGY AND STUDY SELECTION

Studies published in English were identified from PubMed. The following keywords were used in the search strategy: (allergy OR atopy) AND (tumor/tumour OR cancer OR malignancy) AND (danger signals OR damp OR pamp) AND (NK cells OR ILC OR mast cells OR granulocytes OR APC OR T cells OR B cells OR clinical applications). References published within the 2000–2020 timeframe that had not been otherwise identified in the initial search were added where relevant. We reviewed approximately 500 published studies relevant to this paper.

3 | OVERVIEW

Title

Abstract

Part 1: Introduction to the danger signals: DAMPs, PAMPs and AAMPs

Part 1a. Introduction to the DAMPs and PAMPs in Allergy and Oncology—An overview

Part 1b. Introduction to the allergen-associated molecular pattern (AAMPs)—How allergens can introduce danger?

Part 2: Danger signals in NK cells and ILC

Part 2a: Allergy

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Part 3: Danger signals in mast cells and granulocytes

Part 3a. Allergy

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Part 4: Danger signals and antigen-presenting cells

Part 4a. Allergy

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Part 5: Danger signals in T cells and B cells

Part 5a. Allergy

Part 5b. Oncology

Part 6: Clinical applications addressing danger signals

Part 6a. Allergy and clinical immunology

Part 6b. Oncology

Part 7. Conclusion

The chief danger in life is that you may take too many precautions.

Alfred Adler

I know that every good and excellent thing in the world stands moment by moment on the razor-edge of danger and must be fought for.

Thornton Wilder

4 | PART 1. INTRODUCTION TO DANGER SIGNALS: DAMPs, PAMPs AND AAMPs

4.1 | Part 1a. Introduction to DAMPs and PAMPs in allergy and oncology

Danger is metaphor with deep transcendent meaning for our lives at the cellular, tissue and organismal levels. So-called danger signals can originate from either exogenous (pathogen-associated molecular pattern molecules, PAMPs or allergen-associated molecular pattern molecules, AAMPs),¹ or endogenous (damage-associated molecular pattern molecules, DAMPs). These signals are recognized by the immune system, triggering response in both the innate and

Highlights

1. The immune context under which danger signals are received can promote or prevent immune activation or inflammatory mechanisms which are important determinants in the course of allergic diseases and cancer.
2. Danger signals based on endogenous danger-associated (DAMP), exogenous pathogen (PAMP) and allergen-associated (AAMP) molecular pattern molecules, initiate immune responses, however, acuity, chronicity and immune context may influence the course of pathologies such as allergy and cancer.
3. Allergens can introduce danger, and targeting AAMP-induced signalling can be considered to overcome inflammatory responses in allergy and cancer.
4. Immune cell-derived mediators and danger signals involved in allergic disorders (hypersensitivity versus immune tolerance), also impact disease evolution in malignancies (pro-tumour versus anti-tumour activity), and the connected activities between these processes in both disease fields (AllergoOncology) require further study.

adaptive compartments,² with varying effects depending on their acuity or chronicity. Charles Janeway introduced the infectious non-self-model, where PAMPs are recognized as infectious non-self.³ However, this concept could not explain pathogenic self-recognition. Later in 1994, Polly Matzinger introduced the concept of the Danger Model, postulating that the immune system does not distinguish between self and non-self, but discriminates between 'dangerous' and 'safe' by recognition of pathogens or alarmin signals from injured or stressed tissues.⁴ Based on this model, Walter Land et al.⁵ proposed the concept of Danger Associated Molecular Patterns (DAMPs).

Pathogen-associated molecular pattern molecules are small molecular motifs well-conserved within a class of microbes. They are recognized by Toll-like receptors (TLRs) and other pattern recognition receptors (PRR) (Table 1). PRR are expressed on the cell surface or on the membrane of intracellular organelles of both innate and adaptive immune cells. PRR also include nucleotide-binding and oligomerization domain NOD-like receptors (NLRs), AIM2-like receptors (ALRs) and retinoid acid-inducible gene-I (RIG)-like receptors (RLRs), intracellular proteins that survey the cytoplasm for signs revealing the presence of not only pathogen-encoded molecules but also of pathogen-encoded activities termed 'patterns of pathogenesis'.⁶

Several types of molecules can act as PAMPs. Bacterial lipopolysaccharides (LPS), consistently present in the cell membranes of Gram-negative bacteria, are considered prototypic PAMPs. LPS are recognized by TLR4 coupled with CD14 and Myeloid Differentiation factor 2 (MD-2). Other PAMPs include (a) bacterial lipoproteins and peptidoglycan recognized by TLR2; (b) parasite

TABLE 1 List of danger signals (PAMPs and DAMPs) and their receptors

Exogenous pathogen-associated molecular pattern molecules (PAMPs)	Receptors (PRR)
Bacterial lipoproteins, for example, lipoteichoic acid (gram pos.) and peptidoglycan (gram pos.), Pam3CSK4	TLR1, TLR2
Poly(I:C)	TLR3
Single-stranded RNA,	TLR7, TLR8
Double-stranded RNA	TLR3
LPS	TLR4 coupled with CD14 and MD-2
Flagellin	TLR5
CpG motifs	TLR9
Endogenous Damage-associated molecular pattern molecules (DAMPs or alarmins)	Receptors (PRR)
HMGB1 protein	RAGE, TLR2, TLR4
Heat shock proteins, For example, HSP27, HSP70	CD14, CD91, Scavenger receptors, TLR4, TLR2, CD40
Reactive oxygen intermediates, for example, Hydrogen peroxide	Intracellular redox-sensitive proteins, for example, DNA, enzymes, fatty acids
Laminins, fibronectin, Tenascin C	Integrins
hyaluronan	TLR2, TLR4, CD44
S100 proteins (calgranulins)	RAGE
Extracellular nucleotides (ATP, ADP, adenosine)	PI, P2X and P2Y receptors (ATP, ADP) A1, A2A, A2B and A3 receptors (adenosine) Ecto-enzymes CD39/CD73
TSLP	CRLF2, IL7Ralpha
Acid uric crystals	CD14, TLR2, TLR4
IL-33	ST2

flagellin recognized by TLR5; (c) lipoteichoic acid from Gram-positive bacteria, recognized by TLR2 and TLR6; (d) nucleic acid variants, usually associated with viruses, such as single-stranded RNA, recognized by TLR7 and TLR8, or double-stranded RNA, recognized by TLR3; (e) unmethylated deoxycytidyl-phosphate-deoxyguanosine (CpG) motifs, recognized by TLR9.⁷ Furthermore, the epithelium as a general barrier between an organism's interior and exterior environments is a critical location, where PRR recognize PAMPs and mount a local immune response.⁸

Damage-associated molecular pattern molecule are endogenous molecules released by degranulating, stressed or dying cells, which undergo necrosis, apoptosis or autophagy. The high-mobility group box 1 (HMGB1) protein is the prototype of DAMPs. HMGB1 is recognized by TLR2, TLR4 and the receptor for advanced glycation end products (RAGE).⁹ Other DAMPs are heat shock proteins, reactive oxygen intermediates, extracellular matrix breakdown products such as fibronectin, heparan sulphate, biglycan, fibrinogen, oligo-saccharides of hyaluronan and hyaluronan fragments, tenascin-C, cardiac myosin and S100 proteins. Secondary mediators including some neuromediators and cytokines, such as interferons, serve to amplify the response to DAMPs. Non-protein DAMPs include ATP, uric acid, heparan sulphate and denatured DNA. The activation of PRRs by DAMPs is key in the pathogenesis of tissue injury, repair and

regeneration in several of acute and chronic inflammatory diseases including allergic disorders, asthma, atherosclerosis, neuroinflammation, and more recently, malignancy.¹⁰⁻¹³

Accumulating evidence has led to recent advancements designed to manipulate exogenous and endogenous DAMP signal pathways in immunotherapy, both in allergic and oncologic diseases. Table 2 provides an overview of the most relevant danger signals from the areas of allergy and oncology.

In this Position Paper, we provide a comprehensive overview of danger signals in immune responses in allergy and in oncology and we put forward the importance of considering how these should be evaluated to inform both fields. Here, we focus on individual immune cell types. Non-hematopoietic cells, such as epithelial cells, endothelial cells or stromal cells, are considered beyond the scope of this manuscript. We highlight and discuss potential clinical applications addressing danger signals. We also describe new concepts where the homeostasis of different patterns of associated compartments of the immune system may predispose and set a tolerogenic (or oncogenic) or immunogenic (or allergenic) state. This interplay of innate, humoral and cellular compartments may serve to further understand the complex network of immune regulation between danger signals in allergy, oncology and the connection between them (AllergoOncology) (Figure 1A,B).

BOX 1 Examples of unknown mechanisms of danger signal interactions with immune cells in allergy and oncology**Unmet needs****2: NK cells and ILC**

- a: Allergy To decipher the function of allergens with their AAMP, PAMP and DAMP signals on modulating expression of activating and inhibitory molecules of NK cells and ILCs. How epithelial stress and damage at the mucosal interface can interact with DAMP receptors (IL-33R/ST2) and TSLPR on ILC and NK cell functions for better preventive measurements.
- b: Oncology Contrasting pro- or anti-tumoral activities of innate cells when activated by DAMPs appear to be dictated by the individual microenvironment and specifically cancer type, histology. The mechanism of how DAMPs regulate innate arms of immunity to enhance their anti-tumour functions require further study in specific patient settings.
- Innate cells play two predominant roles in the tumour microenvironment, the initial as 'first responders', allowing rapid sensing of tissue damage or injury, and recruiting and maturing an adaptive immune response. The latter is as entrained effectors, responding to adaptive effectors, amplifying and enhancing antitumour effects.

3: Mast cells and granulocytes

- a: Allergy To further identify granulocyte mediators with potential defensive responses against danger signals.
- b: Oncology To further elucidate the mechanism by which DAMPs (e.g., IL-33, ATP, DNA/CpG motifs, HMGB1, GM-CSF) in the clinical setting influence tumour growth by promoting survival of granulocytes and modulating adaptive immune cells within the tumour.

4: Antigen-presenting cells

- a: Allergy To further investigate how the response of DCs and macrophages to AAMPs, PAMPs and DAMPs influence allergic sensitization, and the resolution of the allergic inflammation. For instance, how danger signals modulate M2/M2b polarization and, in concert, the tissue microenvironment.
- b: Oncology DCs and TAMs exhibit both anti- and a pro-tumoral effects, influenced by the different status of activation and by the TME. To overcome tumour evasion and reset the DC and TAM immune responses against tumours, it is necessary to understand which and how PAMPs and DAMPs re-polarise these APCs towards a DC1- and M1-like phenotype, respectively, and consequently drive a tumoricidal TME.

5: T cells and B cells

- a: Allergy To understand the role of type-2 alarmins and their differences as well as yet undiscovered elements between B and T cells and the epithelial barrier.
- b: Oncology In response to danger signals stimulation, B cells, as other immune cells, can have pro or antitumour effects depending on the cancer type and especially on the immune context. At present, there is a significant need for more studies aiming to get a holistic view of the immune infiltrate in cancer, which may be achieved using the recently developed high throughput methods for proteogenomics and spatial proteogenomics.
- The most recent insights in tumour immunobiology and response to checkpoints suggest that B cells, at the very least as sentinels of so-called tertiary lymphoid structures (TLS), portend a favorable prognosis.

4.2 | Part 1b. Allergen-associated molecular pattern (AAMPs): how can allergens introduce 'danger'?

