2 Basophils in Tumor Microenvironment and Surroundings

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Abstract

Basophils represent approximately 1% of human peripheral blood leukocytes. Their effector functions were initially appreciated in the 1970s when basophils were shown to express the high-affinity receptor (FcεRI) for IgE and to release proinflammatory mediators (histamine and cysteinyl leukotriene C_4) and immunoregulatory cytokines (i.e., IL-4 and IL-13). Basophils in the mouse were subsequently identified and immunologically characterized. There are many similarities but also several differences between human and mouse basophils. Basophil-deficient mice have enabled to examine the in vivo roles of basophils in several immune disorders and, more recently, in tumor immunity. Activated human basophils release several proangiogenic molecules such as vascular endothelial growth factor-A (VEGF-A), vascular endothelial growth factor-B (VEGF-B), CXCL8, angiopoietin 1 (ANGPT1), and hepatocyte growth factor (HGF). On the other side, basophils can exert anti-tumorigenic effects by releasing granzyme B, TNF-α, and histamine. Circulating basophils have been associated with certain human hematologic (i.e., chronic myeloid leukemia) and solid tumors. Basophils have been found in tumor microenvironment (TME) of human lung adenocarcinoma and pancreatic cancer. Basophils played a role in melanoma rejection in basophil-deficient mouse model. By contrast, basophils appear to play a pro-tumorigenic role in experimental and human pancreatic cancer. In conclusion, the roles of basophils in experimental and human cancers have been little investigated and remain largely unknown. The elucidation of the roles of basophils in tumor immunity will demand studies on increasing complexity beyond those assessing basophil density and their microlocalization in TME. There are several fundamental questions to be addressed in experimental models and clinical studies before we understand whether basophils are an ally, adversary, or even innocent bystanders in cancers.

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Abbreviations

ANGPTs	Angiopoietins
APCs	Antigen-presenting cells
BAFF	B-cell-activating factor
BSA	Bovine serum albumin
CAFs	Cancer-associated fibroblasts
CML	Chronic myeloid leukemia
DCs	Dendritic cells
DMBA	7,12-Dimethylbenz(a)athracene
DT	Diphtheria toxin
FcεRI	High-affinity receptor
LTC_4	Cysteinyl leukotriene C_4
PAF	Platelet-activating factor
PD-1	Programmed cell death-1
PDAC	Pancreatic ductal adenocarcinoma
PD-L1	Programmed death-ligand 1
PGD_2	Prostaglandin D_2
TDLNs	Tumor-draining lymph nodes
Th2	T helper 2
TME	Tumor microenvironment
T_{reg}	T regulatory cell
TSLP	Thymic stromal lymphopoietin
uPA	Urokinase plasminogen activator
VEGF-A	Vascular endothelial growth factor-A

2.1 General Aspects

Basophils, first described by Paul Ehrlich in 1879 [1], represent less than 1% of human peripheral blood leukocytes. Their effector functions were not appreciated until the 1970s when basophils were shown to express the high-affinity IgE receptor (FcεRI) for IgE and release of histamine [2–4]. The difficulties in purifying sufficient numbers of human basophils and the absence of basophil-deficient animals hampered the advance of basophil research. Basophils share some characteristics with mast cells, including the presence of similar but distinct basophilic granules in the cytoplasm [5], surface expression of FcεRI, and release of proinflammatory mediators, such as histamine and cysteinyl leukotrienes [6, 7]. Basophils circulate in the peripheral blood and are rarely present in peripheral tissues unless inflammation occurs in mice [8] and in humans [9–13]. The life span of basophils is relatively short (≅2.5 d in mice) [14], and therefore newly generated basophils are constantly supplied from the bone marrow to the peripheral blood [15]. Mouse basophils were clearly characterized by Dvorak et al. as a granular cell population in murine bone marrow with some ultrastructural characteristics similar to mammalian basophils [16]. Recent development of basophil-deficient mice [17–19] has enabled us to examine the in vivo roles of basophils in a variety of immune settings.

In the past, basophils were regarded erroneously as blood-circulating mast cell precursors that could migrate to peripheral tissues and mature into tissue-resident mast cells. There is compelling evidence that basophils and mast cells are distinct cell lineages differentiated from hematopoietic stem cells in the bone marrow [7, 20, 21]. Like other myeloid lineages, basophils develop from hematopoietic stem cells in the bone marrow [15]. It has been suggested that human basophils develop from common basophil-eosinophil progenitors [22, 23]. IL-3 is the most important growth and activating cytokine for human and mouse basophils [24]. Murine basophils can be generated in vitro by culturing bone marrow cells in the presence of IL-3 or thymic stromal lymphopoietin (TSLP) [25]. IL-3-elicited and TSLP-elicited murine basophils differ in terms of gene expression, phenotype, and functions, suggesting heterogeneity among the basophil population [26]. Basophils can be detected in mice deficient for both IL-3 and TSLP signaling, indicating that neither is essential for

basophil development. It has been suggested that approximately 10% of human basophils express the TSLP receptor [7] and the TSLP increases histamine release from basophils [27]. By contrast, a collaborative study demonstrated that human basophils do not express the IL-7Rα [28] and do not respond to TSLP [28, 29]. The above findings emphasize some of the differences between human and mouse basophils [7, 30, 31].

2.2 Basophils as a Source of Cytokines, Chemokines, Angiogenic Molecules, and Granzyme B

Human basophils, differently from mast cells, produce a restricted profile of cytokines [7, 21]. A variety of immunologic stimuli induce the release of substantial amounts of IL-4 [32–36]. Activated human basophils also produce IL-13 [37–39]. IL-4 and IL-13 are potent mediators for type 2 immunity with both overlapping and distinct functions [40]. Schroeder and collaborators first demonstrated that human basophils secrete IL-3 exerting strong autocrine priming effects on these cells [24]. Activation of human basophils induces the release of several proangiogenic molecules. For instance, immunologically activated human basophils release VEGF-A, the most potent proangiogenic molecule [41, 42]. Angiopoietins (ANGPTs) are a family of growth factors that play a role in angiogenesis and lymphangiogenesis [43]. Human basophils constitutively express ANGPT1 and ANGPT2 mRNAs [44]. ANGPTs were detected in cytoplasmic vesicles of basophils and their activation induced the release of ANGPT1. Human basophils can also release hepatocyte growth factor (HGF) [45]. The latter findings suggest that human basophils can modulate angiogenesis and lymphangiogenesis [42, 46, 47]. Basophils also produce CXCL8 [48] which can contribute to epithelial-to-mesenchymal transition in tumors [49]. Interestingly, human [50] and mouse (Schiavoni and Mattei, unpublished observations) basophils release granzyme B which possesses cytotoxic effects on cancer cells [51, 52]. Mouse, but not human [53], basophils represent an important source of TNF-α [18]. Mouse [54, 55], but not human, basophils produce IL-6 [48]. These findings highlight some of the similarities and differences between human and mouse basophils as a source of cytokines.

2.3 Are Mouse and Human Basophils Antigen-Presenting Cells (APCs)?

Activated human [32, 33] and mouse basophils [25, 53] produce large quantities of IL-4. In mice it has been shown that, under certain experimental conditions, basophils migrate to lymph nodes and secrete IL-4, promoting the differentiation of naive $CD4^+$ T cells toward Th2 cells [56]. Three independent groups reported that murine basophils express MHC class II (MHC-II) and costimulatory molecules (i.e., CD80, CD86, and CD40), which are necessary for antigen presentation to naive T cells [57–59]. These studies suggested that mouse basophils can function dually as antigen-presenting cells (APCs) and IL-4-producing cells, driving Th2 cell differentiation, even in the absence of classical APCs [i.e., dendritic cells (DCs)]. By contrast, subsequent studies demonstrated the critical role of DCs, but not basophils, in Th2 differentiation [60–62]. Thus, the functional significance of basophils as APCs remained highly controversial [63]. The group of Karasuyama recently reported an unexpected mechanism of MHC-II acquisition by mouse basophils [64]. These cells express little or no MHC-II by themselves, but they can capture peptide-MHC-II complexes from DCs through a mechanism called trogocytosis, in a cell contact-dependent manner. Thus, MHC-II-dressed mouse basophils can provide peptide-MHC-II complexes and IL-4 to naive $CD4^+$ T cells that in turn differentiate to Th2 cells. This finding tends to reconcile, at least in part, some of the discrepancies observed in previous studies.

Resting human peripheral blood basophils express little or no HLA-DR, but they can be induced to express it when activated in vitro with

stimuli, such as cytokines [59, 65–67]. Nevertheless, human basophils did not induce antigen-specific T-cell proliferation [67–69]. Human peripheral blood basophils do not express HLA-DR and co-stimulatory molecules (CD80 and CD86) [68, 70, 71]. It would be interesting to investigate whether human basophils can acquire peptide-HLA-DR complexes from DCs through trogocytosis and function as APCs, as observed with murine cells.

2.4 Basophil-Deficient Mice

For decades the absence of basophil-deficient mouse hampered the advance of basophil research. During the last years several models of basophil-deficient mice have been developed. Initial experimental studies employed in vivo administration of antibodies that deplete basophils in mice to study the role of these cells. These antibodies recognize either the FcεRI (clone MAR-1) [72] or the activating receptor CD200 receptor 3 (CD200R3) (clone Ba103), which are both expressed by basophils and mast cells. Although both antibodies can efficiently deplete basophils in vivo, they can also activate mast cells and can cause anaphylaxis [62, 73]. Furthermore, the depletion of basophils by Ba103 is FcR dependent and might therefore activate myeloid cells and natural killer (NK) cells [74]. MAR-1 also depletes a subset of FcεRI-expressing DCs [60]. Several functions have been attributed to basophils based on studies using these depleting antibodies [59, 75]. For example, this experimental approach has led to the conclusion that basophils have a role as APCs during Th2 cell polarization [58, 59]. Similarly, it has been suggested that basophils can cause IgG_1-mediated anaphylaxis [76] and that they contribute to protective immunity against *Trichuris muris* [57]. More recently, several new mouse strains with constitutive or diphtheria toxin (DT)-inducible depletion of basophils have been generated [77]. Genetically engineered basophil-deficient mouse models include $Mcpt8^{DTR}$ [8], Mcpt8Cre [62], Basoph8 [78], BAS-TRECK [79], and $Runx1^{P1N/P1N}$ mice [80]. These new genetically engineered basophil-deficient mice allowed to deepen our knowledge on the in vivo role of these cells in different pathophysiological conditions.

2.5 Peripheral Blood Basophils and Human Cancer

Basophilia is frequently observed during the accelerated phase of chronic myeloid leukemia (CML) [81]. The transcription factor IKAROS is absent or reduced in bone marrow blasts from most patients with advanced CML [82]. Forced expression of the dominant-negative isoform of IKAROS in $CD34^+$ cells from patients with chronic CML resulted in disrupted IKAROS activity and enhanced ability to differentiate into basophils [82]. The latter findings suggest that a loss of IKAROS contributes to myeloid disease progression in CML with basophilia. It has been reported that basophils from patients with CML specifically express abundant HGF, which promotes CML cell expansion in an autocrine fashion [45]. A study using a mouse model of CML demonstrated that basophil-like leukemia cells contribute to CML development by providing the chemokine CCL3 [83]. In this model CML development induced a marked accumulation of basophil-like leukemia cells that produced CCL3 in the bone marrow. Basophil-derived CCL3 negatively regulated the proliferation of normal hematopoietic stem/progenitor cells and supported the predominant expansion of leukemia cells [84]. Indeed, basophil depletion prevented the development of CML. Basophilia appears to be an independent risk factor for evolution of myelodysplastic syndrome to acute myeloid leukemia [85, 86].

Circulating basophils have also been associated with certain solid tumors [87]. For instance, basopenia appears to be associated with worse prognosis of colorectal cancer [88]. By contrast, peripheral blood basophils have no predictive role in breast cancer [89] and oral squamous cell carcinoma [90]. In a mouse model of breast cancer, circulating basophils appeared to exert a protective role in the formation of metastases [91].

2.6 Basophils in Tumor Microenvironment of Human Lung Adenocarcinoma

There is compelling evidence that basophils can migrate into the sites of inflammation in mice [8] and in humans [9–12, 92]. Basophils can also be recruited into TMEs by several chemotactic molecules produced by tumor and immune cells [6, 41, 93–97] (Fig. 2.1). Lavin and collaborators compared the immune landscape in peripheral blood and in TME of patients with early (stage I) lung adenocarcinoma by single-cell analysis [13]. Basophils were present in both TME and noninvolved lung parenchyma as early as in stage I adenocarcinoma. They found quantitative and qualitative differences in basophils present in peripheral blood when compared to cells in TME and noninvolved lung tissue. Interestingly, a small percentage of basophils in TME and in noninvolved lung parenchyma expressed PD-L1. This study elegantly demonstrated, as early as in stage I disease, that lung adenocarcinoma lesions were accompanied by marked alteration of immune cells, including basophils, in TME.

