Inflammatory cytokines and immunosuppressive cells in tumor metastasis

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Abstract: Power load forecasting is very important for power dispatching. Accurate load forecasting is of great significance for saving energy, reducing generating cost and improving social and economic benefits. In order to accurately predict the power load, based on BP neural network theory, combined with the advantages of Clementine in dealing with big data and preventing overfitting, a neural network prediction model for large data is constructed.

1. Introduction

Tumor metastasis accounts for more than 90% of cancer mortality, however, current research still knows little about the biological process of tumor metastasis. Although in the past few decades, the treatment methods for cancer have made continuous progress, the mortality rate of cancer has shown a downward trend; For example, in the past ten years, immunotherapy has become an effective means of cancer treatment; However, the existing treatment methods still cannot effectively inhibit tumor metastasis, and the survival period of patients with metastatic tumors or cancer recurrences will not exceed 5 years, and they are facing serious health threats. How to treat tumor metastasis has always been a common challenge faced by basic biologists and clinical therapists.

Tumor metastasis is a complicated and inefficient process. In the biological cascade of tumor metastasis, tumor cells must overcome several obstacles to establish macroscopic metastasis; including loss of cell adhesion, increased cell motility and invasiveness, entry into the circulatory system and survival, and entry into new tissues and eventually colonization of distant organs. There are a variety of factors that drive the metastasis of tumor cells; for example, the accumulation of internal changes in tumor cells themselves can lead to tumor metastasis, and various components in the tumor microenvironment can also promote tumor cell metastasis when acting on cancer cells. The tumor microenvironment usually includes extracellular matrix, various inflammatory cells and cytokines, immune cells, blood vessels, lymphocytes, and fibroblasts. In the 19th century, Rudolf Virchow discovered the presence of white blood cells in tumor tissues, thereby establishing a link between inflammation and cancer development, and proposed the hypothesis that inflammation may promote tumor growth. At present, chronic inflammation is recognized as an important sign of cancer, and at least 25% of cancers are related to chronic inflammation. In most cases of malignant tumors, chronic inflammation does not lead to tumor growth, but promotes tumor progression and metastasis by providing a favorable microenvironment; Including TGF-β, TNF-α, IFN-γ, IL-4, IL-6 and other inflammatory cytokines participate in tumor progression and promote tumor cell metastasis[1]. In addition, convincing evidence shows that the host's immune system also plays an important role in tumor progression. It can not only inhibit tumor development, but also help tumor cells escape immune surveillance to promote tumor growth and metastasis; The immunosuppressive cells that play an important role in this process include myeloid-derived suppressor cells (MDSC), regulatory T cells, tumor-associated macrophages (TAM), regulatory dendritic cells (DCreg), and neutrophils , regulatory B cells, etc[2]. Here, we mainly discuss the mechanism of tumor metastasis mediated by related inflammatory cytokines and immunosuppressive cells, and propose some tumor treatment strategies for these inflammatory cytokines and immune cells.

2. Inflammatory cytokines are involved in multiple stages of metastasis

2.1 Epithelial-mesenchymal transition

Epithelial-mesenchymal transition refers to the biological process in which epithelial cells are transformed into cells with a mesenchymal phenotype through specific procedures. It is an evolutionarily conserved biological process. Epithelial-mesenchymal transition is generally related to tumor metastasis. Through epithelial-mesenchymal transition, tumor cells enhance the ability of migration and invasion, and gain resistance to apoptosis stimuli, which ultimately leads to tumor metastasis. The complex biological process of EMT has been considered as a key sign of carcinogenesis. After years of research, more and more evidences have shown that malignant tumor cells at the tumor border have developed their invasion and stem cell characteristics through epithelial-mesenchymal transition. Tumor cells that have obtained stem cell characteristics have obvious therapeutic resistance, and tumor cells have acquired its transfer characteristics. It is reported that the signal pathways in tumor cells including TGF-β, TNF-α, NF-κB, Notch, Wnt and Hedgehog can cause EMT [3, 4]. TGF-β is a secreted cytokine. Although TGF-β exerts a tumor suppressor effect by inducing cell growth arrest and apoptosis in the early stage of tumorigenesis, in the later stage, TGF-β promotes the growth and development of tumors by initiating the EMT process. TGF-β can activate the EMT process through Smad-dependent and Smad-independent pathways [5]. SMAD is an intracellular transcriptional effector of TGF-β family receptor signal transduction [6]. Changes in E-cadherin levels are one of the main biomarkers of EMT. Snail, Zeb, and Twist are transcriptional inhibitors of E-cadherin expression. Smad mediates the EMT process induced by TGF-β by inducing the expression of Snail, Zeb, and Twist [7]. In the Smad-independent pathway, ERK has been shown to play an important role. In the process of cytoskeleton remodeling, ERK forms a SHC-GRB2-ERK complex with SHC and GRB2, which plays an important role in TGF-β-induced tumor metastasis [8]. Studies have shown that NF-κB is also one of the effective inducers to activate EMT. NF-κB initiates the EMT program by activating Akt. Akt can effectively regulate the expression of Snail, resulting in a decrease in the expression level of E-cadherin protein on tumor cells, resulting in decreased adhesion between tumor cells and improved metastasis ability [9].

