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M2 Macrophage Polarization: Signaling Pathways, Metabolic Reprogramming, and Targeting Strategies in Cancer Therapy

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Abstract:

In the microenvironment of the tumor, there are two subpopulations of tumor associated macrophages (TAMs) with opposite functions: proinflammatory M1 macrophages and immunosuppressive M2 macrophages. Among them, M2-like macrophages' primary function in TME is inhibiting immune response and promoting tumor progression. In order to combat the immunosuppressive effect of M2-like TAMs, this article examines the variables linked to TAM polarization as well as possible tactics for directing TAM repolarization to the M1 pro-inflammatory phenotype for cancer treatment. This article systematically expounds how to intervene tumor progression by targeting the polarization of M2 macrophages, including: 1) An outline of M2 macrophages' function in the TME; 2) The signaling pathways related to TAM polarization (such as STAT family signaling pathway, PI3K/Akt signaling pathway), the reprogramming of cellular metabolic pathways, and the involvement of tumor derived exosomal ncRNA were introduced; 3) A variety of methods to target TAM's orientation to the pro-inflammatory M1 phenotype are discussed, such as signaling pathway inhibition, metabolic intervention, exosomes and other targeting strategies. Therefore, targeting M2 macrophage polarization is an effective strategy to reverse tumor progression, providing a new perspective for cancer therapy.

Keywords: Macrophage polarization; Signaling pathways; Metabolic reprogramming; Exosomes; Targeted therapy

I. Introduction

Macrophages, an essential component of the innate immune system, are vital for controlling the inflammatory response and facilitating tissue healing. These cells show heterogeneity and can adjust their

phenotype and function by sensing the complex signals of the microenvironment. This functional diversity is mainly achieved through the polarization process. Macrophage polarization can be divided into two opposing phenotypes: pro-inflammatory M1 type and immunosuppressive M2 type. In the tumor microenvironment (TME), tumor associated macrophages (TAMs) primarily serve an M2-like tumor-promoting role, controlling a number of malignant outcomes, including angiogenesis, immunosuppression, and tumor spreading [1]. Therefore, TAMs have become a hot spot in cancer treatment research. In recent years, various new therapeutic methods, such as immune checkpoint inhibitors (ICIS) and chimeric antigen receptor T (CAR-T) cell therapy, have achieved durable clinical responses. However, studies have shown that M2 macrophages may lead to the failure of CAR-T cell therapy as well as immune checkpoint blockade treatment by inhibiting T cell and antigen-specific T cell functions [2]. Due to the immunosuppressive effect of M2 like TAMs in TME, targeting M2 macrophage polarization to reverse tumor progression may provide ideas for cancer treatment.

Based on the immunosuppressive effect of M2 macrophages, this review article aims to elaborate the role of M2 like TAMs in the TME, introduce the regulatory elements related to the polarization of TAMs, such as signaling pathways, metabolic reprogramming, tumor derived exosomal ncRNAs, and discuss the targeting methods for the repolarization of TAMs, such as signaling pathway inhibition, metabolic intervention, targeting macrophage and cancer cell-derived exosomes and other strategies. On this basis, this review also combed the advantages and disadvantages of targeting strategies, analyzed the challenges in clinical translation, and proposed a combination treatment strategy combining TAM targeted therapy with other antitumor therapies.

II. The role of M2 macrophages in TME

M2 macrophages in the TME promote tumor growth and exhibit anti-inflammatory properties. Angiogenesis, immunosuppression, and metastasis are the three categories into which M2 like TAMs' tumor-promoting functions can be separated. M2 like TAMs release matrix metalloproteinases (MMPs), growth factors (VEGF), and other cytokines that can block T cells and natural killer (NK) cells, suppress immunological responses, and encourage angiogenesis and cell metastasis. However, other M2-like TAM-produced factors, notably heme oxygenase-1 (HO-1) and cyclooxygenase-2 (COX-2), improve tumor immunosuppression, promote tumor development, and contribute in carcinogenesis and angiogenesis through several routes [1]. By secreting pro-lymphangiogenic substances and undergoing transdifferentiation into lymphoepithelial cells, M2 like TAMs can also promote tumor lymphangiogenesis. Angiogenesis and lymphangiogenesis play key roles in metastasis initiation. Malignant cells can spread in tissues in vivo through newly formed blood vessels, affecting cancer treatment [3].