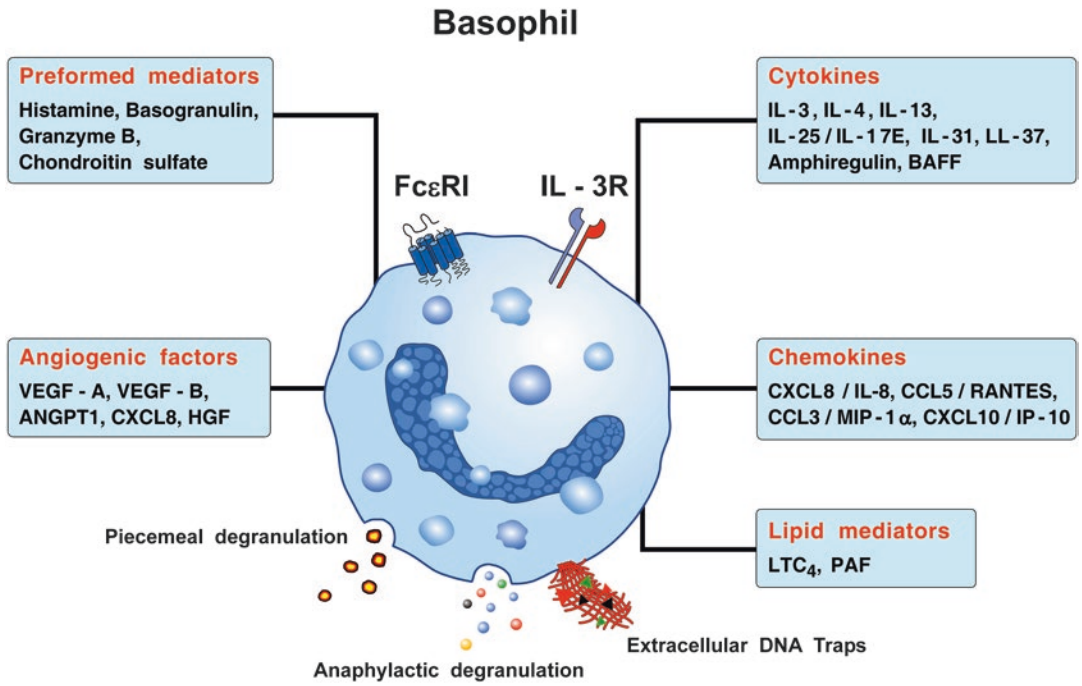

Fig. 2.1 Proinflammatory and immunoregulatory mediators released from human basophils. These cells express a variety of receptors that regulate their development, homeostasis, and effector functions on the cytoplasmic surface. Basophils express the high-affinity receptors for IgE (FcεRI) which bind IgE with high affinity. These cells also express the α-chain (IL-3Rα/CD123) and a common βc (CD131) that bind IL-3, which plays a major role in basophil development [137, 138]. Secretory granules of basophils contain histamine complexed with chondroitin sulfate, basogranulin [139], granzyme B [50], and tryptase at levels of less than 1% of human mast cells. Immunologic activation of basophils leads to the release of histamine, basogranulin, and granzyme B and the production of IL-4 [32, 33, 35, 36, 140], IL-13 [37–39], IL-3 [24], VEGF-A and VEGF-B [41], ANGPT1 [44], and HGF [45]. Basophil activation induces the de novo synthesis of cysteinyl leukotriene C_4 (LTC_4) [141] and platelet-activating factor (PAF) [142]. Human basophils produce several chemokines [48] and, under specific conditions, can release IL-25/IL-17E, IL-31, LL-37, amphiregulin, and B-cell-activating factor (BAFF) [7, 143–145]. Human basophils activated by a variety of IgE- and non-IgE-mediated stimuli rapidly release membrane-free granules to the external microenvironment (anaphylactic degranulation). Basophils infiltrating the sites of inflammation can release packets of granule contents (piecemeal degranulation) [5]. Human basophils are also able to form extracellular DNA traps upon IL-3 priming and subsequent immunologic activation [146, 147]

A recent elegant study found that during lung development basophils acquire a unique phenotype, due to local exposure of specific signals (i.e., IL-33, GM-CSF), which regulates alveolar macrophage maturation and function [55]. The authors found that basophils represented a significant proportion of immune cellular composition during lung development. These cells broadly interacted with immune (e.g., monocytes, macrophages, neutrophils, ILCs) and nonimmune cells (e.g., endothelial cells, epithelial cells, fibroblasts) through the production of several cytokines (e.g., IL-4, IL-6, IL-13, TNF-α). Interestingly, the gene expression profile of lung basophils differed from that of blood-circulating basophils and was characterized by a unique gene signature including *IL6, IL13, Cxcl2, Tnf, Osm, and Ccl4*. The authors attributed the modulation of phenotype of lung basophils mainly to IL-33 and with minor contribution of GM-CSF. Moreover, lung basophils promoted M2 polarization of lung macrophages. Finally, the authors reported that basophils isolated from both the lung and the TME of mice implanted with B16 melanoma cells expressed several cytokines (e.g., *IL4, IL6, Osm, IL13*). This important study demonstrates that lung basophils acquire the expression of several cytokines and growth factors, critical for immune and nonimmune cell functions due to the exposure to lung-specific signals. Collectively, the results of these two important studies indicate that tissue-resident basophils can acquire distinct features from peripheral blood basophils and can play important roles in lung development and presumably in human lung cancer.

Schroeder and collaborators recently demonstrated that highly purified human basophils release histamine and secrete IL-4/IL-13 when co-cultured with the epithelial cell line, A549, an adenocarcinoma of lung origin [29]. This study further determined that an IgE-binding lectin (expressed on the A549 cells) was likely responsible for this activation of basophils, with all indicators pointing to galectin-3. Indeed, a follow-up study from the same group showed that A549 clones generated to be deficient in galectin-3 protein no longer activated basophils for these responses [98]. In addition, basophils co-cultured with microspheres coated with galectin-3 protein [but not bovine serum albumin (BSA) or galectin-9] likewise secreted IL-4/IL-13. However, when added exogenously as a soluble protein, galectin-3 only marginally activated basophils and only at relatively high concentrations, suggesting that the lectin may better facilitate cellular activation when immobilized on a matrix, whether epithelial cells (A549) or microspheres. While more studies are needed, the significance of these findings currently points to the fact that galectin-3 is now implicated as a biomarker and/or factor contributing to the pathogenesis of a wide range of conditions, particularly in cancer and cardiovascular disease, but also in autoimmunity (lupus erythematosus), wound healing, and asthma [99]. Evidence that galectin-3 modulates the immune responsiveness of basophils (and potentially other IgE-bearing cells) could offer novel insight into how these cells might be activated in the absence of specific IgE/allergen interactions. Indeed, this mechanism of activation could prove relevant to the recent findings showing IL-4-producing basophils in lupus erythematosus [100] and cancer [101].

2.7 Basophils in Experimental Melanoma

The role of basophils has been evaluated in a mouse model of melanoma [102]. A model of T_{reg} depletion was associated with increased production of IL-3, which caused basophil infiltration in the TME. This model was associated with complete rejection of tumors, which was found to be dependent on chemokines (i.e., CCL3 and CCL4) produced by infiltrating basophils. These chemokines caused tumor infiltration of $CD8^+$ T cells, which presumably exerted cytotoxic effect. Administration of MAR-1 (i.e., anti-FcεRI) to deplete basophils prevented the rejection of tumors. The authors

concluded that basophils were required for tumor eradication. As previously mentioned, MAR-1 can partially deplete also mast cells and DCs that express FcεRI. Thus, the role of basophils in melanoma rejection will need to be confirmed using genetically engineered basophil-deficient mice.