Recent data suggest that danger signals can be derived from allergens such as from pollen, house dust mite and *Staphylococcus aureus* enterotoxin B (SEB) (Table 3), inducing antigen-specific IgE production in atopic individuals. How capable a protein is in producing this response is often described as allergenicity and may depend on several factors. Allergens somewhat unusual ability to provoke an immune response is determined by their intrinsic functional properties. During sensitization as well as during the effector phase, it is important that some allergens possess proteolytic functions that

breach innate defence barriers, such as epithelial skin layers, leading to an interaction with effector cells such as mast cells, endothelial cells, epithelial cells or stromal cells. This results in inflammation or, when IgE is produced, in typical allergic symptoms such as rhinitis. Examples of allergens with proteolytic functions are dust mites allergens, which are involved in pectin degradation by means of hydrolytic enzymes, or non-hydrolytic enzymes such as the pectin lyase from tree pollen. The major house dust mite allergen Der p 1 exhibits cysteine protease and endopeptidase activity which facilitates barrier disruption leading to activation of caspase-1 activation and induction of IL-1 β and IL-18 release. Additionally, house dust mite-induced activation of the NLR family pyrin domain-containing 3 (NLRP3) inflammasome may play a pivotal role in the pathogenesis of

TABLE 2 Danger signals in allergology and oncology

Allergy involvement	Type of 'danger signal'	Oncology involvement
Activates mast cells and eosinophilic inflammation. Studies with anti-TSLP are underway. ILC2 cells express alarmin receptors: IL-33R/ST2 (suppression of tumorigenicity 2), TSLPR.	TSLP	Pro-tumorigenic in some models, anti-tumorigenic in other studies
Activates mast cells and eosinophilic inflammation.	ATP	ATP from dying cells also activates P2X7R in DCs, leading to pro-inflammatory IL-1 β secretion through the NLRP3 inflammasome, again targeting CD8+ T cells
Activates mast cells and eosinophilic inflammation. Studies with anti-IL-33 are used as treatment in various allergy models.	IL-33	Pro-tumorigenic in some models, anti-tumorigenic in other studies
Allergenic lipocalin peptides bind DAMP formyl peptide receptors 3 (FPR3) expressed by monocyte-derived DCs and stimulate the Th2 microenvironment	Formyl peptide receptors 3 (FPR3)	Reactive oxygen species-dependent Epidermal growth factor receptor (EGFR) tyrosine phosphorylation
Triggers the production of CCL2, a Th2-related chemokine	HMGB1	Leads to production of pro-inflammatory cytokines, regulates monocyte recruitment, angiogenesis and immune suppression. May also lead to NK cell activation. HMGB1-induced TLR4 activation on Tregs decreases IL-10, forkhead box P3 (FOXP3) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expression
n.d.	HSP27	Allows the formation of the metastatic niche for secondary tumour growth
Promotes pulmonary type 2 immunity to mite allergens at mucosal surfaces	Serum amyloid 3 and A1 (SAA1)	Allows the formation of the metastatic niche for secondary tumour growth
Induce specific IgE production	Different allergens (pollens, house dust mites)	n.d.
Activates mast cells and eosinophils	Papain	Inhibition of NF κ B/AMPK signalling and p- AKT, p-ERK, p-Stat3
Activates mast cells and eosinophils	Staphylococcus aureus enterotoxin B	Downregulates the expression of Transforming Growth Factor-Beta (TGF- β) signalling transducers
Enhances influx of inflammatory cells in lung epithelia in allergic mouse models	Adenosine	Stimulation of the DAMP adenosine and its receptor A2A on B cells can block signalling downstream of TLR4 and the B-cell receptor (BCR) which inhibit B-cell survival and can also promote VEGF-C expression, leading angiogenesis and metastasis
Induction of strong Th1 immune response to counterbalance allergen-driven Th2 response	DNA/CpG motifs	TLR9 dependent activation of antigen-specific anti-cancer immune responses via plasmacytoid DC
Modulates the immune response from Th2 to Th17 to Treg	LPS	Required for DC activation, which can then sense DAMPs released through the activation of specific cell surface receptors. LPS activation of TLR4 in Tregs enhances their immunosuppressive activity and proliferation

Abbreviation: N.d., not determined yet

atopic dermatitis (AD).¹⁴ Mutagens in skin cancer models have also been demonstrated to provoke $\gamma\delta$ T-cell-dependent IgE production, suggesting an unusual linkage between atopy and oncology.^{15,16}

Lack of barrier-protective factors may act in this sense as immune adjuvants. Examples are mutations in the filaggrin protein in AD in which percutaneous allergen exposure, and thus sensitization, may occur; and MHC haplotype variability, which may alter or amplify T-cell activating signals, thus increasing the likelihood of developing allergic responses.¹⁷

Allergens seem to possess particular features that facilitate immune activation. Most allergens are 5–100 kDa size proteins or glycoproteins but are clustered in very few protein families (Table 3). Many are dimers, oligomers or tend to form aggregates, thereby forming the so-called AAMPs.¹ Thereby, they can interact with soluble pattern recognition receptors, such as the hexameric serum amyloid A, and initiate inflammation.¹⁸ The potential sources of allergens are numerous, from foods to plants and arthropod faeces. Some proteins contribute to adjuvant functions.

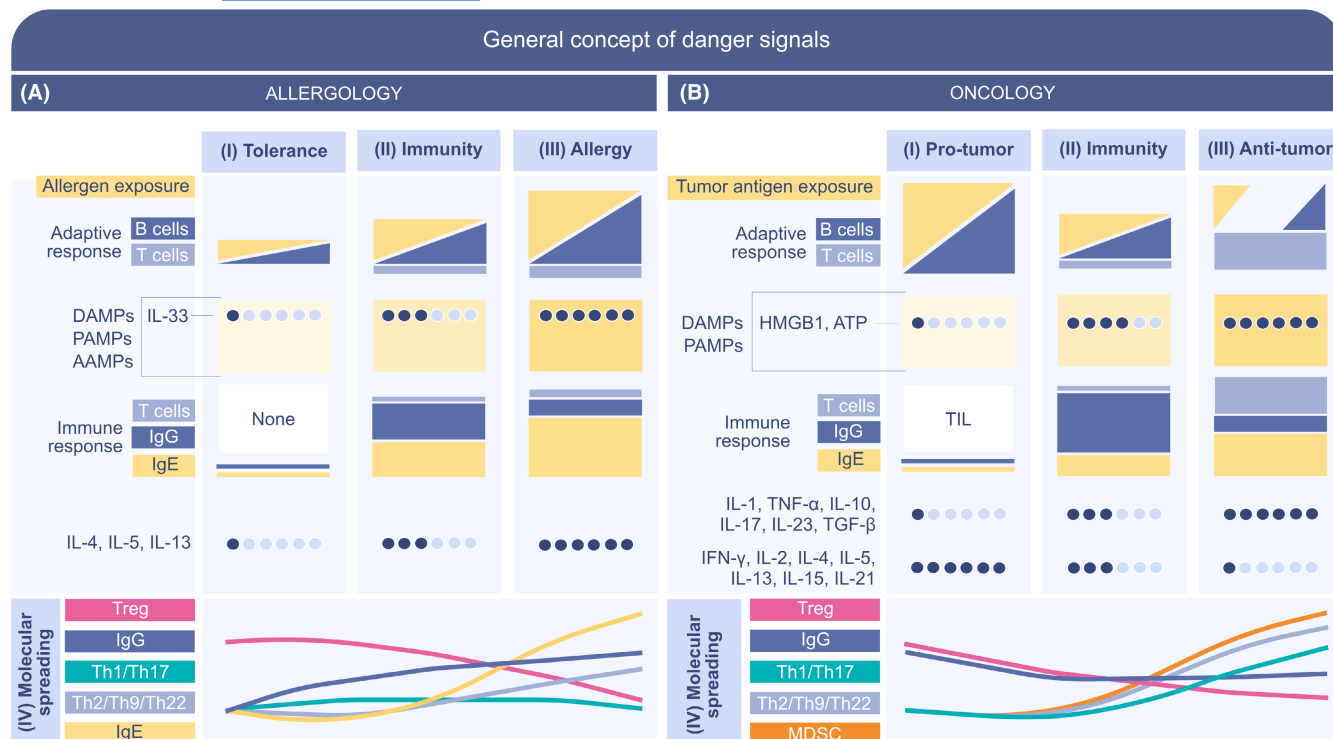


FIGURE 1 General concept of Danger signals. (A) in Allergy. (I) Immune tolerance which is a state of unresponsiveness to a specific antigen or group of antigens, appears in the absence of damage-associated molecular pattern molecules (DAMPs), so-called danger signals, and it is present and only if a tolerogenic immune response is maintained. Regulatory T cells are responsible of maintaining tolerance among other cellular mechanisms. (II) Host immunity requires a balance between inhibitory and activating signals resulting in B-cell-produced immunoglobulins, IgG and IgE, and immune cell-derived cytokine pattern molecules including IL-4, IL-5, IL-13 and IL-33, among others. (III) Exogenous (PAMP or AAMP) or endogenous (DAMP) danger signalling results in humoral and cellular immune responses, including strong cytokine-mediated orchestration of T-cell responses with a Th2-shift and a pronounced B-cell-derived IgG to IgE class switch, creating a clinically allergic phenotype. (IV) Molecular repertoire is involved in different phases of the immune response, whose drivers or predominant cells are largely unknown. T-cell and B-cell repertoire is randomly generated (the 'Adaptome'). Epigenetic changes upon exogenous impact, microbiome, genomic, mutagenic alterations or proteases from allergens are considered likely alterations which can drive allergy. (B) in Oncology. (I) Tumours can arise following primary genomic instability (e.g., paediatric cancers) or secondary genomic instability (e.g., following chronic inflammation as in adult tumours). DAMPs (i.e., HMGB1) or PAMPs can support tumour progression, inhibit immune surveillance and promote tumour-associated immune escape mechanisms. Cell death and release of DAMPs may also trigger chronic inflammation and thereby promote the development and progression of tumours. Dysfunctional tumour-infiltrating lymphocytes (TIL) or tumour cells maintain an immune incompetent microenvironment via secretion of TGF β , IL-10, IL-6 and others. Tregs maintain a tumour-tolerant environment by secreting both IL-10 and TGF β . (II) Immune competence. The humoral and cellular immune responses are in balance and protect from tumour antigens, genetic or epigenetic tumour-promoting events employing a range of cytokines and antibodies. (III) DAMPs (i.e., ATP) may exert protective functions by alerting the immune system to the presence of dying tumour cells, thereby triggering immunogenic tumour cell death and T-cell activation signals. (IV) Molecular spreading arises during chronic inflammation. The 'Adaptome' is shaped by epigenetic changes and the microbiome. MDSC (Myeloid-derived suppressor cells)

Enterotoxin produced by staphylococcal bacteria plays a role in AD via breaching the innate barrier by forming pores in cell membranes. It acts as a superantigen to non-specifically activate adaptive immunity. Others are proteins involved in innate defence and specifically target immune cells. Animal-derived lipocalins or the pathogenesis-related protein 10 (PR-10) proteins possess immune regulatory properties when they transport ligands such as flavonoids, lipids, vitamins and steroids, but initiate danger signals in their unbound form.^{19,20} The heat shock proteins which are another allergenic protein family eliciting immunological danger and being allergenic.

