

# The involvement of tumor-associated macrophages in carcinogenesis

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## ABSTRACT

The Tumor Microenvironment (TME) contains a significant amount of Tumor-Associated Macrophages (TAMs), a highly changeable heterogeneous population with complex impacts on carcinogenesis and development. TAMs release a wide range of cytokines, chemokines, and proteases that encourage extracellular matrix remodeling, tumor cell proliferation and metastasis, tumors vascular and lymph angiogenesis, and immunosuppression. TAMs

with various morphologies have varying effects on the growth and metastasis of tumors. TAMs are a particularly desirable target to suppress tumors growth and metastasis in tumors immunotherapy because they play a crucial role in the formation and development of malignancies. The association between TAMs and the tumors microenvironment is discussed in this article along with its applications in tumor therapy.

**Key Words:** *Macrophages; Solid tumors; Immune response; Cancer cells; Tgf-B; Cytokine; Tumor-associated macrophages*

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## INTRODUCTION

The tumor creates a special microenvironment since it is surrounded by immune cells, neovascularization and its endothelial cells, Cancer Associated Fibroblasts (CAFs), and Tumor-Associated Macrophages (TAMs) as well as a significant amount of malignant epithelial cells. Now, the complex alterations in carcinogenesis and development cannot be entirely explained by the genetic and biological defects of tumors cells alone. As a result, more and more research is focusing on how the tumour microenvironment affects the growth of tumors.

The majority of inflammatory cells seen inside tumors are macrophages, commonly referred to as tumor-associated macrophages. They are heavily implicated in the inflammatory response of tumors and their content can make up more than 50% of the mass of solid tumors. To treat malignancies, target tumors cells alone are insufficient. As a common target, tumors therapy should target both tumors cells and their microenvironment.

TAMs play a substantial role in the tumors microenvironment and are highly desirable targets for tumor immunotherapy.

In order to identify new approaches for treating tumors, this paper discusses the current role of TAMs in carcinogenesis and its relevant applications in tumor therapy.

TAMs' precise genesis has been the subject of debate. According to recent studies, bone marrow monocytes are the main source of TAMs

in mouse models. These cells are drawn to inflammatory signals provided by cancer cells in primary and metastatic tumours, where they develop into TAMs and hasten tumour growth. However, TAMs may also originate from embryonic macrophages, particularly from macrophages deposited in the yolk sac, in malignancies such gliomas and pancreatic cancer. Tumor growth is aided by TAM that is only produced by embryonic macrophages. TAMs differentiate into various tumor-related phenotypes in various tumour microenvironments in both situations.

TAMs can be split into pro-inflammatory M1 type and anti-inflammatory M2 type groups with M2 type macrophages being further differentiated within each group. There are four more subgroups of macrophages: M2a, M2b, M2c, and M2d A subset of M1 macrophages known as traditionally activated macrophages, IFN-gamma (IFN-) along with other pro-inflammatory cytokines and immune-stimulating cytokines including IL-12 and IL-23 induces M1 macrophages. Additionally, it can trigger a Th1 immune response, which can increase inflammation and anti-tumor immunological activity. Additionally, it eliminates infections, destroys tumors cells, and has anti-tumor effects. Surrogate activated macrophages are M2 macrophages. They are activated by IL-4 or IL-4 plus IL-13, secrete IL-10, IL-1 receptor antagonists (IL-1RA), and a number of chemokines, as well as exhibit high levels of arginase, mannose receptor, scavenger receptor, and other receptors. M2 macrophages have a limited

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capacity to deliver antigens and primarily activate Th2 type Tumor growth is facilitated by Th2 type immune responses, which are primarily involved in cell proliferation, angiogenesis, immunosuppression, tissue repair, and interstitial formation.

