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EAACI POSITION PAPER

Granulocytes and mast cells in AllergoOncology—Bridging allergy to cancer: An EAACI position paper

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Abstract

Derived from the myeloid lineage, granulocytes, including basophils, eosinophils, and neutrophils, along with mast cells, play important, often disparate, roles across the allergic disease spectrum. While these cells and their mediators are commonly associated with allergic inflammation, they also exhibit several functions either promoting or restricting tumor growth. In this Position Paper we discuss common granulocyte and mast cell features relating to immunomodulatory functions in allergy and in cancer. We highlight key mechanisms which may inform cancer treatment and propose

Abbreviations: ACT, adjuvant chemotherapy; ADCC, antibody-dependent cellular cytotoxicity; AEC, absolute eosinophil count; ATP, adenosine triphosphate; ATRA, all-trans retinoic acid; ATX-LPA, autotaxin (ATX) and lysophosphatidate (LPA); BAFF, B cell activating factor; BAT, basophil activation test; BPI, bactericidal/permeability-increasing protein; CAR, chimeric antigen receptor; CC, cervical carcinoma; CCL-, chemokine (C-C motif) ligand; CCR3, CC-chemokine receptor 3; CSF3R, colony stimulating factor 3 receptor; CRC, colorectal cancer; CXCL, chemokine (C-X-C motif) ligand; DAMPs, danger associated molecular patterns; DC, dendritic cell; DFS, disease free survival; DPP IV, dipeptidyl Peptidase IV; EC, esophageal cancer; EDN, eosinophil-derived neurotoxin; EETs, eosinophil extracellular traps; EGF, epidermal growth factor; ELR, eosinophil-to-lymphocyte Ratio; EPX, eosinophil peroxidase; ERK1/2, extracellular signal-regulated kinase 1 and 2; ERS, endoplasmic reticulum stress; FATP2, fatty acid transporter protein 2; FGF, fibroblast growth factor; GBC, gallbladder cancer; GC, gastric cancer; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSCs, hematopoietic stem cells; HDN, high-density neutrophils; HMGB1, high mobility group box 1; HER2, human epidermal growth factor receptor 2; IL, interleukin; IL-5 R, interleukin-5-receptor; ICAM1, intracellular adhesion molecule 1; ICB, immune checkpoint blockade; IDO, indoleamine 2,3-dioxygenase; iEOs, inflammatory eosinophils; IHC, immunohistochemistry; ILC2s, group 2 innate lymphoid cells; iRAEs, immune-related adverse effects; IT, immunotherapy; ITAM, immunoreceptor tyrosine-based activation motif; IRF5, interferon regulatory factor 5; LAD2, leukocyte adhesion deficiency 2; LDN, low-density neutrophils; LFA1, lymphocyte function-associated antigen 1; MBP, major basic protein; MCD, mast cell density; MCps, mast cell progenitors; MDP2, myeloid differentiation protein-2; MHC, major histocompatibility complex; MMP, matrix metallopeptidase; MUC4, mucin-4; mRRC, metastatic renal cell carcinoma; MRGPRX2, mastocyte-related G-protein coupled receptor member X2; NADPH, nicotinamide adenine dinucleotide phosphate; NBC, neutrophil blood count; NER, neutrophil-to-eosinophil ratio; NE, neutrophil elastase; NETs, neutrophil extracellular traps; NGF, nerve growth factor; NK cells, natural killer cells; NLR, neutrophil-to-lymphocyte ratio; NLRs, nucleotide oligomerization domain (NOD)-like receptors; NSCLC, non-small cell lung cancer; OC, ovarian cancer; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PDGF, platelet-derived growth factor; PERK, protein kinase RNA (PKR)-like endoplasmic reticulum kinase; PFS, progression-free survival; PGE2, prostaglandine-E2; PMN-MDSCs, polymorphonuclear myeloid-derived suppressor cells; PNE, post-operative number eosinophils; PPR, pattern recognition receptors; RLR, retinoic acid-inducible gene-I (RIG-I)-like receptors; ROS, reactive oxygen species; rEOS, resident eosinophils; SAR, survival time after recurrence; Siglec-8, sialic acid-binding immunoglobulin-like lectin 8; TIL, tumor infiltrating lymphocyte; TRAIL, TNF-related apoptosis-inducing ligand; TSLP, thymic stromal lymphopoietin; TLRs, toll-like receptors; TGF- β1, transforming growth factor beta 1; TANs, tumor-associated neutrophils; TATE, tumor-associated tissue eosinophilia; TDLNs, tumor-draining lymph nodes; TES, tumor infiltrating eosinophils; Th2, type 2 T helper cells; TIM, tumor-infiltrating mast cell; TME, tumor microenvironment; TOLLIP, toll interacting protein; UPR, unfolded protein response; UTC, unconventional T cells; VEGFA, vascular endothelial growth factor A.

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pertinent areas for future research. We suggest areas where understanding the communication between granulocytes, mast cells, and the tumor microenvironment, will be crucial for identifying immune mechanisms that may be harnessed to counteract tumor development. For example, a comprehensive understanding of allergic and immune factors driving distinct neutrophil states and those mechanisms that link mast cells with immunotherapy resistance, might enable targeted manipulation of specific subpopulations, leading to precision immunotherapy in cancer. We recommend specific areas of investigation in AllergoOncology and knowledge exchange across disease contexts to uncover pertinent reciprocal functions in allergy and cancer and allow therapeutic manipulation of these powerful cell populations. These will help address the unmet needs in stratifying and managing patients with allergic diseases and cancer.

KEYWORDS
AllergoOncology, allergy, basophils, cancer, eosinophils, granulocytes, mast cells, neutrophils

1 | INTRODUCTION

AllergoOncology is an emerging multi-disciplinary field that strives to unravel the links between cancer and allergy.[1] Allergies are traditionally linked to Type 2 granulocyte colony-stimulating fact (Th2) responses, however, different disease endotypes often relate to Type 1 (Th1) or Type 3 (Th17)-driven pathophysiological mechanisms.[2] Unravelling diverse functions of immune cells within the wide range of allergic and malignant diseases presents significant challenges.

Granulocytes, including basophils, eosinophils, and neutrophils, together with mast cells, are key immune cells contributing to several allergic conditions, via multiple, significantly differing, roles across disease pheno-endotypes. In principle, activated in response to allergens, mast cells and basophils release inflammatory mediators, leading to the characteristic allergy symptoms and plays roles in tissue remodeling, contributing to chronic allergic inflammation. Eosinophils contribute to tissue damage and inflammation through granule protein and lipid mediator release, and neutrophils are involved in late-phase allergic reactions and chronic allergic inflammation.[3] While these cells and their mediators are commonly associated with allergic diseases and response to infections, including in anti-parasitic immunity, they have also been ascribed several tumor-promoting and contrastingly, tumor-restricting activities.[4] The complexity and heterogeneity of mechanisms underlying allergic diseases, translate into disparate effects in relation to cancer, in keeping with the diverse environments across cancer types and anatomical locations in which these cells reside or are recruited. Thus, we propose that the field requires detailed study of granulocytes and mast cells in the wider allergy and cancer contexts to help uncover key and reciprocal roles in disparate disease settings.

In cancer, the pro- or anti-tumor functions of granulocytes, mast cells and their subpopulations can be heavily influenced by the origin and anatomical location of the cancer and the immune contexture of the tumor microenvironment (TME).[5] Allergy diagnosis tests, such as the basophil activation test (BAT), have been increasingly applied in oncology to evaluate hypersensitivity to therapeutic agents, such as chemotherapies and biologics.[6] Markers of neutrophil, eosinophil and basophil activation have also been studied in oncology to evaluate immune responses, including in the TME. Current knowledge of tumor immune surveillance and a wide range of immunomodulating roles attributed to different granulocyte populations has been applied to develop anti-tumor therapies. Personalized medicine in AllergoOncology therefore aims to enhance anti-tumor functions of granulocytes and mast cells, while moderating their pro-tumor functions for the development of promising therapeutic cancer strategy.[7]

In this Position Paper, we extract the current state of the art knowledge on common features of granulocytes and mast cells and their immunomodulatory functions in allergy and in cancer, and highlight several juxtaposing roles. We discuss the unmet needs in this emerging field and propose specific areas to focus research. Drawing from these insights, the knowledge exchange in the different disease contexts is expected to provide novel markers and contributions of these cell populations to address the unmet needs and future directions in the field of AllergoOncology.

2 | GRANULOCYTES AND MAST CELLS: BIOLOGICAL ATTRIBUTES IN IMMUNE DEFENSE AND ALLERGY

Neutrophils, eosinophils, basophils and mast cells are derived from the myeloid lineage. They are characterized by the presence of cytoplasmic granules and vesicles containing various effector molecules and a multilobulated nucleus. While neutrophils, eosinophils and basophils differentiate and mature in the bone marrow and represent the most abundant cell type in peripheral blood (i.e., polymorphonuclear leukocytes), mast cell progenitor cells

circulate from the bone marrow to various strategic tissues where under the influence of stem cell factors locally produced by many cells in the tissue, they differentiate into mature mast cells. Thus, they are found in nearly all human tissues (being CD117/c-Kit and tryptase their best immunohistochemical markers), but particularly abundant in the skin and mucous membranes, predominantly near blood vessels and nerves.[8] Differentiation of granulocyte subtypes and mast cells is regulated by different lineage-specific cytokines and depends on a network of regulatory factors including transcription factors, microRNAs, and long non-coding RNAs (i.e., IL-5, IL-3, IL-33, and granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling).[9]

Several morphologically and functionally distinct granulocyte populations according to characteristics of their cytoplasmic content: neutrophils, eosinophils, and basophils, represent 40%–60%, 1%–4% and <1% of circulating leukocytes, respectively.[3] Mature granulocytes and mast cells express a wide array of surface molecules involved in differentiation, migration, survival, and activation.[10–12] The life span of granulocytes is <24 h and can be extended when these cells have migrated in tissues, while that of mast cells can be several months. Several chemotactic factors can influence granulocyte migration, depending on the dynamic changes within a tissue microenvironment (i.e., members of the eotaxin family and IL-5 for eosinophils).[13] Furthermore, circadian rhythms (i.e., biological timing mechanisms that generate 24-h/daily rhythmicity of biochemical, physiologic, and behavioral functions) influence cellular and humoral components of the immune system, with granulocytes exhibiting circadian oscillations in their numbers in blood in humans.[14] In homeostasis, neutrophil infiltration into most tissues is circadian, but not in the intestine or the liver. Neutrophils perform different functions in a circadian-independent manner, that is, in the intestine, they control granulocyte colony stimulating factor (G-CSF) production to mobilize hematopoietic stem cells (HSCs). Nevertheless, in other tissues they regulate circadian processes, such as transcriptional programs and tumor invasion in the lung.[15] The circadian influence in other tissues is not well-defined.[16] Existing evidence indicates that the circadian clock functions as a gate that governs many aspects of the cancer-immunity cycle.[17,18]