In a series of ongoing experiments, we have investigated the direct antitumor activities of bone marrow-derived murine basophils following activation with IL-33, an alarmin known to activate the tumoricidal functions in eosinophils [103]. We observed that activation of basophils with IL-33 results in upregulation of granzyme B transcripts (Fig. 2.2a) and surface expression of the degranulation marker CD63 (Fig. 2.2b). In addition, when IL-33-activated basophils were co-cultured with B16.F10 murine metastatic melanoma cells, we found substantial restriction of tumor cell growth, compared to melanoma cells cultured with resting basophils (Fig. 2.2c). These preliminary observations suggest that under proper stimulation basophils can acquire tumoricidal properties and indicate that basophils may orchestrate antitumor immune responses at multiple levels. These interesting findings deserve further investigations in vitro and in vivo.

2.8 Basophils in Experimental and Human Pancreatic Cancer

Ann Dvorak demonstrated the presence of basophils in the stroma of pancreatic cancer showing distinctive ultrastructural morphological features of piecemeal degranulation [5]. The role of basophils and their mediators in experimental and human pancreatic cancer has been elegantly investigated by Protti and collaborators [101]. In a large cohort of pancreatic ductal adenocarcinoma (PDAC), they found basophils expressing *IL4* in tumor-draining lymph nodes (TDLNs) of PDAC patients. Basophils in TDLNs served as an independent prognostic biomarker of patient survival after surgery. The authors confirmed the recruitment of basophils in TDLNs in a mouse model of pancreatic cancer. In this model activated cancer-associated fibroblasts (CAFs) released TSLP which activated DCs. These cells induced IL-3 release from $CD4^+$ T cells. IL-3 activated basophils to produce IL-4. CCL7, produced by DCs and $CD14^+$ monocytes, was, at least in part, responsible for basophils migration from arterial blood into TDLNs. In this setting, basophils were the major source of IL-4 presum-

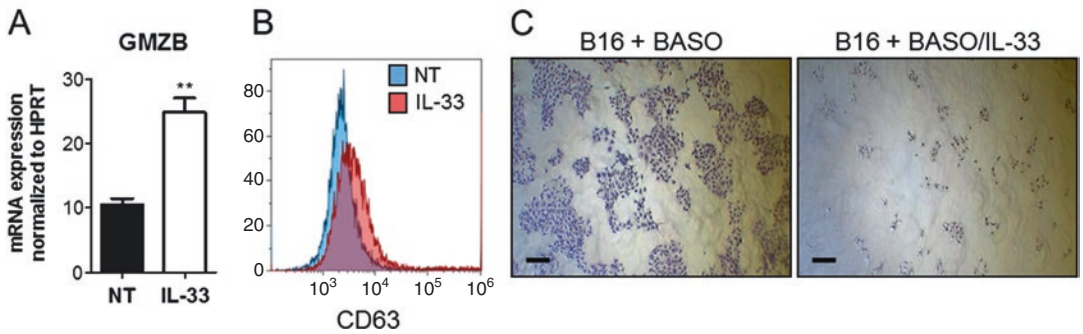

Fig. 2.2 Activation of basophils with the alarmin IL-33 promotes tumoricidal functions. Basophils were generated by culture of murine bone marrow cells in medium containing IL-3 (2 ng/mL) for 10 days. Basophils were then harvested and cultured in medium alone or with added IL-33 (100 ng/mL) for 18 h. (**a**) qRT-PCR analysis of expression of granzyme B. Mean expression values in triplicate samples ± SD are shown. $^{**}P < 0.01$, Wilcoxon's *t* test. (**b**) Flow cytometry analysis of surface CD63 expression. (**c**) Growth of B16.F10 melanoma cells after 24 h co-culture with basophils alone or with added IL-33 (100 ng/mL). At the end of the co-culture, adherent tumor cells were stained with crystal violet to visualize tumor-covered area. Scale bar, 150 μm

ably contributing to both Th2 and M2 polarization in pancreatic cancer. The authors concluded that basophils and their mediator (i.e., IL-4) play a relevant pro-tumorigenic role in PDAC progression.

2.9 Conclusions and Outstanding Questions

Although peripheral blood basophils represent less than 1% of human leukocytes, there is compelling evidence that they can infiltrate the site of inflammation [9, 10, 18, 92, 104]. Importantly, basophils can be found in TME in human gastric cancer [11, 12] in early lung adenocarcinoma [13] and in PDAC [101]. Moreover, basophils can be identified in experimental melanoma [102] and in TDLNs in a model of pancreatic cancer [101]. The mechanisms regulating the trafficking of basophils into TDLNs, and their contributions to the evolving microenvironment of the metastatic niche, remain poorly understood. Single-cell RNA-seq will be necessary to characterize the basophils in TDLNs.

