Tumor-Associated Macrophages in the Prospect of Development of Targeted Anticancer Therapy

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Abstract—The tumor-associated macrophages (TAM) form about 80% of the total stromal leucocytes’ population in solid tumors. TAM multidirectional influence on tumor growth is the consequence of phenotypic and functional heterogeneity of this cell population. The exceptional role of TAM in tumor progression makes them an attractive model for development of the methods of directed antitumor therapy. In this review, the main groups of the antitumor therapy methods, which include the use of TAM, which are directed towards the suppression of tumor angiogenesis, and which are also directed to reactivation of antitumor action of mononuclear phagocytes, are analyzed.

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INTRODUCTION

The most important macrophage functions are: host defense from pathogens aggression and elimination of the host’s malignant cells. However, presence of macrophages in neoplastic tissue leads to their alternative polarization and transformation into the cells-allies of a malignant neoplasm. The mononuclear phagocytes that were involved and polarized in the tumor’s growth area facilitate the proliferation of tumor cells and play an important role in their invasion into surrounding tissues and also in formation of local and distant metastases.

Phenotypic and functional heterogeneity of macrophages is caused by the pluripotent nature of their functions. Macrophages belong to the category of mononuclear phagocytes. They are derived from the myeloid precursors that are localized in bone marrow, the spleen, and also in the fetal liver. Myeloid precursors are developed to the stage of promonocytes and, then, are differentiated to monocytes. Newly formed monocytes (“inexperienced” macrophages) leave the unique environment of the bone marrow and enter the blood. In circulating blood they are exposed to a plethora of agents (including cytokines, chemokines, adrenergic and cholinergic agonists, hormones, immunoglobulins, fatty acids, et al.), which are capable of impacting their functional and phenotypic characteristics [1, 2]. Circulating monocytes selectively home to different tissues under the influence of chemokines or other tissue-specific homing factors; by virtue of adhesion, they home to vessel endothelium. Adhesion of circulating monocytes to vessel endothelium is mediated by interaction of ligands such as LFA-1 on the surface of monocytes and by the molecules of intercellular adhesion (ICAM-1, E- and P-selectins) on the surface of endothelial cells. After extravasation, the monocytes migrate into tissue; under the influence of its microenvironment they differentiate transforming into resident macrophages and remain there throughout 30–90 days. After that, they die or emigrate into a regional lymph node. Phenotypic and functional heterogeneity is the distinctive feature of macrophages, it is mediated both by the tissue microenvironment and by natural activating stimuli. Key phenotypic markers are found on the surface of resident macrophages in different tissues; however, a marker’s expression level in various tissues is different – it depends on the tissue’s function specialization: CD14 is found on a membrane of circulating macrophages of high quality, but it is practically absent in alveolar macrophages; Fc\gamma Rs are widely found in peritoneal macrophages and are suppressed in the womb’ resident and deciduous membrane cells [3, 4]. Independently of constitutive or induced migration, the ligands, to which macrophages are bound, cause an effect on macrophages: transformed host cells, modified molecules, exogenous agents, etc. These ligands are identified by different surface cell receptors; in each certain case this leads to stimulation of phagocytosis, endocytosis, intracellular signaling, complex changes in activation or inhibition of various genes, and synthesis of over 150 biologically active mediators [5]. According to the Th1/Th2 dichotomy of the immune response, there are at least two tendencies in macrophage activations: classic (M1) and alternative (M2). The interplay between macrophages and the inflammatory agents such as pathogen-associated microbe structures or proinflammatory cytokines (for instance, IFN-\(\gamma\)) leads to proinflammatory (classic) activation of these cells, which is consequently followed by secretion of the proinflammatory cytokines, reactive oxygen species, nitrogen oxide, etc. In total,
such macrophage activation leads to development of the inflammatory process and to induction of the Th1-type immune response [6]. Over-proinflammatory activation of macrophages could serve as a pathogenic factor of some human diseases (gout, ischemic disease, et al.). The alternative macrophage activations lead to development of the Th2-type immune response. Such macrophages practically lose cytotoxic activity. In spite of the MHCI-molecules formation, they are not capable of complete antigen-presentation. Instead of this, such cells accomplish the functions of regulatory cells. The classic and alternative activation of macrophages lead to distinctly directed arginine metabolism. During the classic activation, the iNOS metabolizes arginine with NO formation, whereas, during the alternative activation, the Arg-1 arginase enzyme is synthesized and it polymerizes arginine to urea and ornitine (a precursor of polyamines and proline). Polyamines are involved in the processes of cell growth, and proline is a key component of collagen [7]. Alternatively activated macrophages are divided into three subgroups depending on the polarizing stimuli: M2a stimulated by IL4 along with IL13, M2b activated by immune complexes in the presence of IL1β or bacterial lipopolysaccharide; M2c activated by IL10, TGF-β or glucocorticoids [8]. This way of macrophage activation is involved in the processes of morphogenesis such as wound healing, reconstruction of endometrium during menstruation, and others. The alternative macrophage activation transforms them into tolerogenic antigen-presenting cells with regulatory properties. Generation of growth factors and cytokines by these cells activates cell proliferation and angiogenesis. The alternative macrophage activation facilitates the progress of some human diseases like atherosclerosis and cancer [9].