Granulocytes and mast cells respond to different stimuli such as IgG and/or IgE-mediated activation, cytokines, neuropeptides, danger-associated molecular patterns (DAMPS) or alarmins, complement and hypoxic conditions. This is mediated by a broad array of pattern recognition receptors (PRR, like Toll-like receptors (TLRs), nucleotide oligomerization domain (NOD)-like receptors (NLRs) and retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs)), complement and Fc receptors that can influence their participation in immune responses (Table S1).[10–12] Although some differences among granulocyte subtypes and mast cells exist, granules mainly contain serine proteases, acid hydrolases, cationic proteins, metalloproteases, and others for example, histamine, heparin, and proteases, rapidly released upon cell activation. In addition, leukotrienes, prostaglandins and an array of chemokines and cytokines are newly synthesized and released following cell activation (Table S2). Moreover, neutrophilic and eosinophilic granulocytes have nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity which can produce toxic oxygen radicals. Following activation, the granule content can be released via three main mechanisms: exocytosis, piecemeal degranulation and cytolysis. Exocytosis is the release of granule or vesicular contents, into the extracellular space resulting from the fusion of the granule directly with the plasma membrane (classical exocytosis), or from intracellular granule–granule fusion prior to interaction with the plasma membrane (compound exocytosis). Piecemeal degranulation occurs when activated cells selectively release granule contents, such as cytokines and other granule proteins, while remaining viable, that is, do not empty as completely or as explosively as would be anticipated if exocytosis is taking place. Finally, cytolysis is also classified as a form of degranulation because the release of intact cell granules can occur (p.e., neutrophil and eosinophil extracellular DNA traps release).[11,13] Such variety of secreted mediators help potentiate a wide range of functions through different pathways: damaging and killing of pathogens (intracellularly or extracellularly), activation of the endothelium and regulation of trafficking and activity of other leukocytes (i.e., promoting recruitment and activation of monocytes and dendritic cells (DCs), T cells, neutrophils, and Natural killer (NK) cells early in infections[3]), contribution to tissue-remodeling upon infection, and influencing both innate and adaptive immune responses, as well as hematopoiesis.[9] IgE-mediated and TLR-mediated mast cell responses can mobilize DCs to migrate to lymph nodes, promoting T cell-DC interaction and Th2 polarization.[10,11] The complexity and heterogeneity of these mechanisms translate to disparate effects and consequences of granulocytes and mast cells in relation to allergies and in different cancers (Figure 1).

Neutrophils, as the most abundant leukocytes of innate immunity, rapidly respond to tissue injury and infection via a multitude of functions due to their panoply of preformed cytolytic granules (Table S2). Their main immune functions comprise degranulation, phagocytosis, and the release of neutrophil extracellular traps (NETs) or NETosis. Neutrophils can also present cognate antigen to T cells and can also mediate antibody-dependent cellular cytotoxicity (ADCC), mainly via IgG and IgA antibodies whose Fc receptors are expressed on the cell surface.[19] Eosinophils, present in low levels in the periphery, have also relevant cytotoxic effects to pathogens (including helminths, bacteria, viruses, and fungi), tumor cells and respiratory epithelial cells. Upon parasitic infections, eosinophils can play both anti- (directly or by enhancing adaptive immune response through antigen presentation) or pro- pathogen roles (i.e., in *Trichinella spiralis* infection and *Heligmosomoides polygyrus*).[20] Eosinophil extracellular traps (EETs) have a protective effect by limiting the migration of pathogens and antimicrobial activity to a controlled range. Multiple clinically relevant allergens trigger EET formation. Chronic inflammation can lead to the overproduction of EETs, which can induce and exacerbate allergic asthma through multiple mechanisms.[21,22]

	Allergy	Similarities	Cancer
Mast cell	• Found in microenvironment (including lymph nodes) • Symptoms mediated by IgE activated mast cells (release of inflammatory mediators). Mostly, Allergen-IgE-FcεRI cross-linking induces cell activation leading to allergic symptoms, but not exclusively (IgG, MRGPRX2, etc.).	• Release of danger signals (DAMPs or alarmins) • Recruit immune effectors cells (T cells, neutrophil, NK cells) • Activated via alarmins and adenosine.	• Accumulation associated with cancer growth and therapy resistance in solid tumors. • Peri-tumoral and lymph node infiltrations associated with improved prognosis. • Virus infected cells selectively recruit NK cells and positively modulate their function. • Activated via anti-tumor antibodies.
Eosinophil	• C-C motif chemokines induce tissue migration during inflammation, (i.e, GI tract or lungs during homeostasis and allergic inflammation (eotaxin-CCR3 axis). IL-5 primes eosinophils to migrate in response to eotaxins. • Involved in chronic allergic and atopic conditions and associated with curative processes. • EETs in BAL fluid are associated with the severity of asthma, and asthma progression through neuro-immune signals and EPX.	• MBPs type I/II can disrupt the lipid bilayer (cytotoxic to helminths and tumor cells). • Quickly expand and infiltrate inflamed tissues. • Distinct populations for recruited or tissue-resident cells. • ECP and EDN are ribonucleases with antiviral activity. • Lipid bodies characteristic of activated eosinophils serve as reservoirs for inflammatory mediators during inflammatory responses.	• TATE due to chemotactic factors and DAMPs. • Pro- (Hodgkin's lymphoma), or anti-tumorigenic (solid tumors) - augmented by mediators. • Innate tumor sensing and killing with Igs. • Prognosis associated with eosinophilic presence and plasticity (cancer type dependent). • Treg induction.
Basophil	• Important source of IL-4 release that stimulates ILC2, recruits eosinophils, and augments differentiation of naïve T cells to Th2. • Infiltration of tissues may contribute to allergic disease and act to worsen disease control: in the lung in asthma, in nasal polyps in CRS, including those with AERD, in which basophils tend to have higher rates of degranulation, correlating with disease severity. • Through release of IL-4 and IL-13, basophils can recruit and activate keratinocyte proliferation and differentiation; leading to barrier dysfunction observed in atopic dermatitis or CSU.	• BAT used to evaluate hypersensitivity to allergens and therapeutic agents • Influenced by Th2-biased inflammatory signals • Surface expression of the full tetrameric form (αβγ2) of the high-affinity receptor (FcεRI) • Releasing preformed mediators	• Identified in a broad range of TMEs • Limited understanding of the role in cancer • Associated with patient survival outcomes (pro- or anti-tumoral, dependent on cancer type)
Neutrophil	• FcgRIIIb also plays an important role in anaphylaxis. • Progression of allergic diseases. • Infiltrate allergen-induced reaction and serve as APCs to allergen-specific $CD4^+$ T cells. • Express higher levels CD49d, CXCR4, CD11b in atopic asthma. • Activated $CD16^{hi}CD62L^{dim}$ neutrophils are increased in pollen season. • Certain pollen species attract them to the airways in a TLR4-,MDP2- and CXCR-2-dependent manner. Neutrophils internalize and degrade birch pollen Bet v 1 and induce proliferation and cytokine production of Bet v 1-specific effector T cells. Also, grass pollen can stimulate neutrophil immune responses through inducing the secretion of IL-8. • Major source of oncostatin M contributing to mucosal barrier dysfunction. • Release MMP-9 and show increased respiratory burst and production of ROS in asthma. • NETosis and enucleated cytoplasts associated with Th17 response and neutrophilic asthma.	• Promotes type 2 immune responses	• May have a role in tumorigenesis • Biomarkers, such as NLR, proposed as a risk stratifier and treatment guide • Either pro- or anti-tumoral effects in TME (dependent on cancer type) • Association between TANs and overall patient survival (dependent on cancer type)

FIGURE 1 Granulocytes and mast cells: Main traits and functions in allergy and cancer. Key examples of similar and distinct roles of mast cells, eosinophils, basophils, and neutrophils in the different contexts of allergy and cancer. AERD, aspirin-exacerbated respiratory disease; APC, antigen presenting cell; BAL, bronchoalveolar lavage; BAT, basophil Activation Test; CRS, chronic rhinosinusitis; CSU, chronic spontaneous urticaria; DAMPS, danger associated molecular patterns; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; EET, eosinophil extracellular trap; EPX: Eosinophil peroxidase; GI, gastrointestinal; Igs, immunoglobulins; IL, interleukin; MBP, major basic protein; MDP-2, myeloid differentiation protein-2; NETosis, formation of neutrophil extracellular trap; NK, natural killer; NLR, neutrophil-to-lymphocyte ratio; ROS, reactive oxygen species; TAN, tumor associated neutrophil; TATE, tumor-associated tissue eosinophilia; TLR, toll-like receptor; TME, tumor microenvironment.

Among them they can activate pulmonary neuroendocrine cells via the CCDC25-ILK-PKCα-CRTC1 pathway, which is potentiated by eosinophil peroxidase (EPX), subsequently amplifying allergic immune responses via neuropeptides and neurotransmitters. With this, EETs integrate immunological and neurological cues to drive asthma progression. Very recently, a link between eosinophils and the autotaxin and lysophosphatidate (ATX-LPA) signaling axis has been described.[23] Due to overexpression of ATX, the ATX-LPA axis plays a crucial role in cancer cell proliferation and growth, motility, invasion, and tumor tissue angiogenesis and therapy outcome in different cancer types, such as glioblastoma, melanoma, liver, breast and renal cancers.[24–26] Recently, ATX–LPA signaling

was shown to shape the TME by inhibiting eosinophil recruitment, resulting in increased tumor growth in pancreatic ductal adenocarcinoma (PDAC).[27] In addition, eosinophils have been reported to play a role in immunoregulation (interacting with a variety of immune cells such as T cells, MCs, DCs, and B cells), tissue homeostasis, wound healing and tissue remodeling.[20,28] Mast cells and basophils contribute to allergic reactions and anaphylaxis often, but not exclusively, mediated by IgE. Basophils are the rarest granulocytes but with many similarities with tissue-resident mast cells[12]) which constitutively express high levels of the tetrameric high-affinity IgE receptor FcεRI. Eosinophils also express trimeric FcεRI, but at much lower levels and predominantly intracellularly. Allergen-IgE-FcεRI cross-linking induces cell activation leading to allergic symptoms and initiation of inflammatory reactions due to the release of an array of acute and delayed inflammatory mediators (Table S1). Basophils are primed by and secrete IL-3 which supports their development and functions in allergic diseases.[10] During basophil degranulation, activation markers, such as CD63 and CD203c are upregulated, as measured by flow cytometry (i.e., BAT).[29] Upregulation of CD63 is reported to directly correlate with histamine release and inversely correlate with intracellular diaminoxidase.[30,31] Like BAT, passive mast cell activation test ((p)MAT) is a tool to measure mast cell activation by different allergen sources, including drugs,[32] but is executed with human mast cells derived from healthy donor peripheral blood $CD34^+$ progenitor cells or LAD2 cell lines, sensitized overnight with patient sera. Afterwards cells are challenged with the antigen/allergen of interest and cell activation is assessed. This method is particularly relevant because cell activation through newly uncovered mast cell surface receptors, such as Mastocyte-related G-protein coupled receptor (GPCR) member X2 (MRGPRX2) which respond to small molecules and basic peptides independently of IgE, can be analyzed. Recent detection of these receptors has broadened the possibilities of potential interactions between mast cells and the TME.[33] Furthermore, the capacity of mast cells for antigen sensing has recently been linked to allergen avoidance behavior.[34,35]

