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Chemokines, cytokines and exosomes help tumors to shape inflammatory microenvironment

K.-S.N. Atretkhany [a,b], M.S. Drutskaya [a,b], S.A. Nedospasov [a,b,c], S.I. Grivennikov [a,d,*], D.V. Kuprash [a,b,**]

[a] Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, 119991 Moscow, Vavilova Str. 32, Russia
[b] Biological Faculty, Lomonosov Moscow State University, 119234, Moscow, Russia
[c] German Rheumatology Research Center (DRFZ), Berlin, Germany
[d] Fox Chase Cancer Center, Cancer Prevention and Control Program, Philadelphia, PA, USA

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ABSTRACT

Relationship between inflammation and cancer is now well-established and represents a paradigm that our immune response does not necessarily serves solely to protect us from infections and cancer. Many specific mechanisms that link chronic inflammation to cancer promotion and metastasis have been uncovered in the recent years. Here we are focusing on the effects that tumors may exert on inflammatory cascades, tuning the immune system ability to cause tumor promotion or regression. In particular, we discuss the contributions of chemokines, cytokines and exosomes to the processes such as induction of inflammation and tumorigenesis. Overall, tumor-elicited inflammation is a key driver of tumor progression and an essential component of tumor microenvironment.

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1. Introduction

Inflammation was appropriately added to one of the ten hallmarks of cancer (Hanahan and Weinberg, 2011). Tumor cells accumulate mutations in several critical genes involved in cell growth regulation, such as tumor-suppressor genes or oncogenes. The original hypothesis that the emergence of tumors is strongly associated with site- or tissue-specific chronic inflammation, was first postulated by Rudolf Virchow more than a century ago (Mantovani, Allavena, Sica, and Balkwill, 2008). Different types of inflammation, depending on the causative agent, can contribute to tumorigenesis (Grivennikov, Greten, and

Abbreviations: G-CSF, granulocyte colony-stimulating factor; HIF-1, hypoxia-inducible factor 1; IGF2, insulin-like growth factor 2; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MDSC, myeloid-derived suppressor cells; MIF, macrophage migration-inhibitory factor; MMP, matrix metalloprotease; PD-L1, programmed death-ligand 1; STAT, signal transducer and activator of transcription; TAM, tumor-associated macrophages; TGFβ, transforming growth factor beta; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

* Correspondence to: S.I. Grivennikov, Fox Chase Cancer Center, Cancer Prevention and Control Program, Philadelphia, PA, USA.
** Corresponedence to: D.V. Kuprash, Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, 119991, Moscow, Vavilova Str. 32, Russia. Fax: +8 499 135 14 05.
E-mail addresses: sergey.grivennikov@fccc.edu (S.I. Grivennikov), kuprash@eimb.ru (D.V. Kuprash).

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Karin, 2010). These include therapy-induced inflammation (touched upon at the end of this review), tumor-elicited inflammation, inflammation caused by environmental stimuli and, perhaps most famous, chronic inflammation preceding tumor development. Here we focus on several aspects of tumor-induced inflammation and the ability of a growing tumor to recruit and exploit the immune system in such a way that it contributes to tumor growth, progression and metastasis. This type of tumor-associated or tumor-elicited inflammation is largely dependent on cytokine and chemokine production by tumor cells and other cellular components of tumor microenvironment (Fig. 1, Tables 1, 2). Evolutionary, this type of inflammation is probably selected to aid tissue repair and regeneration, however, these processes are usurped during the course of tumorigenesis to help tumor growth and progression instead. Chemokines and cytokines further play a role in orchestrating specific immune, inflammatory and stromal cell recruitment. They also essentially serve as direct growth and migratory factors for cancer cells, including those that remain confined within the tumor and those that travel towards the distant sites of metastasis (Fig. 2).

Recent advances in exosome research led to understanding of the important role that these vesicles may play in tumor microenvironment. Exosomes secreted by tumor cells provide physical means to transfer a variety of (normally) intracellular molecules into the surrounding cells, including immune and inflammatory cells, where these molecules exert regulatory effects. Tumor cells often give rise to a large number of exosome particles, therefore exosomes may represent a novel link between cancer and inflammatory cells, an important mechanism for the induction of tumor-induced (elicited) inflammation. Tumor progression can also be sustained by injury signals coming from dying (necrotic) cells due to hypoxia or as a result of primary tumor resection.