2.2 Invasion and infiltration

Tumor cells passing through the endothelium of blood vessels or lymphatic vessels into the circulatory system is a necessary step for distant metastasis. This process is called infiltration. There are many factors that cause tumor cell infiltration, such as non-tumor cells in the tumor microenvironment, proteases and various signaling molecules. These cells and molecules play an important role in promoting tumor cells to enter the circulatory system. The process of tumor infiltration involves the destruction of basement membrane and the remodeling of extracellular matrix. In the process of extracellular matrix remodeling, irreversible proteolysis and cross-linking occurred. This process is coordinated and completed by a variety of enzymes, including serine proteases, matrix metalloproteinases (MMP) and cysteine cathepsin. These proteolytic enzymes are jointly secreted by tumor cells, stromal cells and infiltrating immune cells. Studies have confirmed that mast cells, neutrophils and macrophages can secrete proteolytic enzyme during ECM remodeling. In breast cancer research, mast cells are recruited into the microenvironment of breast tumors and secrete tryptase, which increases the rate of lymph node metastasis and the incidence of breast cancer [10]. Similarly, in a breast cancer model, Vasiljeva et al. found that under the influence of IL-4, the expression of the cysteine protease cathepsin B (CTSB) secreted by macrophages increased, leading to an increase in lung metastasis [11]. Studies have confirmed that in the process of tumor development, the level and activity of cathepsin secreted by macrophages are regulated by IL-4, and IL-4 is produced by T cells [12]. In the tumor microenvironment, IL-4 and IL-13 secreted by immunosuppressive $CD4^+$ T cells can promote the transformation of macrophage phenotype from M1 to M2, and promote lung metastasis of breast cancer [13]. Macrophages play an important role in the process of tumor metastasis. Through the NF-κB and STAT3 signal transduction pathways, cytokines secreted by other immune cells, including IL-6, TNF-α, etc., up-regulate the expression level of MMP in tumor cells [14].

2.3 Circulation and extravasation

The metastatic cascade of tumors includes four processes: invasion, infiltration, extravasation, and the continued growth of metastasis to the secondary site. The tumor metastasis cascade is very inefficient. In the end, only about 0.01% of circulating tumor cells can survive and form tumors at the secondary site. There are many factors that lead to the low survival rate of circulating tumor cells (CTC), mainly including the influence of mechanical shear stress and the killing of CTC by the immune system. Palumbo et al. found that tumor cell-associated tissue factor (TF) can protect circulating tumor cells from recognition by NK cells, thereby increasing the survival rate of circulating tumor cells [15]. The inflammatory mediators released by tumor cells and tumor-related stimuli can increase the survival rate of circulating tumor cells. For example, TNF-α and IL-6 secreted in the microenvironment of tumor cells can increase the survival probability of cancer cells in the circulation. In the study of bone metastasis of breast cancer cells, TNF-α and IL-6 act as osteoclast activating factors on osteoclasts, promote the secretion of RANKL, induce the formation of osteoclasts, and endow breast cancer cells with osteolytic metastasis [16, 17]. Chemokines including CXCR4, CCR4, CCR7 and CCR9 guide the migration of metastatic cancer cells in the circulatory system [18]. CXCR4 and CCR7 are the main chemokine receptors on tumor cells. High levels of CXCR4 and CCR7 in tumor patients usually show a poor prognosis. CXCL12 and CCL21 are the ligands of circulating tumor cell chemokine receptors CXCR4 and CCR7, respectively. Their combination not only promotes the attachment of tumor cells, but also prevents the death of circulating tumor cells by regulating the pro-apoptotic protein Bmf and anti-apoptosis protein Bcl-xL [19]. Studies have reported that inflammation-induced cell adhesion molecules (CAM) promote the adhesion of circulating tumor cells to the endothelial cell walls of organs at the metastasis site, thereby promoting tumor metastasis. Metastasis of tumor cells from lymph nodes to distant organs may be an indirect way of tumor metastasis, and metastatic cells in lymph nodes may have a higher survival rate.