III. Related mechanisms of targeting TAMs

A research area that has steadily grown is focusing on M2 macrophage polarization in an effort to disrupt the immunosuppressive mechanism of M2 like TAMs. The signaling pathways and other determinants associated with TAM polarization are reviewed in this section.

A. Signaling Pathways Linked to the Polarization of Macrophages

Numerous signaling pathways, including as the PI3K/Akt signaling pathway, the STAT family, and others, are linked to the crucial function that TAMs play in the evolution of tumors. Knowing the importance of each pathway in macrophage polarization is essential since it could inspire M2 to M1 macrophage transformation tactics.

1) STAT family signaling pathway: The various aspects of the mammalian immune system are influenced by transcription factors from the JAK (Janus kinase) family and STAT (signal transduction and transcriptional activator) family. Of them, IFN-γ primarily stimulates the STAT1 signaling pathway and encourages M1 macrophage polarization. Conversely, IL-4/13 and IL-10 promote M2 macrophage polarization by activating STAT6 and STAT3, which is linked to tissue healing and immunological tolerance [1]. The STAT6 signaling pathway mediated by IL-4/13 is crucial in initiating and maintaining the M2 phenotype. IL-4/13 initiates signal transduction by binding to the IL-4 receptor alpha chain on the surface of macrophages. After the receptor formed by binding binds to its own ligand, it recruits and activates the coupled Janus kinase to phosphorylate it, and these phosphorylated sites become the anchoring sites of STAT6. After being recruited to the receptor complex, STAT6 is also phosphorylated by Janus kinase and undergoes dimerization before entering the nucleus. In the nucleus, STAT6 dimers act as transcription factors that identify and attach to particular DNA sequences found in target genes' enhancer or promoter regions, thereby activating transcription of a range of M2 related genes and polarizing macrophages into the M2 phenotype. The similar IL-10/STAT3 pathway activates JAK1 and TYK2 kinases through IL-10 receptors, leading

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to phosphorylation of STAT3. Additionally, phosphorylated STAT3 penetrates the nucleus, where it suppresses the production of pro-inflammatory genes linked to M1 and promotes the expression of a number of genes connected to immunosuppression and anti-inflammatory responses. IFN-γ stimulates M1 polarization by triggering the STAT1 signaling pathway, according to the study of Huffaker TB et al. M2 macrophage polarization results from IL-6's activation of the STAT3 signaling pathway in the tumor model of colorectal cancer [4,5]. Programmed cell death 1 (PD-1) increases phosphorylation of STAT6 to promote M2 polarization while reducing phosphorylation of STAT1 to decrease M1 polarization [6].

2) The signaling pathway PI3K/Akt: Phosphatidylinositol 3-kinase (PI3K) / protein kinase B (Akt) signaling pathway is one of the core signaling pathways regulating cell growth, proliferation, exercise, metabolism and survival. Environmental stimuli such as PAMPs, cytokines / chemokines, and hormones can activate PI3K. Phosphatidylinositol-4,5-bisphosphate (PIP2) on the cell membrane is catalyzed by PI3K upon activation to produce phosphatidylinositol-3,4,5-trisphosphate (PIP3). As a second messenger, PIP3 recruits and activates the downstream key effector kinase Akt. Akt plays a regulatory role by phosphorylating its numerous downstream substrates, such as promoting the production of anti-inflammatory cytokine IL-10. In terms of macrophage polarization, PI3K/Akt pathway tends to promote M2 phenotype and inhibit M1 related inflammatory response. Through the activation of the PI3K/Akt signaling pathway, PCSK9 was reported to boost colon cancer cell proliferation, motility, and invasion in vitro and to induce the polarization of M2 macrophages [7]. The PI3K-γ pathway inhibitor and CSF-1R downregulation in the pancreatic tumor model effectively polarized TAMs from the M2 to M1 phenotype, triggering the anti-tumor immune response and preventing tumor growth [8].The aforementioned indicates that M2 polarization and a poor outcome in cancer treatment are linked to the PI3Kγ/Akt signaling pathway.

