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Cancer Immunol Res 2014;2:1-8.

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Abstract

Eosinophils have long been known to infiltrate tumors, and in most cases, this is associated with an improved prognosis. However, the reasons behind this infiltration and the mechanism of action of the eosinophil have remained elusive. In this article, we explore the biology of eosinophils and examine their function in homeostasis and disease states, specifically focusing on what is currently known about the association of the eosinophil with cancer. *Cancer Immunol Res; 2(1); 1–8. ©2014 AACR.*

Disclosure of Potential Conflicts of Interest

M.E. Rothenberg has an ownership Interest in Immune Pharmaceuticals and Receptos; is a consultant/advisory board member of Immune Pharmaceuticals, Norvatis, Pluristem Therapeutics, and Receptos; and has royalty to reslizumab (Teva Pharmaceuticals). No potential conflicts of interest were disclosed by the other author.

CME Staff Planners' Disclosures

The members of the planning committee have no real or apparent conflicts of interest to disclose.

Learning Objectives

Eosinophils, discovered over 150 years ago, are present in various lesions, and tumor-associated tissue eosinophilia has been correlated with both good and bad prognosis for cancer. Upon completion of this activity, the participant should gain a basic knowledge of the biology of eosinophils, and their potential roles in homeostasis and in diseases. A broader understanding of these granulocytic leukocytes and their interaction with other immune cells will inform research on their potential to affect tumors and to improve cancer therapy.

Acknowledgment of Financial or Other Support

This activity does not receive commercial support.

Eosinophil Biology

All vertebrates have eosinophils, which are blood cells identified by the capacity to incorporate acidophilic stains and characterized by large secretory granules within the cytoplasm. However, there are variations across species in eosinophil origin, differentiation, and development. In general, eosinophils are granulocytic leukocytes derived from bone marrow hematopoietic progenitors. Mature eosinophils enter the blood stream and migrate to seed various tissues and organs, where they reside and help maintain homeostasis. In multiple disease states, inflammatory mediators, including cytokines and chemokines, stimulate the migration of eosinophils from the bone marrow, their localization to affected sites, and their activation in response to infection and tissue damage (reviewed in refs. 1–3). This cancer immunology primer focuses on aspects of eosinophil biology with the potential to inform research on endogenous and therapy-induced host responses to cancer.

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doi: 10.1158/2326-6066.CIR-13-0196

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Receptors and their ligands

Eosinophils express a large number of surface molecules, including adhesion molecules, chemokine receptors, cytokine receptors, immunoglobulin receptors, Toll-like pattern recognition receptors (TLR, PRR), and siglec-lectin receptors (reviewed in refs. 1–3). Three cytokines, interleukin (IL)-3, IL-5, and granulocyte macrophage colony-stimulating factor (GM-CSF), are critical for regulating eosinophil development. IL-5 is necessary and sufficient for the selective expansion of eosinophils (4) as systemic levels elicit both blood and tissue eosinophilia, whereas localized production promotes tissue eosinophilia. Conversely, IL-5 deficiency leads to a marked reduction in the levels of eosinophils in the blood and peripheral tissues (5). In addition to eosinophils, IL-3 and GM-CSF also regulate the development of other hematopoietic cells such as neutrophils, mast cells, dendritic cells, and macrophages. Moreover, eosinophils not only express receptors for these and other cytokines but also produce cytokines to maintain their own activation and survival (Fig. 1).

The three canonical eosinophil chemokines are eotaxin-1 (CCL11), eotaxin-2 (CCL24), and eotaxin-3 (CCL26), which act mainly via the CC chemokine receptor 3 (CCR3) that is expressed at relatively high levels on eosinophils (6,7). Other important soluble factors that impact eosinophils include IL-2, CCL5 (RANTES), CCL7, and CCL13 [monocyte chemotactic protein 3 and 4 (MCP-3 and MCP-4); reviewed in refs. 1, 2]. It is important to note that IL-13 is a major inducer of eotaxins and