In neutrophils, FcγR expression, especially the low affinity FcγRIIIb, has been reported to play an important role in anaphylaxis.[36] Neutrophils also contribute to the development and progression of allergic diseases[37] including allergic asthma[38] (Figure 1). Neutrophils and neutrophil-derived products influence the underlying allergic type 2 immune response and the cardinal features of allergic asthma.[39] Studies depicting neutrophils as biomarkers during allergic development, exacerbation, and as part of pathogenesis are sparse. Neutrophil FcεRI expression has been reported to be minimal at most in both patients with asthma and non-allergic individuals and consequently not regulated by serum IgE, unlike other human $FcεRI^+$ cells.[40] However, rhinovirus infection is reported to drive dsDNA release, associated with NETs and induction of type 2 immunity, leading to asthma exacerbation[41,42]; and neutrophils have been defined as biomarkers for non-type 2 asthma, referred to as neutrophilic asthma, and activated neutrophil subsets ($CD16^{high}$ $CD62L^{dim}$) are increased in blood and nasal fluids of allergic patients during the pollen season.[43]

3 | GRANULOCYTES AND MAST CELLS IN AllergoOncology

3.1 | Mast cells: allergic inflammatory cells with increasingly appreciated roles in cancer

Alongside their widely described roles in allergic diseases, multiple danger signals based on endogenous DAMPs or alarmins (e.g., IL-33, Thymic stromal lymphopoietin (TSLP), Adenosine triphosphate (ATP), DNA/CpG motifs, high mobility group Box 1 (HMGB1)), adenosine, hypoxia, and low pH in the TME activate mast cells to discharge their mediators with disparate pro-tumorigenic or anti-tumor activities.[44] As a result, both positive and negative impacts of mast cells in cancer have been increasingly recognized (Figures 2 and 3, Tables 1 and 2). Their roles in cancer growth and expansion remains controversial, with beneficial and detrimental effects reported in different cancer-specific contexts and likely related to different characteristics such as the anatomical location of the tumor, the specific cancer type, and the inflammatory conditions of the TME.[45]

Mast cell infiltration (mast cell density, MCD) has been associated with enhanced cancer growth and clinical therapy resistance in solid tumors (Tables 1 and 2), including melanoma,[46] breast cancer,[47] non-small cell lung cancer (NSCLC),[48] prostate cancer,[49] and colorectal cancer (CRC).[50] Furthermore, increased numbers of tumor-infiltrating mast cells (TIMs) were found in skin tissue of patients with primary cutaneous lymphoma,[51] patients with progressive cutaneous lymphoma compared to patients with a stable course, and in patients with the most severe cutaneous T-cell lymphoma. An autocrine/paracrine loop between SCF^+/$c\text{-}Kit^+$ mast cells has been described to promote cutaneous melanoma progression.[52] Contrastingly, positive associations with survival have also been reported in various cancers[53–55] (Table 1). Conditions with both elevated mast cells and increased blood vessel density could indicate areas of mast cell release of vascular endothelial growth factor A,[56] and recruitment of effector cells into tumor tissues. In childhood classical Hodgkin lymphoma, mast cell, eosinophil and B cell signatures were enriched, whereas macrophage and stromal signatures were more prominent in adult disease, opening an opportunity for risk-stratification at diagnosis.[57] Not only the abundance but the phenotype/signature of TIMs, that is, activated vs resting for instance, seem to determine the positive or negative effect towards cancer.

Communication of mast cells with tumor cells and other cells in the TME may lead to changes in mast cell responses and differentiation into different mast cell phenotypes.[58–60] Particular mast cell gene signatures have been identified in certain tumors, such as head and neck squamous cell carcinoma,[61] lung adenocarcinoma,[62] and

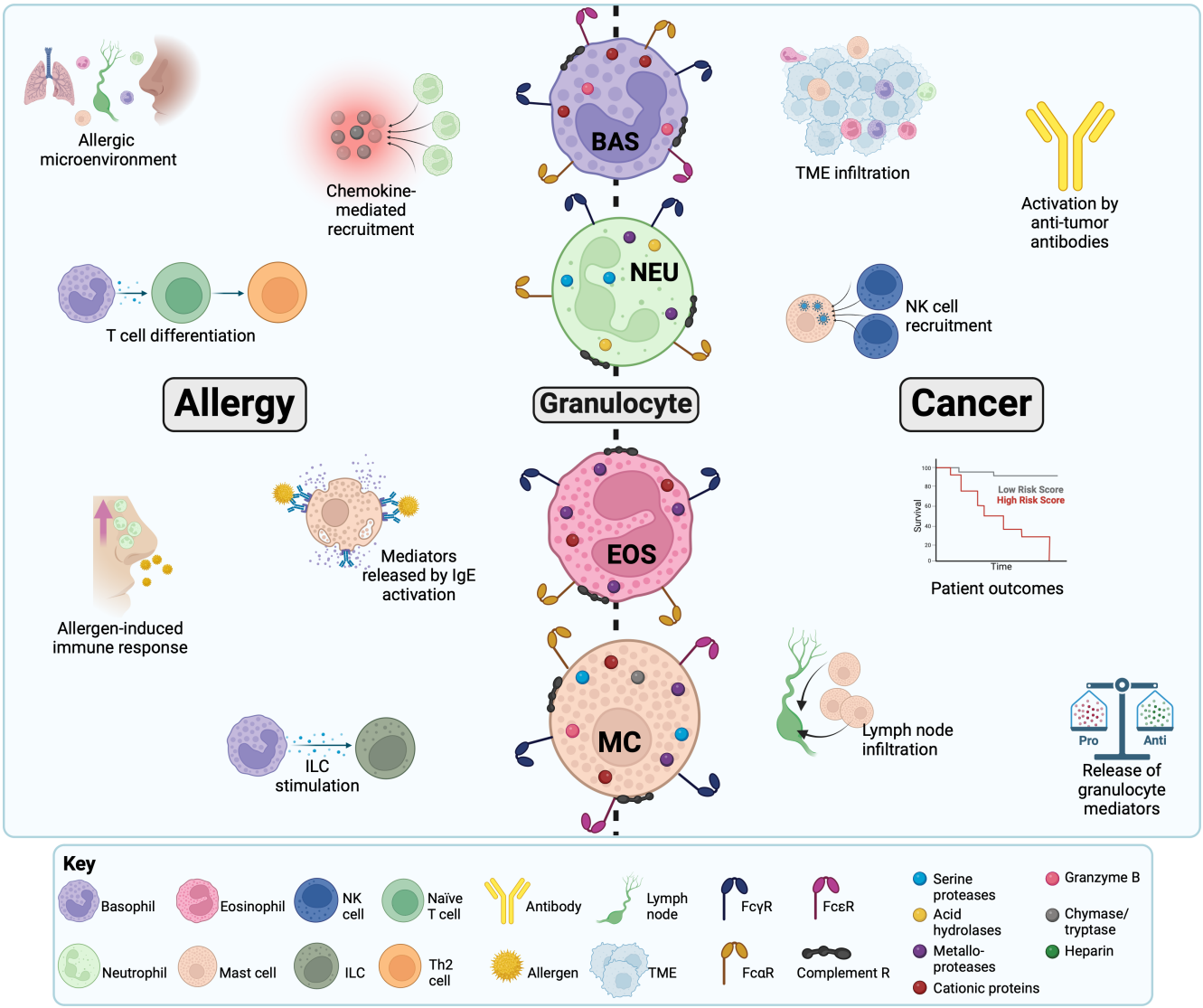

FIGURE 2 Granulocytes and mast cells in AllergoOncology. Composite schematic representing basophils, eosinophils, neutrophils and mast cells and their key functions in allergy and in cancer. Each cell segment is shown with its respective membrane-bound receptors and intracellular cytokines. With some differences among granulocyte subtypes and mast cells, the granules are mainly loaded with serine proteases, acid hydrolases, cationic proteins, metalloproteases, and other proteins—For example, histamine, heparin, and proteases. In addition, these cells can release leukotrienes, prostaglandins, and an array of chemokines and cytokines that are newly synthesized following cell activation. Such variety of secreted mediators allow them to exert a wide range of functions: Damaging and killing of pathogens, regulation of trafficking and activity of other leukocytes and contribution to tissue-remodeling. Granulocytes and mast cells express different Complement and Fc receptors that can influence their participation in immune responses. In Allergy: Basophils, eosinophils, neutrophils and mast cells are found in the allergic microenvironment; eosinophils are recruited towards chemoattractants to tissues, depending on the dynamic changes within a tissue microenvironment; mast cells and basophils drive differentiation of naïve T cells to Th2 and stimulate ILC2s; mast cell and basophil activation by allergen-IgE immune complex formation triggers release of mediators, including histamine and chymase/tryptase; allergens can also stimulate neutrophil immune responses, especially through the low affinity IgG receptor FcγRIIIb, they play a role in anaphylaxis but neutrophils contribute to the development and progression of allergic diseases, infiltrating the airways and skin during allergen-induced late-phase-reaction and can serve as antigen-presenting-cells to allergen-specific $CD4^+$ T cells. Furthermore, certain pollen species attract neutrophils to the airways where they internalize and degrade pollen allergen and induce proliferation and cytokine production of specific effector T cells. Neutrophils, especially activated subsets, were found to be increased in blood and nasal fluids from allergic patients during the pollen season. In Cancer: Basophils, eosinophils, neutrophils and mast cells are found in the TME, and may be engaged and activated by anti-tumor antibodies; mast cells can selectively recruit NK cells and modulate their function; granulocyte and mast cell numbers and activation can be associated with altered patient risk and prognosis (see Table 1); mast cell infiltration into lymph nodes may be associated with cancer outcomes; granulocytes and mast cells release an array of mediators which may be either pro- or anti-tumoral which is likely dependent on the particular TME. Neutrophils can also present cognate antigen to T cells and can also mediate antibody-dependent cellular cytotoxicity (ADCC), mainly via IgG and IgA antibodies whose Fc receptors are expressed on the cell surface. ILC, Innate Lymphoid Cell; NK, natural killer; TME, tumor microenvironment.