B. Metabolic Reprogramming Associated with Macrophage Polarization

Through metabolic reprogramming, immunological and tumor cells can control energy to support cell division and growth. M2 macrophages mainly utilize Fatty acid oxidation (FAO) and oxidative phosphorylation (OXPHOS) to generate energy and exhibit anti-inflammatory properties. The kinase target (mTOR) pathway is a central regulator of macrophage metabolism and polarization. Through the induction of transcription factor IRF4, mTORC2 works in concert with the STAT6 pathway to enhance glucose metabolism in order to boost OXPHOS and FAO. This, in turn, increases the polarization of M2 macrophages in TAMs, resulting in immunosuppression of TME. Furthermore, lipid metabolism also plays a role in macrophage polarization. PPARs, part of the nuclear hormone receptor superfamily, are key regulators of lipid metabolism and can promote M2 polarization. PPAR α and PPAR δ are highly expressed in oxidized tissues, controlling OXPHOS and energy homeostasis. Adipocyte activity and lipid storage are influenced by PPAR γ, which is abundantly expressed in white adipose tissue. It has been reported that PPAR α and PPAR γ can enhance macrophage polarization toward M2 phenotype [9]. The above shows that M2 macrophages can effectively utilize a variety of energy substrates (such as fatty acids) to adapt to the TME.

C. Tumor Derived Exosomal ncRNAs Associated with Macrophage Polarization

Macrophage polarization is induced by exosomal ncRNAs generated from tumors. On the contrary, TAM derived exosomal ncRNA promotes tumor proliferation, metastasis, and angiogenesis. Tumor derived miR-934 exosomes regulate the interaction between colorectal cancer cells and TAMs and induce macrophage M2 polarization by downregulating PTEN expression and activating PI3K/AKT signaling pathway [10]. By competitively binding to the target miR-1-3p, the exosome circATP8A1 generated from gastric cancer cells promoted macrophage M2 polarization and activated the STAT 6 pathway. Overexpression of circATP8A1 promotes the proliferation, migration and invasion of gastric cancer cells [11]. The above indicates that tumor derived exosomal ncRNAs also play a role in macrophage polarization.

IV. Targeting TAM to repolarize to M1 pro-inflammatory phenotype strategy

According to the influencing factors mentioned above, we discussed a variety of strategies to target M2 macrophage polarization, including signaling pathway inhibitors, metabolic interventions, and exosomes.

A. Signaling Pathway Inhibitors

In recent years, the number of new therapeutic drugs targeting inhibition of molecular signaling pathways has increased significantly. One of the most commonly dysregulated signaling pathways in cancer is the PI3K/AKT pathway, which was previously discussed. Pan PI3K inhibitors, isotype selective PI3K inhibitors, dual PI3K/mTOR inhibitors, and Akt inhibitors are examples of small molecule inhibitors that target the PI3K/AKT sig-

naling pathway and have garnered a lot of interest. Pan PI3K inhibitors contain numerous molecular targets and can provide a broader range of activities, but the possibility of both off-target and on-target toxicity may also increase [12]. Clinical trials have shown that BAY 80-6946 is highly selective and potent, and can induce apoptosis of a subpopulation of tumor cells abnormally activated by PI3K, showing antitumor activity [13]. Isoform specific PI3K inhibitors have stronger precise targeting and lower toxicity. The most widely used medication to suppress Akt in advanced solid tumors is capivasertib, a strong and specific inhibitor of three Akt isoforms [12]. The signaling pathway inhibitors mentioned above can effectively inhibit the transformation of macrophages to M2 type, and then reverse tumor progression.

B. Metabolic Interventions

The immune metabolism and polarization of macrophages play an important role in the development of various diseases. Among them, arginine catabolism plays a central role in promoting immunosuppression. Through the actions of arginase (Arg1) and nitric oxide synthase (NOS) in cells, arginine primarily generates urea, L-ornithine, and nitric oxide. According to the research report, M2 macrophages may limit T cell use of arginine by breaking it down, which would prevent antitumor immunity. This is because Arg1 expression has accumulated in the TME. Research has indicated that CB-1158, a small molecule inhibitor, can inhibit arg1, which in turn inhibits immune escape and reduces tumor growth [14]. Furthermore, smoke can alter the oral mucosa's local immune metabolic microenvironment, promote abnormal cell proliferation, decrease apoptosis, activate glutamine transporters in macrophages, promote intracellular transport of glutamine, and result in active glutamine metabolism. It can also promote M2 polarization [15]. Therefore, blocking arginase and promoting glutamine transport may become an effective treatment for a variety of cancers.