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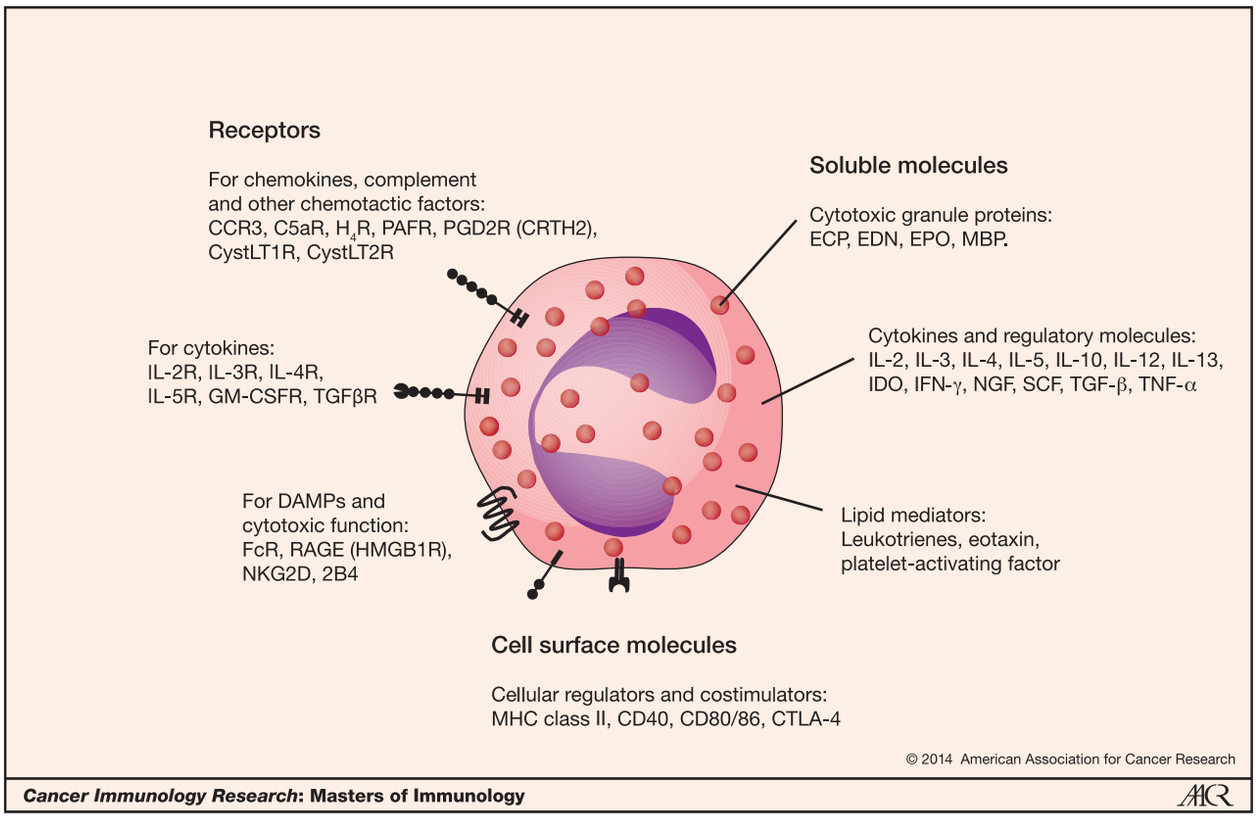

Figure 1. Surface and secreted molecules of eosinophils. Eosinophils express cell surface molecules important for adhesion and antigen presentation and receptors for immunoglobulin, stress-induced pattern recognition, chemokines, and cytokine signaling. Eosinophils also secrete a wide variety of molecules important for their immune function, including cytotoxic granule proteins, cytokines, chemokines, lipid mediators, neurotransmitters, and DNA traps.

that recent attention has focused on the key role of innate helper lymphoid cells (ILC) in regulating eosinophils by producing IL-5 and IL-13, particularly under homeostatic conditions in the gastrointestinal (GI) tract (8).

