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Tumor Associated Macrophages (TAMs) In the World of Cancer

" *The Most Difficult Thing in Life Is To Know Yourself*"
Thales

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Abstract

Cancer is a disease extremely difficult to defeat. Besides tumor cells, the microenvironment is influencing progress and metastasis. Recently, it has been discovered that macrophages may promote progress of the tumors. Those tumors associated macrophages (TAMs) are still not completely defined and their role not fully described. If the phenotype of the macrophages can influence the outcome of the tumor disease, the focus should be on TAMs and their potential in development of personalized therapy in fighting metastatic tumors.

Abbreviations: TAMs: Tumor Associated Macrophages; CSF-1: Colony Stimulating Factor 1; M-CSF: Macrophage Colony Stimulating Factor; ECM: Extracellular Matrix; EGF: Epidermal Growth Factor; TNF: Tumor Necrosis Factor; VEGF: Vascular Endothelial Growth Factor; MMP: Matrix Metalloproteinases; TGFβ: Transforming Growth Factor β; NFkB: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B cells

Introduction

Steps necessary for the change from normal to malignant cell include numerous alterations in cell physiology. For example, cancer cells gain mutations and do not respond to external inhibitory signals. Additionally, changes in their DNA allow them to proliferate without need for the external growth factors [1,2]. Moreover, surrounding environment in necessary for the progression of tumors. In 1863, Rudolf Virchow proposed that tumor initiates at the site of chronic inflammation and that tissue injury with inflammation may increase cell proliferation and cancer progression [3]. In 1986, Dvorak made an expression "tumors are wound that never heals", thus comparing tumor with parasites evoking wound healing response to obtain the surrounding stroma for their survival and growth [4,5]. Inflammation may involve macrophages, neutrophils, pro-inflammatory cytokines, vasoactive amines and reactive oxygen species (ROS) [6]. Although, in immunocompetent hosts, immunogenic cancer cells are regularly eliminated by the cells of the immune system and weakly immunogenic variants grow to form tumors [2], tumor microenvironment changes the function of macrophages from the pro-inflammatory (i.e. tumoricidal) to pro-tumoral phenotype, thus macrophages promote tumor development [7]. The main features of macrophages are heterogeneity and plasticity. Two extreme phenotypes are M1, that are classically activated macrophages characterized by IL-12^{high}IL-23^{high}IL-10^{low} and on the other end M2, characterized by IL-10^{high}IL-12^{low}IL-23^{low} [8]. The hypoxic tumor microenvironment through production of lactic acid and Hypoxia-inducible factor 1-alpha (HIF-1α), induces an M2-type polarization [8,9]. It has been suggested that tumor associated macrophages (TAMs), component of the stroma of progressing tumors, express characteristics of M2-phenotype [8].

Tumor Associated Macrophages (TAMs)

Tumor-associated macrophages (TAMs) are present in the tumor microenvironment and considered necessary for the tumor progression and metastasis [10]. In humans, TAMs are usually identified by expression of CD163, CD204, or CD206 on the cell surface [11]. In lung, breast, and thyroid cancer tissue samples there was higher CD163-positive macrophage densities than in normal tissues. Moreover, CD163-positive macrophage density negatively correlates with five-year cancer survival rate in several human cancers (10). TAMs originate from the bone marrow monocytes. Monocyte infiltration in tumors is dependent on chemokines (e.g. CCL2, CCL5, CXCL12) and the growth factor, the colony stimulating factor 1 (CSF-1), also known as macrophage colony stimulating factor (M-CSF) [12]. There are two ways how TAMs support tumor progression. Firstly, TAMs positively influence tumor growth, angiogenicity, and extracellular matrix (ECM) degradation, and secondly, suppress potential antitumor immune response [13]. Tumor growth is supported by production of cytokines and growth

factors (IL-6, low concentrations of Tumor necrosis factor, TNF and Epidermal growth factor, EGF). Furthermore, TAMs secrete pro-angiogenic factors, such as Vascular endothelial growth factor (VEGF) and IL-8 [12].

The hypoxic microenvironment influences the increased expression of endothelin 1 and 2 by tumor cells, that stimulate the release of Matrix metalloproteinases (MMP2 and MMP9) from macrophages, promoting ECM degradation [14]. It was already shown, that endothelin 1 is implicated in the fibrotic process and that induces M2-phenotype in cultured human macrophages [15]. Moreover, TAMs produce IL-10 and Transforming growth factor β (TGFβ), also known as immune suppressing cytokines. Additionally, production of chemokines CCL20 and CCL22, recruit regulatory T cells (Treg) thus negatively influences the immune reaction against tumor antigens [12]. IL-10-immunosuppressive role may be due to its ability to inhibit Nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) activity, since NFkB plays a central role in the control of inflammation and immunity [16].

Metastasis is also promoted by TAMs. Migration of tumor cells from tissues to blood vessels is dependent on EGF signalling. TAMs and tumor cells are stimulated by CSF-1 and EGF, respectively, thus the "lock-step" migration through ECM is activated [17]. From the peripheral blood of patients with breast, pancreatic, or prostate cancer, circulating cancer-associated macrophage-like cells were isolated using precision microfilters under low-flow conditions. These cells were not found in healthy individuals, while in cancer patients were bound to circulating tumor cells. Cells were expressing epithelial, monocytic and endothelial protein markers, thus showing that TAMs play a role in tumor cell migration [11]. Localization of TAMs is also implying its role in the tumor migration. TAMs are usually located in the areas of tumor invasion and in the perivascular areas, the place where cancer cells intravasate in the blood or lymphatic circulation [18]. During mammary gland development, macrophages promote collagen fibrillogenesis. Fibrillar collagen 1 has been shown to speed up the movement of macrophages and tumor cells, for up to ten times the speed comparing to their movement through the tumor stroma [19].

We can suggest that movement of macrophages is dependent on tumor environment. It has already been shown that macrophages can use, both mesenchymal and amoeboid mode of migration and additionally the mode between the two, [20]. It has already been described that tumor cells can use mesenchymal or amoeboid migration during metastatic spread [21]. In the absence of macrophages, breast carcinoma (SUM159PT) cells layered on Matrigel, infiltrated the matrix using the mesenchymal migration mode, with the activation of MMPs. On the other hand, in the presence of macrophages, tumor cells used amoeboid mode of migration. There is a possibility that tumor cells could follow macrophages using amoeboid movement, when ECM is already remodelled by macrophages activity [18].

Tumor Associated Macrophages in Human Cancers and Conclusion

The localization of TAMs in colorectal tumors has different influence on patients' survival. It seems that TAMs infiltrating tumor, promote its progression, while TAMs outside tumor nests, relate to good prognosis [12]. In triple negative breast cancer, high numbers of infiltrating macrophages are associated with a significantly higher risk of distant metastasis and decreased disease-free and overall survival. In endometrial adenocarcinoma, the presence of TAM relates to advanced disease staging, high tumor grade, increased lymph vessel density, lymphovascular space invasion, and lymph node metastasis [19]. A high density of infiltrated TAMs is associated with aggressiveness of gastric cancer, as well [11]. Personalized treatments are the future in fighting tumors. TAMs can both promote and inhibit cancer progression. Determining TAMs heterogeneity and defining parameters influencing it can be an important step in producing more personalized treatment for cancer patients [9].

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