C. Targeting Exosomes Produced from Cancer Cells and Macrophages

Exosomes can carry various miRNAs and play an important role in cell communication. After being absorbed by recipient cells, exosomes release the cargo they carry into the cytoplasm, thus realizing the regulatory effect on target cells. Through the inhibition of KDM6B expression in macrophages, the promotion of M2 polarization, and the inhibition of M1 polarization, cancer cell-derived miR-138-5p exosomes were able to achieve tailored regulation of cancer cells in a breast cancer model [16]. As a miR-455-5p ceRNA, lncRNA growth inhibition specific 5 (GAS5) suppresses the STAT3 pathway and causes polarization to change from M2 to M1 [17]. The above shows that targeting macrophages and cancer cell-derived exosomes can realize the transition from M2 type to M1, which is a feasible strategy to target M2 repolarization.

V. Discussion

In recent years, the strategy of targeting signaling pathways has been widely used. These methods can also regulate signaling pathways and provide more regulatory targets by directly inhibiting signaling pathways through small molecules or indirectly inhibiting post-translational modifications such as phosphorylation and acetylation by blocking signaling pathways. In addition, some drugs with effects on cellular metabolism (such as fatty acid synthesis inhibitors) have shown the potential to regulate TAMs function and enhance antitumor immunity in preclinical models. However, clinical transformation still faces challenges. The key lies in the timing and targeting of selective regulation methods of TAMs metabolism to avoid adverse effects on other immune cells or normal tissues. In addition, in clinic, targeting macrophages and cancer cell-derived exosomes is a promising targeted drug carrier. They have the ability to penetrate biological barriers, have better biocompatibility and lower immunogenicity, and can continuously, efficiently and stably transport the contents in the blood. However, the therapeutic efficacy of natural exosomes may be poor due to their inadequate targeting and ease of clearance in vivo [18]. Meanwhile, the manufacture of exosomes also remains a challenge. Despite the promising prospect of TAM targeted therapy, clinical translation still faces many challenges and limitations.

First, TAMs are heterogeneous and plastic. TAMs are not a single group, and their phenotypes and functions vary according to tumor type and microenvironment. Therefore, it is extremely difficult to develop a broad-spectrum and effective TAM targeting strategy. For example, the highly diverse TME of pancreatic ductal adenocarcinoma significantly limits the effectiveness of many therapies [19]. Second, there are difficulties in drug delivery and targeting. At present, how to effectively deliver drugs to tumor sites and selectively act on TAMs while minimizing the impact on other cells is still a major problem. For example, limiting arginine metabolism within T cells inhibits their cytotoxic functions and induces cell cycle arrest [20]. Finally, there are limitations in clinical translation. Due to the gap between preclinical models and human body, many strategies that perform well in preclinical models have poor effect or excessive toxicity after entering clinical trials. Therefore, combination therapy --

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combining TAM targeted therapy with other anti-tumor therapies (such as chemotherapy, radiotherapy, ICIS, etc.) is considered as a promising direction to improve cancer treatment outcomes. Clinical data indicate that combined cancer immunotherapy has enhanced therapeutic efficacy and reduced drug resistance compared with monotherapy. For example, PI3K γ inhibitors combined with PD-L1 antibody and chemotherapy, CD47 antibody combined with other anti-tumor antibodies have shown that combination therapy has more potential than monotherapy. Therefore, future research needs to pay more attention to: first, using advanced technologies such as single-cell omics, we can deeply understand the subpopulations, functions, metabolic characteristics and dynamic evolution of TAMs in different tumor types and treatment stages at the single-cell level and spatial dimension, and find more specific therapeutic targets. Second, develop drugs that can precisely regulate specific TAMs subpopulations. Third, explore the best combination of TAM targeted therapy with ICI, chemotherapy, radiotherapy and other emerging therapies and conduct clinical experiments to achieve more effective and safer cancer immunotherapy.