In addition to receptors for cytokines and chemokines, eosinophils also express receptors for mediators of recruitment to tissues, including cysteinyl leukotriene 1 and 2 (CysLT1R and CysLT2R), prostaglandin D2 (PGD2R), and the platelet-activating factor (PAFR; refs. 9, 10). PGD2R is also known as the "chemoattractant receptor-homologous molecule expressed on T helper type 2 (T_H2) cells" (CRTH2) and appears to direct both T_H2 cell and eosinophil/basophil recruitment (11). Eosinophils also express high levels of the histamine H_4 receptor, which has been shown to be important in chemotaxis and activation (12).

Granule proteins

The cytotoxic activity of eosinophils is mediated through secretory granules. Eosinophil granules comprise a crystalloid core composed of major basic protein 1 and 2 (MBP-1, MBP-2) and a matrix composed of eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and eosinophil peroxidase (EPO; ref. 13).

The cytotoxic effect of the MBPs is likely from increased membrane permeability via surface charge interactions (reviewed in ref. 1). ECP has cytotoxic, helminthotoxic, and ribonuclease activity. ECP induces toxic pores in the membranes of target cells, facilitating the entry of other cytotoxic molecules. EDN also has ribonuclease activity and is an endogenous ligand of TLR2 that can activate myeloid dendritic cells via the TLR2/MyD88 signaling pathway (14). EPO catalyzes the oxidation of halides, pseudohalides, and nitric oxide to form reactive oxygen and nitrogen species, which can promote oxidative stress and subsequent cell death by apoptosis and necrosis (reviewed in refs. 1, 2).

Infection

An archetypal function of eosinophils is a role in host defense against parasites. Eosinophils can mediate antibody-dependent cellular cytotoxicity (ADCC) against helminths (reviewed in ref. 1). The eosinophil granule proteins ECP and EDN degrade single-stranded RNA viruses via ribonuclease activity; viruses including rhinovirus, respiratory syncytial virus (RSV), and parainfluenza virus induce eosinophil release of EPO in the presence of CD4 T cells and antigen-presenting cells (15). Eosinophils appear to be important in the innate immune response during bacterial sepsis originating from an intestinal source. In response to bacteria, the complement component C5a, or CCR3 ligands, eosinophils expel mitochondrial DNA traps that contain ECP and MBP (16).

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Regulatory cells

Eosinophils interact with various innate immune cells (the most prominent of which are mast cells and myeloid-derived dendritic cells) and adaptive immune cells (primarily T cells) (reviewed in refs. 1, 2). Eosinophils express MHC class II and co-stimulatory molecules (CD40, CD80/86, CTLA-4) that regulate T-cell activation, cytokine secretion, and proliferation (17–19). They can process and present a variety of antigens derived from bacteria, viruses, parasites, and allergens to promote T-cell proliferation. Eosinophils can produce and secrete most cytokines capable of promoting T-cell proliferation and activation. These leukocytes are also involved in T-cell polarization via indoleamine 2,3-dioxygenase (IDO), which promotes polarization via T_H1 cell apoptosis (20) and is important for regulatory T-cell (Treg) skewing (21). The secreted granule protein EDN can enhance antigen-specific T_H2–biased immune responses (14). EDN can also induce the migration and maturation of dendritic cells. There is evidence of eosinophil trafficking into the draining lymph nodes with localization in the T-cell–abundant paracortical regions (reviewed in ref. 1).

Eosinophils can also regulate mast cell functions through the release of granule proteins and cytokines. MBP, EPO, and ECP trigger mast cells to release histamine, TNF-α, IL-8, GM-CSF, and prostaglandin 2 (PGD-2). Chymase, a mast cell protease, triggers production of eosinophil-derived stem cell factor (SCF), which is a crucial mast cell growth factor. Eosinophils secrete nerve growth factor (NGF), a cytokine involved in mast cell survival and activation (reviewed in refs. 1, 22). Interestingly, patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome (HES) characterized by elevated serum tryptase levels are more likely to develop end-organ fibrosis (23), suggesting that mast cells may have an important role in eosinophil-mediated fibrosis. In addition, eosinophils are a major source of TGF-β, a molecule known to have broad immunoregulatory roles on multiple immune cell types, including macrophages, T_H1, T_H2, and B cells (24).

Roles in homeostasis

The GI tract, spleen, lymph nodes, thymus, mammary glands, adipose tissue, and uterus are rich in eosinophils. Their presence in these organs during normal conditions suggests a role for eosinophils in some homeostatic processes (reviewed in refs. 1, 2).