2. Induction of inflammation within tumors

One of the key questions which ties together oncogenic transformation, induction of pro-inflammatory intratumoral responses and increased tumor growth and progression is how chemokine/cytokine producing cells "sense" oncogenic transformation, i.e. how tumor-specific signals and tumor-restricted molecular mechanisms cause activation of inflammatory responses. How "tumor elicited inflammation" is induced at molecular and cellular levels? These molecular signals and events should probably be directly linked to the key steps of oncogenic process, including oncogenic mutations and other common denominators of tumor induction. Then, the ability of most tumors to induce inflammatory microenvironment regardless of heterogeneity and variations among individual tumors could be explained.

One of the common factors in many solid tumors is hypoxia. Due to high proliferation, defective blood vessels, acidification, abnormal vasculature tumor cells create hypoxic conditions which can activate hypoxia-inducible factor 1 (HIF-1), a heterodimeric protein that consists of constitutively expressed HIF-1β, and either one of the two HIF-α isoforms: HIF-1α or HIF-2α. (Palazon, Goldrath, Nizet, and Johnson, 2014; Semenza, 2014). Growth factors released by tumors and tumor microenvironment stimulate HIF-1α synthesis through activation of PI3K and MAPK signaling pathways. In addition, the major mechanism of HIF-1α upregulation and function is related to the fact that the lack of oxygen in hypoxic conditions stabilizes HIF-1α protein via inhibition of prolyl-oxidases required for HIF-1α degradation. For example, binding of insulin-like growth factor 2 (IGF2) and transforming growth factor beta (TGFβ) to their cognate receptors leads to HIF-1α activation, which in turn transcriptionally activate genes encoding these factors in an autocrine fashion. Proinflammatory cytokines can also activate HIF expression, for example, tumor necrosis factor (TNF) induces expression of HIF in macrophages via NFκB activation (Albina et al., 2001) and interleukin-6 (IL-6) enhances HIF-1α mRNA expression through activation of signal transducer and activator of transcription (STAT) 3 (Dang et al., 2011). Activation of Toll receptors may also contribute to HIF-1α expression through activation of NFκB-signaling (Shengwei et al., 2016). HIF-1 is very important for tumor growth and metastasis due to its involvement in transcriptional activation of genes responsible for proliferation, survival, glucose metabolism, angiogenesis, invasion and metastasis. Most relevant for the topic of our discussion, HIF is involved in regulating cancer-associated inflammation by directly regulating the expression of chemokines and cytokines. For example, HIF-1α in hypoxic tumor cells drives the production of chemokines and chemokine receptors responsible for myeloid cell recruitment, such as CXCR4, CXCL12 and CCL5 (Schioppa et al., 2003; Du et al., 2008; Lin et al., 2012). Convergence of HIF-1α and NFκB pathways can increase proinflammatory functions, survival of neutrophils, and migration and proinflammatory cytokine expression by

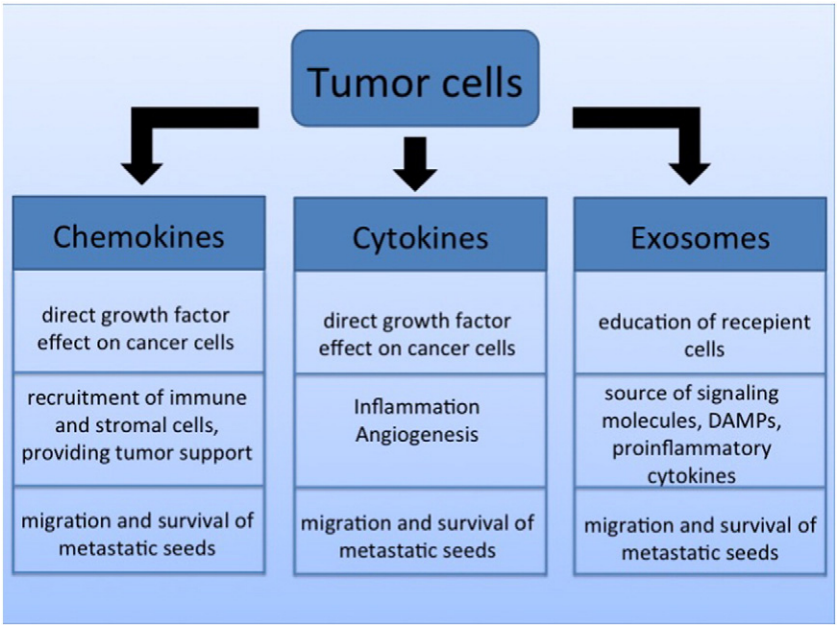

Fig. 1. Secretion of various mediators by tumor cells leads to increased tumor growth and metastasis (see text for details).