Human basophils release several angiogenic factors such as VEGF-A and VEGF-B [41], CXCL8 [49], ANGPT1 [44], and HGF [45]. CXCL8 and TNF-α can induce epithelial-to-mesenchymal transition [49, 105]. IL-4 and IL-13 can favor M2 polarization of tumor-associated macrophages [106, 107]. On the other side, basophils can exert anti-tumorigenic effects by releasing granzyme B [51, 52] and TNF-α [18] that possess cytotoxic effects on cancer cells. Moreover, histamine promotes DC maturation and can inhibit experimental tumor growth [108–110]. These findings suggest that basophils have the potential to play an anti-tumorigenic or a pro-tumorigenic role in tumor immunity (Fig. 2.3).

There is increasing evidence that basophils in peripheral blood differ from those found in TME [13]. This is not surprising because peripheral blood basophils circulate at physiological pH and normoxia, whereas peritumoral and intratumoral basophils are embedded in a hostile microenvironment characterized by increased levels of lactate, PGE_2, adenosine, IFN-α, and a low pH [111–114], which can profoundly influence basophil phenotype [115, 116]. Studies on basophil biology are usually performed at physiological pH and normoxia. It will be important to investigate how the tumor milieu activates/modulates the production of mediators and the expression of receptors in tumor-infiltrating basophils. Analyses of basophils in TDLNs have only recently began [101]. High-dimensional analysis, particularly single-cell RNA-seq, will be necessary to characterize basophils in TDLNs and in TME.

There is increasing evidence that immune cells in TME can play different roles in early and late stages of tumorigenesis [115, 117–120]. Basophils have been identified in the immune landscape of tumor and noninvolved lung tissue in early lung adenocarcinoma [13]. The hypothesis that basophils and their mediators play diverse roles in different phases of tumor initiation and growth deserves investigation.

Several models of basophil-deficient mice have been described. Initial studies were conducted using administration of antibodies (i.e., MAR-1 and Ba103) that transiently deplete basophils [72, 121]. However, these models can interfere with other immune cells [60, 74]. Recently, several mouse strains with constitutive or inducible depletion of basophils have been described. Studies using antibody-depleted basophils [102] and genetically engineered models [101] yielded apparently discordant findings on the role of basophils in cancer. Results obtained with basophil-deficient mouse models should be interpreted with caution because even new mouse mutants showed some hematological abnormalities. Perhaps, future studies attempting to evaluate the basophil role in a complex and heterogeneous disorder, such as cancer, should be performed using more than one model of basophil deficiency.

IgE is an ancient and highly conserved immunoglobulin isotype found in mammals. There is evidence that IgE has evolved to provide protection against infections and environmental toxins [6, 18, 122, 123]. Basophils express FcεRI which binds IgE [2, 4]. IgE has been suggested to play a protective role in tumor growth [124, 125]. In a