The GI system is the predominant location of eosinophils. The majority of peripheral eosinophils traffic into the lamina propria of the GI tract in all segments except the esophagus, and this trafficking occurs independent of classic lymphocytes and enteric flora but is dependent on a new class of immature lymphoid cells, referred to as type 2 innate lymphoid cells (ILC2), as ILC2 make abundant amounts of the classic T_H2 cell cytokines IL-4 and IL-13. Thus, eosinophil trafficking has a unique mode of regulation compared with other leukocytes. This localization is regulated by the constitutive expression of eotaxin-1 and the circadian expression of IL-5 and IL-13 by ILCs (8).

The uterus is home to a large number of eosinophils, which are mainly localized to the endometrial stroma and at the endometrial–myometrial junction. Eotaxin-1–deficient mice have a deficiency of eosinophils in the uterus and delayed estrus onset. In the mammary gland, increased eotaxin-1 expression co-occurs with eosinophil infiltration into the terminal end bud. The presence of eosinophils in the mammary gland has been associated with formation of the terminal end bud and the branching of the ductal tree.

Thymic eosinophils are recruited during the neonatal period. Subsequently, an increase in thymic eosinophil levels corresponds to the onset of thymic involution. Interestingly, thymic eosinophils may be able to present antigens, and their temporal and spatial regulation in the thymus suggest a possible role in negative selection of double-positive $CD4^+CD8^+$ thymocytes, perhaps through the promotion of apoptosis.

In adipose tissue, eosinophils are important for the maintenance of glucose metabolic homeostasis. A loss of adipose tissue–associated eosinophils leads to insulin resistance and fat accumulation due to a decrease in the level of alternatively activated macrophages, which requires the eosinophil production of IL-4 and IL-13 (25).

Disease states

Eosinophils are involved in numerous inflammatory fibrotic pathologies. The eosinophil granule proteins MBP, EPO, and ECP are toxic to diverse tissues, and hypereosinophilia is known to induce tissue damage and dysfunction in the brain, heart, skin, and lung (reviewed in refs. 1–3, 26).

Eosinophils are important for the development of asthma-associated airway hyperresponsiveness (AHR; ref. 27; reviewed in refs. 1, 2) and are a principal source of CysLTs in the asthmatic bronchial airway (28). These leukotrienes can initiate mucus hypersecretion, AHR, and edema. MBP has also been shown to be cytotoxic to airway epithelial cells and may be at least partly responsible for the tissue damage associated with eosinophil infiltration in bronchial mucosa in asthma. Importantly, eosinophils have been implicated in the regulation of pulmonary T-cell responses (29) and appear to be required for complete T_H2 lymphocyte cytokine production and allergen-induced mucus production in the lung (30). Within the past few years, attempts have been made to further classify asthma phenotypes; one subtype is eosinophilic asthma, which is often a severe, steroid-refractory disease (31). Multiple studies have supported the use of anti–IL-5 therapy for patients with this form of asthma (reviewed in refs. 2, 3, 26). Moreover, peripheral blood eosinophils and eosinophil granule protein levels are increased and correspond with disease activity in most patients with atopic dermatitis, and eosinophil granule proteins have been shown to be deposited in lesional skin (32).

Eosinophil accumulation in the GI tract is a common characteristic of numerous disorders, including gastroesophageal reflux disease, inflammatory bowel disease, drug reactions, helminthic infections, HES, eosinophilic GI disorders (EGID), and allergic colitis (reviewed in refs. 2, 3, 26). EGIDs, including eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), and eosinophilic gastroenteritis (EGE), often occur without peripheral blood eosinophilia, indicating the significance of GI-specific mechanisms for regulating local eosinophil levels. While absent in the normal esophagus, eosinophils

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markedly accumulate in the esophagus of patients with EoE. A number of experimental models have provided evidence that eosinophils are key effector cells in EGIDs and contribute to the disease pathology (33).

