Proceedings of the 3rd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/85/2025.20109

The Role of JAK-STAT in Tumor-associated Macrophage Polarization

Yuting Zhang[1,a,*]

[1]*Xiamen NO.1 High School of Fujian, Xiamen, China*
a. ytzhang09@outlook.com
**corresponding author:*

Abstract: The polarization of tumor-associated macrophages (TAM) in the tumor microenvironment (TME) is closely related to the proliferation, invasion, immune escape and chemotherapy resistance of tumor cells. Promoting M1 macrophage polarization and inhibiting M2 macrophage polarization have become new strategies for tumor treatment. The JAK/STAT pathway is involved in the regulation of TAM polarization. Cytokines in TME, tumor-inhibiting chemicals and Chinese medicines and their extracts can regulate TAM polarization by activating or inhibiting JAK/STAT pathway. Activation of JAK-STAT1 and JAK-STAT5 can induce M1 polarization and inhibit tumor development. Activation of JAK-STAT3 and JAK-STAT6 can induce M2 polarization and promote tumor development. Activation of JAK-STAT1 and inhibition of JAK-STAT6 can induce polarization of M2 to M1. Therefore, it is possible to inhibit tumor development by exploring drugs that can activate the JAK-STAT1 and JAK-STAT5 pathways or inhibit the JAK-STAT3 and JAK-STAT6 pathways. In this paper, the relationship between JAK/STAT pathway and TAM polarization is reviewed, which provides ideas and optimization suggestions for the development of tumor targeted therapeutic drugs.

Keywords: Tumor-associated macrophages (TAM), Macrophage polarization, JAK-STAT, Tumor microenvironment (TME).

1. Introduction

In 2022, there were approximately 19.96 million new cases of malignant tumors worldwide, with a death toll of approximately 9.7 million. It has become a major disease that endangers human health and affects the quality of human life [1]. Although modern medicine has made significant progress in the diagnosis and treatment of malignant tumors, the prognosis is poor. Therefore, developing new treatment strategies to improve the treatment effectiveness of malignant tumors is a major scientific issue that urgently needs to be addressed. Regulating the tumor microenvironment (TME) to prevent the development of tumors and treat malignant tumors has been the main direction of malignant tumor research in the past decade. Tumor associated macrophages (TAMs) are important innate immune cells in TME. TAMs are related to the occurrence, development, angiogenesis, and metastasis of tumors, and participate in the proliferation, invasion, immune escape, and chemotherapy resistance of tumor cells. They are potential therapeutic targets for tumors. Regulating the function of TAMs in malignant tumors is a new direction for immunotherapy. Previous studies have confirmed that the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway is one of the

DOI: 10.54254/2753-8818/85/2025.20109

important cancer pathways, which can regulate the occurrence and development of tumors through multiple pathways by modulating its downstream targets. The JAK/STAT pathway is related to the TAMs polarization. Down regulating the JAK/STAT3 to reduce the macrophages2 (M2) polarization can reduce the growth and metastasis of tumor cells [2]. Therefore, studying the TAMs polarization mediated by regulating the JAK/STAT pathway would be a priority research area in the development of targeted anti-tumor drugs [3].

As so far, there have been a large number of studies on the role of JAK-STAT in polarization of TAMs, most of which have not been clinically validated. The mechanism of JAK-STAT in TAMs polarization, key driving factors, and how to make new drugs exert ideal effects in complex TME are urgent issues that need to be addressed. This article will take the JAK/STAT pathway in TAMs as the starting point, introduce macrophage polarization and JAK/STAT pathway, explain the role of this pathway in TAMs polarization, explore the intervention of tumor treatment methods through this pathway, summarize the research results of intervening TAMs polarization by regulating the JAK/STAT in recent years, and provide ideas for future targeted cancer therapy.

2. TAM polarization affects tumor occurrence and development

Macrophages are innate immune cells differentiated from mononuclear cells derived from bone marrow. Diversity and plasticity are classic features of macrophages. Macrophage polarization refers to the process in which mature macrophages (M0) produce different functional phenotypes under special TME stimulation. The polarization of macrophages plays a crucial role in defending against pathogens, regulating inflammation, repairing tissues, and maintaining body homeostasis. TAM is the main immune cell in TME. Polarized macrophages can be divided into M1 and M2 based on their immune functions. M1 and M2 can change each other under different TME [4]. The phenotype of macrophage types can be evaluated and identified by comparing and analyzing M1 markers (CD16/32, IL-1 β, IL-6, TNF - α, etc.) and M2 markers (CD206/mrc-1, IL-10, etc). M1 promote inflammation and eliminate tumor cells. TAM mainly exists in the form of M1 in the early stages of tumor formation., the proportion of M2 macrophages increases due to the favorable factors for M2 differentiation in TME of most late stage tumors [5]. Promoting angiogenesis, tissue reconstruction, and damage repair are the functions of M2. An increase in M2 promotes tumor growth, invasion, and metastasis. An increase in the proportion of M2 in TME promotes tumor growth, invasion, and metastasis. Engulfing and killing target cells are functions of M1. The ratio of M1 in TME is positively correlated with the survival time of cancer patients [6]. Therefore, immunotherapy strategies targeting TAMs, such as inducing M1 polarization and inhibiting M2 polarization, is a very promising cancer treatment method.

3. The JAK-STAT plays an important role in TAM polarization

The JAK/STAT is a highly conserved pathway. The JAKs gene is a non receptor protein tyrosine kinase family, including four members: JAK1, JAK2, JAK3, and TYK2. The signal transducer and activator of transcription (STAT) family includes seven transcription factors (TFs), including STAT1, STAT2, STAT3, and so on. JAKs initiate receptor tyrosine phosphorylation when extracellular factors bind to natural receptors on the TAMs cell membrane. And then promoting STATs proteins recruit and phosphorylate. Phosphorylated STATs dimerizate and accumulate in the nucleus as TFs, regulating the expression of multiple genes. JAK/STAT is a common pathway used to transduce signals from the extracellular to the intracellular. Abnormal activation of the JAK/STAT is associated with some malignant tumors and inflammatory diseases [7]. A Disintegrin and Metalloproteinase with Thrombospondin motifs-10 (ADAMTS10), secreted by gastric cancer cells, regulates ROS in macrophages through JAK/STAT, inhibits M2 polarization, suppresses gastric cancer cells'

DOI: 10.54254/2753-8818/85/2025.20109

proliferation, migration and invasion, and promotes apoptosis of cancer cells [8]. JAK/STAT pathway can affect the occurrence, development, invasion, and metastasis of tumors by regulating the polarization of TAMs in TME. Therefore, the JAK/STAT pathway in TAM is being explored as a potential therapeutic target for cancer patients [9].

4. JAK-STAT regulates TAM polarization

The JAK and STAT families can form various pathways. Each of them has different effects on TAM polarization. The effects of various JAK/STAT pathways on TAM polarization are summarized in this section.

4.1. JAK/STAT1

JAK/STAT1 is involved in cell differentiation and apoptosis processes, as well as in tumors, chronic inflammation, and autoimmune diseases. More and more evidence suggests that STAT1 is a central TF regulating macrophage polarization and a key TF in M1 macrophage polarization. Activation of STAT1 polarizes macrophage function towards M1 [10,11]. T lymphocyte immunoglobulin mucin-3 (Tim-3) and TAMs derived extracellular vesicle miR-889-3p lead M2 polarization by inhibiting STAT1, resulting tumor promoting [12]. Tripartite motif-containing protein 65 (TRIM65) is an intracellular ubiquitin E3 ligase, plays a role in tumor development by regulating TAMs polarization in the TME [13]. TRIM65 is upregulated in 16 types of cancer, and high levels of TRIM65 are closely associated with higher tumor grade, poorer prognosis, and macrophage immune infiltration levels in cancer patients. The phosphorylation level of JAK1/STAT1 in TAM decreasing induce M2 polarization and promote tumor deterioration. Knocking out TRIM65 activates the JAK1/STAT1 pathway in macrophages, promoting M1 polarization and inhibiting M2 polarization, thereby suppressing tumor development (Figure 1) [3]. The above studies indicate that JAK1/STAT1 is a key pathway for TAM polarization, therefore, targeted drugs that activate the JAK1/STAT1 pathway in TAMs can be researched to inhibit tumor development. For example, Lenvatinib (LEN) is a small molecule multi-target kinase inhibitor, which exhibits effective anti-tumor activity. LEN treatment inhibits the expression of M2 markers (including arginase-1, IL-10, TGF - β, and CD206) and promotes the expression of M1 markers (such as IL-6, IL-1 β, and CD86). Activation of STAT1 promotes M1 polarization, inhibiting M2 polarization and tumor development [10]. However, side effects such as gastrointestinal discomfort and heart failure may occur after taking LEN medication, therefore, the development of safe and non-toxic targeted therapeutic drugs urgently needed.