Tumor-associated macrophages (TAMs) are formed from the circulating monocytes recruited to the growth zone of a malignant neoplasia, because one of the physiologic functions of the immune system is identification and rendering of the transformed cells. Most monocytes, which are transformed to TAMs, are recruited to the tumour’s growth zone from circulation with the use of CCL2 (MCP-1) and CCL5 (RANTES) chemokines [10, 11]. The CCL2 biological effect on tumor growth possesses a peculiarity of dose dependency: a low level of its expression is associated with tumor progression; a high level of its expression is associated with tumor regression, which is probably mediated by the M1 macrophages into the tumor’s growth zone [12]. CCL5 is generated by the naive T-cells and also by the cells of some tumors. This chemokine causes the monocytes migration into the tumor’s growth zone; it also causes the expression of a group of chemokines for myeloid cells such as CCL2, CCL3 (MCP-1x), CCL4 (MCP-1β), and CXCL8 (IL8) [13, 14]. The malignant neoplasia cells are characterized by production of the other chemokines too: CCL8 (MCP-2), CCL-18 (MIP-4), CCL-22 (chemokine of the macrophage’ origin) [15]. Recruiting of monocytes into a tumor is also under the control of cytokines; CSF-1 and VEGF play a key role in this process. Generation of the cytokines mentioned above is characteristic to many types of tumors such as ductal carcinoma, colorectal cancer, ovary cancer, and many others. CSF-1 stimulates proliferation, differentiation and viability of mononuclear phagocytes, and also facilitates malignant tumor infiltration by monocytes [16]. The VEGF level in the tumor’s growth zone correlates with the TAMs content. This cytokine stimulates migration of circulating monocytes into the tumor’s growth zone and mediates homing of myeloid cells into the regions of tumor neovascularization causing CXCL-12 (stromal cells’ factor-1) expression by the structural tumor cells [17]. ET-1, ET-2, and ET-3 endothelins are the effective factors recruiting mononuclear phagocytes into the tumor’s growth zone. Besides the capacity to stimulate proliferation and invasion of malignant cells, ET-1 possesses a chemoattractive activity according to monocytes and neutrophils. ET-2 mediates recruiting of macrophages into the tumor, their localization in the hypoxic zone, and activation of these cells to produce biologically active compounds, which facilitate tumor progression; for instance, matrix metalloproteases 2 and 9 [18].

The functions of macrophages in the tumor’s growth zone are widely diversiform and, sometimes, paradoxical. It was supposed that for a long time the top-priority and only function of TAMs was a direct cytotoxic effect on malignant cells, and also phagocytosis of apoptotic cells and cell debris. Today, knowledge about the functions of TAMs is much wider. It is known that the monocytes recruited to the tumor’s growth zone are capable of being functionally diversified in two populations: M1-cells, which are involved in activation of anti-tumor immunity, and M2-cells, which facilitate tumor progression [19-21].

Activation of the anti-tumor immune response of M1-TAMs is connected with a tissue’s stroma reconstruction, which conducts tumor growth. During the process of reconstruction, the anti-inflammatory mediators are expressed; these mediators recruit monocytes and also dendritic cells and natural killers to the tumor’s growth zone that leads to significant increasing of the IFN-γ and IL12 levels inside the zone. The recruited monocytes immediately differentiate into the M1-macrophages, and the monocytes are also activated to form IL12, which stimulates natural killers and dendritic cells to generation of IFN-γ. Under the IFN-γ effect, TAMs are stimulated to cytotoxic activity and to formation of reactive oxygen species and NO involved in apoptosis activation. Lysosomes are the main targets of reactive oxygen species in cells (including malignant cells). Oxidation causes destabilization of lysosome membranes, which leads to the release of lysosome enzymes and to cell damage. For the purpose of protection, the process of autophagy is activated in cells; however, prolonged oxidative stress leads to so called “autophagic cell death”, which is now classified as a related to apoptosis form of programmed cell death [22–24]. TNF-α, which is produced by phagocytes,