Cancer Immunology, Immunotherapy (2019) 68:823–833
https://doi.org/10.1007/s00262-018-2255-4

FOCUSSED RESEARCH REVIEW

Opposing roles of eosinophils in cancer

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Received: 9 August 2018 / Accepted: 28 September 2018 / Published online: 9 October 2018

Abstract

Eosinophils are a subset of granulocytes mostly known for their ability to combat parasites and induce allergy. Although they were described to be related to cancer more than 100 years ago, their role in tumors is still undefined. Recent observations revealed that they display regulatory functions towards other immune cell subsets in the tumor microenvironment or direct cytotoxic functions against tumor cells, leading to either antitumor or protumor effects. This paradoxical role of eosinophils was suggested to be dependent on the different factors in the TME. In addition, the clinical relevance of these cells has been recently addressed. In most cases, the accumulation of eosinophils both in the tumor tissue, called tumor-associated tissue eosinophilia, and in the peripheral blood were reported to be prognostic markers for a better outcome of cancer patients. In immunotherapy of cancer, particularly in therapy with immune checkpoint inhibitors, eosinophils were even shown to be a potential predictive marker for a beneficial clinical response. A better understanding of their role in cancer progression will help to establish them as prognostic and predictive markers and to design strategies for targeting eosinophils.

Keywords Eosinophils · Cancer · Prognostic marker · Immunotherapy · PIVAC 17

Abbreviations

AEC	Absolute eosinophil count
CCL	CC-chemokine ligand
CCR	CC-chemokine receptor
CRC	Colorectal cancer
CXCL	C-X-C-chemokine ligand
DAMPs	Damage-associated molecular patterns
DFS	Disease-free survival
DPP4	Dipeptidylpeptidase 4
ECP	Eosinophil cationic protein
EDN	Eosinophil-derived neurotoxin
GI	Gastrointestinal
HMGB1	High-mobility group box 1 protein
HPF	High power fields
ICI	Immune checkpoint inhibitor
MBP	Major basic protein
MM	Malignant melanoma
OSCC	Oral squamous cell carcinoma
PAMP	Pathogen-associated molecular patterns
PFS	Progression free survival
REC	Relative eosinophil count
Siglec	Sialic acid-binding immunoglobulin-like lectin
TATE	Tumor-associated tissue eosinophilia
Th2	Type 2 Th cells

This paper is a Focussed Research Review based on a presentation given at the *Seventeenth International Conference on Progress in Vaccination against Cancer* (*PIVAC 17*), held in Loutraki, Corinthia, Greece, 27th–30th September, 2017. It is part of a *Cancer Immunology, Immunotherapy* series of *PIVAC 17* Focussed Research Reviews.

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Introduction

In recent decades, cancer research has widened from the analysis of tumor cells and their genetic alterations towards a broader investigation including the TME. Tumor growth is not only dependent on malignant cells, but also on chronic inflammation maintained by surrounding cells, including leukocytes, fibroblasts and endothelial cells. Tumor-infiltrating host cells can either conduct protumor or antitumor functions by secreting soluble factors such as cytokines and chemokines [1]. Eosinophils represent one subset of the

leukocytes infiltrating tumors. Compared to other immune cells in the TME, such as T cells, macrophages, neutrophils, MDSC and DC, the function of eosinophils is poorly investigated. There is an undisputable need for a more detailed analysis of their impact on tumor development since eosinophils have been described to act as regulatory and effector cells within the TME [2–4]. Moreover, they are known to produce a wide range of factors influencing other leukocytes. The classical view on eosinophils only combatting parasites and inducing allergies must be revisited [5].

In this review, we discuss the biology of eosinophils, their modulation of tumor growth and the mechanisms of such modulation. Furthermore, the potential properties of eosinophils as a marker for survival or therapy response in cancer patients as well as strategies of targeting eosinophils will be analyzed.