VI. Conclusion

Through the analysis of the immunosuppressive effect of M2 TAMs in TME, this study systematically combs its regulatory mechanism and the targeted intervention strategy of repolarization, and discusses its potential and challenges in clinical transformation and combination therapy. The results showed that M2 macrophages could promote angiogenesis, immunosuppression and metastasis in TME; The polarization of M2 like TAMs is involved in a variety of signaling pathways, metabolic reprogramming, and exosomal ncRNA. Regulating these factors can effectively change the phenotype of TAMs; Strategies targeting Tam repolarization, such as targeted inhibitors of STAT family and PI3K/Akt signaling pathways, interventions in arginine catabolism and glutamine metabolism, and strategies targeting macrophages and cancer cell-derived exosomes, have shown potential in treatment for cancer. However, combination therapy may show to be a successful strategy to enhance therapeutic effect and overcome drug resistance because of the heterogeneity and adaptability of TAMs, problems in clinical transformation, and other obstacles. Future research can pay more attention to finding specific therapeutic targets, developing more precise drugs and exploring safer and efficient combination treatment strategies, providing more possibilities for cancer immunotherapy.

References

[1] Gao J, Liang Y, and Wang L., "Shaping polarization of tumor-associated macrophages in cancer immunotherapy," *Front. Immunol.*, vol. 13, Jun. 30, 2022, Art. no. 888713.

[2] Rodriguez-Garcia A., Lynn R. C., Poussin M., Eiva M. A., Shaw L. C., O'Connor R. S., Minutolo N. G., Casado-Medrano V., Lopez G., Matsuyama T., and Powell D. J. Jr., "CAR-T cell-mediated depletion of immunosuppressive tumor-associated macrophages promotes endogenous antitumor immunity and augments adoptive immunotherapy," *Nat. Commun.*, vol. 12, no. 1, Feb. 9, 2021, Art. no. 877.

[3] Boutilier A. J. and Elsawa S. F., "Macrophage polarization states in the tumor microenvironment," *Int. J. Mol. Sci.*, vol. 22, no. 13, Jun. 29, 2021, Art. no. 6995.

[4] Huffaker T. B., Ekiz H. A., Barba C., Lee S. H., Runtsch M. C., Nelson M. C., Bauer K. M., Tang W. W., Mosbruger T. L., Cox J. E., Round J. L., Voth W. P., and O'Connell R. M., "A Stat1 bound enhancer promotes Nampt expression and function within tumor associated macrophages," *Nat. Commun.*, vol. 12, no. 1, May 11, 2021, Art. no. 2620.

[5] Zhong Q., Fang Y., Lai Q., Wang S., He C., Li A., Liu S., and Yan Q., "CPEB3 inhibits epithelial-mesenchymal transition by disrupting the crosstalk between colorectal cancer cells and tumor-associated macrophages via IL-6R/STAT3 signaling," *J. Exp. Clin. Cancer Res.*, vol. 39, no. 1, Jul. 11, 2020, Art. no. 132.

[6] Yao A., Liu F., Chen K., Tang L., Liu L., Zhang K., Yu C., Bian G., Guo H., Zheng J., Cheng P., Ju G., and Wang J., "Programmed death 1 deficiency induces the polarization of macrophages/microglia to the M1 phenotype after spinal cord injury in mice," *Neurotherapeutics*, vol. 11, no. 3, pp. 636–650, Jul. 2014.

[7] Wang L., Li S., Luo H., Lu Q., and Yu S., "PCSK9 promotes the progression and metastasis of colon cancer cells through regulation of EMT and PI3K/AKT signaling in tumor cells and phenotypic polarization of macrophages," *J. Exp. Clin. Cancer Res.*, vol. 41, no. 1, Oct. 14, 2022, Art. no. 303.

[8] Li M., Li M., Yang Y., Liu Y., Xie H., Yu Q., Tian L., Tang X., Ren K., Li J., Zhang Z., and He Q., "Remodeling tumor immune microenvironment via targeted blockade of PI3K-γ and CSF-1/CSF-1R pathways in tumor associated macrophages for pancreatic cancer therapy," *J. Control. Release*, vol. 321, pp. 23–35, May 10, 2020.

[9] Xiao S., Qi M., Zhou Q., Gong H., Wei D., Wang G., Feng Q., Wang Z., Liu Z., Zhou Y., and Ma X., "Macrophage fatty acid oxidation in atherosclerosis," *Biomed. Pharmacother.*, vol. 170, Jan. 2024, Art. no. 116092.

[10] Zhao S., Mi Y., Guan B., Zheng B., Wei P., Gu Y., Zhang Z., Cai S., Xu Y., Li X., He X., Zhong X., Li G., Chen Z., and Li D., "Tumor-derived exosomal miR-934 induces macrophage M2 polarization to promote liver metastasis of colorectal cancer," *J.*

Hematol. Oncol., vol. 13, no. 1, Nov. 19, 2020, Art. no. 156.
[11] Deng C., Huo M., Chu H., Zhuang X., Deng G., Li W., Wei H., Zeng L., He Y., Liu H., Li J., Zhang C., and Chen H., "Exosome circATP8A1 induces macrophage M2 polarization by regulating the miR-1-3p/STAT6 axis to promote gastric cancer progression," *Mol. Cancer*, vol. 23, no. 1, Mar. 8, 2024, Art. no. 49.
[12] Glaviano A., Foo A. S. C., Lam H. Y., Yap K. C. H., Jacot W., Jones R. H., Eng H., Nair M. G., Makvandi P., Geoerger B., Kulke M. H., Baird R. D., Prabhu J. S., Carbone D., Pecoraro C., Teh D. B. L., Sethi G., Cavalieri V., Lin K. H., Javidi-Sharifi N. R., Toska E., Davids M. S., Brown J. R., Diana P., Stebbing J., Fruman D. A., and Kumar A. P., "PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer," *Mol. Cancer*, vol. 22, no. 1, Aug. 18, 2023, Art. no. 138.
[13] Liu N., Rowley B. R., Bull C. O., Schneider C., Haegebarth A., Schatz C. A., Fracasso P. R., Wilkie D. P., Hentemann M., Wilhelm S. M., Scott W. J., Mumberg D., and Ziegelbauer K., "BAY 80-6946 is a highly selective intravenous PI3K inhibitor with potent p110α and p110δ activities in tumor cell lines and xenograft models," *Mol. Cancer Ther.*, vol. 12, no. 11, pp. 2319–2330, Nov. 2013.
[14] Steggerda S. M., Bennett M. K., Chen J., Emberley E., Huang T., Janes J. R., Li W., MacKinnon A. L., Makkouk A., Marguier G., Murray P. J., Neou S., Pan A., Parlati F., Rodriguez M. L. M., Van de Velde L. A., Wang T., Works M., Zhang J., Zhang W., and Gross M. I., "Inhibition of arginase by CB-1158 blocks myeloid cell-mediated immune suppression in the tumor microenvironment," *J. Immunother. Cancer*, vol. 5, no. 1, Dec. 19, 2017, Art. no. 101.
[15] Zhu Y., Zhang S., Sun J., Wang T., Liu Q., Wu G., Qian Y., Yang W., Wang Y., and Wang W., "Cigarette smoke promotes oral leukoplakia via regulating glutamine metabolism and M2 polarization of macrophage," *Int. J. Oral Sci.*, vol. 13, no. 1, Aug. 9, 2021, Art. no. 25.
[16] Xun J., Du L., Gao R., Shen L., Wang D., Kang L., Chen C., Zhang Z., Zhang Y., Yue S., Feng S., Xiang R., Mi X., and Tan X., "Cancer-derived exosomal miR-138-5p modulates polarization of tumor-associated macrophages through inhibition of KDM6B," *Theranostics*, vol. 11, no. 14, pp. 6847–6859, May 3, 2021.
[17] Chi X., Ding B., Zhang L., Zhang J., Wang J., and Zhang W., "lncRNA GAS5 promotes M1 macrophage polarization via miR-455-5p/SOCS3 pathway in childhood pneumonia," *J. Cell. Physiol.*, vol. 234, no. 8, pp. 13242–13251, Aug. 2019.
[18] Zhang Y., Bi J., Huang J., Tang Y., Du S., and Li P., "Exosome: A review of its classification, isolation techniques, storage, diagnostic and targeted therapy applications," *Int. J. Nanomedicine*, vol. 15, pp. 6917–6934, Sep. 22, 2020.
[19] Finan J. M., Guo Y., Goodyear S. M., and Brody J. R., "Challenges and opportunities in targeting the complex pancreatic tumor microenvironment," *JCO Oncol. Adv.*, vol. 1, Dec. 18, 2024, Art. no. e2400050.
[20] Dussold C., Zilinger K., Turunen J., Heimberger A. B., and Miska J., "Modulation of macrophage metabolism as an emerging immunotherapy strategy for cancer," *J. Clin. Invest.*, vol. 134, no. 2, Jan. 16, 2024, Art. no. e175445.