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Review

The kinship of neutrophils and granulocytic myeloid-derived suppressor cells in cancer: Cousins, siblings or twins?

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ABSTRACT

Neutrophils in the tumor host may promote tumor progression by enhancing angiogenesis, invasion and metastasis. Granulocytic myeloid-derived suppressor cells (MDSC) share many features with neutrophils. Classically, MDSC are viewed as and defined as immunosuppressive cells. In this article we summarize and critically review evidence for a role of MDSC in promoting angiogenesis, invasion and metastasis of solid tumors. We also attempt to provide a critical evaluation of the relationship between neutrophils and G-MDSC in the tumor host with a particular focus on human cancer.

1. Introduction

As early and rapidly responding immune cells neutrophils are indispensable to combat infections. In addition, neutrophils are also key effector cells in inflammation and inflammatory diseases. As outlined below solid tumors share many features with microbial infections and chronic inflammatory diseases.

1.1. Cancer, microbes, neutrophils and inflammation

Immune cells recognize microbes via so-called pattern recognition receptors (PRR). These PRRs can be expressed in various compartments and localizations including the cell surface, endosome or cytoplasm. During an infection these PRRs are activated by distinct structural components of microbes [1]. Triggering of PRRs results in immune activation which aims to sense and eliminate the infectious agent.

In addition to microbial structures these PRRs also respond to so-called damage-associated molecular patterns (DAMPs). DAMPs are cellular structures and molecules, which are released during unscheduled, non-apoptotic, cell death [2]. This type of cell death and uncontrolled release of normally intracellularly deposited molecules is a frequent phenomenon in solid tumors. Continuous uncontrolled release of DAMPs will then lead to the activation of PRRs on cells of the tumor microenvironment. As a result, cellular signaling pathways originally developed to alert the host in response to microbial infection become constantly activated in progressive tumors through cellular DAMPs. It is therefore not surprising that immune cells involved in the clearance of infections (such as neutrophils) are regularly recruited to solid tumors.

The continuous presence of DAMPs together with damaged and stressed cells in the malignant tissue also results in a state of chronic inflammation. In non-malignant tissue stressed and damaged cells elicit cellular repair processes, which ultimately lead to the resolution of the original damage or stress. In cancer, however, the "malignant" stressor cannot be cleared – Dvorak poignantly illustrated this fact by coining the famous phrase "tumors as wounds that never heal" [3]. More recently, this process has been redefined and termed "cancer-related inflammation" and many soluble and cellular mediators involved have been identified [4]. As neutrophils constitute a key component of the innate inflammatory response, it is not surprising that they are readily recruited to tumors in response to factors released from chronic cancer-related inflammation.

Further evidence which links neutrophils to cancer is the role of microbes in cancer initiation and progression. Based on epidemiological studies it is now generally accepted that chronic infections can accelerate or even induce the development of cancer [5]. Prototypic examples for this include hepatic viruses, hepatitis and hepatocellular carcinoma, schistosomiasis and bladder cancer as

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well as *Helicobacter pylori* and gastric cancer among many others. While chronic pathogenic infections are mainly and clearly linked to the development of malignant lesions, a role for microbiota (normally non-pathogenic microbes populating a specific tissue or body region) in the promotion of tumor progression has only recently begun to emerge. For example, it has been suggested that microbiota residing in the gastrointestinal tract drive tumor progression. In a murine model of genetically driven tumor initiation the development of malignant lesion was associated with barrier defects. These defects enabled gastrointestinal microbiota to make contact with immune cells eventually driving the tumor-promoting inflammatory immune cell function [6]. Similarly, in a model of azoxymethane-exposed, IL-10-deficient colitis-associated cancer the malignant progression was driven by bacteria-induced inflammation [7]. Collectively, these and related studies suggest that a deregulated microbiotic tissue environment, as it occurs in cancer, may enable otherwise non-harmful microbes to recruit inflammatory cells and initiate tumor-promoting inflammatory processes [8].

1.2. Neutrophils and tumor progression

Over the last decade tumor-promoting inflammation has established itself as an enabling characteristic of malignant disease [9]. Many key soluble and cellular mediators involved in this process have been identified. Among them are neutrophils and myeloid-derived suppressor cells [10]. While the function of MDSCs is mainly associated with immunosuppression (see below), neutrophils have been found to regulate key mechanisms of tumor progression such as angiogenesis, invasion and metastasis. Table 1 summarizes key mediators and mechanisms utilized by PMN during these processes. A particular prominent mediator, which drives angiogenesis, is MMP-9. Release of TIMP-free MMP-9 results in enhanced bioavailability of matrix sequestered VEGF, a major pro-angiogenic growth factor. Next to MMP-9, oncostatin M, CXCL8 and Bv8 have been demonstrated to promote angiogenesis if produced by neutrophils. A far greater number of mediators seem to be involved in the enhancement of invasion and metastasis. While MMPs, oncostatin, CXCL8 and Bv8 are also involved, additional neutrophil products driving tumor growth, invasion and metastasis include HGF, TGF-beta, APRIL and elastase. The reader is referred to the reviews by Dumitru et al., Tecchio et al., and Tazzyman et al. in this themed issue for details and further reference [11–13].