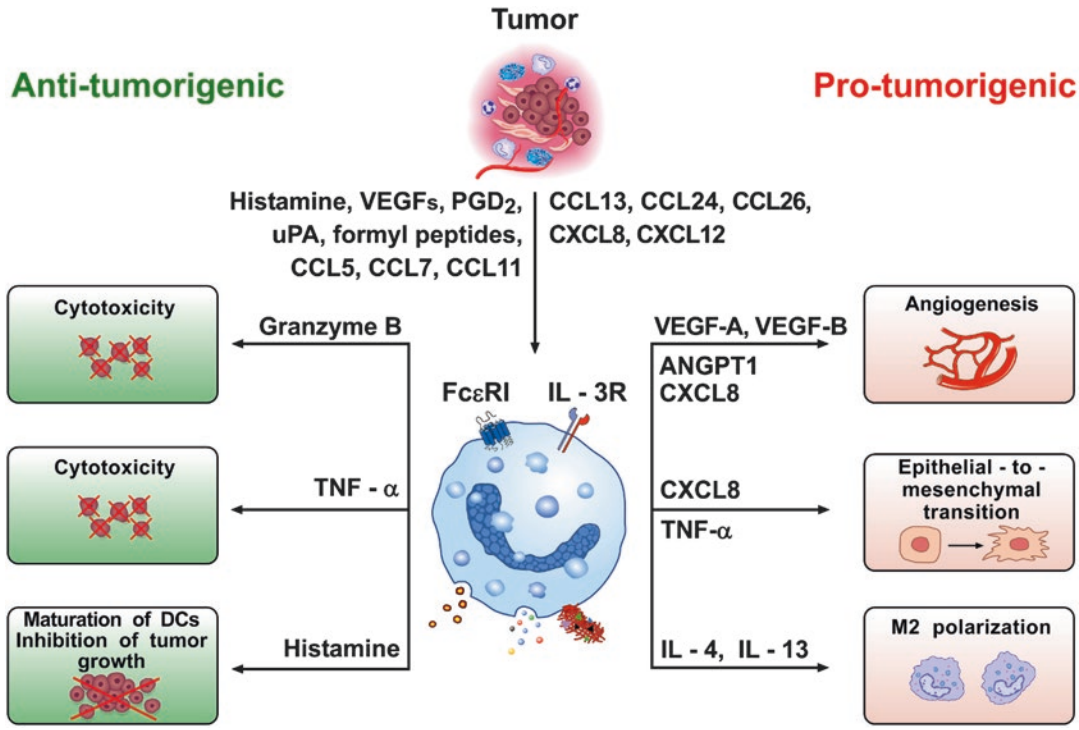

Fig. 2.3 Basophils can be recruited into tumor microenvironments (TMEs) by several chemotactic molecules [e.g., VEGFs, histamine, prostaglandin D_2 (PGD_2), urokinase plasminogen activator (uPA), formyl peptides, CCL5, CCL7, CCL11, CCL13, CCL24, CCL26,CXCL8, CXCL12] produced by tumor or immune cells [6, 41, 93–97]. Basophils in the TMEs can exert anti-tumorigenic and/or pro-tumorigenic roles. Basophils can exert direct tumor cytotoxic effects via granzyme B [50] and TNF-α [18]. Histamine promotes dendritic cell (DC) maturation and inhibits tumor growth [108–110]. On the other side, basophils represent a potentially major source of several angiogenic molecules (VEGF-A, VEGF-B, ANGPT1, CXCL8, and HGF) [44, 45, 48]. CXCL8 and TNF-α can induce epithelial-to-mesenchymal transition [49, 105]. IL-4 and IL-13 can favor M2 polarization of tumor-associated macrophages [106]

mouse model of skin tumorigenesis, topical exposure to a common xenobiotic and carcinogen (i.e., 7,12-dimethylbenzatracene: DMBA) caused a potent IgE response that provided protection against carcinogenesis [126]. Although the mechanism by which IgE inhibited tumor growth in this model remains to be determined, the authors speculated that it "might involve soluble factors and/or cytotoxicity mediated by basophils." Further studies should investigate the role, if any, of IgE-mediated activation of basophils in experimental and human tumors.

Tumor cells evade host immune attack by expressing several checkpoints, such as programmed cell death-1 (PD-1) and PD-1 ligands (PD-L1 and PD-L2) [127, 128]. Monoclonal antibodies targeting the PD-1/PD-L1 pathway unleash antitumor immunity and have revolutionized the treatment of cancer [129, 130]. PD-L1 is also expressed on the surfaces of various immune cells such as macrophages and DCs [13, 131–133], mast cells [13, 134, 135], and basophils in TME [13]. Recent evidence indicates that PD-L1 expressed in immune cells within TME, rather than on tumor cells, plays an essential role in immune checkpoint blockade therapy [132, 133]. Moreover, secreted PD-L1 can interfere with immune checkpoint therapy in cancer [136]. An interesting task will be to investigate the role of PD-L1$^+$ basophils in TME in the context of immune checkpoint blockade.

In conclusion, the roles of basophils in experimental and human cancer have been little investigated and are currently largely unknown.

The elucidation of basophils in tumor immunity will demand studies on increasing complexity beyond those assessing basophil density and their microlocalization in TME. There are several unanswered fundamental questions to be addressed in experimental models and clinical studies before we understand whether basophils are an ally, adversary, or even innocent bystanders in cancers.

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