2.4 Niche before tumor metastasis

Whether a cancer cell will metastasize depends not only on the cell itself, but also on the distant microenvironment called the metastatic niche. In 1889, Stephen Paget discovered that circulating tumor cells would only grow in places with suitable soil, and proposed the famous Paget theory, the "seed soil theory." A large number of studies have shown that metastasis niche helps to enhance the survival and reproduction of tumor cells. In the early stage of metastatic growth, cancer cells establish an inflammatory microenvironment in distant organs, which is the key to supporting the metastatic growth of tumor cells. Studies have reported that tumor cells at the primary site mobilize BMDCs to establish a local microenvironment at the distant metastatic site. In the study of breast cancer metastasis to the lung, researchers confirmed that $Gr\text{-}1^{+}CD11b^{+}$ cells have been recruited into the lungs of breast cancer hosts before the tumor cells reach the lungs. $Gr\text{-}1^{+}CD11b^{+}$ cells inhibit the production of IFN-γ in the lungs before metastasis, IFN-γ is one of the key cytokines of tumor immune defense; At the same time, $Gr\text{-}1^{+}CD11b^{+}$ cells increase the inflammatory cytokines in the pre-metastasis niche by establishing an inflammatory microenvironment, induce a large amount of matrix metalloproteinase 9 (MMP9), promote vascular remodeling, and lead to increased tumor cell extravasation [20]. Lysyl oxidase (LOX) is a tumor-derived factor secreted by hypoxia. The expression of LOX is regulated by hypoxia-inducible factor (HIF). Studies have shown that inhibiting LOX can eliminate tumor metastasis in mice with breast cancer tumors; In addition, LOX can also regulate the activity of fibronectin (FN) by activating focal adhesion kinase (FAK), thereby establishing a metastatic niche that is conducive to the growth of metastatic tumor cells [21]. Cytokines related to bone metastasis of tumor cells, IL-6, IL-11 and TNF-α, are secreted by immune cells. It is worth noting that the tropism of organs in the process of tumor cell metastasis depends on a variety of different mechanisms, and the specific effects of these mechanisms on the tropism of metastatic organs still need to be further studied.

3. Immunosuppressive cells promote tumor metastasis

Exploring the relationship between the immune system and cancer progression has always been a research hotspot in the field of tumor immunology. Tumor cells evade immune surveillance and the metastasis of tumor cells leads to the malignant progression of tumors, and may cause the failure of clinical cancer immunotherapy. Existing evidence has shown that the immune system plays a dual role in cancer. It can not only monitor and kill tumor cells to inhibit tumor development, but also interact with components in the tumor microenvironment to promote tumor growth and metastasis. Although innate and adaptive immune molecules and cells can effectively identify and kill cancer cells, that is, cancer immune surveillance, cancer cells have developed a variety of different mechanisms to evade immune surveillance. For example, immunosuppressive cells can help tumors escape anti-tumor immune response. Tumor cells establish an immunosuppressive tumor microenvironment by recruiting immunosuppressive cells into the tumor microenvironment and releasing immunosuppressive cytokines (such as VEGF, TGF-β). Immune cells recruited by tumors can obtain phenotypic and functional changes, from inhibiting tumor status to promoting tumor status. After years of research, it has been discovered that myeloid-derived suppressor cells (MDSC), regulatory T cells, tumor-associated macrophages (TAM), regulatory dendritic cells (DCreg), neutrophils, regulatory B cells, etc. can promote tumor progression [2].