Allergens may carry danger signals that support allergenicity. Examples are pollen-associated lipid mediators (PALMs) released by pollen grains, which attract and may activate eosinophils and

neutrophils and modulate dendritic cell (DC) function,²¹ and HMGB1, which binds to RAGE. Advanced glycation end products (AGEs), which RAGE recognizes, are also present in foods such as cooked meat, oils, cheese and other foods with high sugar content. A combination of potential food allergens and AGEs may thus lead to sensitization and food allergies.²²

Extrinsic microenvironmental factors, which alter normal defence mechanisms may also contribute to allergenicity.¹⁷ Bacterial LPS, an example of a Th1 adjuvant, acts through PRR including TLRs, nucleotide-binding oligomerization domain-containing proteins (NOD), Dectin and DC-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN/CD209).¹⁷ Helminth-derived molecules, an example of a Th2 adjuvant, may also skew the immune system towards Th2.

TABLE 3 Danger signals associated with molecular allergens (AAMPs) or typical for allergen families

Allergen-family	Paradigms (alphabetic)	Source	Mechanism of danger signal	Physiological function
With transport function				
PR-10	<ul style="list-style-type: none"> • Aln g 1 • Bet v 1 • Cor a 1 • Fag s 1 • Pla a 1 • Api g 1 • Ara h 8 • Cor a 1 • Dau c 1 • Fra a 1 • Gly m 4 • Mal d 1 	<ul style="list-style-type: none"> • Alder • Birch trees • Hazelnut • Beech • PlataneCross-reactive plant food: • Celery • Peanut • Hazelnut • Carrot • Strawberry • Soy • Apple 	<ul style="list-style-type: none"> • Exposure of AAMPs by dimer formation • Like lipocalins, PR-10 pollen allergens sequester iron and are produced in response to plant stress, like microbial attack. Their withdrawal of iron from immune cells favours the survival of Th2 cells. • Their withdrawal of iron from immune cells favours the survival of Th2 cells. • Some lipid ligands hinder proteolytic digestion of food allergens, promote their thermal stability and absorption (e.g., Ara h 8) 	<ul style="list-style-type: none"> • Pathogenesis-related
Lipocalins	<ul style="list-style-type: none"> • Bos d 2,5 • Can f 1,2,4,6 • Cav p 1 • Equ c 1 • Fel d 4, 7 • Mus m 1 • Ory c 1 • Phod s 1 	<ul style="list-style-type: none"> • Cattle • Dog • Guinea pig • Horse • Cat • Mouse • Rabbit • Hamster 	<ul style="list-style-type: none"> • AAMPs by dimer formation • These innate defence molecules sequester iron from the environment, thereby skewing immune cells towards Th2, as Th1 are more susceptible to iron deficiency. • Lipid binding protects against degradation and enhances LPS/TLR4 signalling 	<ul style="list-style-type: none"> • Transport function
Subgroup of lipocalins: fatty acid binding proteins (FABPs)	<ul style="list-style-type: none"> • Der p 13 • Der f 13 • Blo t 13 	<ul style="list-style-type: none"> • Mites 	<ul style="list-style-type: none"> • AAMP bind to hexameric Serum amyloid A, the complex activates the SAA1-binding receptor, formyl peptide receptor 2 (FPR2). 	<ul style="list-style-type: none"> • Function: transport and metabolism of large-chain fatty acids
Secreto-globulin, Utero-globin	<ul style="list-style-type: none"> • Can f Fel d 1-like • Fel d 1 • Ory c 3 	<ul style="list-style-type: none"> • Dog • Cat • Rabbit 	<ul style="list-style-type: none"> • Yet not clear, potentially binding TLR4 ligands and Th2 activation via TLR4 and TLR2. 	<ul style="list-style-type: none"> • Hormone binding
(Beta)-Expansins	<ul style="list-style-type: none"> • Cyn d 1 • Lol p 1 • Phl p 1 • Phl p 2 	<ul style="list-style-type: none"> • Bermuda grass • Ryegrass • Timothy grass 	n.d.	<ul style="list-style-type: none"> • Xylan-binding • Cell wall relaxation • Fruit ripening • Antimicrobial
NPC2 (Niemann-Pick type C2)	<ul style="list-style-type: none"> • Can f 2 • Cat NPC2 • Der p 2 • Der f 2 	<ul style="list-style-type: none"> • Dog • Cat • house dust mite • storage mite 	<ul style="list-style-type: none"> • Lipid binding molecules • Replace MD-2 subunit from TLR4 complex, initiate Th2 signals 	<ul style="list-style-type: none"> • Nutrient transfer
Parvalbumins (α and β)	<ul style="list-style-type: none"> • Cyp c 1 • Clu h 1 • Dal s 1 • Gad m 1 • Raj c • Sco s 1 	<ul style="list-style-type: none"> • Carp • Herring • Salmon • Codfish • Ray • Mackerel 	<ul style="list-style-type: none"> • Calcium sequestration 	<ul style="list-style-type: none"> • Participate in muscle relaxation • Regulator of neuronal signal transmission
Ole e 1 Ole e 1-like	<ul style="list-style-type: none"> • Frau e 1 • Lig v 1 • Ole e 1 • Pla l 1 	<ul style="list-style-type: none"> • Ash • Privet • Olive • plantain 	<ul style="list-style-type: none"> • AAMPs by dimer formation. 	<ul style="list-style-type: none"> • Zn²⁺ binding • Signal transduction during germination and growth • Immune activator
Tropomyosins	<ul style="list-style-type: none"> • Ani s 3 • Blo t 10 • Pen m 1 • Per a 7 	<ul style="list-style-type: none"> • Anisakis • Blomia tropic. • Black Tiger Shrimp • Cockroach 	<ul style="list-style-type: none"> • AAMPs by repetitive epitope display 	<ul style="list-style-type: none"> • Troponin/Actin binding • Regulator of muscle contraction

(Continues)

TABLE 3 (Continued)

Allergen-family	Paradigms (alphabetic)	Source	Mechanism of danger signal	Physiological function
Troponins	• Cra c 6	• Brown shrimp	• AAMPs by repetitive epitope display	• Calcium binding, • Tropomyosin/Actin binding • Regulator of muscle contraction
Polcalcins	• Aln g 4 • Phl p 7	• Alder • Tim. Grass	n.d.	• Calcium binding • Growth regulation
Profilins		• Pollen • Plant food	n.d.	• Calcium binding • Actin binding • Locomotion and shape regulator
Manganese superoxide dismutase	• Alt a MnSOD • Asp f 6 • Mala s 11 • Pis v 4	• Alternaria • Aspergillus • Malassezia • Pistachio	n.d.	• Manganese-binding • Anti-inflammatory • Transform reactive oxygen species into molecular oxygen
Oleosins	• Ara h 15 • Cor a 12	• Peanut • Hazelnut	• Bind phospholipids, creating an oil body—potentially supporting mucosal uptake	n.d.
With barrier breach function				
Cysteine proteases	• Der p 1 • Der f 1 • Papain • Bla g 1	• House dust • storage mites • Plant food • German cockroach frass proteases	• Direct lytic effect: Degrade extracellular matrix proteins and lead to an inflammasome response in the skin and release of IL-33. • Activate G-protein-coupled protease-activated receptors (PARs)	n.d.
Aspartate proteases	• Bla g 2	• Cockroach • Alternaria fungus	• Aspartate protease activation of protease-activated receptor (PAR)-2	n.d.
Arginine kinases	• Der p 20 • Bla g 9 • Pen m 2	• House dust mite • Black tiger shrimps	n.d.	• Mg ²⁺ binding • Couple energy production with cellular function
Alpha-Gal (mammalian meat allergy)	• α-Gal	• Cat Fel d 5 • Ticks bite • Red meat	• Presumably AAMPs by repetitive epitope display	n.d.
With carrier, barrier breach and regulatory function				
2S-Albumins	• Ana o 3 • Ara h 2 • Ara h 6 • Ber e 1 • Cor a 14 • Fag e 2 • Gly m 8 • Jug r 1 • Maci S2 albumin • Pap S2 albumin • Pis v 1 • Ses i 1 • Sin a 1	• Cashew nut • Peanut • Peanut • Brazil nut • Hazelnut • Buckwheat • Soy • Walnut • Macadamia nut • Poppy • Pistachio • Sesame • Mustard	• Destabilization of membranes resulting in leakage • Presumably, the lipids inside may act on innate cells (iNKTs)	• Lipid binding • Seed storage • Pathogenesis-related
7/11S Globulins (vicilins/legumins)	• Ara h 1 • Cor a 11 • Gly m 5 • Jug r 2 • Jug r 6 • Pis v 3	• Peanut • Hazelnut • Soy • Walnut • Walnut • Pistachio	• Exposure of AAMPs by trimer/hexamer formation • Destabilization of membranes resulting in leakage • Globulins interact with phosphatidylcholine, which hinders their digestion and activates DCs	

TABLE 3 (Continued)

Allergen-family	Paradigms (alphabetic)	Source	Mechanism of danger signal	Physiological function
LTPs (Lipid transfer proteins)	• Fra a 3	• Plants, nuts, fruits	• Destabilization of membranes resulting in leakage	• Lipid binding • Trafficking
nsLTPs (nonspecific Lipid transfer proteins)	• Pru p 3 • Api g 2	• Fruits • vegetables	• Destabilization of membrane	• Lipid binding • Signal transduction regulation • Cell wall organization • Antimicrobial activity
Phospho-lipases	• Ves v 1 (PLA1) • Ves v 2 (PLA2)	• Wasp • Wasp	• Cleaves fatty acids, important for downstream activation of the inflammatory arachidonic acid pathway • Potential interaction with cell membranes of inflammatory cells	• Ca ²⁺ binding
Pectate lyases	• Amb a 1 • Cup a 1 • Cry j 1	• Ragweed • Arizona cypress • Jap. Cedar	• AAMPs by repetitive epitope display	• Calcium binding • Pectate lyase activity

Abbreviations: AAMPs, Allergen-Associated Molecular Patterns; N.d., not determined yet.

Additionally, irritants may serve as adjuvants. This is the case for environmental pollutants including particulate matter, such as diesel exhaust particles (DEPs) and viral infections. These may alter the development of allergic sensitization through immunomodulatory effects such as altering antigen-presenting cell (APC) functions and influencing cytokine profiles.¹⁷ The concept of allergens expressing AAMPs may open new opportunities for therapeutic interventions targeting AAMP/receptor downstream signalling, in an analogy to danger signals currently being investigated and already applied in anti-tumour treatment.

5 | PART 2: DANGER SIGNALS IN INNATE LYMPHOID CELLS (ILCS) AND NATURAL KILLER (NK) CELLS

5.1 | Part 2a. Allergology

While there is controversial evidence for a role of ILC1 and NK cells in asthma, ILC2 are now known to be an integral part of the type 2 response that occurs in allergic diseases. ILC2 are key players sensing epithelial stress and damage occurring at the mucosal interface through expression of DAMP receptors (IL-33R/ST2 (suppression of tumorigenicity 2) and TSLPR).²³ Together with basophils and mast cells, ILC2 provide early signals to other cell types involved downstream in the allergic response (DC, eosinophils, macrophages).²⁴ Furthermore, IL-17-derived ILC3 have been associated with asthma exacerbation in obese individuals^{25,26} (Figure 2A).

5.2 | Part 2b. Oncology

ILCs have been reported in many tumour types and have been shown to exert both tumour-protective and tumour-promoting

capabilities. These functions likely depending on their specific subsets (ILC1, ILC2, ILC3 or LTi), in a way that is similar to the different CD4+ T helper cell subsets.²⁷ Since ILCs display high plasticity, their functions are determined mainly on their immediate environment, such as the organ/tissue type, the cancer type and the nature of immune cells they are in contact with (reviewed by²⁸).

ILCs express a variety of sensors for danger signals such as ST2, IL-17RB or TSLPR. The DAMP IL-33, known for its modulation of tumour-associated ILC2, is the most documented activator of ILCs.²⁹ IL-33-mediated ILC2 expansion conferred effective anti-tumour immunity against pancreatic cancer, particularly in combination with PD-1 checkpoint blockade.³⁰ Furthermore, tumour models genetically manipulated to secrete endogenous IL-33 showed increased accumulation of ILC2s secreting CXCL2/1 which promoted tumour apoptosis via CXCR2 activation.³¹ In contrast, in a breast cancer model, a time-dependent increase of endogenous IL-33 in primary tumours and development of metastases was associated with an increase IL-13-producing ILC2 and immunosuppressive cells including M2 macrophages in the tumour microenvironment (TME).³² The IL-33-related immunosuppressive properties of ILC2 were also demonstrated to depend on the ecto-enzyme CD73 which in concert with CD39, converts extracellular ATP to adenosine, an inhibitor of anti-tumoural immunity.²⁸ Similar effects were described during chemotherapy and radiation therapy before allogeneic hematopoietic stem cell transplantation. As such, therapy-mediated tissue damage induced extracellular ATP release, sensed by resident ILC3 expressing the ecto-enzymes CD73/CD39, results in immune tolerance manifested by reduced graft-versus-host disease (GvHD).³³

NK cells also play pivotal roles in anti-tumour innate immune responses via cytotoxic functions and cytokine and chemokine secretion. PAMP and DAMP signals can modulate the expression of activating and inhibitory ligands of NK cells, resulting in disparate, anti-tumour or pro-tumour effects, respectively. For example, TLR5 stimulation

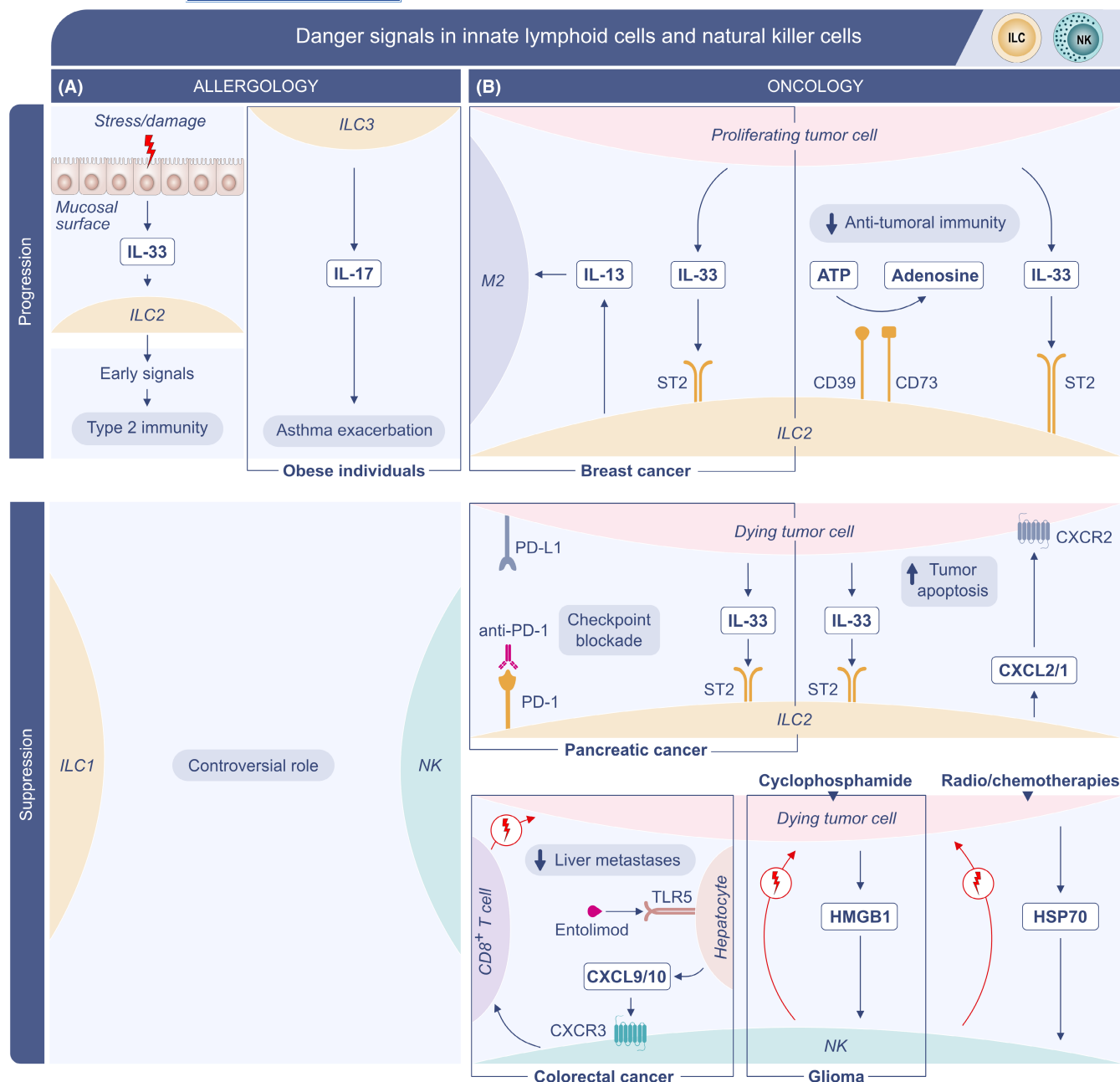


FIGURE 2 Implication of danger signals in innate lymphoid cells (ILC) and natural killer (NK) cells in Allergology and Oncology. (A) Schematic depicting of ILC2 as key players in type 2 immunity providing early signals to other cell types involved downstream in the allergic response; and IL-17-derived ILC3 involved in 'obese-asthma' exacerbations, with a controversial role of ILC1 and NK in the suppression of allergic response (Part 2A of the Position Paper). (B) Schematic depicting the ILC and NK role in oncology with progression and suppression activity depending on their specific subsets, (determined by e.g., cancer type) and the danger signals which interact with, respectively (Part 2B of the Position Paper). ATP, Adenosine 5'-triphosphate; CD39, Ectonucleoside triphosphate diphosphohydrolase-1; CD73, Ecto-5'-nucleotidase; PD-1, Programmed cell death protein 1; CXCL2/1, Chemokine (C-X-C motif) ligand 2/1; CXCR2, Chemokine (C-X-C motif) receptor 2; HMGB1, High-mobility group box protein 1; HSP70, Heat shock protein 70; IL, Interleukin; M2, M2 polarized Macrophage; ST2, Suppression of tumorigenicity 2

via entolimod, a TLR5 agonist, improved survival in a murine model of colorectal cancer metastasis to the liver. These anti-tumour effects were associated with increased NK cell homing to the liver and NK cell-mediated activation of DCs, which in turn stimulated CD8⁺ T cells.³⁴ In a glioma mouse model, HMGB1 release induced by the immunogenic chemotherapeutic cyclophosphamide resulted in NK cell activation.³⁵

Furthermore, stress-, radiotherapy- or chemotherapy-induced membrane and exosome-associated HSP70 could act as DAMPs to activate NK cell-mediated cytotoxicity *in vitro* and *in vivo*.²⁹ Conversely, the anti-inflammatory DAMP, adenosine, decreases NK cell maturation and cytotoxic functions, by impairing perforin and IFN γ release, resulting in tumour growth and metastatic spread³⁶ (Figure 2B).

6 | PART 3 DANGER SIGNALS IN MAST CELLS AND GRANULOCYTES

6.1 | Part 3a. Allergology

Mast cells (MCs), eosinophils (Eos), neutrophils and basophils are armed with an array of PRRs (e.g., TLRs, NLRs, RLRs, ALRs, C-lectin receptors). MCs are key sentinels of danger signals because of their presence in nearly all body barrier tissues, while Eos seemingly share this function mainly in the gut. IL-33 derived from epithelial cells bound to MC via its specific ST2 receptor plays a crucial role in the exacerbation of allergic diseases.³⁷

Mast cells activation is fundamental for the recruitment and activation of blood granulocytes, especially in allergic reactions. Allergens bind to IgE /FcεRI complexes on MCs and basophils, resulting in cellular activation and release of a vast array of preformed and newly formed mediators. Additionally, some allergens ('pseudoallergens') can cause 'direct' MC and granulocyte activation. For example, MCs and Eos can be activated by SEB binding to CD48 and TLR2,³⁸ and papain binding to protease-activated receptor 2 (PAR-2),³⁹ thereby modelling the danger mechanism of mite allergen Der p 1.⁴⁰ Interestingly, neutrophils, which do not play a major role in Th2 immunity, are recruited to the airways by direct binding of pollen or animal dander to TLR4, MD-2 and CXCR2.⁴¹ Moreover, MCs and blood granulocytes can be activated by DAMPs released from epithelial cells following cell damage, an event that occurs in allergic reactions. Epithelial-derived molecules that may activate MCs and granulocytes include DAMPs, such as TSLP, ATP and IL-33.^{42,43} In regard to allergic immune responses, TSLP is released by skin, gut and lung epithelial cells in response to danger signals and has been linked to MC activation and eosinophilic inflammation.⁴⁴ Basophils can also be activated by epithelial cell release of DAMPs that either directly activate basophils or synergize with IgE-driven activation on the basophil surface to trigger IL-4 and IL-13 production.^{45,46} Furthermore, B-cell-derived IgD binds to mast cells and basophils to activate these cells to produce antimicrobial factors mounting an respiratory immune defence.^{47,48}

Importantly, MCs and blood granulocytes contain potent preformed pro-inflammatory mediators in their cytoplasmic granules that can promptly mount a 'defensive' response against danger signals such as *Staphylococcus aureus* enterotoxin B.⁴⁹ Examples include tumour necrosis factor α (TNF α) and proteases for MCs, eosinophil peroxidase (EPO) for Eos and myeloperoxidase for neutrophils (Figure 3A).

6.2 | Part 3b. Oncology

The tumour-promoting or tumour-restricting abilities of innate immune cells, including MCs, basophils, Eos and neutrophils, within the tumour microenvironment (TME), may be modulated by DAMPs of which IL-33, ATP, DNA/CpG motifs and HMGB1 are widely studied.

Under the influence of IL-33, MCs and basophils can indirectly favour neoplastic development via modulation of tumour-resident myeloid cells. In a mouse model of gastric cancer, MCs responded to tumour-derived IL-33 through the release of other factors such as GM-CSF, CCL3 and IL-6, attracting macrophages that supported tumour growth.⁵⁰ Similarly, under the influence of IL-33 and GM-CSF, lung-resident basophils promoted polarization of alveolar macrophages towards anti-inflammatory phenotypes with tumour-supporting potential.⁵¹ Conversely, basophils can be activated by IL-33, along with IL-3 and IL-18 to secrete CCL3 and CCL4, which can attract CD8+ T cells into tumours, resulting in increased rejection of melanoma tumours in vivo.⁵² Several studies revealed that IL-33 can directly activate cytolytic eosinophil function against cancer cells in multiple murine models of cancer, such as hepatocellular,⁵³ breast⁵³ and colorectal⁵⁴ cancer. This activity is associated with the ability of eosinophils to clear DAMPs through the release of potent peroxidases. In addition to these potential roles of IL-33, inflammatory proteases released by MCs and neutrophils can cleave secreted IL-33, modulating its biological activity and its subsequent influence on tumour immunity,⁵⁵ and mounting a 'defensive' response.⁴⁹

HMGB1 secretion by neoplastic cells can trigger the recruitment and pro-tumoral functions of neutrophils. HMGB1 release by ultraviolet-damaged keratinocytes supported melanoma genesis and promoted lung metastases, a mechanism dependent on the recruitment and the subversion of neutrophils towards a pro-angiogenic state via TLR4 activation.⁵⁶ In addition, hypoxia promoted the release of HMGB1 by primary tumours favouring lung metastasis through the activation of CD62L^{dim} neutrophils in a mouse model of triple-negative breast cancer. TLR2 signalling pathway activation by HMGB1 directed CD62L^{dim} neutrophils to produce and release neutrophil extracellular traps, which in turn promoted cancer metastasis.⁵⁷ Neutrophils respond to cell death and the release of DAMPs by limiting the immune role of T cells; this may constitute a means by which the tumour adapts to cell death signals that promote reparative proliferation to exert local immunosuppression (Figure 3B).