Biology of eosinophils

Eosinophils represent a subpopulation of granulocytes and are phenotypically characterized by their bilobed nuclei, large specific granules, and their capability to be stained by acidophilic dyes. They mature in the bone marrow upon specific stimuli and are then released into the peripheral bloodstream. Eosinophils can further migrate into various organs such as lung, thymus, adipose tissue and especially the gastrointestinal (GI) tract [6]. Tissue-resident eosinophils execute different functions, often based on their cytokine release [7] via exocytotic degranulation. However, even under homeostatic conditions, the distinct role of eosinophils in different tissues remains uncertain and needs to be further explored.

Mature eosinophils express a wide range of surface receptors involved in adhesion, activation, migration and pattern recognition [5]. Sialic acid-binding Ig-like lectins 8 (Siglec)-8 in human [8] and Siglec-F in mice [9] are predominantly expressed on eosinophils. Although Siglec-8 was detected also on basophils [8] and Siglec-F was found on alveolar macrophages [10], both surface molecules are considered as eosinophil markers [8, 9]. In addition, eosinophils express the IL-5 receptor alpha subunit and the CC-chemokine receptor (CCR) 3, also known as CD125 and eotaxin receptor, respectively. Although not uniquely expressed on eosinophils, these two receptors define the eosinophil phenotype and can serve as markers in combination [5]. Both receptors play a pivotal role in the activation process.

Next to their surface receptor repertoire, eosinophils can be characterized by their intracellular content and, in particular, by their specific granules that contain major basic protein (MBP) and eosinophil peroxidase, as well as the ribonucleases eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin (EDN) [11]. Furthermore, eosinophils store lipid bodies containing lipid mediators such as leukotrienes, prostaglandins and platelet-activating factor [5].

It has been demonstrated that IL-5, which is largely produced by type 2 Th cells (Th2) [12] and type 2 innate lymphoid cells [13], plays a crucial role in eosinophil proliferation, activation and survival. The expansion and trafficking of human eosinophils were shown to be critically dependent on IL-5 [14]. The importance of this cytokine was demonstrated by applying anti-IL-5 mAbs in patients with severe asthma and eosinophilia, leading to a reduction of eosinophil numbers in the peripheral blood [15]. Eosinophil migration was found to be supported by eotaxins, a group of chemokines that can recruit eosinophils synergistically with IL-5 [16]. The effect of eotaxins is based on their binding to CCR3 expressed on eosinophils [17].

Human eosinophils can also be activated via the signaling through pattern-recognition receptors such as TLR and nucleotide-binding oligomerization domain-like receptors [18].

Functional properties of eosinophils

After activation and migration to the target site, eosinophils implement their functions through different mechanisms. The most prominent one is degranulation, which is performed mainly as a controlled transport of specific vesicles to the cell surface, and therefore, called "piecemeal degranulation" [19]. Through the release of cationic proteins and ribonucleases, activated eosinophils have direct cytotoxic effects especially on pathogens like viruses and bacteria in vitro [20, 21]. The cationic proteins were found to be components of extracellular traps [22] and to exert antibacterial effects in vivo, resembling the function of neutrophil extracellular traps [23].

Furthermore, eosinophils release cytokines by degranulation to modulate other leukocyte subpopulations [5]. Eosinophils were shown to produce Th2-type chemoattractants to orchestrate Th2 cells into the lung under allergic conditions in mice [24]. Moreover, they were reported to support the survival of plasma cells in the bone marrow by secreting a proliferation-inducing ligand and IL-6 [25]. The role of eosinophils as immune regulatory leukocytes may even be executed by direct cell-to-cell contact as shown by in vitro ultrastructural studies of mast cell–eosinophil interaction [26]. In addition, eosinophils are able to exert antigen presenting functions, resulting in T cell activation [27]. Although they are considered "non-professional" APCs, they express MHC class II and the costimulatory molecules CD80 and CD86 [28].

Eosinophils participate in innate immunity by recognizing pathogen- and damage-associated molecular patterns (PAMPs/DAMPs) leading to degranulation [18]. In adaptive immunity, they play a role in the recruitment of other leukocytes, direct interaction with them, and antigen presentation to T cells [27]. Their capability of combatting parasites is among their most prominent properties and was confirmed in several studies in vivo [29]. In addition, they also execute antibacterial and antiviral functions, which was shown in *Pseudomonas aeruginosa* infections in mice [30], respiratory syncytial virus infections [31] and HIV infections [32].