Cancer

Multiple studies have shown an improved prognosis with tumor-associated tissue eosinophilia (TATE) or evidence of eosinophil degranulation in various types of solid tumors, including colon tumors (34, 35), oral squamous cell carcinoma (SCC; ref. 36), esophageal SCC (37), nasopharyngeal carcinoma (38), penile cancer (39), laryngeal carcinoma, pulmonary adenocarcinoma, bladder carcinoma (40), and prostate cancer (41). This beneficial influence of eosinophils in diverse tumors appears to be independent of other standard prognostic factors (e.g., stage, age, sex, alcohol or tobacco history, histologic grading, vascularization, vascular invasion, and neural invasion).

In contrast, TATE is associated with poor prognosis in Hodgkin lymphoma. Interestingly, a large portion of the Hodgkin lymphoma tumor mass consists of an inflammatory infiltrate, suggesting significant immune dysregulation by this B-cell tumor (42). There have been conflicting reports of TATE as a poor prognostic indicator in other solids tumors (oral SCC and cervical carcinoma), although it has been suggested that this discrepancy may be related to differences in study methods and design (43). There is at least one eosinophil-knockout mouse model that shows TATE as a risk factor for experimentally induced oral SCCs (44).

Antitumor responses

Antitumor cytotoxic responses via degranulation are suggested by the observation of granule proteins in the local vicinity of tumors (45), but the tumoricidal effects of eosinophils are not well understood. In mice with peripheral blood eosinophilia, there is a substantial decrease in both tumorigenicity and tumor progression concomitant with an abundant tumor eosinophilia. In comparison, mice with decreased levels of eosinophils (*CCL11*$^{-/-}$) or mice that are completely eosinophil deficient (*IL5*/*CCL11*$^{-/-}$ and Δ*dblGATA*) exhibited increased tumorigenicity in association with reduced tumor eosinophilia (46). In humans, eosinophils are frequently observed following immunotherapy with IL-2 (47, 48), IL-4 (49, 50), GM-CSF (51), or tumor vaccination (52).

Necrosis

TATE may develop early and persist throughout tumor development but may be especially prominent in necrotic areas (53). Indeed, cancerous tissues with associated necrosis can induce eosinophil migration *in vitro* and *in vivo* (53, 54). Injection of melanoma cells into mice causes an abundant eosinophilia within the necrotic and capsule regions versus areas of viable tumor (see Fig. 2).

Cytokines

Some tumor cells produce IL-5, IL-3, eotaxin-1, and thymus and activation-regulated chemokine (TARC or CCL17), which can collectively act on the differentiation and/or migration of eosinophils (55–58). In oral cavity SCCs, eosinophils are the main source of eotaxin (59), showing an autocrine-like mechanism for tissue eosinophilia.

In a mouse melanoma tumor model, the immunotherapy-mediated clearance of CTL-resistant lung tumor by T_H2 cells was dependent on eotaxin and STAT. The elimination of these tumors was associated with eosinophil degranulation (60). In another mouse model, tumor cells that were engineered to express IL-4 were rejected or showed reduced growth following implantation into syngeneic hosts. These IL-4–expressing tumor cells induced an eosinophil and macrophage-rich tumor infiltrate, and eosinophils were critical for tumor killing (50). Consistent with these results, the administration of recombinant IL-4 to patients with cancer in phase 1 clinical trials showed evidence of eosinophil degranulation in a dose-dependent manner (49).

IL-2 immunotherapy is used to treat both melanoma and renal cell carcinoma. The antitumor effect of systemic IL-2 therapy is also correlated with degranulation of eosinophils within the tumors (47, 48); this degranulation may occur via antibody-dependent mechanisms (61). In addition, IL-25 has been shown to have antitumor activity *in vivo*; IL-25 treatment leads to eosinophilia, which is correlated with tumor suppression (62).

Damage-associated molecular patterns and cytotoxic cellular receptors

Study of eosinophil recruitment in solid tumors has shown that eosinophil tissue infiltration is mediated by factors released directly from necrotic tumor cells (63). One of the contributing factors is the eosinophil-derived cytokine high-mobility group box 1 (HMGB1; ref. 64). HMGB1 binds to the receptor for advanced glycation end products (RAGE) on eosinophils and triggers eosinophil degranulation (65).

