The role of tumor-associated macrophages in solid malignancies – an overview of current knowledge

Jozef Murić, Jaroslava Chyliková, Jozef Skarda, Maria Miklosova, Vojtech Kamarad

Tumor-associated macrophages are an important part of the tumor microenvironment. The presence of certain populations of macrophages within tumor tissue may be associated with either better or worse disease prognosis. The study of these cells is currently receiving a great deal of attention, with the most important topics of investigation raised being: the typification of subpopulations of tumor-associated macrophages; identification of the prognostic significance of population density and distribution of macrophages in the tumor microenvironment; ways to influence macrophage activity, migration and differentiation within the tumor. The answers to these questions can improve the efficiency of immunotherapy for malignancies. The presented article briefly reviews recent findings on tumor-associated macrophages in solid malignancies.

Key words: tumor microenvironment (TME), tumor-associated macrophages (TAMs), resident tissue macrophages (NTAMs), classically activated macrophages (M1), alternatively activated macrophages (M2)

INTRODUCTION

Malignant tumor tissue consists of tumor stroma and tumor parenchyma, which together form a tumor microenvironment (TME). The survival, growth and invasion of tumor parenchymal cells depend on their interactions with stromal cells, which consist of non-malignant cells of different cell types.1-5

Macrophages are an important part of the tumor microenvironment.6-28; different populations of macrophages coexist within and around the tumor. In general terms, these are populations of tumor-associated macrophages (TAMs) as well as macrophages belonging to resident tissue macrophages, thus classified as non-tumor-associated macrophages (NTAMs). Garrido-Martín et al. report that TAMs in primary lung carcinomas have completely different transcriptional characteristics compared to NTAMs that are present in the surrounding non-tumor lung parenchyma of the same lung resection as in patients treated primarily surgically.4 These findings demonstrate that TAMs undergo modifications as a result of the tumor tissue microenvironment.2-4,6,8,10,12,13,19,24

TAMs control and mediate many processes and interactions within the tumor, as well as interactions between the tumor and the host organism.2-4,6,11. They enter the tumor tissue microenvironment primarily by migration and transformation of circulating monocytes6,13. although some subpopulations of macrophages arise from precursor cells independently of monocytes2,4,8,9,11.

It is well known that, in the tumor microenvironment, macrophages demonstrate ambivalent behavior as a result of their different differentiation2-4,6-8,10,12-15,18. Phenotypic diversity and functional plasticity are characteristic features of macrophages which allow them to perform a wide range of often conflicting tasks2-4,6-8,10,12-15,17,18. Important macrophages effector functions are phagocytosis, antigen presentation, secretion of variety signaling molecules. So they may affect antitumor immune response, angiogenesis and also inflammation.

Under the influence of various signals, macrophages can alter the range of expressed genes, the spectrum of surface membrane molecules and the production of metabolites and mediators. We are talking about the polarization of macrophages2,8,11,12,17,18,29. Classically activated macrophages are pro-inflammatory and have an inhibitory effect on the tumor; they are referred to as M1 macrophages. Alternatively activated macrophages are anti-inflammatory and they promote the persistence, or progression, of the tumor respectively. They are referred to as M2 macrophages2-4,6-8,10,12,13,19,20,24.

Recent studies point to the pitfalls of the rigid division of TAMs into the classes of M1 and M2 macrophages6,29-31. Traits of the M1 and M2 phenotypes are not mutually exclusive, even in a particular cell6,8,16,20,30. Garrido-Martín et al. demonstrated that in some patients with primary lung adenocarcinomas and squamous-cell carcinomas, a portion of M2 macrophages showed strong simultaneous expression of M1 markers (M1hotTAMs),

Corresponding author: Jaroslava Chylikova, e-mail: jaroslava.chylikova@osu.cz

© 2021 The Authors; https://creativecommons.org/licenses/by/4.0/

Received: September 16, 2021; Revised: September 16, 2021; Accepted: December 1, 2021; Available online: December 17, 2021

Department of Pathology, Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic and Department of Clinical and Molecular Pathology, Faculty of Medicine and Dentistry, Palacky University, Olomouc, Czech Republic

Corresponding author: Jaroslava Chylikova, e-mail: jaroslava.chylikova@osu.cz
these were identified using CXCL9. The presence of M1hotTAMs in the tissue microenvironment of primary lung carcinoma was associated with intense tumor infiltration by resident cytotoxic tissue memory cells CD8 + TRM and with concomitant better survival. Although the mechanisms leading to T cell colonization of the tumor are only partially known, M1hotTAMs play an important role. They have a high expression of CXCL9, CXCL10, CXCL11 and CXCL12; these molecules are potent chemotactants and activators of T cells. The presence of M1hotTAMs in the tumor is associated with a higher rate of CD8+ and CXCR3+ T cell infiltration. Higher population density of tumor infiltrating T cells within non-small cell lung carcinoma is associated with a better prognosis of the disease. M1hotTAMs also express a large number of surface antigen presenting molecules. The high rate of presentation of tumor antigens contributes to the maintenance of T cell infiltration of the tumor.