7 | PART 4 DANGER SIGNALS AND ANTIGEN-PRESENTING CELLS (APCS)

7.1 | Part 4a. Allergology

DCs and macrophages initiate and maintain allergen-driven Th2 immune responses in the airways, with IL-4 as a key driver for alternative activation of macrophages and for the pathogenesis of asthma.⁵⁸ Macrophage features and functions are insufficiently studied in human allergic diseases (most studies so far have been conducted in murine models). Allergic asthma is associated with increased infiltration of alveolar macrophages (AM) with an alternatively activated (M2) rather than the classically activated (M1) phenotype.⁵⁹ Damage and activation of the respiratory epithelium through DAMPs, such as those induced by viruses⁶⁰ and uric acid⁶¹ generated during tissue damage, probably induce ingress of DCs from the bone marrow.

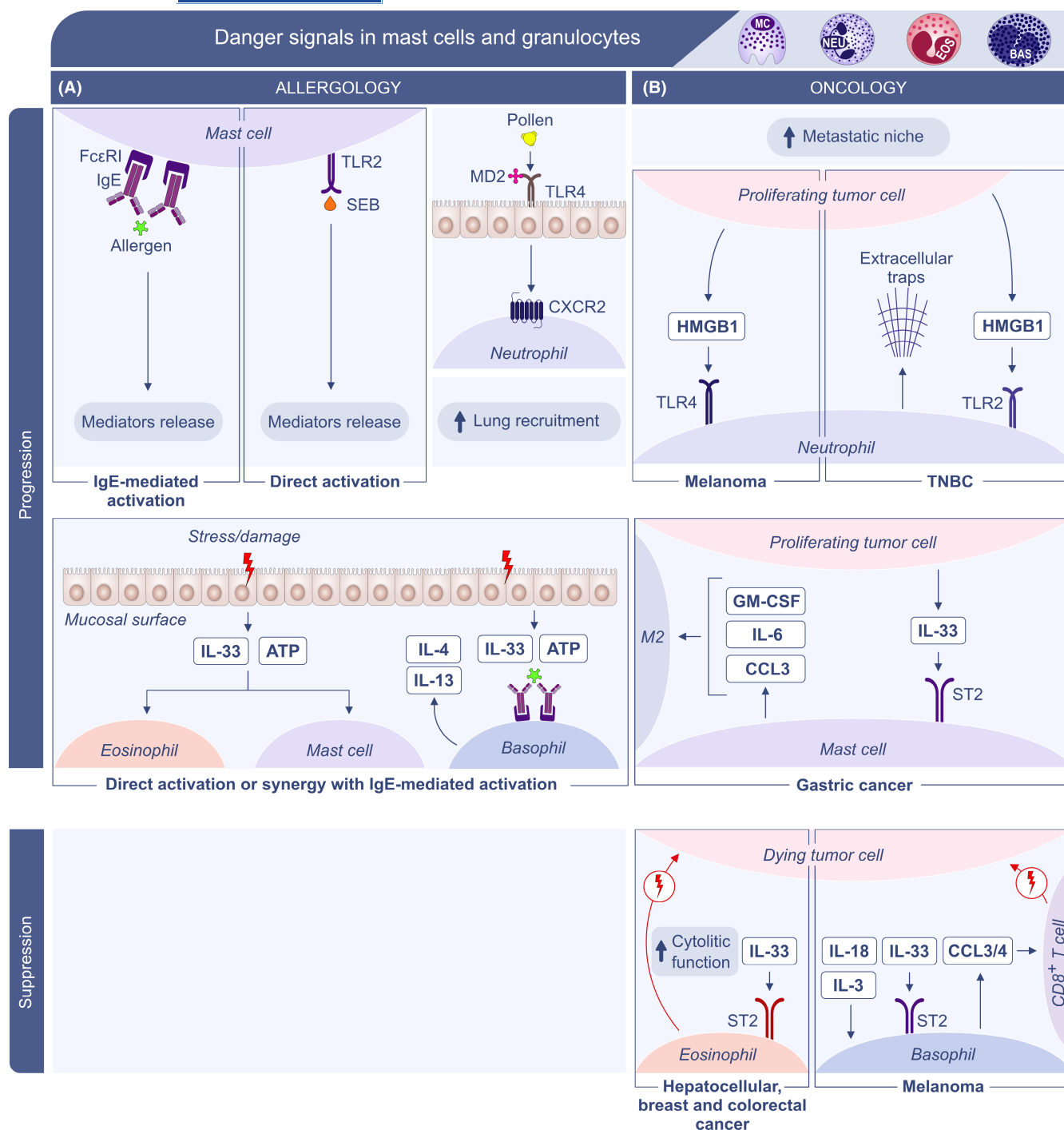


FIGURE 3 Implication of Danger signals in Mast cells and Granulocytes in Allergology and Oncology. (A) Schematic depicting allergic diseases progression driven by mast cells, basophils, eosinophils and neutrophils activated by allergens (AAMP) and epithelial damage (DAMP) through the FcεRI and 'direct' activation (Part 3A of the Position Paper). (B) Schematic depicting oncologic disease progression and suppression by mast cells, basophils, eosinophils and neutrophils activity based on their interaction with DAMPS such as IL-33, ATP, DNA/CpG motifs and HMGB1 with different behaviour determined by cancer type; for example, pro-angiogenic activity of neutrophils in melanoma and the release of extracellular TRAPS in triple-negative breast cancer; the tumour grow activity of MCs stimulated by IL-33 in gastric cancer; the cytolitic function of eosinophils in various cancer types and basophils activated by IL-33, recruiting CD8+ T cells inducing rejection of tumour cells in melanoma (Part 3B of the Position Paper). ATP, Adenosine 5'-triphosphate; BAS, Basophil; CCL3, C-C Motif Chemokine Ligand 3; CXCR2, Chemokine (C-X-C motif) receptor 2; Eos, Eosinophil; FcεRI, Fc epsilon RI or high-affinity IgE receptor; GM-CSF, Granulocyte-macrophage colony-stimulating factor; HMGB1, High-mobility group box protein 1; IL, Interleukin; IgE, Immunoglobulin E; MC, Mast cell; MD-2, Myeloid differentiation factor 2; M2, M2 polarized Macrophage; Neu, Neutrophil; SEB, Staphylococcus aureus enterotoxin B; TME, tumour microenvironment; TLR, Toll-like receptor 2/4; TNBC, Triple-negative breast cancer; ST2, Suppression of tumorigenicity 2

PAMPs, such as LPS, are required for DC activation and triggering immune responses.^{62,63} In atopic dermatitis (AD), TLR2-mediated sensing of *Staphylococcus (S) aureus* is strongly impaired in Langerhans cells and inflammatory DCs and contributes to immune deviation in AD and lack of *S. aureus* clearance.⁶⁴

DCs and macrophages can sense DAMPs released through the activation of specific cell surface receptors (Table 1). For example, P2X7R expression is higher in M2-type than in M1-type AMs; P2X7R activation by ATP can induce M2-type AM polarization and inhibit M1 AM polarization, while blocking of P2X7R has the opposite effect.⁶⁵ However, DAMP signals are also involved in the polarization of macrophages towards an immunoregulatory, that is, M2b phenotype. Increased production of HMGB1, a Th1-associated DAMP, in the plasma of severely burned patients during the acute phase can trigger the production of CCL2, a Th2-related chemokine. CCL2 can stimulate macrophages towards M2b-like polarization,⁶⁶ the same phenotype involved in IgG4-related tolerance induced by allergen immunotherapy (AIT)⁶⁷ (Figure 4A). APCs express a wide variety of PPRs (for DAMPs, PAMPs and AAMPs). Investigation of homeostatic versus allergic states can help identify targets to inhibit inflammation associated with allergy.

7.2 | Part 4b. Oncology

Modulation of antigen-presenting capacity by various danger signals is starting to be understood as an important feature of tumour evasion. Harold Dvorak's comparison of the TME to an impaired wound healing process placed DAMPs into the limelight as prime modulators of APC functions during tumour defence. Tumour proliferation triggers substantial cell death-associated DAMPs, and DCs and tumour-associated macrophages (TAMs) frequently orchestrate the downstream immune response.^{68,69} The main consequences of DAMP-mediated modulation of antigen presentation in tumours are as follows: (i) shifting of primary T-cell responses, (ii) modulating effector T-cell responses and/or (iii) influencing the APC-derived cytokine milieu. This response can either manifest as immunogenic cell death (ICD), whereby DAMP engagement of APCs induces antigen-specific anti-cancer immunity; or alternatively, as tolerogenic cell death (TCD), through immunologically silent clearance of cancer cells and their associated antigens.⁶⁸ The balance between these two states is delicate and frequently influenced by the phenotype of the APCs engaging DAMPs.⁷⁰⁻⁷²

In the context of triggering immunogenic cell death, chronic exposure to DAMPs within the TME can contribute to the migration and maturation of DCs, which induce anti-cancer responses by presenting cancer antigens to T cells.⁷³ Dying cancer cells release nucleic acids sensed by PRR on DCs, that trigger RIG-I/MDA5 and cGAS-STING pathway activation, leading to IFN secretion and DC cross-priming of naïve CD8+ T cells in tumour-draining lymph nodes.⁷⁴ Furthermore, ATP from dying cells stimulates tumour and immune cells to release further ATP which activates P2X7R and the NLR-NLRP3 inflammasome in both macrophages and DCs, leading

to pro-inflammatory IL-1 β and TNF secretion and increasing Th1 and CD8+ T-cell immunity.^{75,76}

In contrast, DAMPs can establish a pro-tumorigenic response, by inducing macrophage polarization to M2-like phenotypes resulting in poor cancer prognosis. HMGB1, with its thiol group in a reduced state, binding to CXCL12 expressed by TAMs, induces chemotaxis via CXCR4 and regulates monocyte recruitment, angiogenesis and immune suppression.⁷⁷ Moreover, HMGB1, interacting with RAGE,^{70,72} or via the HMGB1-TLR2-NOX2-autophagy axis,⁷¹ promotes the monocyte differentiation to anti-inflammatory pro-tumour M2-like macrophages, allowing the formation of a metastatic niche for secondary tumour growth. This has been described in lung cancer with released HSP27 interacting with macrophage-associated TLR3, and in breast cancer by induction of serum amyloid A3 (SAA3) interacting with TLR4.⁷⁷ Furthermore, M2 TAM subsets exhibit high expression of ectonucleotidases, CD39 and CD73, which scavenge ATP and hydrolyse it to adenosine,⁷⁸ promoting immunosuppression by driving a TCD response, and potentiating TAM pro-tumour functions, such as vascular endothelial growth factor (VEGF)-mediated angiogenesis⁷⁶ (Figure 4B). After chemotherapy or radiotherapy, tumour-derived DAMPs activate innate cells that produce pro-inflammatory cytokines. However, chronic inflammation on the one hand leads to autoimmunity, while on the other hand ultimately increases the population of immunosuppressive cells in the tumour microenvironment.⁷⁷ It was shown that infiltration of leukaemia cells into the bone marrow rewires the tissue environment to inhibit the phagocytic capacity of macrophages. Resistance to macrophage-mediated killing can be overcome by combination of therapeutic antibodies and chemotherapy.⁷⁹ Besides, tumour-derived DAMPs elevate the expression of immune checkpoint molecules that allow tumours to evade immune responses.