Cancer cells are also known to upregulate stress molecules such as MHC class I–related chain A (MICA), MICB, and the UL16-binding proteins (ULBP). While the cognate NKG2D receptor is normally associated with natural killer (NK) cells and NK cell cytotoxic activity, eosinophils can also be stimulated to express this receptor. Moreover, a blocking anti-NKG2D antibody has been shown to inhibit eosinophil-mediated tumor cytotoxicity (66). Eosinophils have been shown to express 2B4, another receptor that is normally associated with NK cells. Eosinophil 2B4 activation resulted in cytotoxicity against two tumor cell lines, the mouse mastocytoma P815 and EBV-infected B-cell lines (67).

Eosinophil degranulation and cytotoxicity

Eosinophil lysates are cytotoxic to B16 melanoma cells (60). In a colon carcinoma cell line, direct contact between eosinophils and tumor cells was necessary to induce cytotoxicity. This interaction was shown to involve the adhesion molecule CD11a/CD18 and ECP, EDN, TNF-α, and granzyme A (68). Furthermore, eosinophil-derived MBP may be present in histologic sections of lung metastases (60).

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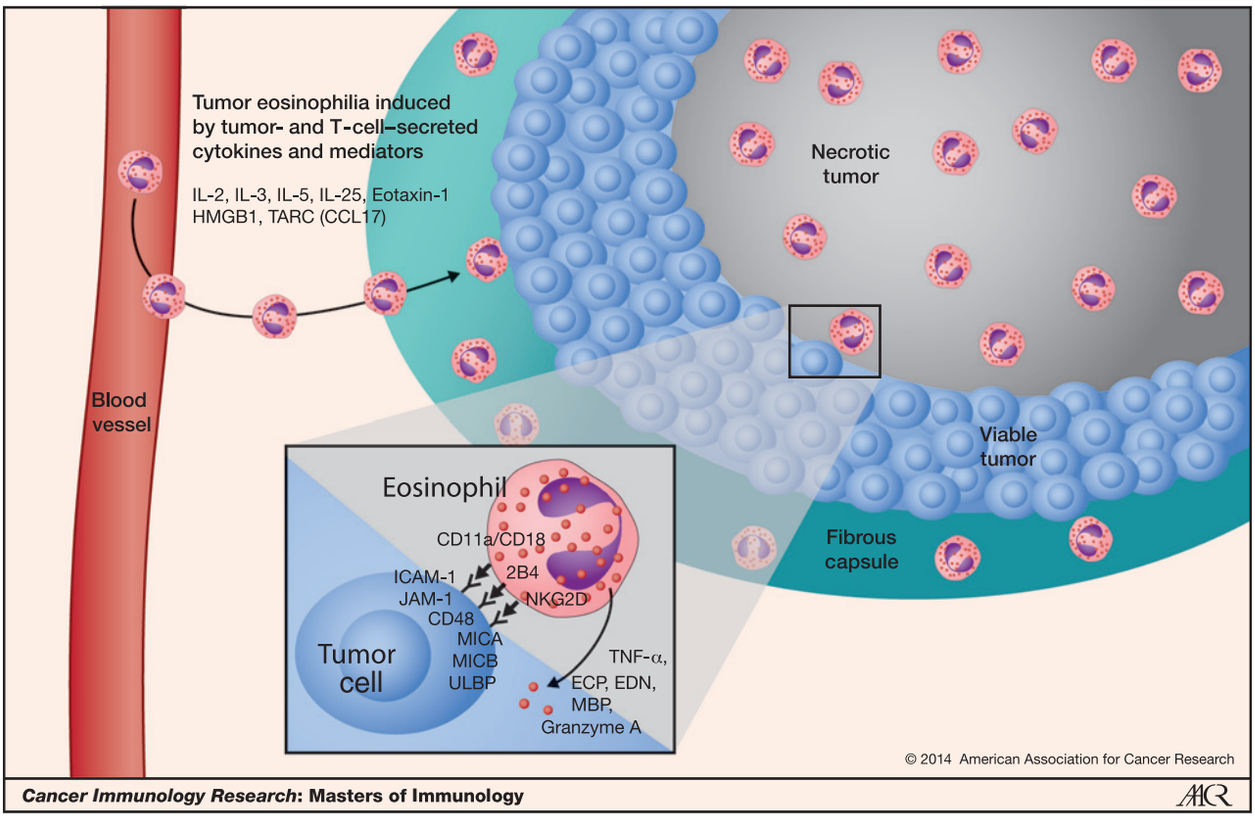