3.1 Myeloid-derived suppressor cells (MDSC)

Bone marrow-derived suppressor cells (MDSCs) are usually produced and secreted by the bone marrow and are immature bone marrow cells. In the process of tumor development, MDSCs are recruited to the tumor site to establish an immunosuppressive tumor microenvironment around the tumor and promote tumor progression. MDSC exerts immunosuppressive function by inhibiting T cell proliferation, cytokine production and cytotoxicity. MDSC can inhibit the release of IFN-γ and IL-2 from T cells to produce immunosuppression. In the periphery, MDSC exerts immunosuppressive function by producing or regulating immunosuppressive metabolites. For example, MDSC inhibits T lymphocytes through the metabolism of L-arginine, human granulocyte arginase inhibits T cell proliferation and cytokine synthesis and release, arginase-mediated consumption of arginine results in the stagnation of activated T lymphocyte proliferation, resulting in immunosuppression[22]. Studies have confirmed that the use of arginase-1 inhibitors can effectively restore the anti-tumor immunity of T cells. MDSC can also inhibit the activation of T cells by consuming cystine and cysteine; The activation of T cells depends on cysteine, in the presence of MDSC, cystine in the microenvironment is consumed and cysteine is not replenished, ultimately inhibits the activation of T cells[23]. Recruitment and regulation of other immunosuppressive cells is a major mechanism of MDSC-mediated peripheral immunosuppression. Ghiringhelli et al. found that MDSC induces the development of Treg cells by secreting IL-10 and IFN-γ[24]. In breast cancer research, MDSC inhibits the production of IL-12 by macrophages and promotes the conversion of macrophages to the M2 phenotype that promotes tumor development[25]. Different from the periphery, MDSCs in tumor tissues have a stronger ability to directly inhibit T cells, which is related to the abundant presence of arginase-1 and immunosuppressive cytokine in the tumor microenvironment. MDSC not only has an immunosuppressive effect, but can also promote tumor angiogenesis and ultimately promote tumor metastasis.

3.2 Regulatory T cells

Thymus-derived regulatory T cells that express FOXP3 and CD25 are immunosuppressive cells. The infiltration of a large number of Treg cells into tumor tissue usually leads to poor prognosis of cancer patients and poor quality of life in the later stage. Studies have confirmed that the removal of Treg cells can effectively enhance the anti-tumor immune response. According to reports, breast cancer cells recruit Treg cells at the primary tumor site by regulating the secretion of prostaglandin E2, leading to $CD8^+$ T cell apoptosis and bone metastasis of cancer cells[26]. Treg cells suppress the T cell immune response through IL-2. IL-2 is produced by activated T cells. Exogenous IL-2 ensures the

survival and proliferation of Treg cells. Treg cells express high-affinity IL-2 receptors, resulting in insufficient amounts of IL-2 acting on T cells, inhibits the activation and proliferation of T cells[27]. Treg cells can not only regulate T cells, but also control NK cells, macrophages and other immune cells through body fluids or cell-to-cell contact. In the study of lung metastasis of breast cancer, the secretion of β-galactoside binding protein (βGBP) by Treg cells induced the apoptosis of NK cells, leading to an increase in lung metastasis of breast cancer cells; Treg cells can also inhibit the cytotoxicity of NK cells by secreting transforming growth factor-β (TGF-β), leading to an increase in lung metastasis[28]. Under hypoxic conditions, tumor cells promote the recruitment of Treg cells by inducing the expression of CCL28, and promote tumor angiogenesis by secreting VEGFA[29].

