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Review

Initiative action of tumor-associated macrophage during tumor metastasis

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Abstract

Tumor-associated macrophages (TAMs) are a significant component of the microenvironment of any solid tumors in the majority of cancers, associated with unfavorable prognosis. TAMs emerge as attractive targets for therapeutic strategies aimed at reprogramming their protumor phenotype into an effective antitumor activity.

In this review article, we present an overview of mechanisms responsible for TAMs recruitment and highlight the roles of TAMs in the regulation of tumor angiogenesis, invasion, metastasis, immunosuppression, and chemotherapeutic resistance. We describe the interplay between Th17 cells and other immune cells in the tumor microenvironment, and we assess both the potential antitumorigenic and pro-tumorigenic activities of Th17 cells and their associated cytokines. Understanding the nature of Th17 cell responses in the tumor microenvironment will be important for the design of more efficacious cancer immunotherapies. Finally, we discuss TAM-targeting therapy as a promising novel strategy for an indirect cancer therapy.

Keywords: Tumor-associated macrophage; Th17 and Tregs cells; Inflammation; Metastasis

1. Introduction

Cancer is a disease characterized by rapid growth of cells in the body, often in the form of a tumor. There was an estimation of 8.2 million deaths from cancer in the world in 2012, of which, 4.7 million (57%) deaths occurred in males and 3.5 million (43%) in females, giving a male: female ratio of 10:8 [1]. According to The National Central Cancer Registry (NCCR) of China, it was estimated that there were 34,319 new cases diagnosed as oral cavity cancer in China. In 2010, among the diagnosed cases, there were 14,652 cases resulting in deaths due to oral cavity cancer. In 2010, the crude incidence and mortality rate of oral cavity cancer was 1.11/100,000, accounting for 0.75% of overall cancer deaths, ranked the 20th in all cancer sites [2].

The innate immune cells that play a broad role in host defense and the maintenance of tissue homeostasis are macrophages [3]. In general, we can classify macrophages into two subsets: the classical M1 and the Alternative M2 macrophages [4]. The phenotype M1 is driven by the Th1 cytokine interferon-γ, bacterial moieties such as lipopolysaccharide (LPS), and Toll-like receptor (TLR) agonists. The production of pro-inflammatory factors such as IL-6, IL-12, IL-23, and tumor necrosis factor-α(TNF-α) are their characteristic feature. Conversely, the M2 macrophages exert anti-inflammatory and pro-tumorigenic activities. Within the tumor, macrophages are a major stromal component, where they commonly termed tumor-associated macrophages [5,6]. The localization of TAMs in a human sample is usually determined by marking the expression of CD163 and CD68 proteins. The infiltration of macrophages is largely related to poor prognosis of malignant tumors [6]. Cancer metastasis or metastatic tumor is a

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process in which cancer cells spread from the primary tumor (where it started) to different area(s) of the body. Cancer metastasis is the primary cause of morbidity and mortality which is responsible for about 90% of total cancer deaths [7].

This review is aimed to provide an overview of the action, function and reaction of the tumor-associated macrophages during tumor growth, and its role in metastasis process. This review will also throw some lights on anti-cancer therapy and drugs delivery process by TAMs. It is not the intent of this review to provide an in-depth description of each macrophage, types and classification of tumors and metastasis of various tumor as each topic itself can be a lengthy review. It hoped that this review can serve as a lead for readers who are interested in the recent development of the functions of TAMs during tumor metastasis.

2. Tumor-associated myeloid cells: differentiation pathways

The cellular content of solid tumors is characterized by the presence of a leukocyte infiltrate including lymphocytes and myeloid cells from early stages. Recent evidence indicates that among leukocytes, myeloid cell populations represent a prominent component, both regarding number and functions, supporting tumor growth and progression and has prognostic value [8]. Tumor-associated myeloid cells (TAMC) contain five distinct myeloid populations- (1) Tumor-associated macrophages (TAM), (2) Monocytes expressing the angiopoietin-2 (Ang-2) receptor Tie2 known as Tie2-expressing monocytes or (TEM), (3) Myeloid-derived suppressor cells (MDSC), (4) Tumor-associated neutrophils (TAN), and (5) Tumor-associated dendritic cells (TADC) [8].