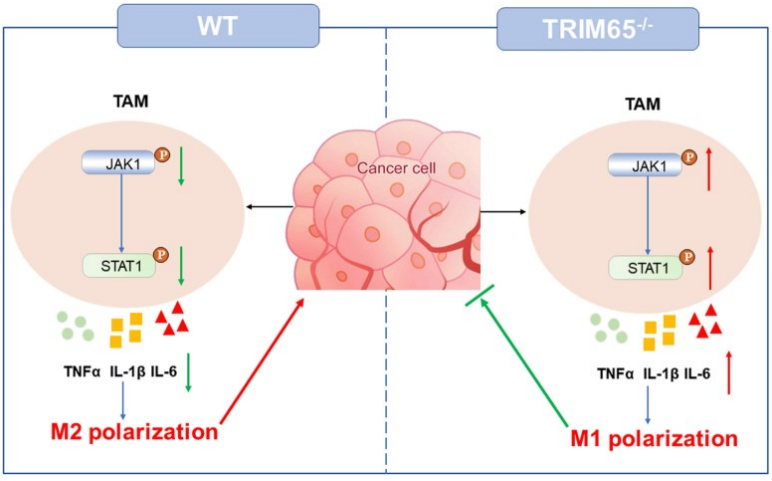

Figure 1: TRIM65-JAK/STAT axis mediates macrophage M1/M2 polarization [3].

DOI: 10.54254/2753-8818/85/2025.20109

4.2. JAK/STAT3

Extensive research has shown that STAT3 is closely related to human tumors, participating in the regulation of macrophage polarization [14]. Reducing JAK/STAT3 activity can alter macrophage function, inhibit tumor growth and metastasis. STAT3 inhibitor WP1066 inhibits STAT3 phosphorylation, which can reduce M2 polarization, thus inhibiting the development of breast cancer. IL-6, IL-10, VEGF, and HSP90α in TME induce M2 polarization by activating the JAK2/STAT3 pathway, promoting tumor cell infiltration [14,15]. Exogenous addition of lipopoly saccharide and paclitaxel also has the same effect. Targeted inhibition of the JAK/STAT3 and suppression of M2 polarization is considered an effective way for the treatment of malignant tumor patients. 2-Methoxyestrol (2-ME) is a normal metabolite of estrogen in the body and has been clinically tested for the treatment of breast, kidney, ovary, prostate, and multiple myeloma. It is an anticancer drug with strong anti-angiogenic activity. 2-ME inhibits M2 polarization by inhibiting STAT3 activation, resulting reduced breast cancer development [2]. However, 2-ME is a poorly soluble drug in water, and oral administration has a first pass effect on the liver, leading to rapid metabolism, low bioavailability, and difficulty in maintaining blood drug concentration. Therefore, further research and clinical application are needed to develop its long-acting drugs. Research has shown that certain traditional Chinese medicines (TCMs) and their extracts can regulate TAM polarization and treat tumors by affecting the JAK2/STAT3. For example, Cucurbitacin B is the main active monomer of Cucurbitaceae plants and has been widely used in the treatment of malignant tumors. It controls M2 polarization by targeting the JAK2/STAT3 pathway to inhibit tumor metastasis. Taraxacum mongolicum extract can promote the transformation of M2 into M1 and inhibit the deterioration of breast cancer by inhibiting the IL-10/STAT3/PD-L1 pathway [16,17]. Therefore, targeted drugs that inhibit JAK/STAT3 can be developed to suppress M2 polarization or promote M2 to M1 polarization, slowing down the progression of tumor diseases. TCM and its extracts are a safe and effective treatment method.