3.3 Macrophages

Tumor-associated macrophages are the main cell type in the tumor environment, accounting for about 30%-50% of the mass of tumor tissue. Macrophages are derived from immature monocytes released from the bone marrow. Monocytes are recruited into the tumor microenvironment and induced by IL-4 and IL-13 to differentiate into tumor-associated macrophages[30]. Macrophages are divided into non-polarized M0 macrophages, suppress tumor M1 macrophages, and promote tumor M2 macrophages. In fact, TAM is characterized by an immunosuppressive M2-like phenotype, M2 macrophages promote tumor growth and metastasis by affecting the tumor microenvironment. Tumor cells polarize the macrophages around the tumor tissue to the M2 phenotype in a variety of ways. For example, IL-4 and IL-13 promote M2-like polarization of macrophages by promoting STAT6 signaling[31]; IL-4 and IL-10 secreted by tumor cells can also induce M2-like polarization of macrophages[32]; Transforming growth factor β (TGF-β) secreted by tumor cells activates smad2/3 and PI3K/AKT signals to induce M2-like polarization of macrophages[33]. TAM promotes tumor development and metastasis in a variety of ways. TAM activates the NF-κB signaling pathway in tumor cells by secreting TNF-α, enhancing tumor cell survival and cell invasiveness[34]. TGF-β secreted by TAMs can also cause tumor cells to undergo epithelial-mesenchymal transition. FOXQ1 is overexpressed in many cancers. It binds to the promoter region of E-cadherin to inhibit the expression of E-cadherin. TGF- β promotes the expression of FOXQ1 and leads to the occurrence of EMT, thereby promoting the metastasis of tumor cells[35].

3.4 Other immunosuppressive cells

In terms of cancer, tumor-associated neutrophils (TAN) also follow the Th1/Th2 paradigm and exhibit N1 (tumor suppression) or N2 (tumor promotion) phenotypes[36]. Neutrophils release neutrophil elastase (NE) and matrix metalloproteinases (MMP8/9) in the tumor microenvironment to induce extracellular matrix remodeling, promote tumor angiogenesis, and lead to tumor cell metastasis[37]. Studies have reported that regulatory B cells can inhibit the proliferation of $CD4^+$ and $CD8^+$ T cells, and secrete TGF-β to transform $CD4^+$ T cells into a regulatory T cell phenotype[38].

4. Treatment strategy and conclusion

More and more evidences have shown that inflammatory cytokines and immunosuppressive cells promote tumor progression and metastasis through different mechanisms. This means that inflammatory cytokines and immunosuppressive cells are potential targets for tumor targeted therapy. It is a valuable treatment option for key inflammatory cytokines and immunosuppressive cells such as TGF-β, TNF-α, IL-4, IL-6, IFN-γ, MDSC, TAM and Tregs at different stages of cancer progression. For example, targeted inhibition of TGF-β can effectively reduce epithelial-mesenchymal transition[39]; inhibition of IL-4 levels in the tumor microenvironment can reduce cathepsin levels, and inhibit the M2-like transformation of macrophages, reducing lung metastasis of breast cancer[13]; inhibiting the levels of chemokines CXCR4 and CCR7 can effectively reduce the adhesion of tumor cells in the circulatory system and lead to the death of tumor cells[19]; LOX is also a potential target of tumor immunotherapy, inhibition of LOX can eliminate tumor metastasis in mice with breast cancer tumors growing in situ[21]; MDSCs recruited into the tumor microenvironment usually promote tumor

development and metastasis, how to reduce the level of MDSCs in the tumor microenvironment is also an effective treatment; reducing the level of IL-2 secreted by T cells can inhibit the survival and proliferation of Treg cells[27]; targeted inhibition of IL-4, IL-10, and IL-13 can effectively reduce the M2-like polarization of macrophages and so on[32]. The mechanisms by which inflammatory cytokines and immunosuppressive cells promote tumor development and metastasis still require further research and the development of new cancer treatment strategies.

A variety of cancer treatment strategies can be designed for different inflammatory cytokines and immunosuppressive cells, bringing hope to the survival of cancer patients. Nevertheless, there are still many problems and challenges in the immunotherapy of cancer. For example, whether there are differences in the tumor microenvironment between different tumor types or patients with different tumors, or what causes these differences; In addition, in the tumor microenvironment, the relationship between different inflammatory cytokines and immunosuppressive cells and cancer cells is still unclear; While targeting to suppress inflammatory cytokines and immunosuppressive cells, how to not destroy their normal physiological functions; Simultaneously targeting a variety of inflammatory cytokines and immunosuppressive cells may be the most ideal cancer treatment strategy. In general, the biological process of tumors from occurrence and development to metastasis requires continuous exploration.

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