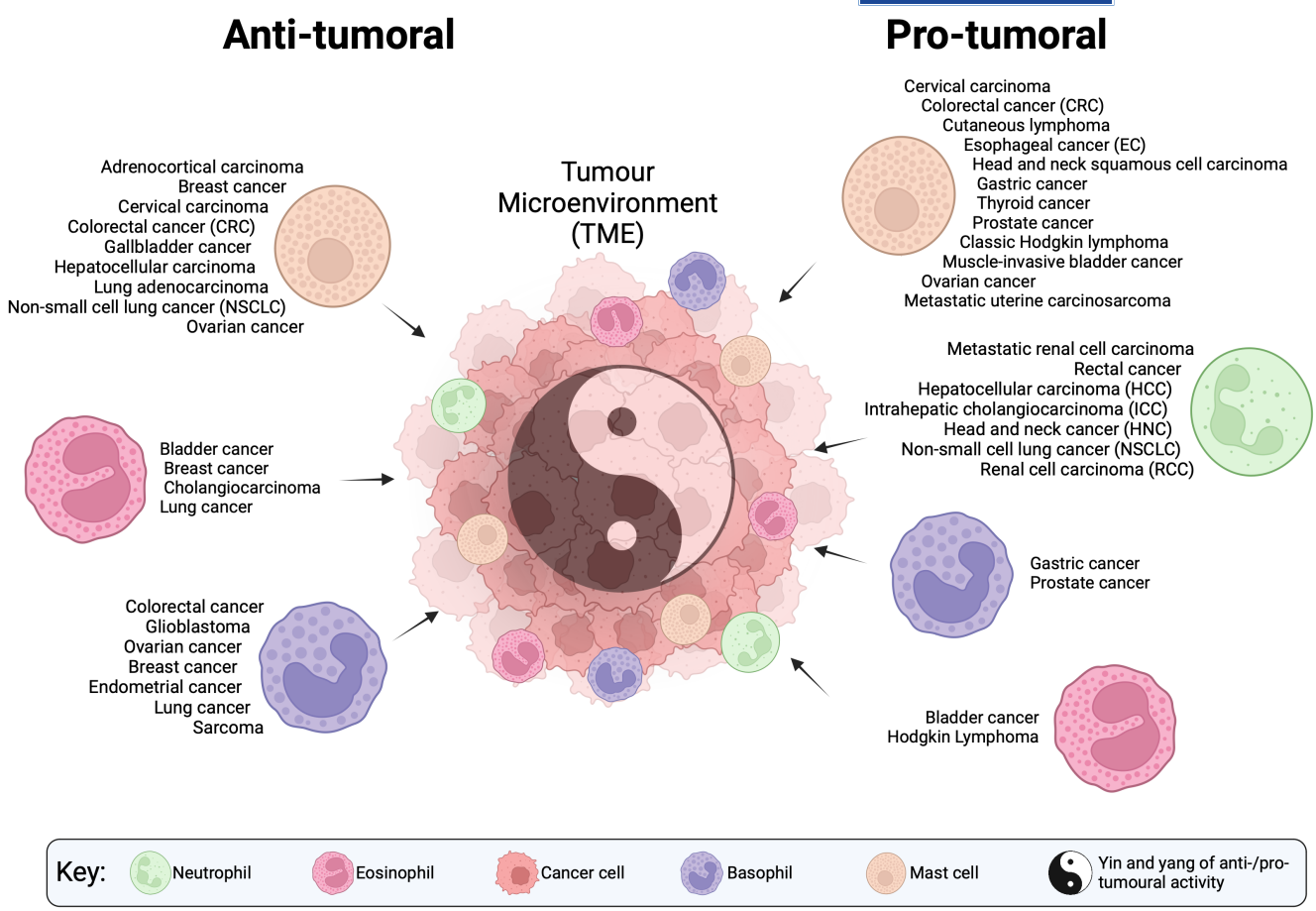

FIGURE 3 Pro-tumoral and anti-tumoral roles of granulocytes and mast cells in cancer. Key examples of the "yin and yang" anti–/pro-tumoral activities associated with granulocytes and mast cells within the tumour microenvironment (TME) of different cancers. Basophils and mast cells exhibit both anti- and pro-tumoral influences within the TME of certain cancers, whilst eosinophils and neutrophils largely play solely anti- and pro-tumoral activities in the TME of certain cancers, respectively.

adrenocortical carcinoma,[63] to be associated with prognosis and immunotherapy response.

3.2 | Eosinophils and their possible roles in cancer

Studies on eosinophils have mainly focused on their role in helminth infections and allergic diseases, but peripheral eosinophilia in cancer patients has been documented for over 120 years (Figure 1). In lung cancer, CRC and melanoma, eosinophil infiltration in the TME (i.e., tumor-associated tissue eosinophilia (TATE)) is likely partially dependent on signaling through the IL-5 receptor (IL-5R) alpha-CCR3 signaling axis.[64] In addition, IL-25 and IL-33 regulate IL-5 production by innate lymphoid cells (ILCs) and may affect eosinophil priming and migration into lungs that harbor metastases.[65] Eosinophils are also recruited to regions of dying cells and hypoxia within tumors when DAMPs, such as HMGB1 and IL-33, are present. This process can be triggered by the expression of CCL-13 and CCL-4 by HMGB1, and by the expression of CCL-11 by IL-33, as potent inducers of type 2 T helper cells (Th2). Recent studies have shown that the microbiota can also influence eosinophil migration to the TME.[64,66]

Both TATE and peripheral blood eosinophilia have been associated with both favorable and poor prognosis in different disease contexts and model systems (most recent human epidemiological studies are summarized in Table 1 and Figure 3) and immunotherapy outcome (Table 2).[64,67–69] However, most of the evidence comes from exploratory studies with small numbers of patients where eosinophil counts from different samples were calculated. Thus, systematic analyses of eosinophil phenotypes are needed for clarification of their role. There has been also controversy regarding the role of eosinophils in the TME, being the interplay eosinophils-adaptive immune response key in decrypting their effect on cancer.[66] A given microenvironment does not instruct eosinophils to perform a single and rigid end-stage function. Distinct eosinophil subpopulations have been described in the context of allergy and cancer in mice and humans, with different phenotypes for those populations recruited to the TME compared with the tissue-resident subsets. For instance, there is a general heterogeneous transcriptome signature between colitis-associated cancer eosinophils compared with normal colonic eosinophils in mice, indicating plasticity in the eosinophilic response, as is already demonstrated for macrophages and

TABLE 1 Epidemiological studies of granulocytes and mast cells in cancer addressing risk and prognosis in humans.

Cell type	Biomarker	Cancer type	Tumoral effect (anti/pro)	Impact on prognosis and/or cancer risk	References
Mast cell (MC)	High tumor-infiltrating mast cells (TIM)/Intratumoral mast cells/Mast cell density (MCD)	Adrenocortical carcinoma	Anti-tumoral	Higher TIM infiltration positively correlated with patient's outcome	180
		Breast cancer (Luminal A and B)	Anti-tumoral	High TIMs are good prognostic factors for Overall Survival (OS)	181
		Breast cancer	Anti-tumoral	Resting dendritic and resting mast cells were the most significant immune infiltration-related cells and were highly expressed in low-risk group	182
		Cervical carcinoma (CC)	Pro-tumoral	High TIMs in CC tissue was associated with worse OS in patients	183
			Anti-tumoral	Low levels of infiltration of CD8+ T cells, activated T memory cells and resting and activated mast cells (especially in metastasis) was associated with worse OS in patients	184
		Colorectal cancer (CRC)	Anti-tumoral	In late-stage CRC, high resting mast cells was associated with better OS	185
			Anti-Pro-tumoral	MCD improved survival in stages II and III CRC patients receiving adjuvant chemotherapy Multiple immune pathways were enriched in low MCD group while cytokines/chemokines promoting anti-tumor immunity were highly expressed in such group MCD was negatively correlated with CD8+ T cells infiltration	186
			~~Anti~~Anti-tumoral	Infiltration density of MCs in CRC tissues was positively correlated with improved patients' prognoses	139
		Cutaneous lymphoma	Pro-tumoral	TIM significantly increased in primary cutaneous T-cell lymphoma and in primary cutaneous B-cell lymphoma Higher counts of TIM in patients with a progressive course compared to patients with a stable course TIM numbers correlated positively with different stages of cutaneous T-cell lymphoma TIM numbers correlated with microvessel density in cutaneous lymphoma	51
		Esophageal cancer (EC)	Pro-tumoral	TIM significantly increased at the late stage of EC and a high percentage of MC indicated a poor OS. TIM accumulation and infiltration of CD8+ T cells were shown to be negatively correlated	187,188
			Pro-tumoral	TIM combined with Nrf2 mutation could be a marker to predict prognosis and immunotherapy response	189
		Gallbladder cancer (GBC)	Anti-tumoral	High TIM infiltration was linked to the immune surveillance by recruiting and activating CD8+ T cells and a predictor of therapeutic response of gemcitabine-based adjuvant chemotherapy	190

TABLE 1 (Continued)

Cell type	Biomarker	Cancer type	Tumoral effect (anti/pro)	Impact on prognosis and/or cancer risk	References
		Head and neck squamous cell carcinoma	Pro-tumoral	MCD is an independent factor of prognosis and reflects an unfavorable outcome.	140,191
		Gastric cancer (GC)	Pro-tumoral	In stage III patients, $CD8^+$ T cells, $CD68^+$ macrophages, and $CD117^+$ mast cells infiltrated more when poor prognosis CD117+ mast cells have the same trend of predicting significance for prognosis in the RNA and protein levels	192
		Hepatocellular carcinoma	Anti-tumoral	Patients lacking TIMs displayed larger tumors and higher tumor recurrence rates	193
		Lung adenocarcinoma	Anti-tumoral	Elevated MC abundance is associated with enrichment of $CCR2^+$ cytotoxic T cells and favorable prognosis, including therapeutic response to tyrosine kinase inhibitor therapy	194
		Non-small cell lung cancer (NSCLC)	Anti-tumoral	Higher frequency of TIMs correlated with a better OS and progression-free survival (PFS)	195,196
		Thyroid cancer	Pro-tumoral	Mast cell percentage associated with tumor size, stage and distant metastasis. High TIMs facilitate progression by inhibiting $CD8^+$ T cell function through Galectin-9	197
		Prostate cancer	Pro-tumoral	A high level of MCs infiltration was associated with a significant decrease in the two-year recurrence-free survival rates, associated with a higher level of osteopontin expression	198
			Pro-tumoral	High extramural MC counts are associated with a higher risk of adverse prostate cancer outcome (development of metastases)	199
		Classical Hodgkin Lymphoma	Pro-tumoral	Eosinophil, B-cell, and mast cell signatures were enriched in children, whereas macrophage and stromal signatures were more prominent in adults	57
		Metastatic renal cell carcinoma (mRCC)	Anti-tumoral	High mast cell density together with $CD4^+$ and $CD8^+$ Tumor-Infiltrating Lymphocytes (TILs) associated with better OS	200
		Muscle-invasive GBC	Pro-tumoral	Patients with higher stromal TIMs had a significant worse OS and recurrence free survival. High stromal TIMs were negatively correlated with $CD8^+$ T cells	201
		Ovarian cancer (OC)	Anti-tumoral	In advanced (stage III/IV) patients, peri-tumoral and/or lymph node mast cell infiltration has been associated with more favorable prognosis, OS	55
			Pro-tumoral	The proportions of M2 macrophages and mast cells were greater in malignant than in benign ovarian neoplasms Larger proportions of cells expressing M2 macrophages were related to worse prognoses for malignant ovarian neoplasia	202