4.3. JAK/STAT6

STAT6 is a powerful target for anticancer drugs, and its activation promotes M2 polarization [11]. Clinical evidence shows that high levels of STAT6 expression in colorectal cancer patients are positively correlated with poor clinical prognosis [18]. Inhibiting M2 polarization by suppressing the activation of STAT6 is an effective targeted therapy for tumors. 23 Hydroxybetulinic acid (23-HBA) is an active ingredient in Pulsatilla chinensis, which inhibits the Jak2/STAT6, suppresses M2 polarization, reduces IL-10 secretion, inhibits the STAT3/Bcl-2 of cancer cells, enhances the therapeutic effect of rectal cancer, and weakens chemotherapy resistance in colorectal cancer [19]. Garcinone E is a natural flavonoid found in the skin of mangosteen fruit. Garcinone E induces cell apoptosis and inhibits cancer cell migration. Research shows that Garcinone E can inhibit the growth and metastasis of breast cancer by inhibiting the activation of STAT6, reducing the M2 proportion, increasing the M1 proportion [20]. Therefore, inhibiting the JAK/STAT6 can suppress M2 polarization, induce M1 polarization, thus tumor growth and metastasis can be inhibited.

4.4. JAK/STAT synergizes to regulate TAM polarization

Each JAK-STAT is not acting alone, but coordinating with each other to regulate TAM polarization and tumor development. For example, activating the STAT5 / NF - κ B, inhibiting the STAT6 pathway in macrophages, promoting M1 polarization, and effectively preventing peritoneal metastasis of colorectal cancer. When pancreatic cancer (PC) cells are co-cultured with monocytes, the growth of PC cells are inhibited by inhibiting the activities of STAT2, STAT3 and STAT6 and activating STAT5 to promote M1 polarization. Tumor necrosis factor superfamil-15 (TNFSF15) acts

DOI: 10.54254/2753-8818/85/2025.20109

on TAMs in three ways: firstly, it promotes the differentiation of bone marrow cells into M1 by activating STAT1/3; Secondly, it promotes the differentiation and polarization of M0 into M1 by activating the MAPK/Akt/ STAT1/3 pathways; Thirdly, it can mediate the M2 polarizated into M1 by activating STAT1/3 and inactivating STAT6, leading to the enrichment of M1 in TME and achieving the characteristic of inhibiting tumor development (Figure 2) [9].

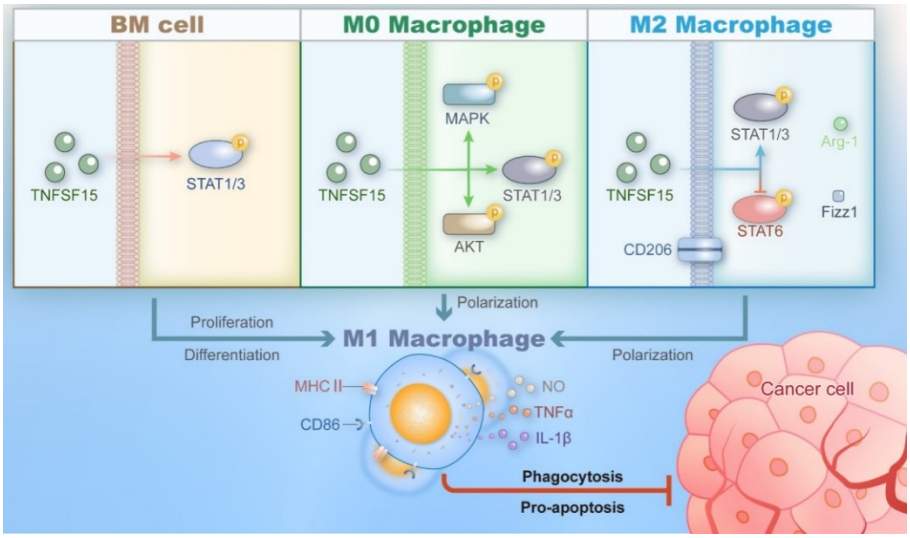

Figure 2: TNFSF15 induced M1 polarization of various origins [9].