Most cancers have a predominance of M2 cells, and TAMs are M2 subtypes. M1 polarized macrophages infiltrated by tumors typically have an IL-12 high IL-10 low phenotype during the course of tumour formation, which promotes the immune response and results in tumour cell division. TAMs typically change to the M2 phenotype during the formation of advanced cancers, encourage tumour infiltration and metastasis, and produce a favourable milieu to support tumour survival, tumour growth, and angiogenesis. One of the crucial elements of the tumour microenvironment is the TAM. TAMs typically polarise into M2 macrophage because TME can impair immunological function. In the tumour stroma, M2 type TAMs are widely distributed and are capable of producing a high number of immunosuppressive chemokines and factors. By decreasing antigen presentation and obstructing T cell activity, it can reduce tumour immunity.

TAMs can impede the normal progression of antigen presentation, for example, by secreting cytokines and inflammatory mediators like IL-10, Transforming Growth Factor Beta (TGF- $\beta$ ), Prostaglandin E2 (PGE2), and Matrix Metalloproteinase 7 (MMP-7). This impairs T cells' capacity to recognise or even eradicate tumour cells, which results in the development of an immunosuppressive microenvironment. Among these, TGF- $\beta$  and IL-10 are crucial components of the immunosuppressive milieu. TGF- $\beta$  is an immunosuppressive cytokine that can impair the activity of immune cells such T cells, dendritic cells, and Natural Killer cells (NK). TGF- $\beta$  may reduce the ability of NK cells to destroy tumours by inhibiting the NKp30 and NKG2D receptors, which are involved in NK cell membrane-mediated cytotoxicity. TGF- $\beta$  also reduces CD8+ T cells' capacity to fight tumors. Granzyme A, Granzyme B, IFN- $\gamma$  and FAS ligand are a few of the cell-lysing genes whose expression is being inhibited by this method. Causes the population of Treg cells to grow even more. TGF- $\beta$  also inhibits DC transfer and boosts apoptosis, which decreases antigen presentation, downregulates adaptive immunological responses, and encourages CD4+ T cell development into Th2 cells. TGF- $\beta$  may also cause tumour cells to overexpress IL-10, which activates Th2 immune activity while suppressing Th1 immune activity. This upsets the balance between Th1 and Th2 and eventually prevents the immune system from destroying tumour cells. According to studies, inhibiting TGF-mediated signalling pathways in the TME could enhance the immune system's capacity to eradicate malignancies. A flexible cytokine called IL-10 promotes tumour growth and permits cancerous cells to avoid immune control. Another tumor-derived chemical, PGE2, which controls TAM polarisation via the EP2 and EP4 receptors, is connected to TAMs' capacity to release IL-10. TNF- $\alpha$ , IL-6, and IL-12 production of pro-inflammatory cytokines can be suppressed by IL-10 by reducing the activity of NF- $\kappa$ B. IFN- $\gamma$  may potentially be suppressed by IL-10. When melanoma cells are exposed to IL-10 for 48 hours to 72 hours, up to 100% of homologous CTL-mediated HLA-A2.1 restricted tumour cell specific lysis is totally inhibited. Researchers also discovered that blood IL-10 levels were positively connected with the formation of tumours, indicating that IL-10 is crucial to the growth of tumours. TAMs have a rigorous relationship with angiogenesis, which

is crucial in the development and genesis of tumours. We all know that angiogenesis is crucial for the development and spread of malignant cancers. The process of producing neovascularization from the currently present vascular system is known as tumour angiogenesis. In addition to providing oxygen and nutrients for tumour growth, the development of neovascularization also creates an ideal environment for tumour spread. There is mounting evidence that TAMs are important in controlling angiogenesis. Vascular Epithelial Growth Factor (VEGF), Fibroblast Growth Factor (FGF1), Platelet-Derived Growth Factor (PDGF), Hepatocyte Growth Factor (HGF), Placental Growth Factor (TGF) expressed by TAMs and tumour cells, matrix Metalloproteinases (MMP-9, MMP-2), interleukin (IL)-8, interleukin (IL)-1, and other cytokines play significant synergistic roles throughout the process, of which According to research, lung cancer macrophages' M2 polarisation can increase their expression of VEGF, which in turn promotes tumour angiogenesis.