Figure 2. Tumor–eosinophil interactions. Eosinophils infiltrate both the necrotic and fibrous capsules of tumors. Known tumor-associated cytokines related to eosinophil accumulation include IL-2, IL-3, IL-5, IL-25, GM-CSF, eotaxin-1, and HMGB1. Cellular contact and cytotoxicity have been shown for CD11a/CD18 and 2B4 and assumed for NKG2D. The granule proteins ECP, EDN, and MBP have been shown to be involved in tumor cytotoxicity following their release in tumors.

Hypereosinophilic syndromes

HES and chronic eosinophilic leukemia (CEL) are malignancies characterized by sustained, idiopathic hypereosinophilia (>1,500 eosinophils/L). The term CEL is used when the leukemia is a clonal population. A subset of patients with HES have a fusion of the genes encoding FIP1-like 1 (*FIP1L1*) and the platelet-derived growth factor receptor α (*PDGFRA*) as a result of an 800-kb deletion on chromosome 4 (4q12; ref. 69). The fusion product has dysregulated tyrosine kinase activity. In mice, the *FIP1L1-PDGFRA* fusion gene is not sufficient to induce HES but requires IL-5 overexpression (70). Patients with HES respond well to the tyrosine kinase inhibitor imatinib mesylate, which blocks PDGFR signaling (69, 71, 72). Treatment with imatinib mesylate in other patients with HES who lack the fusion protein may also cause a dramatic reduction of eosinophil numbers, suggesting that other, not-yet-identified kinase(s) are also sensitive to imatinib mesylate.

Graft-versus-Host Disease

Graft-versus-host disease (GvHD) can occur after stem cell or bone marrow transplantation from an allogeneic donor. Eosinophilia in the blood and tissue is a common feature of GvHD and contributes to the allogeneic response, as revealed in investigations of GvHD in animal models (73, 74). Studies have shown that eosinophilia is a predictor for acute and chronic GvHD (75, 76). However, the prognostic significance remains controversial, as some studies have shown a favorable correlation with survival (77–79) and others have shown the opposite effect (80). Factors that may underlie these differences include variations in diagnostic criteria and a failure to adequately control for steroid use, which may significantly affect eosinophil levels.

Connection between Cancer and Allergy

The relationship between allergy and cancer is controversial. Eosinophils from allergic donors induce higher levels of tumor cell apoptosis compared with eosinophils from nonallergic donors (68), raising the possibility that the increased activation of eosinophils in allergic patients may mediate antitumor effects. Consistent with this idea, there is some evidence to suggest a possible inverse relationship with allergy for some cancer types, including glioma, pancreatic, and colon cancers; however, in other cancers (asthma/lung cancer and atopic dermatitis/skin cancer), these two pathologies may be positively associated (81). Overall, the interplay of allergy and cancer is complex and may involve the relative importance of chronic inflammation, immunosurveillance, and immunomodulatory therapy for allergic disease.

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Conclusions

In summary, eosinophils are associated with areas of tissue remodeling and cell turnover during both homeostasis and disease. In tumors, eosinophils are associated with necrotic areas, and there is evidence for the cytotoxic effect of eosinophils on tumor cells both *in vitro* and *in vivo*. Finally, TATE appears to be protective for the most part, but whether this finding is a direct correlation or merely an associated phenomenon requires further studies. We hope that this primer will encourage cancer specialists to investigate the presence of blood and/or tissue eosinophilia during cancer development, thereby promoting research that exploits the tumor-regulating potential of eosinophils to improve cancer therapy.

Authors' Contributions

Writing, review, and/or revision of the manuscript: M.E. Rothenberg, B.P. Davis

Received November 6, 2013; accepted November 12, 2013; published online January 3, 2014.

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