In summary, inducing M1 polarization in TME can inhibit tumor development. Inducing M2 polarization can promote tumor development. Different JAK-STATs are regulated in TAM, resulting in different phenotypes. The activation of JAK-STAT1 and JAK-STAT5 can induce M1 polarization and inhibit tumor development. The activation of JAK-STAT3 and JAK-STAT6 can induce M2 polarization and promote tumor development. Activating JAK-STAT1 and inhibiting JAK-STAT6 can polarize M2 towards M1. Therefore, targeted development of JAK-STAT1 and JAK-STAT5 activators and JAK-STAT3/JAK-STAT6 inhibitors can be explored to inhibit tumor growth and metastasis (Figure 3). The main directions of future research include: 1) Regulating cytokines in TME. 2) Knockout or overexpression of genes related to the JAK-STAT. 3) Development of safe and long-lasting targeted chemical drugs. 4) The development and utilization of TCM and its extracts.

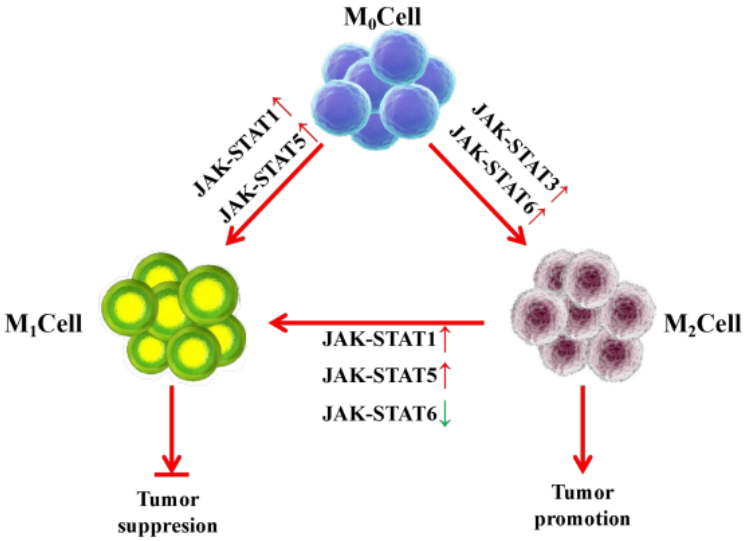

Figure 3: JAK-STAT and TAM polarization.

DOI: 10.54254/2753-8818/85/2025.20109

5. Conclusion

Multiple factors in TME participate in TAM intracellular signaling through the JAK-STAT, regulating TAM polarization. Therefore, It is possible to achieve specificity, clarification, and simplification of TAM polarization control, and provide targets for the development of new drugs through analysis and research on the regulatory sites of the JAK-STAT. It is expected to improve the clinical outcomes of patients with malignant tumors by targeting the JAK-STAT regulators in the polarization mechanism of TAM. More specific new drugs will be developed based on the further research on the JAK-STAT in the future.

References

[1] *Bray, F., Laversanne, M., Sung, H., et al. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 74(3), 229-263.*

[2] *Deswal, B., Bagchi, U., Santra, M. K., et al. (2024). Inhibition of STAT3 by 2-Methoxyestradiol suppresses M2 polarization and protumoral functions of macrophages in breast cancer. BMC Cancer, 24(1), 1129.*

[3] *Jiang, M., Wang, D., Su, N., et al. (2024). TRIM65 knockout inhibits the development of HCC by polarizing tumor-associated macrophages towards M1 phenotype via JAK1/STAT1 signaling pathway. International Immunopharmacology, 128, 111494.*

[4] *Wang, S., Liu, G., Li, Y., et al. (2022). Metabolic reprogramming induces macrophage polarization in the tumor microenvironment. Frontiers in Immunology, 13, 840029.*

[5] *Yunna, C., Mengru, H., Lei, W., et al. (2020). Macrophage M1/M2 polarization. European Journal of Pharmacology, 877, 173090.*