Tumor-associated macrophages are usually the most abundant immune population in the tumor microenvironment due to the early infiltrating leukocyte populations within the tumors [9]. They develop from blood monocytes which actively engaged from the circulation into tumor tissues. Aptly stimulated macrophages can kill tumor cells *in vitro,* shown by early studies; however, TAM, conditioned by the tumor microenvironment, loose the cytotoxic capability and rather exert several pro-tumoral functions, mediating cancer-related inflammation, angiogenesis, immunosuppression, tissue remodeling, and metastasis [9,10].

TAM is a hallmark of myeloid which shows heterogeneous behavior, and the cells overgeneralized in a polarization concept with two extreme M1 and M2 phenotypes with distinct and somehow contrasting functions [11]. Classically activated or M1 macrophages are bacterial products and Th1 cytokines (e.g., LPS/interferon-γ). M1 macrophages strongly produce inflammatory and immune stimulating cytokines, trigger adaptive responses, secrete reactive oxygen species (ROS) and nitrogen intermediates, and have a cytotoxic effect towards transformed cells. In contrast, alternatively activated or M2 macrophages differentiate in response to Th2 cytokines (e.g., interleukin (IL)-4, IL-13) [12]. In conflict with their M1 counterpart, M2 macrophages produce growth factors, leading to tissue repair and angiogenesis activation, which have high scavenging activity, and also acts as inhibitive adaptive immune responses [5,8]. As a result, macrophages are a very heterogeneous cell population, which can display different functions depending on the context. Macrophages can be either immunosuppressive which inhibits inflammation or immune stimulatory at the beginning of the inflammatory response [5,8,13].

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of early myeloid progenitors, immature granulocytes, macrophages, and dendritic cells at different stages of differentiation. It also has the ability to suppress T-cell functions [14]. MDSC accumulate in the blood, bone marrow, and secondary lymphoid organs of tumor-bearing mice. Their presence in the tumor microenvironment has been suggested to have a causative role in promoting tumor-associated immune suppression and local tumor-associated factors promote their activation [15].

MDSC, isolated from blood of patients with glioblastoma, colon cancer, breast cancer, lung cancer, or kidney cancer of human are poorly defined [16,17]. Recent studies of human MDSC projected that they have a characteristic $CD34^+$, $CD33^+$, $CD11b^+$, and $HLA\text{-}DR^-$ profile [18]. Likewise, human MDSC is divided into two main subsets: (1) Monocytic MDSC (M-MDSC) which characterized by the expression of CD14, and (2) Granulocytic MDSC (G-MDSC), which is recognized by positivity for CD15.

A recent study shows that a small number of dendritic (DC) found in most human and murine neoplasms have an immature phenotype (iDC). Likewise, to macrophages and neutrophils, plasticity is the main feature of these cells. DC localized in different forms in tumors; such as, in breast cancer immature $langerin^+$ DC interposed within the tumor mass, whereas more mature $CD83^+$, $DC\text{-}LAMP^+$ DC are limited to the peritumoral area [8,19] (See Fig. 1). Q6

3. Major role of innate immune cells during cancer and anticancer immunity

"The first line of defense" against pathogens and cancers are the innate immune system. They engrossed into the tumor site in any tumor, where they can recognize the transformed cells. Due to the interaction between tumor cells and innate immune cells in the tumor microenvironment, innate immune cells lead to the promotion of tumor growth, angiogenesis, and metastasis. Therefore, before developing any strategies for immunotherapy of cancer, profound knowledge of the innate immune system in tumor immunity and tumorigenesis is a must.

3.1. Natural killer (NK) cells

Natural killer (NK) cells are effectors cells which are considered to play a critical role in the early innate immune response to antitumor immunity [20]. Natural killer cells, by their morphology, their expression of lymphocyte markers, and their origin from the common lymphoid progenitor cell in the bone marrow, were qualified as lymphocytes. CXCL12 and

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