(Continues)

TABLE 1 (Continued)

Cell type	Biomarker	Cancer type	Tumoral effect (anti/pro)	Impact on prognosis and/or cancer risk	References
			Pro-tumoral	Stromal infiltrating mast cells identify immunoevasive subtype high-grade serous OC with poor prognosis and inferior immunotherapeutic response	203
	Circulating mast cell progenitors (MCps)	CRC	Anti-tumoral	Lower levels of circulating MCps in patients with CRC were found, which was significantly related to CRC development After surgery, the frequency of circulating MCps was significantly increased	204
	Activated MC signature	Metastatic uterine carcinosarcoma	Anti-tumoral	Activated MC were significantly downregulated during tumor metastasis (nomogram analysis)	205
		Lung adenocarcinoma	Pro-tumoral	Activated mast cells correlated with less favorable survival, whereas resting mast cells were associated with better OS and disease free survival (DFS)	206
	Resting MC	Prostate cancer	Anti-tumoral	Higher proportions of resting mast cells were associated with worse outcomes	207
		NSCLC	Anti-tumoral	Higher risk score associated with lower resting mast cell infiltration (predictive score containing four resting mast cell-related genes)	208
Eosinophils (EOS)	Tumor-associated tissue eosinophilia (TATE)	GBC	Anti-tumoral	High TATE associated with less tendency to metastasis	209
		Pancreatic ductal adenocarcinoma (PDAC)	Anti-tumoral	Eosinophils were identified in human PDAC specimens, and rare individuals with high intratumor eosinophil abundance had the longest OS Low eosinophils and low eosinophil-to-lymphocyte ratio (ELR) were significant independent factors of poor prognosis	210,211
	Elevated eosinophil count	Breast cancer	Anti-tumoral	Improvement in breast cancer-specific survival in patients with high relative eosinophil count	212,213
	Elevated tumor-infiltrating eosinophils (TIEs)	Breast cancer (Luminal A and B)	Anti-tumoral	Low TIEs risk factors for DFS	181
	Elevated postoperative number of eosinophils (PNE) count	Cholangiocarcinoma	Anti-tumoral	Low-PNE group showed a poorer prognosis with regards to the OS and the survival time after recurrence (SAR) No significant difference in the DFS	214
	EOS% of ≥1.15% and IFNγ of ≥3.75 ng/L	NSCLC	Anti-tumoral	Improved clinical outcomes in patients with advanced NSCLC	64
	TATE and eosinophil infiltration	Hodgkin lymphoma (pediatric)	Pro-tumoral	Patients with marked eosinophil infiltration had worse DFS and tumor invasion	215,216
		GBC	Pro-tumoral	TATE may be one of the probable prognostic signs for local relapse	209

TABLE 1 (Continued)

Cell type	Biomarker	Cancer type	Tumoral effect (anti/pro)	Impact on prognosis and/or cancer risk	References
Basophils	Greater tumor-infiltrating basophils	GC	Pro-tumoral	Worse OS. Inferior response to chemotherapy	77
	Elevated peripheral basophil count	GC	Pro-tumoral	Worse OS and PFS Worse response to anti-PD-1 inhibitor-chemotherapy combination	79
	Elevated activated intra-tumoral basophil (CCR3, CD123, FcεRI, CD63, CD203c, tryptase) gene signatures	GC	Pro-tumoral	Worse OS	6
	Elevated peripheral basophil count	Metastatic prostate cancer	Pro-tumoral	Worse OS	78
	Lower peripheral basophil count	CRC	Anti-tumoral	Shorter OS and DFS	80,81
	Elevated peripheral basophil count	Glioblastoma	Anti-tumoral	Improved PFS	82
	Elevated number of peripheral basophils and peripheral basophil with high capacity for activation	OC	Anti-tumoral	Improved OS	76
	Elevated activated intra-tumoral basophil (CCR3, CD123, FcεRI, CD63, CD203c, +/− tryptase) gene signatures	OC	Anti-tumoral	Improved OS, PFS	76
	Elevated intra-tumoral basophil (CCR3, CD123, FcεRI) gene signature	Breast cancer	Anti-tumoral	Improved OS, PFS	6
	Elevated activated intra-tumoral basophil (CCR3, CD123, FcεRI, CD63, CD203c, +/− tryptase) gene signatures	Endometrial cancer	Anti-tumoral	Improved OS, PFS	6
	Elevated intra-tumoral basophil (CCR3, CD123, FcεRI) gene signature	Lung cancer	Anti-tumoral	Improved OS	6
	Elevated intra-tumoral basophil (CCR3, CD123, FcεRI) and activated intra-tumoral basophil (CCR3, CD123, FcεRI, CD63, CD203c, +/− tryptase) gene signatures	Sarcoma	Anti-tumoral	Improved OS, PFS	6

(Continues)

TABLE 1 (Continued)

Cell type	Biomarker	Cancer type	Tumoral effect (anti/pro)	Impact on prognosis and/or cancer risk	References
Neutrophils	Neutrophil blood count (NBC)	mRCC	Pro-tumoral	High neutrophils: adverse prognostic factor	217
	Neutrophil-to-lymphocyte ratio (NLR)	Rectal cancer	Pro-tumoral	High NLR predict for poor OS	119,120
	Tumor-associated neutrophils (TANs)	Hepatocellular carcinoma (HCC) Intrahepatic Cholangiocarcinoma (ICC) Head and Neck Cancer (HNC) NSCLC RCC	Pro-tumoral	High TAN adverse prognostic effect. High levels of intra-tumoral neutrophils are associated with unfavorable recurrence-free, cancer-specific and OS	218

Abbreviations: CC, cervical carcinoma; CRC, colorectal cancer; DFS, disease free survival; EC, esophageal cancer; ELR, eosinophil-to-lymphocyte ratio; EOS, eosinophils; GBC, gallbladder cancer; GC, gastric cancer; HNC, head and neck cancer; ICC, intrahepatic cholangiocarcinoma; MC, mast cell; MCD, mast cell density; MCps, circulating mast cell progenitors; mRCC, metastatic renal cell carcinoma; NBC, neutrophil blood count; NLR, neutrophil-to-lymphocyte ratio; NSCLC, non-small cell lung cancer; OC, ovarian cancer; OS, overall survival; PC, prostate cancer; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PNE, post-operative number of eosinophils; SAR, survival time after recurrence; TANs, tumor-associated neutrophils; TATE, tumor-associated tissue eosinophilia; TIEs, tumor-infiltrating eosinophils; TILs, tumor-Infiltrating lymphocytes; TIM, tumor-infiltrating mast cells.

neutrophils.[70] In a mouse model of experimental asthma two distinct eosinophil populations, tissue-resident ($CD125^{intSiglec\text{-}Fint}CD62L^{+}CD101^{low}$) and recruited ($CD125^{intSiglec\text{-}Fhi}CD62L^{-}CD101^{hi}$) have been revealed. Studies in the lung also revealed a regulatory phenotype for normal resident eosinophils (rEos) able to inhibit allergen-loaded DC maturation. In contrast, recruited inflammatory eosinophils (iEos) promoted a Th2 cell immune response, that positively correlated with asthma.[71] These regulatory processes may also operate in the TME and the stimulatory state of eosinophils, and their functions, are likely to be heavily influenced by the anatomical location and inflammation conditions across different tumor types.[67] Recently, ultrastructural findings of eosinophil clustering and ETosis add novel mechanistic insights for eosinophil anti-tumoral activity.[72] These differences in eosinophil phenotype and functions in diverse TMEs should be the focus of future systematic studies to clarify the controversy surrounding the use of eosinophils as biomarkers for prediction and prognosis in different cancer types.

3.3 | Presence and potential influence of basophils in tumors

Although basophil activation states and functions can be influenced by Th2-biased, and most likely alternative Th2 inflammatory signals, which are known features of several tumor types, until recently basophils have received little attention in cancer. This may be a reflection of their small numbers in the blood and the small tumor-infiltrating basophil numbers as a proportion of lymphocytes.

In a limited number of studies, basophils have been identified in the TME, of several tumor types including in lung adenocarcinoma patient lesions,[73] tumor-draining lymph nodes (TDLNs) from PDAC patients,[74] and in tumors from mouse models of melanoma.[75] More recently, the presence of basophils and activated basophils in both normal and malignant tissues were indicated by gene expression signatures, including CCR3, CD123, FcεRI, CD203c, and tryptase, and in the case of ovarian cancer were confirmed with protein detection by immunohistochemistry (IHC) (Figure 1).[6,76] Of the cancers studied, cholangiocarcinoma, thymoma, renal, and pancreatic cancers appeared to most clearly express basophil and activated basophil signatures.[6]

Associations between patient survival outcomes and basophils, and their activation state, have also been observed (Table 1; Figure 3). Poor patient outcomes have been associated with greater intra-tumoral basophil infiltration in gastric cancer,[77] and elevated blood basophil counts in metastatic hormone-sensitive prostate cancer.[78] Furthermore, higher peripheral basophil counts were associated with worse response to anti-PD-1 inhibitor and chemotherapy combination treatment (Table 2), worse progression-free survival (PFS) and overall survival (OS), as well as accumulation of intra-tumoral basophils and M2 macrophages in gastric cancer.[79] Conversely, lower circulating basophil counts were associated with worse outcomes in patients with CRC[80,81] and glioblastoma.[82]

TABLE 2 Evidence on the roles of mast cells and granulocytes on immune checkpoint blockade (ICB) outcomes.

Cell	Effect on ICB outcome	Biomarker	Cancer Model	References
Mast Cells	Resistance/Decreased response	Tumor infiltrating mast cells (TIMs, molecular subtypes 1 and 2)	Early–stage lung adenocarcinoma	49
		Activated mast cell density + Nrf2 mutation	Esophageal	189
		Abundance stromal TIMs	Ovarian	203
		Activated TIMs and PD1+ TIMs	Melanoma	219
	Increased response	Resting TIMs	NSCLC	115
Eosinophils	Positive response	Eosinophilia/AEC	Metastatic melanoma (including in stage IV)	220–223
			Several tumor types	224
			mRCC	225
		Intratumoral eosinophil accumulation	Solid tumors	64
Neutrophils	Lower response rate	Elevated neutrophil-to-lymphocyte (NLR) ratio	Melanoma	226
			NSCLC	122
	Responders	Decrease in Neutrophil-to-eosinophil (NER) ratio	mRCC	108,118
	Reduced efficacy	IL-8 in serum	Four phase 3 clinical studies: CheckMate 067 (melanoma); CheckMate 017 (squamous NSCLC); CheckMate 057 (nonsquamous NSCLC); and CheckMate 025 (RCC)	227
	Positive response	$Sell^{hi}$ state neutrophil (enhanced IFN-gene signature)	Lung adenocarcinoma (mouse model)	228

Abbreviations: AEC, absolute eosinophil count; ICB, immune checkpoint blockade; NER, neutrophil-to-eosinophil; NLR, neutrophil-to-lymphocyte; nsqNSCLC, nonsquamous NSCLC; sqNSCLC, squamous NSCLC; TIMs, tumor infiltrating mast cells.