Under homeostatic conditions, the major part of the eosinophil population is resident in the GI tract. However, their function within this tissue remains unclear. It was shown that eosinophils contribute to immune homeostasis in the GI tract by fostering IgA-producing plasma cells and promoting T cell-independent IgA class switching [33]. In the thymus, eosinophils were found to be localized in proximity to immature double-negative thymocytes in the corticomedullary region, suggesting that they play a role in negative T cell selection [34]. Eosinophils were reported to contribute to the metabolic processes in the adipose tissue by promoting alternatively activated macrophages [35].

Eosinophils in various diseases

Besides the impact in infections, eosinophils are associated with atopic disorders such as asthma. In the pathogenesis of asthma, they contribute by releasing MBP, which triggers mast cell and basophil degranulation. Furthermore, they were found to release functional exosomes promoting the progression of asthma [36]. In asthmatic patients, targeting eosinophils can be achieved by humanized anti-IL-5 mAbs, although a clinical improvement is only seen in a subset of patients displaying a persistent sputum eosinophilia before the treatment [37].

Furthermore, there is a link between eosinophils and GI disorders, in particular, eosinophilic esophagitis. This disease is characterized by eosinophilic infiltration of the esophageal mucosa and chronic inflammation mediated by Th2 cells [38].

Eosinophil-related diseases also include hypereosinophilic syndromes defined by eosinophilia and associated organ damage; the accumulation of eosinophils is based on activated eosinopoiesis or an overproduction of eosinophilopoietic cytokines [39]. Another reason for eosinophilia could be primary immunodeficiency, which represents a group of very rare genetic diseases [40].

Eosinophil recruitment in cancer

Although eosinophils were described in relation to cancer more than 100 years ago [41], the mechanisms underlying their accumulation in the peripheral blood or tumor tissue are still not completely understood. The most prominent attractor of eosinophils, IL-5, was demonstrated to be produced by human cancer cells [42] and to recruit eosinophils to the peripheral bloodstream [43]. Furthermore, other factors such as GM-CSF were shown to be produced by tumor cells as well as to recruit and activate eosinophils [44]. Additionally, the Th2 cytokine IL-4 displayed antitumor function in vivo through the induction of eosinophil migration to the tumor site and local eotaxin expression [45, 46]. Moreover, in vivo studies revealed that CC-chemokine ligand 11 (CCL11), also called eotaxin-1, was largely responsible for orchestrating eosinophils within the tumor [47]. This role of eotaxins in cancer can be underlined by their expression in human cancer tissue [48]. In addition to the CCR3-dependent recruiting, eosinophil migration was found to be regulated by CCR1 [49].

Interestingly, it has been demonstrated in a mouse melanoma model that eosinophil recruitment to the tumor belongs to an early inflammation reaction [50]. In this paper, the authors reported that this early migration was rather due to chemotactic factors produced by dying tumor cells than induced inflammatory mediators secreted by $CD4^+$ T cells. Indeed, stress signals such as alarmins or DAMPs are known to attract eosinophils [5, 6]. These DAMPs include the high-mobility group box 1 protein (HMGB1) released by stressed or dying cells, which led to recruitment, survival and activation of eosinophils [51]. Another alarmin, IL-33, was found to have the ability to recruit eosinophils based on the IL-33/ST2-axis in vivo [3]. Furthermore, ATP, acting as a DAMP, was able to attract and activate eosinophils through binding to the P2Y purinergic receptor [52].

Modulation of tumor growth by eosinophils

Numerous studies have addressed the role of eosinophils in fighting cancer, but the experimental studies have revealed conflicting results. Some mechanisms of eosinophil functions in tumors are illustrated in Fig. 1.

Antitumor functions were demonstrated by the injection of IL-4 secreting tumor cells into mice which resulted in tumor regression mediated mainly by eosinophils [45]. In a melanoma mouse model, it was found that elimination of metastasis was based on eosinophil degranulation [46]. The eosinophils were attracted and activated

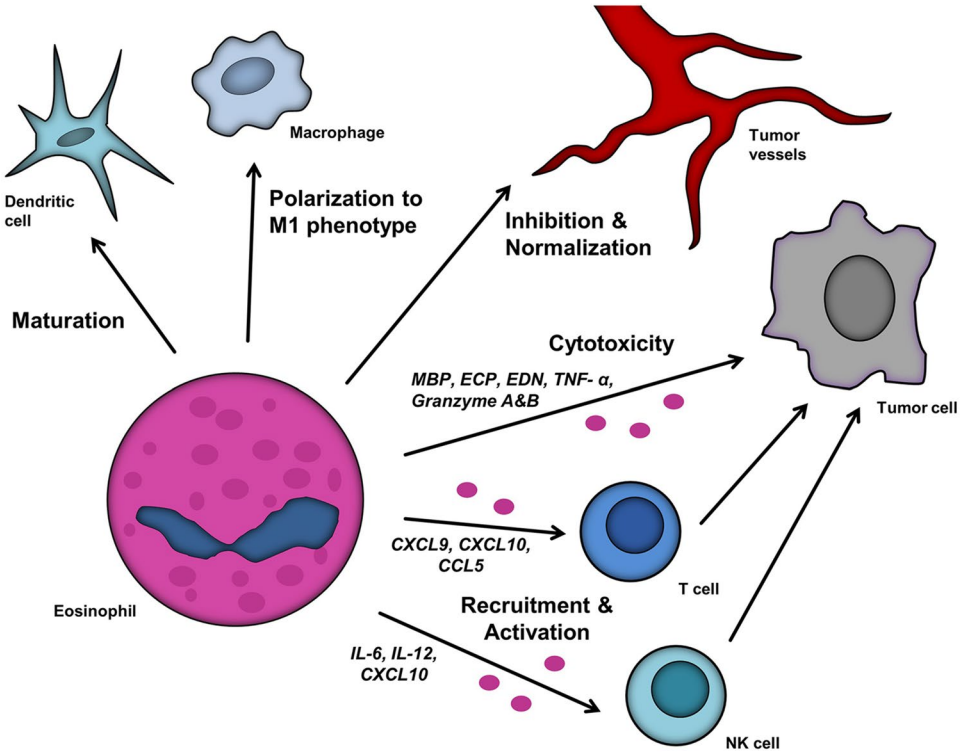

Fig. 1 Impact of eosinophils within the TME. Eosinophils influence other leukocytes, including T cells, NK cells, DC and macrophages, and alter their effect on tumor growth. T cell recruitment and activation is based on the chemokines C-X-C-chemokine ligand (CXCL) 9, CXCL10 and CC-chemokine ligand (CCL) 5, whereas NK cells are attracted by IL-6, IL-12 and CXCL10. Eosinophils modulate tumor vessels and exert direct cytotoxic functions towards tumor cells via major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), TNF-α, granzyme A and granzyme B

by tumor-specific $CD4^+$ T cells. Furthermore, Simson et al. [47] demonstrated an increased tumor incidence and growth of methylcholanthrene-induced fibrosarcomas in mice deficient for either CCL11 or CCL11 and IL-5, with reduced or deficient eosinophil levels, respectively. The tumor-protective effect of IL-5 was histologically proven to be dependent on enhanced eosinophilic infiltration [47].

In contrast, some experimental studies indicated a protumorigenic role for eosinophils. It was demonstrated that the incidence of squamous cell carcinoma induced by 4-nitroquinoline-1-oxide was enhanced in wild-type mice compared to eosinophil-deficient mice [53], indicating that eosinophils might be involved in the promotion of carcinogenesis. In a carcinogen-induced hamster oral squamous cell carcinoma (OSCC) model characterized by tumor-associated tissue eosinophilia (TATE), animals were treated with anti-IL-5 mAbs, resulting in attenuated tumor growth [54], emphasizing the protumoral role of eosinophils. These observations led to the hypothesis that eosinophils may be able to execute both, pro- and antitumor functions, depending on different stimuli in the TME. Such polarized functions in tumor-bearing hosts were also observed for other myeloid cells such as macrophages and neutrophils.