8 | PART 5 DANGER SIGNALS IN T CELLS AND B CELLS

8.1 | Part 5a. Allergy

TLRs are expressed by adaptive immune cells, such as B cells, CD4+ and CD8+, $\gamma\delta$ T cells and CD4+CD25+ regulatory T-cell (Treg) populations.⁸⁰ There is a concentration dependency leading to an immune outcome. For example, an increase in the levels of TLR ligands such as LPS can change the immune outcome from Th2 to Th17 to Treg, and thus, higher doses can counteract allergic responses.⁸¹

Pro-inflammatory Th1 cytokines promote TLR expression, whereas Th2 cytokines appear to dampen TLR expression and function in both resting and Th1 cytokine-primed human intestinal epithelial cells.⁸² Similarly, TLR ligands can directly modulate adaptive immune cell functions. Bacterial lipopeptides Pam3CSK4 (TLR1/TLR2), flagellin (TLR5), and R-848 (TLR7/8) can co-stimulate proliferation and cytokine secretion in human memory CD4+ T cells, whereas TLR3 ligand poly(I:C) and TLR2 ligands increase IFN- γ and IL-6 secretion in T-cell receptor (TCR)-stimulated $\gamma\delta$ T cells. TLR

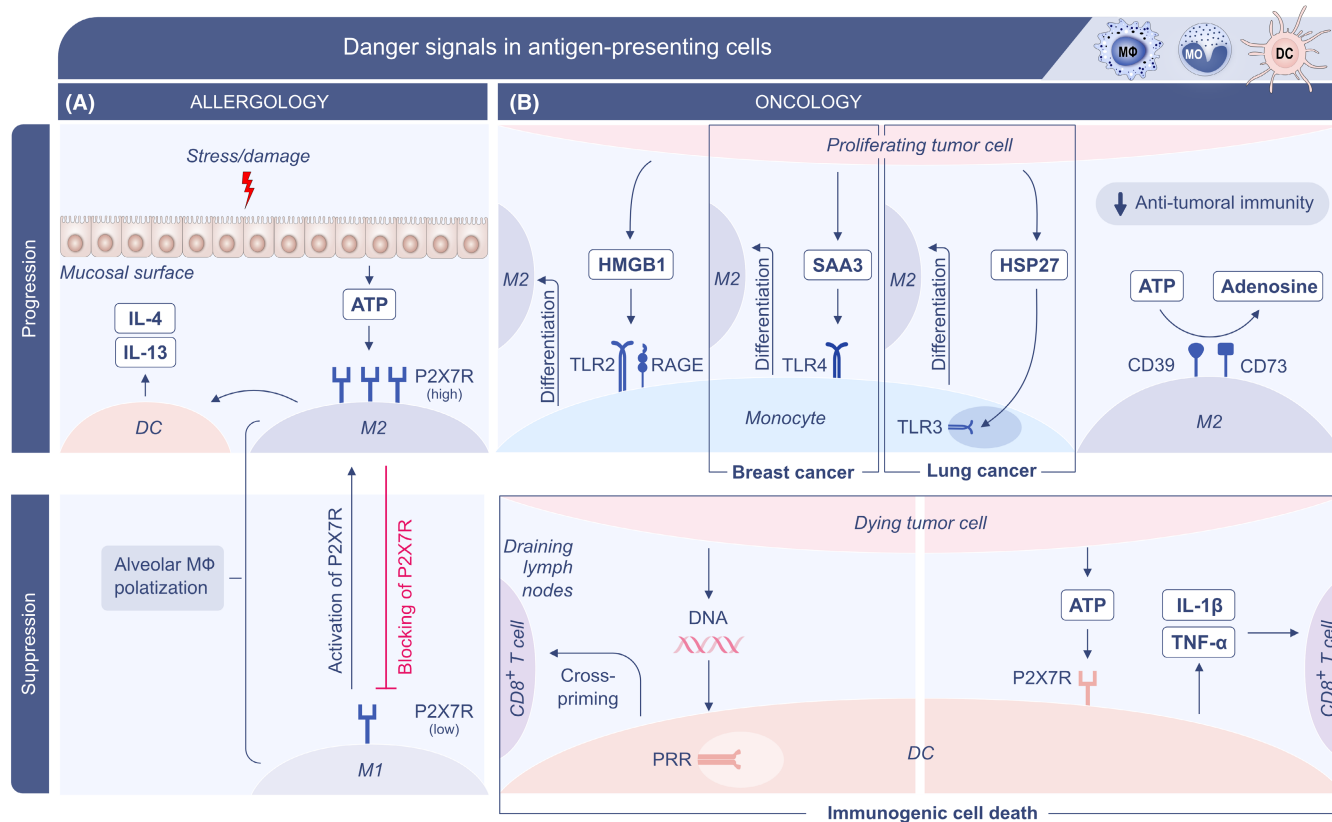


FIGURE 4 Implication of Danger signals in antigen-presenting cells (APC) in Allergy and Oncology. (A) Schematic depicting states of allergic diseases depending on the interaction of DC and macrophages with 'danger signals' (DAMPs) which interact with, inducing progression (DC activation and macrophage polarization to M2) or suppression (macrophages polarization to M1) (Part 4A of the Position Paper). (B) Schematic depicting states of oncologic disease progression/suppression based on the DC and macrophages interaction with DAMPs: the response can either manifest as immunogenic cell death (ICD), creating an antigen-specific anti-cancer immunity (by DC a M2); or alternatively, as tolerogenic cell death (TCD), through immunologically silent clearance of cancer cells, related to macrophage polarization to M1 (Part 4B of the Position Paper). ATP, Adenosine 5'-triphosphate; DC, Dendritic cell; DNA, Deoxyribonucleic acid; CD39, Ectonucleoside triphosphate diphosphohydrolase-1; CD73, Ecto-5'-nucleotidase; HMGB1, High-mobility group box protein 1; HSP27, Heat shock protein 27; IL, Interleukin; Mono, monocyte; M1, M1 polarized Macrophage; M2, M2 polarized Macrophage; P2X7R, P2X purinoceptor 7; PRR, pattern recognition receptors; RAGE, receptors for advanced glycation end products; SAA3, serum amyloid A3; TLR, Toll-like receptor; TNF α , Tumour necrosis factor

ligands have also been implicated in the survival and modulation of the suppressive capacity of Tregs.

In B cells, B-cell receptor (BCR)-mediated and TLR signalling pathways interact and synergize to enable T-cell-independent class switching.⁸³ Importantly for allergic diseases, danger signals are translated by epithelial cells which then produce serum amyloid A and the DAMPs TSLP and IL-33¹⁸ to drive Th2 immune responses. Epithelial cells are also capable of responding to other environmental triggers from changes in ion or oxygen concentration, metabolites from food or microbiome or even sunlight. Interestingly, epithelial cells also commit to a type 1 or type 2 polarized expression profile,⁸⁴ which is characterized by distinct functions. They respond by release of IL-33 which exerts its effects by activating the ST2/IL-1aR receptor, expressed constitutively on Tregs, MCs, Th2 and ILC2 cells, the predominant ILC population in the lung. After binding to its receptor, IL-33 activates NF- κ B, which likely regulates the outcome of diseases such as atopic dermatitis (Figure 5A).

The danger model according to Polly Matzinger⁴ reflects the integration of the adaptive and innate immunity in immune regulation, where APCs activate T and B cells, leading to production of specific antibodies. Those antibodies recognize foreign antigens, which may act as danger to the organism. As such, immunoglobulins play a central role in danger-associated immune responses. As discussed in our previous Position Paper, IgE is not only associated with allergic disorders, parasitosis and specific immunological abnormalities but also epidemiologic and mechanistic evidence indicates a role for IgE-mediated immune surveillance and protection from tumour growth.²⁷ A less well-studied antibody class, immunoglobulin D (IgD), is upregulated in the bronchial mucosa in asthma, and the IgD repertoire shows a high level of somatic hypermutation.^{85,86} Bioinformatics analyses of the IgD repertoire indicate that the somatic mutations in IgD are antigen driven, although less so compared to other isotypes.⁸⁶ Clinical studies demonstrate an association between asthma and infection of the bronchial mucosa

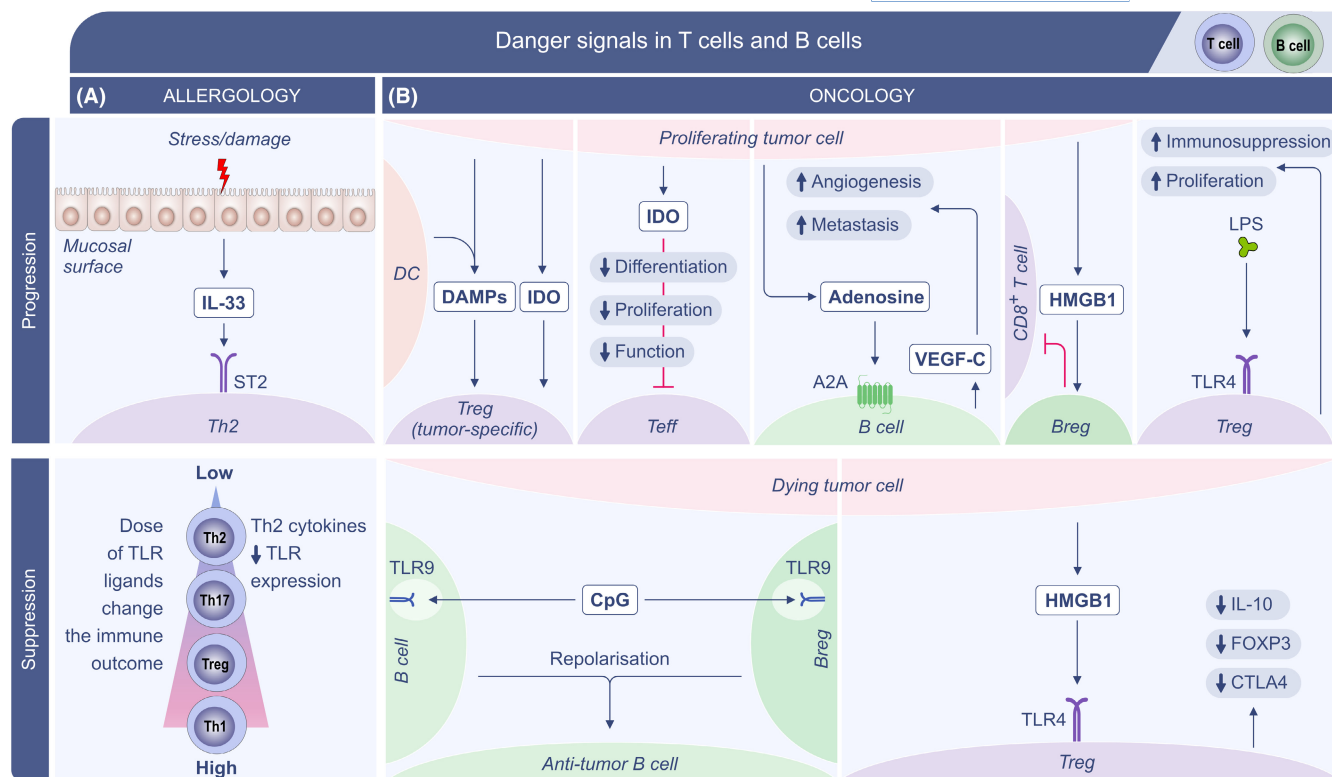


FIGURE 5 Implication of Danger signals in T cells and B cells in Allergology and Oncology. (A) Schematic depicting states of allergy progression based on a predominant Th2 response induced by DAMPs such as IL-33; and suppression induced by Th1, Treg and Th17 immune response related to an increase in the levels of TLR ligands (Part 5A of the Position Paper). (B) Schematic depicting states of oncologic disease based on the interaction of DAMPs and PAMPs which can shape adaptive immunity, potentiating anti-tumour or pro-tumour B-cell phenotypes and in suppressing the proliferation and differentiation of effector T cells and in provoking enhanced suppressor activity of Tregs (Part 5B. of the Position Paper). A2A; Adenosine A2A receptor; B, B cell; Breg, Regulatory B cells; CpG, Deoxycytidyl-phosphate-deoxyguanosine; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; DC, Dendritic cell; Foxp3, forkhead box P3; HMGB1, High-mobility group box protein 1; IDO; Indoleamine 2,3-dioxygenase; IL, Interleukin; LPS, Lipopolysaccharides; ST2, Suppression of tumorigenicity 2; TLR, Toll-like receptor; Teff, Effector T cell; Th, T helper cell; Treg, regulatory T cell; VEGF, Vascular endothelial growth factor