[6] *Zhang, M., He, Y., Sun, X., et al. (2014). A high M1/M2 ratio of tumor-associated macrophages is associated with extended survival in ovarian cancer patients. Journal of Ovarian Research, 7, 19.*

[7] *Mirzaei, S., Paskeh, M. D. A., Okina, E., et al. (2022). Molecular landscape of lncRNAs in prostate cancer: A focus on pathways and therapeutic targets for intervention. Journal of Experimental & Clinical Cancer Research, 41(1), 214.*

[8] *Zhou, J., Li, T., Chen, H., et al. (2022). ADAMTS10 inhibits aggressiveness via JAK/STAT/c-MYC pathway and reprograms macrophages to create an anti-malignant microenvironment in gastric cancer. Gastric Cancer, 25(6), 1002-1016.*

[9] *Zhao, C. C., Han, Q. J., Ying, H.-Y., et al. (2022). TNFSF15 facilitates differentiation and polarization of macrophages toward M1 phenotype to inhibit tumor growth. Oncoimmunology, 11(1), 203291.*

[10] *Sun, P., Li, Z., Yan, Z., et al. (2024). Lenvatinib targets STAT-1 to enhance the M1 polarization of TAMs during hepatocellular carcinoma progression. BMC Cancer, 24(1), 1-14.*

[11] *Chen, C., Zhou, S., Yang, X., et al. (2024). In vitro study of cold atmospheric plasma-activated liquids inhibits malignant melanoma by affecting macrophage polarization through the ROS/JAK2/STAT1 pathway. Biomedicine & Pharmacotherapy, 175.*

[12] *Jiang, X., Zhou, T., Xiao, Y., et al. (2016). Tim-3 promotes tumor-promoting M2 macrophage polarization by binding to STAT1 and suppressing the STAT1-miR-155 signaling axis. Oncoimmunology, 5(9), e1211219.*

[13] *Zhang, S., Li, D., Wang, H., et al. (2024). CAFs-derived exosomal miR-889-3p might repress M1 macrophage polarization to boost ESCC development by regulating STAT1. Cell Biochemistry and Biophysics, 1-14.*

[14] *Xia, T., Zhang, M., Lei, W., et al. (2023). Advances in the role of STAT3 in macrophage polarization. Frontiers in Immunology, 14, 1160719.*

[15] *Fan, C. S., Chen, C. C., Chen, L. L., et al. (2022). Extracellular HSP90α induces MyD88-IRAK complex-associated IKKα/β-NF-κB/IRF3 and JAK2/TYK2-STAT-3 signaling in macrophages for tumor-promoting M2-polarization. Cells, 11(2), 229.*

[16] *Zhang, H., Zhao, B., Wei H., et al. (2022). Cucurbitacin B controls M2 macrophage polarization to suppress metastasis via targeting JAK-2/STAT3 signaling pathway in colorectal cancer. Journal of Ethnopharmacology, 287, 114915.*

[17] *Deng XX, Jiao YN, Hao HF, et al. (2021). Taraxacum mongolicum extract inhibited malignant phenotype of triple-negative breast cancer cells in tumor-associated macrophages microenvironment through suppressing IL-10 / STAT3 / PD-L1 signaling pathways. Journal of Ethnopharmacology, 274, 113978.*

[18] *Cui G., Wang Z., Liu H., et al. (2022). Cytokine-mediated crosstalk between cancer stem cells and their inflammatory niche from the colorectal precancerous adenoma stage to the cancerous stage: Mechanisms and clinical implications. Frontiers in Immunology, 13, 1057181.*

DOI: 10.54254/2753-8818/85/2025.20109

[19] *Fan Z., Cui Y., Chen L., et al. (2024). 23-Hydroxybetulinic acid attenuates 5-fluorouracil resistance of colorectal cancer by modulating M2 macrophage polarization via STAT6 signaling. Cancer Immunology & Immunotherapy, 73(5), Article 83.*

[20] *Nie X., Fu L.Yan F,. et al.(2023) Garcinone E suppresses breast cancer growth and metastasis by modulating tumor-associated macrophages polarization via STAT6 signaling.Phytotherapy Research: PTR,37(10),4442-4456.*