A recent study of Carretero et al. [2] elucidated the role of eosinophils in tumor rejection. The authors observed a tumor regression upon T_{reg} cell depletion associated with tumor eosinophilia in a melanoma mouse model. Further investigation revealed that eosinophils produced chemokines like CCL5, CXCL9 and CXCL10, which recruited $CD8^+$ T cells into the TME. Additionally, the authors observed an induction of macrophage polarization towards the M1-like cells which were previously described to exert anti-tumor effects [1]. Another publication presented evidence of tumor growth delay after injection of IL-33 and attributed this effect to the intratumoral accumulation of eosinophils and $CD8^+$ T cells [3]. Moreover, eosinophils migrated to the lungs, preventing the formation of metastases. Upon depletion of eosinophils with a Siglec-F mAb, $CD8^+$ T cell infiltration was diminished. Furthermore, the authors showed that eosinophils exerted direct cytotoxic effects on tumor cells in vitro [3]. In addition, eosinophils were demonstrated to interact with other immune cells such as NK cells [55] and DC [56].

Interestingly, eosinophils were demonstrated to also affect angiogenesis, which is an essential process for tumor growth. Eosinophils were able to induce normalization of tumor vessels, secreting less angiogenic factors, such as VEGF, in the TME [2]. Furthermore, Xing et al. [57] found that CCL11-induced eosinophils inhibit angiogenesis in a fibrosarcoma mouse model.

Importantly, it was observed that eosinophils can exert direct cytotoxic effects towards tumor cells by releasing granular content. Eosinophil lysate was reported to kill B16 melanoma cells in vitro [3]. Furthermore, eosinophils were shown to release MBP into the tumor tissue in vivo, suggesting that MBP was responsible for the cytotoxic effect [46]. Indeed, in vitro studies demonstrated that eosinophilic

MBP has cytotoxic function against tumor cell lines [58]. Additionally, the tumoricidal effect of MBP was found to be enhanced by the combination with TNF-α in multicellular tumor spheroids [59]. The release of TNF-α together with ECP and EDN was also observed after the co-culture of eosinophils together with colon cancer cells, enhancing cytotoxic activity [4]. In addition, eosinophils exerted cytotoxicity via the release of the apoptosis inducing protease granzyme B [60]. Besides the release of cytotoxic factors, eosinophils were found to build close contacts with viable tumor cells [61]. This cross-talk could be at least partly based on the binding of ICAM-1 on eosinophils to the junctional adhesion molecule A on tumor cells, which was shown for colon cancer cells [62]. Interestingly, the binding was found to be dependent on IL-18, which upregulated adhesion molecules on eosinophils and tumor cells.

On the other side, some publications reported protumor functions of eosinophils. They were shown to recruit T_{reg} cells via production of CCL22 that facilitated pulmonary metastasis in mice [63]. Furthermore, Kratochvill et al. [64] found that eosinophils produce IL-13, thereby driving macrophage polarization towards the M2-like immunosuppressive phenotype. Another immunosuppressive effect of eosinophils was mediated by the production of indoleamine 2,3-dioxygenase, which is capable of inhibiting T and NK cell function [65] as described in NSCLC patients [66]. However, the tumor-promoting role of eosinophils not only involves other immune cells. It was also demonstrated that MBP in a sub-cytotoxic subcytotoxic dose induced angiogenesis by promoting endothelial cell proliferation and enhancing the effect of VEGF [67].

Eosinophils as a prognostic marker for clinical outcome

In the past, various studies have highlighted the involvement of eosinophils in numerous tumor entities and their increasingly important potential utilization as a prognostic marker. They were shown to be related to a beneficial prognosis in most cases, although evidence of association to a non-beneficial prognosis was described [68]. This connection towards the clinical prognosis was either reported for TATE or peripheral eosinophil counts.

A prognostic impact of TATE for OSCC patients has already been described for many years [69]. Several studies revealed a positive correlation between eosinophil infiltration and a favorable prognosis. Dorta et al. [70] showed an association between an increased disease-free survival (DFS) as well as overall survival (OS) and the intensity of TATE. Furthermore, the OS rate was found to be particularly elevated in the case of intratumoral TATE as compared to other regions [71]. Recently, other authors tried to simplify the evaluation of TATE and found a cut-off at four eosinophils per high power field (HPF) with patients having more than four eosinophils per HPF displaying a better survival [72]. However, other publications described eosinophilic tumor infiltration as a marker for an unfavorable prognosis in OSCC patients. TATE was found to predict lymph node metastasis [73] and was demonstrated to correlate with locoregional recurrence [74]. In addition, Alrawi et al. [75] described an impaired survival of patients with high numbers of tumor-infiltrating eosinophils. Interestingly, another publication revealed no significant impact of TATE on the 5- and 10-year survival of OSCC patients [76].

In colorectal cancer (CRC), an infiltration of eosinophils was first described by Moezzi et al. [77]. A link between decreasing eosinophilic infiltration and increasing malignancy of CRC was confirmed by other studies, including in total around 1000 tissue samples [78, 79]. Furthermore, a correlation between high eosinophilic infiltration of the tumor and a beneficial 5-year survival rate in CRC patients was reported [80]. Moreover, the occurrence of CRC was found to be inversely correlated with circulating eosinophils, suggesting a protective role for eosinophils in CRC development [81]. In addition, a retrospective study of CRC patients with stage I-III documented a better OS and DFS in case of a higher eosinophil blood count [82].

The prognostic value of eosinophils has been demonstrated for breast cancer as well. A reduced risk of disease recurrence was described in primary breast cancer patients displaying a higher peripheral eosinophil count [83]. In contrast, it has been reported that high numbers of eosinophils correlate with an impaired DFS in patients treated with the antibody trastuzumab [84].

The association of eosinophils with an unfavorable prognosis has been particularly described for cervical cancer. This tumor entity is characterized by the development from intraepithelial neoplastic lesions. In contrast to CRC, a higher density of eosinophilic infiltration was associated with accelerated tumor progression [85]. Furthermore, TATE was found to be correlated with enhanced tumor depth and size leading to an impaired survival [86]. Interestingly, the authors failed to observe any impact of the peripheral eosinophil count on the survival rate. In contrast, Bethwaite et al. [87] described intensive TATE as a beneficial factor for the 5-year survival rate in cervical cancer patients.

The link between eosinophil counts or eosinophilic tumor infiltration and survival was also studied in patients with other tumor entities. In gastric cancer, high levels of TATE correlated with an improved survival rate [88, 89]. A similar association of TATE with metastasis, recurrence and prognosis can be seen in esophageal cancer [90, 91]. Furthermore, high peripheral eosinophil counts have been shown to be related to an enhanced OS in hepatobiliary cancer [92]. In addition, the eosinophil count was found to be elevated

in patients with renal cell carcinoma that responded to the therapy with tyrosine kinase inhibitor sorafenib [93].

Eventually, eosinophils were found to be associated with a better prognosis in most cases, although further studies should be performed, especially in OSCC, breast cancer and cervical cancer. Nevertheless, the controversial prognostic value reported for eosinophils might be based upon different measures for the intensity of eosinophilia and non-sufficient statistical power.

Eosinophils as a predictive marker in cancer immunotherapy

Eosinophilia is a frequently observed side effect of immunotherapy and has been described for administration of IL-2 [94], IL-4 [95], GM-CSF [96], anti-PD-1- [97] and anti-CTLA-4-antibodies [98]. An enhanced degranulation of eosinophils is shown during treatment with IL-2 [94] and IL-4 [95], supporting a possible involvement of these cells in tumor control.

Recently, the role of eosinophils as a predictive marker has been intensively studied in malignant melanoma (MM) patients treated with immune checkpoint inhibitors (ICI). It was found that a high baseline eosinophil count is correlated with an improved OS in patients treated with the anti-PD1 antibody pembrolizumab [97]. In contrast, our study on MM patients treated with the ICI ipilimumab revealed that not the baseline eosinophil count but rather an early increase in the eosinophil count is linked to an improved clinical response to this immunotherapy [98]. Moreover, we found that the concentration of eotaxin-1 in serum from non-responding MM patients was significantly lower than before therapy, leading to diminished eosinophil count observed in the peripheral blood of non-responders [98]. These results suggest that eosinophils could potentially be used as a predictive marker for clinical response to ICI therapy. Another paper described a trend towards an association of eosinophilia with a better survival rate independent of the treatment [99], emphasizing, however, a prolonged OS in patients treated with an ICI and experiencing eosinophilia. Interestingly, the significance of eosinophils as a predictive marker was also confirmed for uveal MM patients by demonstration of increased OS in patients with higher eosinophil levels during ICI therapy [100].

Similar to MM patients, eosinophils were also described as a potential predictive marker in lung cancer patients treated with ICI. A multivariate analysis of patients with NSCLC and treated with ICI revealed a significant positive correlation between increased baseline eosinophil count and improved OS [101]. However, Shelton et al. [102] found a correlation between a high peripheral eosinophil count and a favorable OS in lung cancer (including SCLC and NSCLC) independent of the treatment.

In addition to MM and lung cancer, a correlation between elevated eosinophil counts during immunotherapy with sipuleucel-T and improved OS was shown in prostate cancer patients [103].

Taken together, eosinophils were shown to be a predictive marker in immunotherapy in different tumor entities. However, further studies on greater patient cohorts would be necessary for the implementation of this parameter into the clinical use. Table 1 summarizes the data on eosinophils as a biomarker.

Eosinophils as a therapeutic target

Several studies on pre-clinical mouse tumor models described the possibility of eosinophil targeting [104]. However, none of these drugs were approved for the application in cancer patients. Interestingly, it has been reported that inhibitors of dipeptidylpeptidase 4 (DPP4) impaired eosinophil trafficking within tumors by blocking posttranslational modifications of chemokines [105]. In hepatocellular carcinoma mouse model, the treatment with the DPP4-inhibitor sitagliptin resulted in an enhanced tumor immunity associated with the regression of tumors. These effects were diminished upon eosinophil depletion or inhibition of their degranulation. Therefore, the authors started a phase Ib clinical study in which patients with hepatocellular carcinoma are treated with sitagliptin prior to surgery [105].

Conclusion

Taken together, eosinophils participate in the regulation of various physiological and pathological processes, including cancer. The accumulation of eosinophils in the TME or in the peripheral blood of cancer patients was already observed a long time ago but has been mainly neglected so far. However, during the last decade the attention to this topic has been constantly increasing due to the challenging recent results showing the role of eosinophils in the tumor defense in vivo (Fig. 1) [2, 3]. Some authors even suggested a possibility of eosinophil polarization into distinct subsets having either immunostimulatory or immunoinhibitory functions [2, 3, 106]. However, more studies would be needed to investigate this possibility in tumor-bearing hosts in vivo. Furthermore, numerous observations have appeared, indicating the possible application of eosinophils as a prognostic biomarker. The intensity of TATE has been correlated with a better clinical outcome for many solid tumors. Furthermore, a high eosinophil blood count was found to be associated with

Table 1 Evidence on eosinophils as prognostic and predictive markers

Tumor entity	*n*	Conclusion	Ref.
OSCC	125	Intense TATE is associated with prolonged DFS and OS TATE is an independent prognostic marker	[70]
OSCC	87	Intense intratumoral TATE is associated with prolonged OS Intratumoral TATE is an independent prognostic marker	[71]
OSCC	99	Medium and high TATE is associated with prolonged OS	[72]
OSCC	71	Intense TATE is associated with occult lymph node metastasis Intense TATE is associated with impaired DFS	[73]
OSCC	14	Intense TATE is associated with locoregional recurrence	[74]
OSCC	87 20	TATE predicts invasiveness of the tumor Intense TATE is associated with impaired cumulative survival	[75]
OSCC	43	No significant association between intensity of TATE and outcome	[76]
CRC	441	Strong stromal eosinophilic infiltration is associated with prolonged 5-year survival TATE is an independent prognostic marker	[80]
CRC	242	AEC is inversely associated with CRC incidence	[81]
CRC	569	Low AEC is associated with impaired OS and DFS AEC is an independent prognostic marker	[82]
Breast cancer	419	High AEC is associated with a prolonged DFS	[84]
Breast cancer	62	Low eosinophil count is associated with prolonged DFS in patients treated with trastuzumab AEC is an independent prognostic marker	[83]
Cervical cancer	61	Moderate and extensive TATE is associated with impaired OS TATE is an independent prognostic marker	[86]
Cervical cancer	73	Moderate and intense TATE is associated with a prolonged 5-year survival	[87]
Gastric cancer	308	Moderate and marked TATE is associated with a prolonged 5-year survival	[88]
Gastric cancer	324	Numerous TATE is associated with a prolonged 5-year survival TATE is an independent prognostic marker	[89]
Eso-phageal cancer	36	High TATE is associated with a prolonged OS TATE is an independent prognostic marker	[90]
Eso-phageal cancer	97	Large number of eosinophils is associated with a prolonged 2- and 5-year survival in patients with lymph node metastasis	[91]
Hepato-biliary cancer	206	High peripheral eosinophils counts are associated with a prolonged cumulative survival	[92]
Renal cell cancer	282	Increase of REC during therapy with sorafenib is associated with a prolonged OS and PFS REC is an independent prognostic marker	[93]
MM	177 346	High AEC and REC associated with prolonged OS of patients treated with pembrolizumab High REC is an independent prognostic marker for a better OS of patients treated with pembrolizumab	[97]
MM	59	Increase in AEC associated with improved clinical response to treatment with ipilimumab Increase in AEC is an independent predictive marker for the clinical response to ipilimumab	[98]
MM	86 40	High REC is associated with a prolonged OS in patients treated with ICI High REC is associated with a better OS in immunotherapy-naïve patients who lived at least 12 months	[99]
uveal MM	86	High REC is associated with prolonged OS of patients treated with ICI REC is an independent prognostic marker	[100]
NSCLC	134	High AEC is associated with a prolonged OS and PFS in patients treated with nivolumab AEC is an independent prognostic marker	[101]
NSCLC & SCLC	358	High eosinophil count associated with prolonged cumulative survival in NSCLC and SCLC Eosinophil count is an independent prognostic marker	[102]
Prostate cancer	377	Increase of eosinophil count during therapy with sipuleucel-T is associated with an induced immune response, cancer-specific survival and prolonged OS	[103]

AEC absolute eosinophil count, *CRC* colorectal cancer, *DFS* disease-free survival, *ICI* immune checkpoint inhibitor, *MM* malignant melanoma, *n* number of patients, *OS* overall survival, *OSCC* oral squamous cell carcinoma, *PFS* progression-free survival, *REC* relative eosinophil count, *Ref.* references, *TATE* tumor-associated tissue eosinophilia

patients' responsiveness to immunotherapy, in particular to ICI [97, 98]. Nevertheless, further investigation in greater cohorts is needed for the definite use of eosinophils as a prognostic or predictive marker. In addition, due to a lot of outstanding questions, an attempt to target eosinophils in cancer therapeutically has not been made yet. This approach should be reconsidered when there are more clinical data and evidence about functional mechanisms.

Acknowledgements The authors wish to thank Elisabeth Cordell for editing the manuscript, Xiaoying Hu for designing figure elements, Rebekka Weber and Zeno Riester for helpful advice. The literature search was assisted by Maurizio Grilli from the library for the Medical Faculty of Mannheim, Ruprecht-Karl University of Heidelberg.

Author contributions SCSS: writing, review and revision of the manuscript, preparation and revision of the figure and table. JU: review and revision of the manuscript. VU: writing, review and revision of the manuscript and revision of the table and figure.

Funding This work was supported by grants from the German Research Council (RTG2099) to J. Utikal and V. Umansky and the Cooperation between German Cancer Research Center (DKFZ) and Ministry of Science, Technology and Space of Israel (MOST) in Cancer Research (CA181 to V. Umansky). This work was kindly backed by the COST Action BM1404 Mye-EUNITER (http://www.mye-euniter.eu). COST is supported by the EU Framework Program Horizon 2020.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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