with the common commensal bacteria, *Moraxella catarrhalis* and atypical *Haemophilus influenzae*.^{87,88} These bacteria express IgD-binding proteins that induce the polyclonal proliferation of naive IgD+B cells and heavy-chain class switch recombination.⁸⁹⁻⁹¹ Class switch recombination and somatic hypermutation are catalysed by the same enzyme (activation-induced cytidine deaminase or AID) and occur together in germinal centre reactions involving both processes of genetic recombination, unique to immunoglobulin genes and TCRs. We suggest that the antigens recognized by IgD antibodies may include local proteins in the bronchial mucosa, such as those expressed by bacteria in asthma patients. It is proposed that the mutual antagonism between the antigens and antibodies signifies a standoff between the bacteria and host in commensalism.^{85,86} IgD is an isotype that is known to interact with innate immune proteins, such as Galectin-9 and CD44 on basophils.⁴⁸ It may therefore not only deliver a stimulus for switching to IgE, but can also amplify Th2 responses and cause the exacerbation of asthma and other inflammatory diseases affecting the lungs, for example, autoimmunity and cancer.

8.2 | Part 5b. Oncology

Danger signals in cancer are employed by tumour cells, including dying tumour cells and the surrounding ones, to orchestrate the TME and create immune tolerance and dysfunction by interacting with APC or T cells directly. The prototypic danger signal HMGB1, found in many tumours, triggers TLR-mediated induction of tumour antigen-specific T cells, which in turn recruit tumour-promoting macrophages or retain CD8+ cytotoxic T cells in an anergic state. Moreover, tumour-derived DAMPs induce tumour-specific Tregs directly or via DC and mount a strong tumour tolerance to engineer an escape from immune control.⁶⁸ The enzyme indoleamine 2,3-dioxygenase (IDO) (produced by immune cells or cancer cells) causes degradation of tryptophan, thereby suppressing proliferation and differentiation of effector T cells and provoking enhanced suppressor activity of Tregs.⁹²

B cells in the TME can have anti-tumour activity, however, regulatory B cells (Bregs) support pro-tumour immune responses. In cancer, stressed and dying cancer cells can release DAMPs and, in some

cases, there could be loss of barrier integrity with consequent flux of PAMPs. DAMPs and PAMPs can shape adaptive immunity, potentiating anti-tumour or pro-tumour B-cell phenotypes.⁹³ Stimulation of the DAMP adenosine and its receptor A2A on B cells can block signalling downstream of TLR4 and the BCR which inhibit B-cell survival and can also promote VEGF-C expression, leading to angiogenesis and metastasis.⁹⁴ The PAMP and TLR9 ligand CpG can induce anti-tumour B-cell phenotypes and repolarize Bregs into B effector cells.⁹⁵ In contrast, immunogenic chemotherapeutic oxaliplatin treatment was associated with increased tumour-infiltrating IgA+PD-L1+IL-10+ B cells which inhibited oxaliplatin-induced tumour regression and anti-tumour CTL in a murine model of prostate cancer.⁹⁶ Furthermore, HMGB1 stimulated Bregs *ex vivo* suppressed CD8+ T-cell activity.⁹⁷

Also, LPS can activate B cells via TLR4-dependent signalling, while cytokine secretion by T cells seems to be unaffected or may have their functions impaired. Unlike the engagement of TLR1/2, LPS activation of TLR4 in Tregs enhances their immunosuppressive activity and proliferation. In contrast, HMGB1-induced TLR4 activation on Tregs decreases IL-10, forkhead box P3 (FOXP3) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expression. The activation of similar kinds of TLRs may thus have a pro-tumour or anti-tumour effect in different types of cancers.

B cells differentiate into plasma cells, which in allergic patients produce high levels of allergen-specific IgE. While elevated serum IgE is generally associated with allergic/atopic conditions, very low or absent IgE may hamper anti-tumour surveillance, indicating the importance of a balanced IgE-mediated immune function. Epidemiologic studies indicate that IgE has a surveillance function in cancer, and since solid tumours are infiltrated by IgE receptor-expressing immune cells, anti-tumour IgE may result in antibody-dependent cell-mediated cytotoxicity (ADCC) and phagocytosis (ADCP) of cancer cells²⁷ (Figure 5B). On the other hand, the impact of anti-IgE therapies (used to treat allergic diseases), in the development of malignant diseases is yet unclear and must be further investigated.

9 | PART 6 CLINICAL APPLICATIONS ADDRESSING DANGER SIGNALS

9.1 | Part 6a. Allergy and clinical immunology

Individual pathways through which danger signals contribute to the pathophysiology of various allergic and immunologic disorders have been described. For instance, several studies have recently demonstrated an important role of endogenous danger signals at the inception and maintenance phase of allergic disease.⁶² For example, generation of danger signals by the reactive drug metabolites represents a proposed mechanism for certain drug-induced cutaneous reactions. Danger signals result in lymphocyte activation with damage of the target cell, whereas in the absence of the stress signal, no activation is provided and tolerance of the drug results.^{98,99} In

addition, since HMGB1 levels are significantly increased in allergic rhinitis,¹⁰⁰ while promoting smooth muscle contraction via TLR4 in the upper airways in allergic asthma,¹⁰¹ a potential therapeutic intervention targeting HMGB1 has been proposed.¹⁰²

Therapeutic strategies to target HMGB1 by binding and neutralizing extracellular HMGB1 currently include small molecule drugs and antibodies which antagonize TLR4 and RAGE (extracellular HMGB1 receptors), as well as decoy receptors.¹⁰³ Some drugs such as metformin which is approved for the treatment of type 2 diabetes, have off-target effects by directly binding HMGB1.¹⁰⁴ Other drugs designed to target HMGB1 have only been tested preclinically in different inflammatory diseases.¹⁰⁵ With regard to allergy treatment, some data exist on the HMGB1 binding compound glycyrrhizin (GLT), a natural anti-inflammatory and antiviral triterpene in clinical use, which inhibits the chemoattractant and mitogenic activities of HMGB1.¹⁰⁶ Topical glycyrrhizin application reduced the content of HMGB1 in nasal fluid of rhinitis patients as well as decreased the number of eosinophils, which would normally release high amounts of HMGB1.¹⁰²

Auto-inflammatory disorders, such as hereditary periodic fevers (HPFs) or cryopyrin-associated periodic syndrome (CAPS), involve mutations in the gene coding for NLRP3, characterized by aberrant inflammasome hyperactivity and constitutive IL-1 β production. These patients present with unexplained and recurrent fever, severe inflammation, arthropathy, chronic urticaria or central nervous system involvement. IL-1 β inhibitor treatment results in dramatic improvement of symptoms.¹⁰⁷ Interestingly, activation by apolipoprotein E (a concentration-dependent pulmonary danger signal) of the NLRP3 inflammasome and subsequent IL-1 β secretion by bronchoalveolar fluid macrophages has been observed in asthmatic subjects.¹⁰⁸ Moreover, NLRP3 inhibitors in asthma models decrease pulmonary inflammation, making NLRP3 a potential therapeutic target in severe asthma.¹⁰⁹ Similarly, activation of the NLRP3 inflammasome by AAMP danger signals originated from dust mites has also been described in the pathogenesis of atopic dermatitis.¹⁴

IL-33 is considered to be a key factor in the development of different allergic disorders, especially asthma¹¹⁰ and atopic dermatitis.¹¹¹ Anti-IL-33 and anti-TSLP agents are being studied as treatments in various allergy models. For example, a phase 2a study of etokimab, an IgG1 anti-IL-33 monoclonal antibody, showed significant clinical improvement in patients with moderate-to-severe atopic dermatitis. Treatment was associated with decreased peripheral eosinophilia and reduction in skin neutrophil infiltration.¹¹² Stimulation of individual cells by alarmins results in production of IL-4 and IL-13.⁴⁶ As such, dupilumab, the monoclonal antibody targeting the IL-4 and IL-13 pathways is used in the treatment for asthma, atopic dermatitis and chronic rhinosinusitis with nasal polyps.¹¹³

Allergen immunotherapy (AIT) is the only disease-modifying therapy for allergic rhinoconjunctivitis, asthma and other allergic conditions. Several adjuvants are used to induce a more rapid, potent and long-lasting AIT immune response, by acting as immunostimulatory agents: aluminium hydroxide, calcium phosphate, microcrystalline tyrosine (MCT) and (monophosphoryl lipid A MPL).¹¹⁴

If aluminium hydroxide is used as an adjuvant in certain subcutaneous immunotherapy (SCIT) protocols, the damaged tissue releases endogenous signals, such as uric acid which may stimulate the NLRP3 inflammasome, a caspase-1 activating complex that induces inflammation. Contrastingly, specific allergen tolerance is achieved through sublingual-specific immunotherapy (SLIT) in the absence of danger signals, where the effector cells are biased towards induction of Th1 and IL-10 producing CD4⁺ Tregs, resulting in tolerance as opposed to inflammation.¹¹⁵

Peptide immunotherapy (PIT) is a new type of allergen-specific immunotherapy, aimed at increasing clinical tolerance to the allergen while reducing the potential risk of systemic allergic reactions. Through PIT, the administered 'immunodominant' peptides from specific allergens in the absence of danger signals (e.g., in the absence of LPS and/or an adjuvant), can generate T-cell tolerance. This is the opposite of administering of the same peptide with an adjuvant, which promotes an inflammatory/immunogenic response. Soluble peptides administered by intranasal, oral, intravenous, subcutaneous and intradermal routes, all have the potential to induce tolerance.¹¹⁶ Another approach towards allergen immunotherapy with potential lower side effects than the current AIT may be administering a mixture of allergens together with immunostimulatory oligodeoxynucleotide sequences (ISS-ODN). These sequences are bacterial DNA motifs containing unmethylated cytosine residues in the sequence CpG, which act via the cytosolic TLR9 receptor in DC and serve as adjuvants that promote a Th1 response.¹¹⁷

9.2 | Part 6b. Clinical applications addressing danger signals in Oncology

9.2.1 | Activating danger signals as a therapeutic approach for cancer

Activation of TLRs by DAMPs or PAMPs can result in the secretion of pro-inflammatory cytokines. Consequently, diverse TLR agonists have been designed as therapeutics against cancers. Successful studies have involved imiquimod, a TLR7 agonist, used in skin cancer, and Bacillus Calmette-Guérin (BCG), a nonspecific agonist of TLR2/TLR4 applied in bladder cancer treatment. Both applications result in increased cytokine production, that is, interferons and interleukins, leading to T-cell activation and anti-tumour responses. However, either hyperactivation or hypoactivation of TLRs supports the survival and metastasis of a tumour.¹¹⁸ In the situation of overactivation, inhibition of TLR signalling may be useful for tumour regression.