Similarly, in ovarian cancer, higher numbers of circulating basophils and basophils with greater capacity for ex vivo stimulation, as well as higher expression of gene signatures denoting activated basophils (CCR3, CD123, FcεRI, CD63, CD203c, with or without expression of tryptase) in the TME have all been shown to be associated with improved survival outcomes.[76] Similarly, higher expression of gene signatures for activated basophils in tumors were associated with greater survival in endometrial cancer and sarcoma, but with worse outcomes in gastric cancer (epidemiological studies of basophils in cancer are summarized in Table 1). Overall, basophils in the circulation and within the TME across different cancers, especially in their activated states, may contribute to anti-tumor immunity and patient survival outcomes. The mechanisms through which basophils may play a role in cancer are not well-understood. Activated basophils may contribute to anti-tumor immunity by release of mediators, such as granzyme B, TNF-α, and histamine. Furthermore, combined anti-tumoral effects may result from crosstalk between basophils and other immune cells. There is an urgent need to gain a more comprehensive view of their roles. Due to new developments whereby optimized BAT discriminates between allergic and merely sensitized/healthy it seems to be a promising in vitro tool in studying basophils in both allergic[83–85] and cancer patients by monitoring hypersensitivity to chemotherapeutics and immunotherapies, and the progress of therapeutic agent desensitization.[76,86,87] Future studies are likely to include greater elucidation of such mechanisms in specific cancers and may utilize such in vitro tools.

3.4 | Neutrophils and their functions in cancer

Neutrophils are the most abundant circulating leukocytes in humans[19] and are known to infiltrate the TME.[88] Neutrophils in cancer were originally described either as anti-tumorigenic (termed N1 or high-density neutrophils (HDN)), or pro-tumorigenic (termed N2 or low-density neutrophils (LDN)). The cancer stage, the tumor type and the local microenvironment are key determinants modulating neutrophil functions. Indeed, tumoricidal capacities of neutrophils may decline over time with tumor growth. Thus, neutrophils may support features of cancer progression such as proliferation, metastasis, angiogenesis, and immunosuppression through multiple mechanisms, among which the role of NETs is growing. Tumors have systemic effects that modulate NETosis. Cancer cells have been proposed to recruit neutrophils to TME, where neutrophils are activated to release NETs that can promote tumor growth, tumor progression, metastasis, and tumor associated thrombosis.[41,89,90] Nevertheless, neutrophils present a higher heterogeneity and plasticity than previously appreciated,[91,92] including in PDAC,[93] melanoma, and lung cancer.[94,95] It is now accepted that different subsets of neutrophils can have differential impact on oncogenesis and consequently on patient survival following treatment[96] (Tables 1 and 2). In TME, the correlation between TANs and patient OS shows contradictory results, though most relevant data in human points at pro-tumoral effects.[88] Moreover, the prognostic significance of TANs was thought to be dependent on tumor histology, and their intra-tumoral or

BOX 1 Open questions and future insights on granulocytes and mast cell mechanisms to be explored in oncology and ICB immunotherapy (IT)

Immune cell type	Oncology	Immunotherapy (e.g., ICB IT)
Mast cells	• Which mast cell activation mechanisms can stimulate the recruitment and pro-inflammatory functions of different immune cells such as T cells, NK cells, macrophages? • What are the regulatory checkpoints that prevent mast cell anti-tumor functions? • Is the location of mast cells in the TME significant in relation to the anti- or pro-tumoral functions of these cells?	• Can Histamine-HRH1 upregulation and its link to T cell dysfunction implicate mast cells in ICB IT resistance? • Could H1-antihistamine treatment during IT help improve clinical outcomes? • Could the balance of resting versus activated mast cell subsets predict IT outcomes in different cancer types? • Could cancer associated antigen specific IgE stimulation re-activate mast cell pro-inflammatory functions in the cancer context? • Could β-tryptase or other released activation mediators be useful biomarkers in monitoring toxicity to chemotherapy and biological drugs?

Eosinophils	• Are known mechanisms of eosinophil recruitment to sites of allergic inflammation (e.g., eotaxin-CCR3, IL-5, CCL-5, CCL-11, IFNγ) also relevant to recruitment of these cells in the TME to promote tumor-associated tissue eosinophilia (TATE)?
	• Can mediators produced by eosinophils in allergic inflammation via which eosinophils exert cytotoxic effects against parasites (e.g., MBP, EPX, IFNγ, TNF, IL-5, IL-33, and CCL-11) also kill cancer cells?
	• EET are favored in chronic allergic inflammation and they can also impact neuroendocrine signaling; could this influence the TME and eosinophil phenotype and activation against cancer?
	• Which mediators (e.g., TSLP), and mechanisms in the TME, influence eosinophil plasticity towards a Th2 phenotype, tolerance (IL-4, IL-5, IL-10, IDO, IL-13) and tumor growth promotion (e.g., EGF, FGFs, NGF, TGF-β1, PDGF, VEGFA)?
	• Identification of a robust mRNA signature for eosinophils and their activation states
		• Could eosinophil levels serve as biomarkers of response to ICB or other IT and/or increased risk of toxicity?
		  • Does this apply to specific IT treatment?
		  • Is this predictive model confined to patients with cancer types known to be responsive to IT?
		  • Could subsets of activated eosinophils help refine predictive models?
		• What are the mechanisms of cross-talk between eosinophils and other immune cells (e.g., IL-5, CCL-5 expressing CD8+ T cells; CCL-11 expressing CD4+ T cells; CXCL-9 and CXCL-10 expressing macrophages) that are critical for eosinophil-mediated anti-tumor functions in IT?
		• Patients receiving eosinophil-depleting treatments should be monitored for cancer prevalence

Neutrophils	• Could differential levels of tumor-associated neutrophils (TANs) or neutrophil-to-lymphocyte ratios (NLR) contribute to disparate clinical outcomes? • Could well-described neutrophil mediators in allergic inflammation (e.g., TGF-β, PGE2, neutrophil-derived proteases, NE, MMP-9) promote cancer growth?	• Can circulating neutrophil-to-lymphocyte ratio (NLR) or neutrophil-to-eosinophil ratio (NER) offer more refined predictive models for ICB response? • Could these be combined with immunological markers such as IL-8 or with neutrophil infiltration in tumors? • Could IT influence neutrophil activation states in the circulation and the TME? • Could an intervention that triggers a neutrophil pro-inflammatory phenotype shift enhance IT response? • Could CAR neutrophils hold promise as a cancer IT modality? • Could IgA class antibodies specific for cancer-associated antigens shown pre-clinically to activate and direct the power of neutrophils to kill tumor cells by ADCC via engagement of Fcα receptors emerge as novel immunotherapy for patients with cancer?

BOX 1 (Continued)

Immune cell type	Oncology	Immunotherapy (e.g., ICB IT)
Basophils	• Are basophils primed by known allergic inflammation signals (e.g., IL-3) in cancer and could these signals influence their activation and functions? • Could Th2 mediators known to be released by basophils in allergic diseases, (e.g., prostaglandins, leukotrienes, IL-4, IL-13) influence the TME and basophil phenotype and activation against cancer?	• Are basophils stimulated by endogenous IgE reactive to anti-cancer drugs via their FcεRI, leading to degranulation and type I hypersensitivity? • Could the BAT become a clinically used tool to be used to predict allergic reactions to anti-cancer drugs? • Could the BAT become a clinically used tool to identify activated basophils to predict prognosis and treatment outcome? • Is the phenomenon of basophil non-responsiveness in BAT the same in allergy and cancer and/or has it pathomechanistic significance?
Unknown mechanisms that may apply to all granulocytes	• Do granulocyte populations, and which ones, alter their phenotypes and shift their functions during cancer evolution? How does this fit within the immunoediting hypothesis model? Could different cell populations be involved in preventing tumor growth during the early disease stages, while being directed to promote tumor expansion and metastasis during advanced disease? • Is there an IFNγ signature for granulocytes and their roles in cancer? • What are the pertinent mechanisms by which DAMPs (e.g., IL-33, ATP, DNA/CpG motifs, HMGB1, GM-CSF) in the clinical setting influence tumor growth by promoting the survival of granulocytes and modulating adaptive immune cells within the tumor?	• Is an activated IFNγ pathway important in the contributions of different granulocyte populations to IT response?

peri-tumoral localization. Possibly the discrepancy related to the prognostic value most likely results from diverging methods applied to define neutrophil subsets, highlighting the importance of ongoing initiatives to adopt consensual nomenclature when investigating these cells.[88,91,96] Future studies may focus on neutrophil phenotypes and their potential for activation by anti-cancer therapeutics.