TAMs also congregate in tumour hypoxic zones, which are identified by hypoxia tension. TAMs' ability to adapt to the hypoxic environment allows them to transmit more angiogenic genes. HIF-1 and HIF-2 play an important role in controlling angiogenesis. TAMs increase the expression of HIF-1 and HIF-2 in the hypoxic tumour microenvironment and the overexpression of this factor can encourage the production of the cytokines mentioned above, including VEGF.

In a study using PyMT mice, doxycycline treatment resulted in a 43% reduction in the number of macrophages in the vicinity of the tumour. using this to reduce the quantity of macrophages Through this level, it is possible to slow the growth of tumours, decrease tumour angiogenesis, and down-regulate the expression of numerous genes that promote angiogenesis. Through research into It was discovered that TAMs play a crucial role in colon cancer tumour formation in an oxidative stress-dependent way, consequently boosting the angiogenic ability of the tumour microenvironment. Neovascularization is encouraged by M2 type immunosuppressive macrophages in the malignant glioblastoma model. According to the study, some TAMs exhibit TIE2 on their surface. These TIE2+ macrophages are linked to tumour angiogenesis and tumour ischemia because they often attach to endothelial cells that express ANG2 (TIE2 ligand, an endothelial cell-specific angiogenic factor). After the recovery is crucial. Lymphangiogenesis and TAMs.

The first stage of the general transfer of tumour cells, called lymphangiogenesis, denotes a bad prognosis for the tumour. The regular operation of the lymphatic system is essential for keeping the body's homeostasis in check as well as for normal metabolism and immunological response. TAMs can significantly speed up lymphangiogenesis through cellular autonomic models and paracrine, according to experimental and clinical investigations. Numerous pre-existing lymphangiogenic factors are among the paracrine effects' many activators.

According to research, macrophages have a role in the development of lymphatic vessels in an inflammatory setting. It was discovered that TAMs have an effect on the proliferation, migration, and capillary-like vessel make-up of lymphatic endothelial cells in the research of TAMs on the occurrence and development of ovarian cancer (LEC). VEGF-C can be released by TAMs. This encourages tumour lymphangiogenesis in addition to helping tumour angiogenesis.

Invasive TAMs in malignant ovarian tumors can encourage lymph angiogenesis by acting on LEC in comparison to a normal ovary. MMP-2 and MMP-9 overexpression in breast cancer can encourage lymph angiogenesis and is intimately linked to lymph node metastases. Maruyama et al. discovered that VEGF-C-expressing CD11b+macrophages can gather in mice corneal stroma and stimulate mouse corneal lymph angiogenesis. TAMs have a significant role in the immunosuppressive microenvironment around tumors. Widespread interest has also been shown in TAMs targeted medication delivery, which may be generally categorized into three categories:

- Reducing or depleting TAMs
  - Encouraging TAM phagocytosis
  - Converting TAMs into tumor-inhibiting macrophages.
- Polarization of TAMs is a popular research topic among them. the targeted Nano carrier that can reprogram TAMs without producing systemic damage by delivering mRNA that has been in vitro translated to encode M1-polarizing transcription factors. In models of glioblastoma, melanoma, and ovarian cancer,

it has been demonstrated that can reverse the immunosuppressive impact. TAMs are reprogrammed into a phenotype that activates anti-tumor immunity and encourages tumor regression by virtue of their tumors support status.

A number of ureido tetrahydrocarbazole compounds have been developed, created, and tested in studies both in vitro and in vivo. Among these, it was discovered that compound 23a may, both in vitro and in vivo, repolarize TAM from M2 to M1 in a dose-dependent manner. A further significant finding is that chemical 23a can considerably slow tumors growth in LLC animal models when tested in vivo. Additionally, research has shown that CHA-encapsulated mannosylated liposomes can improve CHA's immunotherapeutic effectiveness by causing the M2 type to become M1 type. The study to selectively delete particular M2 TAMs offers the opportunity to reduce or deplete TAMs in a way that allows for the eradication of TAMs that promote cancer while preserving TAMs with anti-tumor potential. Using T cell adaptors and EnAd targeting TAMs depletion, a potent therapy that combines direct cancer cell toxicity with the reversal of immunosuppression.