Cytokine & Growth Factor Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Mini review

Chemokine regulation of neutrophil function in tumors

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ARTICLE INFO

Article history:
Received 11 March 2016
Accepted 21 March 2016
Available online xxx

Keywords:
Chemokines
Neutrophils
Inflammation
Cancer

ABSTRACT

The role of neutrophils in cancer and metastasis is still debated and controversial since they have been shown to be endowed with both pro- and antitumor functions. These contradictory results seem to be now explained by recent discoveries of tumor-associated neutrophils plasticity and multiple neutrophil subsets.

Chemokines and chemokine receptors are known to tightly regulate the release of neutrophils from the bone marrow, their passage into circulation and transmigration into the tissues as well as tumor infiltration. It is emerging that chemokine receptors are differentially expressed by neutrophil subsets and they affect not only their recruitment but also their effector functions.

Here we are resuming human and murine data suggesting that therapeutic modulation of neutrophil activity through the targeting of specific chemokines or chemokine receptors can improve their anti-tumoral properties.

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1. Introduction

Neutrophils, also called polymorphonuclear leukocytes (PMNs), are the most abundant leukocytes population in circulation and they are essential effectors of the inflammatory response and defense against pathogens. Even if neutrophils are mostly considered for their anti-microbial function, more recently it has been described their involvement in several additional functions, both in physiological and pathological conditions, being able to regulate and activate the innate and adaptive immune responses [1]. Interestingly it is emerging an important role of neutrophils in cancer biology [2,3].

Cancer cells activate mechanisms similar to the ones that regulate neutrophils recruitment to inflammatory sites, indeed they express various ligand (CXCL8, CXCL5 and CXCL6) for neutrophils receptors CXCR1 and CXCR2 that actively recruit neutrophils to tumor sites. Therefore neutrophils represent an important component of the tumor microenvironment and neutrophilia, recurrent in advanced cancer patients, has been associated with poor prognosis in many tumors.

A recent meta-analysis of published papers indicated that their presence in tumor tissue is associated with poor prognosis [4]. Furthermore an elevated ratio of peripheral neutrophils-to-lymphocytes (NLR) has been recognized as a poor prognostic indicator in various cancers [5].

In addition, neutrophils have been found to have a key role in the establishment of the pre-metastatic niche [6]. Nevertheless, neutrophil role in cancer is still not completely elucidated because both pro- and antitumor functions have been described [7] (Table 1).

1.1. Neutrophils protumoral functions

Tumor associated neutrophils (TANs), recruited to tumor sites by signals produced by cancer cells and tumor microenvironment, are able to sustain cancer progression through several mechanisms. TAN_s are induced to release enzymes, contained in their granules, such as neutrophil elastase (ELA2), neutrophils collagenase (MMP8) and neutrophils gelatinase B (MMP9), that can promote tumor cells invasion by remodeling extracellular matrix (ECM) or directly acting

Abbreviations: PMNs, polymorphonuclear leukocytes; TAN_s, Tumor associated neutrophils; N1, proinflammatory; N2, anti-inflammatory tumor-promoting neutrophils; ELA2, neutrophil elastase; MMP8, neutrophils collagenase; MMP9, neutrophils gelatinase B; ECM, extracellular matrix; RNS, reactive nitrogen species; ROS, reactive oxygen species; HGF, hepatocyte growth factor; PGE2, prostaglandin E2; NETs, neutrophil extracellular traps; PD-L1, programmed death-ligand 1; TRAIL, TNF-related apoptosis-inducing ligand; ICAM-1, intercellular adhesion molecule-1; rTEM, reverse transmigrated neutrophils; LDNs, low density neutrophils; HDNs, high density neutrophils; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; RCC, renal cell carcinoma.

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http://dx.doi.org/10.1016/j.cytogfr.2016.03.012
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Please cite this article in press as: O. Bonavita, et al., Chemokine regulation of neutrophil function in tumors, Cytokine Growth Factor Rev (2016), http://dx.doi.org/10.1016/j.cytogfr.2016.03.012

Table 1
Pro- and antitumoral neutrophil functions.

Antitumoral functions	Mechanism	References
Tumor cell killing	ROS production	[21,22]
	Antibody-dependent cell-mediated cytotoxicity (ADCC)	[24,69]
	Release biologically active TRAIL/APO2 ligand	[26,27]
	Fas-mediated apoptosis of cancer cells	[28]
Induction of adaptive immune response to tumors	OX-40L, 4-1BBL	[29]
	Production of cytokines and chemokines to attract monocytes and lymphocytes	[31]
	Neutrophil extracellular traps (NETs) formation	[30]
Metastasis protection	ROS production	[23]

Protumoral functions	Mechanism	References
Local invasion	Modulation of the ECM by release of neutrophil elastase (ELA2), neutrophil collagenase (MMP8), and gelatinase B (MMP9)	[8]
Angiogenesis	Production of angiogenic factors (VEGF-A)	[10]
	Proteolytic release of EGF, TGFβ, and PDGF from the ECM	[8]
	Production of oncostatin M	[10,11]
Immunosuppression	Arginase 1 production	[17]
	TGF-β production	[19]
	Upregulation of PD-L1 expression	[18]
Metastasis promotion	Premetastatic niche	[6]
	NET formation	[16]
	Leukotrienes production	[15]
DNA damage and genetic instability	Release of ROS and RNS	[12]
Tumor cell proliferation and invasion	Release of ELA2	[14]
	Production of growth factors (e.g. HGF)	[9]
	Leukotrienes production	[15]
	Prostaglandin production	[13]

on tumor cells [8]. Neutrophils were shown to support tumor growth and invasion via secretion of protumoral cytokines and growth factors (EGF, TGFβ, PDGF, HGF, VEGF). For example, hepatocyte growth factor (HGF) has been demonstrated to promote the invasion of human pulmonary adenocarcinoma cells [9]. PMNs can enhance VEGF production and tumor cell invasion even through the production of oncostatin M [10,11], a member of IL-6 family, or releasing MMP9. In addition, granule enzymes are able to proteolytically activate the proangiogenic factors EGF, TGFβ, and PDGF from the extracellular matrix (ECM) [6].

Neutrophils can also enhance tumorigenesis through the release of reactive oxygen species (ROS, by myeloperoxidase and NADPH oxidase activity) and reactive nitrogen species (RNS, by nitric oxide synthase), which can contribute to further DNA damage and genetic instability [12].

Some molecules produced by neutrophils are also able to directly promote tumor cell proliferation. ELA2, prostaglandin E2 (PGE2) and leukotrienes activate intracellular signaling cascades which lead to tumor cell proliferation [13,14]. In particular, leukotrienes support proliferation of metastasis initiating cells in different mouse model of breast cancer [15].

Another mechanism by which neutrophils can promote tumor metastasis is the facilitation of the adhesion of tumor cells to endothelial cells at the extravasation site. This mechanism can be mediated by neutrophil extracellular traps (NETs), chromatin fibers released by activated neutrophils and considered to be one of their antimicrobial mechanism. Tumor cells become trapped within the NETs and increase their adhesion to hepatic and pulmonary microvasculature. NETs can also promote cancer cell proliferation inhibiting apoptosis [16].

Furthermore PMN carry out protumoral activity inhibiting antitumoral immune responses. Indeed upon CXCL8 stimulation, neutrophils produce arginase 1, an inhibitor of T cell function [17]. It was also reported that neutrophils upregulate programmed death-ligand 1 (PD-L1) and suppress T-cell proliferation [18]. Finally, neutrophils were shown to promote tumor growth through the production of TGFβ, a cytokine with immunosuppressive effect on other immune cells [19]. Moreover, they produce chemokines and cytokines that actively recruit tumor-supporting cells to the tumor bed [20].

1.2. Neutrophil antitumoral functions

Despite the predominant outline of neutrophils protumoral functions, other studies revealed the abilities of these cells to have anti tumoral effects. In some cases, mechanisms described having a protumoral role were found to inhibit tumor growth. Indeed it has been shown that, even if ROS contribute to cell dead and tissue damage in the tumor microenvironment, they can be cytotoxic for tumor cells [21,22]. Granot and his colleagues described how neutrophils can inhibit the metastatic seeding of breast carcinoma cells in the lungs by killing tumor cells via the generation of high levels of hydrogen peroxide [23].

Neutrophils are also able to kill tumor cells by antibody-dependent cell-mediated cytotoxicity [24] and they are important effectors of anticancer monoclonal antibodies based therapies [25]. Another killing mechanism is reported for interferon

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