Some epidemiological studies defined neutrophil-to-lymphocyte ratios (NLR) in the periphery as an independent factor to predict cancer risk and a strong prognostic determinant in many cancers, especially in advanced cancers.[97,98] NLR are associated with reduced OS and PFS (reviewed by Ocana et al.[99] and in Table 1).[89] Furthermore, formation of NETs has been demonstrated to predict the development of disease progression in several cancer types.[100]

4 | GRANULOCYTES AND MAST CELLS IN CANCER THERAPY: EFFECT ON IMMUNE CHECKPOINT BLOCKADE (ICB) AND T CELL THERAPY OUTCOMES

Immune checkpoint blockade (ICB) therapies have yielded significant clinical benefits and durable responses in subsets of cancer patients. Outcomes are likely affected by the complex TME, meaning that not all patients benefit.[101–103] Interestingly, mechanisms underlying resistance to therapy include suggested contributions of mast cells, granulocytes, and their secreted mediators[101,104–106] (Box 1). Histamine-HRH1 upregulation in the TME can induce T cell dysfunction and immunotherapy resistance; therefore, histamine release, either from allergic responses or in response to cancer-associated inflammation may be involved in immune regulation. Patients with melanoma and lung cancer taking H1-antihistamines during immunotherapy exhibited improved clinical outcomes. Therefore, antihistamines may achieve a reversal of Th2-skewed inflammation; further studies may ascertain whether such interventions could help overcome T cell exhaustion, reinforcing anti-tumor immunity.[107–110] Mast cells may also provide a target of immune checkpoint blockade. In a model of gastric cancer, inhibition of mast cell-associated PD-L1 resulted in increased T cell activation and restriction of tumor growth.[111]

The main evidence of the role of granulocytes and mast cells on ICB outcome is summarized in Table 2. Mast cells, eosinophils and neutrophils have been implicated in resistance to anti-PD1 therapy as well as the occurrence of associated toxicities (immune-related adverse effects, iRAEs).[104,106,110,112] Specific cell signatures and

abundance in the TME seem to be relevant in several solid tumors to predict therapy outcome and thus disease survival.[103,104,113–115] Indeed, the relative numbers between neutrophils and eosinophils, and with lymphocytes, as well as the interaction with them seems to be relevant. NLR and neutrophil-to-eosinophil ratio (NER) have been proposed as prognostic indicators to identify responders for ICB.[116–128] Studies have shown that intratumoral eosinophil accumulation depends on $CD4^+$ and $CD8^+$ T cells expressing IL-5, CCL-5 (in $CD8^+$ T cells), and CCL-11 (in $CD4^+$ T cells), as well as IFNγ. Furthermore, IFNγ release by eosinophils was essential for anti-CTLA-4 treatment-induced vessel normalization.[129] In addition, IFNγ-dependent chemokines CXCL-9 and CXCL-10 expressed by macrophages were critical for the anti-tumor immune response following dual blockade of PD-1 and CTLA-4, consistent with a requirement for accessory myeloid cells in this process.[64] Eosinophils are showing promising results in chimeric antigen receptor (CAR) T cell therapies, possibly given their support on T cell recruitment and activation.[66] Resistance associated with mast cells was also demonstrated by improved efficacy of anti-PD-1 therapy following depletion of mast cells from a mouse model of melanoma using c-kit specific agents, sunitinib or imatinib.[130]

In the context of antigen-specific T cell immunotherapy, a study conducted in a mouse model of melanoma revealed that resident neutrophils can contribute to the killing of tumor antigen escape variants that are not directly targeted by the transferred T cell therapy.[131] Transcriptomic analyses following immunotherapy, revealed that neutrophils acquired more mature anti-tumorigenic profiles compared to the untreated group. Furthermore, this unique transcriptomic signature was able to further stratify those melanoma patients with more favorable survival. Additionally, characterization of pre- and post-treatment tissue biopsies from a small cohort of cancer patients who received an anti-OX40 antibody in a phase I neoadjuvant trial indicated that this immunotherapy resulted in NET formation, suggesting activation of neutrophils.[131] Furthermore, neutrophil activation is observed in patients treated with T cell immunotherapies.[131,132]

5 | SUGGESTED FUTURE DIRECTIONS

Several features and attributes of mast cells and granulocytes and their immunomodulatory functions in allergy are increasingly appreciated with regards to cancer-associated inflammation (Figures 1 and 3) and cancer immunotherapy response (Table 2). In the immunotherapy and personalized medicine era, these insights are urgently needed to inform therapy and patient outcomes (Boxes 2 and 3).

In allergic diseases and cancers, activated granulocytes and mast cells stimulate the recruitment of innate and adaptive immune cells. Cell localization, density, heterogeneity, and stimulatory signals in the TME may influence the quantity, content, and location of mediator release and contribute to a likely fine balance between their tumor-restricting versus tumor-promoting effects.

For instance, studies pointing at histamine-HRH1 upregulation and T cell dysfunction, at least in advanced disease stages, may link mast cells with immunotherapy resistance. However, it is possible that in a therapeutic setting anti-tumor IgE-mediated activation of mast cells may reverse the regulatory functions of these cells. The successful completion of a Phase I clinical trial of the first-in-class IgE antibody therapeutic recognizing a cancer-associated antigen,[133] may pave the way towards to delving into such complex interactions between granulocytes and mast cells with the TME.

In another example, the potential influence of circadian rhythms on neutrophils needs to be defined in relation to impact on tumorigenesis and progression of cancer. It is also unknown whether this effect also occurs with other granulocytes and/or mast cells. Similarly, the impact of neuroendocrine signaling activation between allergy and cancer by granulocytes, like eosinophils (EETs and ETosis) remains to be fully elucidated. Understanding this coordinated network may aid the development of new behavioral and pharmacological cancer therapies.[134,135]

In allergic inflammation, the eotaxin-CCR3 axis and IL-5 alongside CCL-5, CCL-11 and IFNγ may prime eosinophil migration to tissues, while in asthma, IL-4 or IL-13 also stimulate human eosinophils and endothelial cells to promote further migration, whereas IL-5-induced changes support granulocyte differentiation.[136] Similar mechanisms may promote tumor-associated tissue eosinophilia (TATE). A range of mediators produced by eosinophils in allergic inflammation can exert cytotoxic effects to parasites and cancer cells. Eosinophils from allergic donors appear to be primed to kill cancer cells more effectively and promote $CD8^+$ T cells and pro-inflammatory macrophages likely to exert anti-tumor effects. On the other hand, depending on the dynamic changes within a tissue microenvironment, eosinophils could be switched towards Th2 or tolerant phenotypes. This has been shown in models of allergy, but the same plasticity is likely to reflect their diverse and disparate roles in tumors. Tumors may differentially activate eosinophils via classical allergic mechanisms such as TSLP to secrete Th2 mediators or angiogenesis factors. Together these can promote alternatively activated macrophages, immune tolerance, as well as pro-survival signals on cancer cells to support cancer proliferation and metastatic spread.

With regards to therapies, current evidence does not support an increased prevalence of neoplasia in patients receiving eosinophil-depleting treatments. Continued monitoring of these lifelong therapy interventions may be required for many eosinophil-associated disorders on cancer prevalence. Higher eosinophil infiltration and IFNγ-producing eosinophils promoting pro-inflammatory cells, such as macrophages in the TME, may contribute to checkpoint inhibitor treatment response. While a balance between supporting therapy response and toxicity may need to be considered, future studies will probably provide clarification of the role of eosinophils in cancer, such as by including a robust mRNA signature for eosinophils, something currently missing in the field.

Different subsets of neutrophils can have differential impact on cancer outcomes, and are modulated by tumor type, stage, and local

microenvironment. Neutrophils can directly kill cancer cells and stimulate anti-tumor immune responses, but also promote tumor growth and metastasis through various mechanisms, including via responding and contributing to TGF-β. Produced mediators well described in the process of allergic inflammation such as prostaglandine E2 (PGE2) which may have juxtaposed pro- and anti-tumoral

BOX 2 Potential future therapy strategies based on targeting granulocytes and mast cells

Potential therapeutic strategy	Supporting evidence
Enhance tumor killing capacity of mast cells	• MC suppress tumor growth and induce apoptosis of CRC cells by specifically inducing endoplasmic reticulum stress (ERS) through secretion of cystatin C and activation of the unfolded protein response (UPR).[139] Similar observations have been described in head and neck squamous cell carcinoma.[140] • Virus-infected mast cells have been shown to selectively recruit NK cells and positively modulate their functions through mechanisms dependent on soluble mediators, such as interferons, thus enhancing their tumor killing capacity.[141] • Expression of Fc receptors, including the high affinity IgE receptor FcεRI on the surface of mast cells mark these as anticipatory effector cells ready to promptly respond to tumor antigen-specific antibodies, including IgE. Antibody-mediated bridging of mast cells with cancer cells can lead to cancer cell death via mechanisms such as ADCC. • In the TME, antigens shed by cancer cells, or multiple copies of tumor antigens expressed on cancer cells or on cancer cell fragments, together displaying tumor-associated molecular patterns,[142] can cross-link FcR-bound anti-tumor antibodies, including IgE, triggering mast cell degranulation. Immune complex formation, and mast cell-cancer junctions formed in the presence of therapeutic antibodies in tumors, may potentiate antigen presentation and result in enhanced adaptive immune responses. Cross-linking Fc receptors leading to the release of histamine, proteases, prostaglandins, leukotrienes, and other mediators may support local inflammation and recruitment of immune cells to tumors, potentially resulting in "hot" tumors.
Activation of eosinophils to secrete mediators that promote cytotoxicity of cancer cells and suppress metastatic development	• IL-10 and IL-12 secreted by activated eosinophils inhibited prostate cancer cell growth and enhanced E-cadherin expression, which may suppress metastatic development. • Direct eosinophil-mediated cytotoxicity of cancer cells has been observed in many human and mouse in vitro co-culture models of eosinophils and tumor cell lines.[70,143–148] • A range of mediators including (interferon gamma) IFNγ, IL-5, IL-33, and CCL-11 could augment eosinophil-mediated killing of cancer cells, indicating a role for eosinophil-derived factors in eosinophil-mediated tumor cell cytotoxicity.[70,144–146] • By upregulating the integrin lymphocyte function-associated antigen 1 (LFA1) and intracellular adhesion molecule 1 (ICAM1), IL-18 has been shown to promote eosinophil adhesion to Colo-205 CRC cells.[148] • Eosinophils from allergic donors were more cytotoxic than those from healthy donors or patients with hypereosinophilic syndrome,[148] suggesting that harnessing allergic mechanisms may promote anti-tumor functions in AllergoOncology. • Activation of human and mouse eosinophils by IFNγ increased the killing of CRC cells.[149] • TNF-activated and IFNγ-activated eosinophils induced anti-tumor immunity by infiltrating CD8+ T cells and normalizing blood vessels, which activated pro-inflammatory macrophages known to exert anti-tumor effects.[70,150] • The GM-CSF-IRF5 signaling axis in eosinophils promotes anti-tumor immunity through activation of type 1 T cell responses in CRC. GM-CSF activates interferon regulatory factor 5 (IRF5) in vitro and in vivo and can be administered recombinantly to improve tumor immunity.[151,152] • ATX-LPA signaling suppresses a CCL11-eosinophil axis to promote pancreatic cancer progression. ATX suppresses eosinophil accumulation via an autocrine feedback loop, wherein ATX-LPA signaling negatively regulates the activity of the AP-1 transcription factor c-Jun, in turn suppressing the expression of the potent eosinophil chemoattractant CCL11 (eotaxin-1).[23] An in vivo study showed that intraperitoneal injection of GLPG1690, an ATX inhibitor, suppressed tumor progression in a xenograft model.[24] • Chronic inflammation can lead to the overproduction of EETs, which activate pulmonary neuroendocrine cells via the CCDC25-ILK-PKCα-CRTC1 pathway amplifying allergic immune responses via neuropeptides and neurotransmitters. Inhibition of CCDC25 can induce and exacerbate allergic asthma through multiple mechanisms.[19,20] Downregulation of neuro-immune signaling could have a beneficial impact in cancer.
Enhance eosinophil migration into solid tumors	• Administration of the DPP4 (Dipeptidyl Peptidase IV (DPP IV)) inhibitor sitagliptin increases CCL-11 levels and eosinophil migration into solid tumors, leading to enhanced tumor control, which is dependent on tumor-cell expression of IL-33 and contributes to the effectiveness of checkpoint-inhibitor therapy.[153]