Other DAMPs, including endogenous nucleic acids and intracellular proteins exposed by damaged or dying cells, are important in promoting adaptive antigen-specific immunity. Tumours can avoid immune surveillance by exposing or releasing DAMPs which favour the accumulation of dysfunctional innate immune cells. Targeting these DAMPs released by dying cancer cells can decrease cancer inflammation and tumour progression, and supporting anti-tumour immune responses.¹¹⁹

9.2.2 | Treatment-associated immune-related adverse effects in patients with cancer

Danger signals in oncology can also impair the delivery of first-line therapies to cancer patients. Close to one third of women with ovarian cancer receiving carboplatin present with allergic and anaphylactic reactions after 6–8 exposures to the drugs, precluding their continued treatment.¹²⁰ The presence of BRCA1/2 mutations seems to induce earlier and more severe reactions.¹²¹ Allergic and anaphylactic reactions can occur on first exposure in patients reactive to cremophor or polysorbate 80, which can activate complement, such as observed with taxanes.¹²² Biomarkers such as MC-released beta-tryptase can be detected in blood during type I IgE and non-IgE mast cell-mediated reactions and IL-6 is elevated in cytokine-storm like reactions.^{123,124} A novel procedure has been successfully developed to address danger signals in oncology, rapid drug desensitization (RDD), applicable to all chemotherapies, small molecules and monoclonal antibodies, including checkpoint inhibitor immunotherapies.¹²⁵ RDD can address individual reaction phenotypes, such as type I cytokine-storm like reactions, mixed reactions and delayed reactions, but it cannot address serum sickness-like or delayed severe cutaneous adverse reactions.¹²³ The mechanisms of RDD implicate MC inhibitory pathways, blocking extracellular calcium influx and the release of acute and delayed mediators, stabilizing FcεRI/IgE/antigen complexes on the cell surface, preventing their internalization.¹²⁶

10 | PART 7. UNMET NEEDS AND CONCLUSION

Undoubtedly, danger signals impact the pathologies of both allergy and oncology. Here, we propose that danger signals form part of the links between allergy and oncology and are key topics in AllergoOncology (Box 2). Not only that the PAMPs or DAMPs may influence the immune response but also allergens such as AAMP can act as danger signals, generating different immune responses. Delineating the nature and the broader effects of individual danger signals allows a novel understanding of allergy development and treatment. For example, in light of new discoveries regarding DAMPs, it is possible to re-consider the hygiene hypothesis in genetically susceptible subjects exposed to allergens: in the presence of low-dose DAMP (as well as PAMP and AAMP), there is an enhancement of the allergic response induced by DC and macrophage activation; in the presence of high-dose DAMP (and PAMP) exposure (for example, as occurs on livestock farms, in rural environments in developing countries and in traditional lifestyles), there is a shift towards allergic tolerance.^{127,128} (Figure 1A). Along these lines, these questions may also be relevant with regard to allergen immunotherapy: it is yet unclear whether danger signal molecules may support the induction of tolerance to specific allergens, at what doses and what is the most effective route of administration of immunotherapies. These considerations still require extensive study (Box 2).

In the cancer field, on the other hand, danger signals should be considered not only in relation to a history of allergy, chronic inflammation and autoimmunity linked to the risk of developing cancer but

BOX 2 Examples of unmet needs on the interphase between danger signals and immunity in allergy and oncology to inform patient treatment

Danger signals	Clinical unknowns
AAMPs and their roles in the development of allergy and cancer	<ul style="list-style-type: none"> Can AAMPs as danger signals generate different immune responses in allergy and in cancer?
Low-dose versus high-dose exposure to DAMPs, PAMPs, AAMPs in allergic/malignant diseases	<ul style="list-style-type: none"> Is there an enhancement of the sensitization process in allergy with low-dose exposure? Is there a shift towards tolerance rather with high-dose exposure? Could these pathways be better targeted in allergen immunotherapy? What are the implications of AIT for anti-cancer immunity?
Danger signals and immunogenic cell death	<ul style="list-style-type: none"> Is there a link between danger signals and immunogenic cell death (ICD)? How does this influence the development of allergy? Can this be an immune protective signal in cancer? Could drugs be combined to achieve and enhance the effects of danger signals in triggering and enhancing ICD in cancer (e.g., triggering danger signals +antibody/checkpoint inhibitors)?
PAMPs (TLR ligands) DAMPs (HMGB1, TSLP, IL-33)	<ul style="list-style-type: none"> How do these influence immune cells and their activation states in different environments and anatomic locations? How will these shape the local and systemic inflammatory milieu in allergy and in cancer? Could these serve as biomarkers in different disease settings?
Allergen versus cancer immunotherapy with or without danger signals and clinical outcomes	<ul style="list-style-type: none"> What are the outcomes of immunotherapy given with or without danger signals (e.g., LPS) in allergy and in cancer? Could clinical tolerance to an allergen be induced with the right level of a danger signal or rather in the absence of danger signal? Could the opposite be achieved in a cancer vaccine to promotes an inflammatory/immunogenic response to an antigen? How does the route of administration of immunotherapies (intranasal, oral, intravenous, subcutaneous and intradermal) and associated danger signals influence their potential to induce tolerance or immune activation? Can danger signals influence response to cancer immunotherapy e.g., checkpoint inhibitors?
AAMPs, DAMPs, PAMPs and cancer risk	<ul style="list-style-type: none"> What are the contributions of internal or external danger signals including of AAMPs on cancer risk and on cancer survival? Need for validated measures of allergy history including biomarkers of allergy and immune function, i.e., AAMPs, DAMPs PAMPs, mast cell and other immune cell mediators, IgE levels, MCs, ILC.
Roles of danger signals in tolerance induction to chemotherapies	<ul style="list-style-type: none"> Platins/platinum drugs are haptens which require protein conjugation and repeated exposures to induce antigen-specific IgE production, which can lead to severe allergic reactions including anaphylaxis once crosslinked by drug antigen on IgE bound to mast cells. How can Th2 responses towards small molecules such as platins be elicited in the context of immune dormancy and tolerance of cancer antigens through activation of PD1/PDL1 pathways? Outcomes of desensitized patients with IgE against platins may be more favourable than non-allergic, non-desensitized patients? Could a Th2 phenotype increase immune surveillance? Could IgE desensitization of mast cells generate a favourable environment for tumour recognition and control?

also with regard to clinical responses to targeted treatments and to immunotherapy. It is possible that danger signals can trigger or be the result immunogenic cell death (ICD). Harnessing ICD-triggering danger signals may be a desirable mechanism, which can be used as an add on therapy for cancer. For example, antibody-drug conjugates able to induce ICD may be employed in combination with checkpoint inhibitors as potent strategy for cancer treatment. However, the

balance of cell death, tissue remodelling and immunogenicity to cancer antigens in the presence or absence of additional danger signals is unknown. TLR ligands, TSLP, IL-33 and HMGB1 can influence a range of immune cells and their activation states towards adopting either pro- or anti-tumour roles in different malignant states. These danger signals thus have the capability to shape the local and systemic inflammatory milieu. It is possible that fine tuning of danger

signals such as targeting TLRs or cancer-released DAMPs either as a stand-alone strategy or in combination with targeted therapeutic interventions might turn the odds in favour of anti-tumour immunity. For example, Li et al. have published intriguing data on antihistamines, taken by patients with melanoma, who received checkpoint inhibitor immunotherapy¹²⁹(Figure 1B).

After reviewing different danger signals collectively and their respective recognizing receptors in different subtypes of immune cells, this Position Paper stresses the notion that an individual's immune system can act as a relay station between the body and external or internal threats in a defined manner. An urgent need is evident to understand how these processes are regulated, the relationship between them, and how they can be manipulated in the context of various pathological states. It is important to consider allergens and their DAMP-induced signalling as potential targets to overcome inflammatory responses in allergy. The field of AllergoOncology offers the chance to evaluate how a range of danger signals trigger different immune responses with juxtaposing clinical outcomes in allergy and cancer and how dissecting different clinical phenotypes of common DAMP pathways may lead improvements of the clinical management of these diseases. These considerations may open the door to new therapeutic approaches for allergic and malignant diseases.

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CONFLICT OF INTEREST

All authors have read and approved the Position Paper. Any potential conflicts of interest are listed here: CB: Christoph Bergmann received honoraria for presentations from Allergy Therapeutics, Bencard, HAL Allergy and SCS. CSW: Carsten Schmidt-Weber has received speaker honoraria from Bencard and Allergopharma and has a patent a patent on nasal secretions that is pending. EJJ: Erika Jensen-Jarolim declares inventorship in patents on allergen immunotherapy formulation with Biomedical International R+D, Vienna, Austria, of which she is shareholder. She received honoraria for presentations from Allergy Therapeutics, AllergoPharma, Bencard, Meda, Roxall, ThermoFisher, and consulted previously for MediGene, Germany, Novartis, for Allergy Therapeutics and Dr. Schär. EHS: Esther Steveling has received funds from Bencard and ALK. HJB: Heather J. Bax is employed through a fund provided by Epsilogen Ltd. (formerly IGEN Therapeutics Ltd.) and holds patents on anti-tumour IgE antibodies. DHJ: Debra H Josephs holds patents on anti-tumour IgE antibodies. GJ: Galateja Jordakieva has received lecture honoraria by Bencard Allergie GmbH and Thermo Fisher Scientific. KH: Karin Hartmann has received research funding from Thermo Fisher and consultancy or lecture fees from Allergopharma, ALK-Abello, Blueprint, Deciphera, Leo Pharma, Menarini, Novartis, Pfizer, Takeda and Thermo Fisher. MC:

Marianna Castells is Principal Investigator for Blueprint PIONEER and HARBOR clinical trials, Editorial Board Annals Of Allergy Asthma and Immunology, Author UpToDate, Board of Directors ABAI. MTL: Michael Lotze is currently Chief Cell Therapy Officer at Nurix Biotherapeutics and has an invention disclosure with the University of Pittsburgh relating IgE to $\gamma\delta$ T cells. FRW: Franziska Roth-Walter declares main inventorship on patent EP2894478 (applicant Biomedical International R+D GmbH, Vienna, Austria) and received research funding from Biomedical International R+D GmbH, Vienna, Austria and Bencard Allergie GmbH, Munich, Germany. Moreover, she received lecture honoraria by FOMF, VAEM, Bencard Allergie GmbH, Munich, Germany and Vienna, Austria, and Allergy Therapeutics, Worthing, UK. SNK: Sophia N. Karagiannis is founder and shareholder of Epsilogen Ltd. (formerly IGEN Therapeutics Ltd.) and has received funds from IGEN Therapeutics Ltd/Epsilogen Ltd. Sophia N. Karagiannis holds patents on anti-tumour IgE antibodies. AP, DD, DR, DHJ, DF, EF, EI, EU, FLS, FR, GO, HJG, IA, LV, MJ, MP, MCT, MS, RB and SC declare no conflict of interest.

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