1.3. Myeloid-derived suppressor cells

Next to neutrophils a number of other myeloid cells expand and accumulate in the tumor host. Driven by a large number of chemotactic cytokines, chemokines, DAMPs and even lipid metabolites many of these myeloid cells are recruited to the tumor site and contribute to tumor progression [10]. Among these cells, MDSCs, and in particular so-called granulocytic MDSC, seem to be most closely related to neutrophils.

MDSCs are a rather heterogeneous subset of myeloid cells composed of immature and progenitor cells as well as mature cells either belonging to the mononuclear or the polymorphonuclear type [14]. Based on experimental mouse models MDSCs are subdivided into at least two subsets (in mice) and maybe more (in humans) [15]. In mice the minimum definition for the phenotype of monocytic MDSCs (Mo-MDSC) is the co-expression of CD11b and Ly-6C, while granulocytic MDSC (G-MDSC) co-express CD11b and Ly-6G.

As already indicated by their name, the capability of suppressing the activity of other immune cells (mainly demonstrated regarding effector functions and proliferation of T cells) is a key and defining feature of MDSC. Current research suggests that MDSC contribute to tumor growth and progression primarily by suppressing anti-tumor immune function. Furthermore, MDSC may also induce or activate other regulatory cell types as it has been demonstrated for regulatory T cells [16].

Only a small number of studies investigated the impact of MDSC on other aspects of tumor progression, namely invasion, metastasis and angiogenesis. Stimulated by the accumulating evidence, which suggests a multi-faceted role of neutrophils in promoting various aspects of tumor progression, this article will review the currently available data on a similar function for MDSC, and in particular G-MDSC. We will also introduce the key features and clinical relevance of G-MDSC with a focus on human cancer. Finally, we will try to clarify the somewhat fuzzy relationship of neutrophils and G-MDSC in the tumor host.

2. Immunophenotyping and characterization of MDSC in cancer patients

The term MDSC goes back to 2007 when the so-called myeloid suppressor cells (abbreviated as MSCs) were re-named to myeloid-derived suppressor cells. Firstly, this avoided confusion with mesenchymal stem cells (also abbreviated as MSCs) and secondly, it reflected the heterogeneous nature and subset composition of these cells [17]. For many years the research on MDSC in cancer had been driven by murine studies. Originally described as CD11b/Gr-1 double-positive cells, the Gr-1 antigens Ly-6G and Ly-6C now distinguish G-MDSC and Mo-MDSC, respectively. More recently, a number of additional markers have been associated with the MDSC phenotype [18]. Among those markers are also functionally important molecules such as arginase I and nitric oxide synthase, which mediate the immunosuppressive properties of MDSCs via production of reactive oxygen and nitrogen species as well as the depletion of L-arginine [19]. Other than the expression of characteristic surface or intracellular marker molecules, the immunosuppressive properties are also an important hallmark of MDSC (see Ref. [10] and Table 2 for details). For example, a reduction in extracellular L-cysteine and L-arginine will reduce the proliferative capacity of T cells. Similarly, the release of oxidizing molecules such as peroxynitrite and hydrogen peroxide will interfere with the functionality and zeta chain expression of the T cell receptor.

These findings have prompted the majority of researchers to use MDSC mediated inhibition of T cell proliferation or cytokine release as the principle assay to assign the immunosuppressive function to the MDSC under investigation. However, MDSC may also interfere with other T cell functions and, for example, may induce resistance of tumor cells to lysis by antigen-specific cytotoxic T cells [20]. Also the induction of Treg by MDSC [16] and the inhibition of NK function via down regulation of the activating receptor NKG2D have been reported [21].

Stimulated by murine studies, during recent years, a number of studies set out to identify and characterize MDSC in human cancer patients. As the Gr-1 antigen is not available in humans other combinations of markers were employed. Today, there is no unequivocal immunophenotype or final consensus on how to identify human MDSC in cancer patients. Nevertheless, over the last couple of years a certain set of antigens has evolved by repeated usage in different tumor entities and studies. This set of markers includes CD11b, CD14, CD15, CD33, CD66b and HLA-DR [15,22]. Similar to mice, different subsets of MDSCs have also been described in humans. Human Mo-MDSC are mostly referred to as being $CD14^+$ with negative or low expression of HLA-DR. Mo-MDSC express high amounts of CD11b and CD33. Human G-MDSC are mostly defined as $CD11b^+$ and $CD15^+$ or $CD66b^+$. G-MDSC are negative for HLA-DR, display an intermediate expression of CD33 and a variable expression of CD11b, depending on their maturation

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