BOX 2 (Continued)

Potential therapeutic strategy	Supporting evidence
Enhance the growth-inhibitory potential of neutrophils against early-stage cancer	• In the TME, neutrophils can secrete a large array of chemo-attractive factors to recruit and activate immune cells with anti-tumoral functions. Colony stimulating factor 3 receptor (CSF3R) expression by neutrophils and neutrophil infiltration promoted secretion of IL-12 by macrophages and drove type-1 immune responses through unconventional T cells (UTCαβ) to induce immune resistance against sarcoma and other tumors.[154] • Neutrophils can function as antigen-presenting cells (APCs) to potentiate the proliferation of T cells through the expression of the major histocompatibility complex (MHC) and co-stimulatory molecules.[155] • Neutrophils can directly kill neoplastic cells through the use of cytolytic granules, such as neutrophil elastase (NE), cathepsin-G or H_2O_2/oxidative stress, and to kill antibody-opsonized neoplastic cells by trogoptosis.[156] Expression of Fc receptors renders these cells able to perform ADCC mechanisms against cancer cells via IgG and IgA[137,138] (Table S1).
Enhance basophil activation and release of chemokines	• In a melanoma mouse model, recruitment of T cells into tumors by chemokines released from basophils, such as CCL-3 and CCL-4, led to tumor rejection.[75] • Basophil stimulation of B cells through CD40L and secretion of mediators, such as IL-4, IL-6, IL-13, B cell activating factor (BAFF), and histamine, may augment B cell proliferation, survival, and anti-cancer antibody responses.[157,158]
Blockade of immunosuppressive functions of neutrophils	• Neutrophils are well known for their immunosuppressive function associated with polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) in advance cancer stages. The blockade of MDSC with all-trans retinoic acid (ATRA), fatty acid transporter protein 2 (FATP2), PKR-like endoplasmic reticulum kinase (PERK) and Toll interacting protein (TOLLIP) signaling inhibitors can improve anti-tumor immune responses and immunotherapy outcome.[159]
Control/Reduction of pro-tumoral activities of granulocytes and mast cells: decreasing secretion of growth factors and matrix metalloproteinases, as well as promotion of angiogenesis	• Cervical cancer cells can activate eosinophils, by thymic stromal lymphopoietin (TSLP), and induce the production of IL-4, IL-5, IL-10, and IL-13 by eosinophils, which promote cervical cancer cell proliferation.[160] • In several mouse models of cancer, IL-5 and eosinophils facilitated lung metastasis colonization.[161,162] Epidemiological human studies have shown a link between higher levels of IL-5 in breast carcinomas and poor prognosis in distant metastases.[163] • Eosinophils can potentially promote angiogenesis by storing and secreting an array of growth factors (vascular endothelial growth factor A, VEGFA), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF), fibroblast growth factor (FGF)s, Nerve growth factor (NGF), Transforming growth factor beta 1 (TGF-β1) and some members of the S100 family).[64] • Eosinophil-secreted EPX triggered increased mucin-4 (MUC4) and human epidermal growth factor receptor 2 (HER2) expression which supported cancer cell survival and proliferation through HER2 and its intracellular signaling cascades such as extracellular signal-regulated kinase 1 and 2 (ERK1/2) and has been shown to stimulate tumor growth, survival, and metastasis mouse models.[164–166] • Eosinophils may promote tumor growth by releasing IL-4 and IL-13, which in turn may shape macrophage polarization to alternatively activated M2 phenotypes in the TME, or through indoleamine 2,3-dioxygenase (IDO) production, which is essential for promoting immune tolerance to tumors.[167–169] • Pro-tumoral activities of basophils may include the release of pro-angiogenic and lymphogenic mediators,[170–172] the suppression of anti-tumoral immune mechanisms, such as through interactions with Treg cells,[173] and the modulation of the TME towards an immuno-evasive environment, infiltrated with immunosuppressive cells such as M2 macrophages.[77,79] • Transforming growth factor-beta (TGF-β) promotes a pro-tumoral state, whereas contact with IFNγ favors the anti-tumoral phenotype of tumor associated neutrophils (TANs). • Tumoricidal capacities of neutrophils may decline over time with tumor growth. Neutrophils promote tumorigenesis through the release of reactive oxygen species (ROS) that mediate DNA damage and favor cellular mutational load.[174,175] They directly potentiate cancer cell proliferation via numerous paracrine-signaling pathway. For example, prostaglandine-E2 (PGE2), known for anti-inflammatory, pro-tumoral effects can be secreted by neutrophils to reduce cancer proliferation by direct cell-to-cell contact.[176] • Release of growth factors, laminin degradation by the neutrophil-derived proteases neutrophil elastase (NE) and MMP-9 may support cancer cell proliferation.[177] • An increase in the capacity of neutrophils to release NETs during cancer progression has also been shown to promote tumor progression and metastatic dissemination.[178] • Neutrophils participate in angiogenesis through the release of MMP-9 and S100A8/9 that subsequently activate VEGF.[179]

BOX 3 Unmet needs and proposed research avenues

- Better comprehension of the role of granulocytes and mast cells in cancer inflammation and the cross-talk between cells.
- Systematic analyses of granulocytes and mast cell phenotypes to clarify the controversy surrounding the use of these cells as a biomarkers for prediction and prognosis in different cancer types.
- Stratified studies to explore the associations between granulocytes and mast cells with primary or metastatic disease, and tissue vs organ-specific tumors.
- Robust cell signatures and their respective roles, as well as the factors influencing their development: different subsets and activation status of granulocytes and mast cells can have differential impact on cancer and patient survival as well as on therapeutic toxicities.
- Harmonized and standardized methods to define cell subsets and support to initiatives to adopt consensual nomenclature when investigating and describing phenotypes.
- Understanding of the effect of cancer stage, the tumor type and the local microenvironment (known to be key determinants modulating neutrophil functions) on eosinophils, basophils and mast cells.
- Exploration of the critical aspects for granulocytes and mast cell interactions with the TME, as well as the detailed conditions that trigger specific behaviors of these cells.
- Definitions of the plasticity of granulocytes and mast cells in the context of allergy and cancer.
- Determining the links between granulocytes and mast cells with therapeutic response and resistance (particularly focusing on immunotherapy).
- Understanding and harnessing the consequences of granulocytes and mast cells depletion, to enable targeted manipulation of specific populations and fine-tuned immunotherapy, and development of novel cell-based therapeutical strategies.
- Studies of effects of antigen-specific T cell immunotherapy besides neutrophils.
- Clinically validated and feasible biomarkers, individual parameters or combined, for prognosis and therapy outcome and toxicities.
- The ratios NLR and NER have been proposed as prognostic indicators to identify responders for ICB, nevertheless other ratios involving other granulocytes and mast cells in the TME should be explored.
- Basophils deserve attention from the field despite being scarce in the periphery compared to other cells and in tumor microenvironment. The mechanisms through which basophils may play a role in cancer are not well-understood.
- Improved understanding of the immunomodulatory role of allergy mediators in the circulation of patients with cancer and in the TME. Considering similarities and differences between periphery and TME.
- Further development and clinical validation of in vitro models to assess the roles of granulocytes and mast cells in AllergoOncology (BAT, pMAT), and to support the development of new therapeutic strategies.
- Assessment of the impact of granulocyte and mast cell circadian rhythms in cancer.
- Understanding the coordinated neuroendocrine-immune signaling opens the door to the development of new behavioral and pharmacological cancer therapies.

roles and neutrophil-derived proteases NE and matrix metallopeptidase-9 (MMP-9), participate in angiogenesis and support cancer growth. The relationship between TANs and patient survival is still unclear, but some studies report that increased numbers of neutrophils or neutrophil-to-lymphocyte ratios (NLR) associate with less-favorable survival in certain cancers.

In a therapeutic setting, neutrophils offer opportunities, exemplified by the development of engineered CAR neutrophils as immunotherapy. Importantly, IgG and IgA antibodies specific for cancer-associated antigens may activate and direct neutrophils to kill tumor cells via engagement of cell surface Fcγ and Fcα receptors, respectively, by mechanisms such as ADCC and complement activation.[137,138] While current methods of neutrophil depletion may remove both harmful and beneficial neutrophil states, further investigation is required to understand the different states of neutrophils in tumors and the factors influencing their development. This knowledge will enable targeted manipulation of specific neutrophil subpopulations and a chance to fine tune immunotherapy.

Basophil function is widely studied in allergy, however, understanding these cells in cancer is limited. Many attributes of basophils, including their propensity for activation by allergic inflammation signals such as IL-3, may influence their functions in cancer. Th2 mediators released by basophils in allergic diseases drive stimulation of ILC2s, eosinophils, B cells and differentiation to Th2 cells, but can also influence immune responses in cancer. Importantly, basophils can be stimulated by endogenous IgE reactive to anti-cancer drugs via FcεRI, leading to degranulation and type I hypersensitivity. Allergic reactions to anti-cancer drugs can be predicted and confirmed with the BAT and monitored through mediator release. BAT is an emerging tool in the allergy clinic (i.e., diagnosis and monitoring allergen-specific immunotherapy), but also a promising tool in oncology. Future studies may include more in-depth evaluations of basophils and the BAT in oncology to optimize for routine clinical use.

Thus, further research is needed to determine the critical aspects for granulocytes and mast cell interactions with the TME, as well as the detailed conditions that trigger specific cell behaviors.

6 | CONCLUSION

Emerging and disparate roles of granulocytes and mast cells in cancer prognosis and therapy outcomes (Figure 3; Tables 1 and 2) highlight

the urgent need for a comprehensive understanding of their activation states, interactions with their microenvironment, plasticity and functions in allergy and how these translate to the cancer setting. A better insight into allergy mediators may point to immunomodulatory interactions between granulocytes and mast cells with other components of immune response in patient circulation and the TME.

In addition to epidemiological associations between granulocytes and mast cells with oncology treatment responses and patient survival outcomes (Table 1), these cells and their activation may offer novel avenues for therapy. This may include enhancing their activation to promote several attributes, such as: (a) secretion of mediators that can exert anti-tumoral functions, (b) tumor cell killing capacity, (c) migration of mast cells and granulocytes into tumors, (d) increased interactions with other immune cells, and (e) reduction of pro-tumoral activities of granulocytes and mast cells (evidence for the potential for such approaches are outlined in Box 2).

Improved comprehension of the role of granulocytes and mast cells in cancer inflammation and the cross-talk between cells and mediators, as well as systematic analyses of granulocytes and mast cell phenotypes, is required to clarify and better define the use of these cells as biomarkers for prediction and prognosis in different cancer types and disease stages, and toxicities to therapy (Box 3). Furthermore, uncovering specific immunological mechanisms beyond these observations opens the door to novel therapeutic strategies in AllergoOncology.

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DATA AVAILABILITY STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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