Therefore, expression of M2 markers by macrophages does not necessarily guarantee their immunosuppressive action. Patients with primary lung adenocarcinoma infiltrated with M1hotTAMs had better survival rates regardless of concomitant coexpression of M2 markers.

M1 and M2 TAMs represent heterogeneous groups of cells that can be further subtyped into subgroups with dramatically different transcriptomes.

The population density of macrophages in the tumor microenvironment, as well as their phenotypic and functional differentiation, is influenced by various factors. The tumor produces TDCF (tumor-derived chemotactic factor), which is identical to CCL2 (C-C motif chemokine ligand 2) and increases the migration of monocytes into the tumor. Tumor cell secretion affects the transcriptional profile of macrophages and their polarization, leading to shifts in the balance between M1 and M2 features of macrophages in the tissue. Balance between M1 and M2 macrophages may be influenced by oxygen availability in tumor parenchyma, or by variety of stress conditions such as endoplasmic reticular stress, oxidative stress, osmotic stress and also cytokine stimulation.

Apoptosis and necrosis are important events in the tumor microenvironment. Tumor cell apoptosis promotes M2 and suppresses M1 polarization. At the molecular level, S1P (sphingosine-1-phosphate) and microRNA-375 are possible factors derived from apoptotic cells that influence the polarization of macrophages.

The effect of necrosis is probably complex. Reiter et al. report the potentiation of the antitumor properties of macrophages by necrotic cells through increased NO production. Other studies highlight the absence of inflammatory cytokine production following phagocytosis of necrotic tumor fragments and increased infiltration of necrotic tumor sites by macrophages. These events support tumor progression.

Hypoxia in the tumor microenvironment is associated with the production of hypoxia-induced chemotactic factors. Accumulation of M2 macrophages in hypoxic areas of advanced tumors is known as an angiogenesis promoting factor.
such as atezolizumab, durvalumab or avelumab, and also new PD-L1 inhibitors in clinical developments, although there are likely more numerous mechanisms at play. TAMs express a wide variety of inhibitory immune control checkpoint ligands that are different from those to which immunotherapy is directed. These ligands can induce a state of strong immunosuppression. TAMs can bind a therapeutically administered antibody to its Fc receptor, several times more intensely and for a longer duration than the receptor of the target T cell. By this binding, they weaken the therapeutic effect of the used antibody.

Angiogenesis inhibitors slow the growth of a tumor by compromising its adequate supply of nutrients and remediating the products of its metabolism. During treatment with angiogenesis inhibitors, hypoxia is accentuated in the tumor tissue. Hypoxia potentiates the chemotraction of macrophages into the tumor microenvironment, which in turn produces growth factors, such as VEGF, TNF-α, IL-1β, IL-8 (CXCL8), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), thymidine phosphorylase, MMPs and other molecules important for angiogenesis. The high density of TAMs has been evaluated by several studies, as a poor prognostic factor in relation to treatment with angiogenesis inhibitors. The logical conclusion is that the reduction in the density of TAMs, respectively to the density of some of their populations, in the tumor microenvironment may potentiate the effect of treatment with angiogenesis inhibitors. Dalton et al. reported an improvement in the effect of anti-VEGF monoclonal antibody treatment by zolendronic acid-induced depletion of TAMs in several ovarian cancer tumor models.

CONCLUSION

Macrophages are an important part of the tumor microenvironment. They are characterized by great phenotypic diversity, which predetermines their diverse functions.

Depending on the cell phenotype and functional differentiation, macrophages may potentiate or suppress tumor growth. Investigation of the role of individual populations of macrophages in the development of cancer illness depends on the accuracy of their identification. Expression of a particular trait need not be exclusive and preclude co-expression of the traits of others.

Tumor stromal cells are genetically stable compared to tumor parenchymal cells. They could thus be a beneficial therapeutic target, with more predictable behavior.

Influencing the activity, migration and differentiation of macrophages, due to their key role in the tangle of cell interactions, can be reflected in the overall effectiveness of anticancer treatment. Macrophages thus represent a hope for increasing the effectiveness of existing treatment modalities and possibly for the development of completely new methods in the treatment of malignant diseases.

Author contributions: JM: literature search, manuscript writing; JCH: manuscript writing; MM: critical revision; JS: critical revision; VK: concept, critical revision.

Conflict of interest statement: The authors state that there are no conflicts of interest regarding the publication of this article.

REFERENCES: