Natural products targeting macrophages in tumor microenvironment are a source of potential antitumor agents

Qiu-Ping Liu[a], Yu-Ying Chen[a], Pei An[a], Khalid Rahman[b], Xin Luan[a*], Hong Zhang[a*]

[a] Shanghai Frontiers Science Center of TCM Chemical Biology; Institute of Interdisciplinary Integrative Medicine Research, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China

[b] School of Pharmacy and Biomolecular Sciences, Faculty of Science, Liverpool John Moores University, Liverpool, United Kingdom

[*]**Correspondence:**

Hong Zhang

Email address: zhanghong@shutcm.edu.cn

Phone & Fax: 021-51322720

Address: No. 1200, Cailun Road, Pudong New Area, Shanghai, 201203, China

Xin Luan

Email address: luanxin@shutcm.edu.cn

Phone & Fax: 021-51322428

Address: No. 1200, Cailun Road, Pudong New Area, Shanghai, 201203, China

ABSTRACT

Background: Macrophages are one of the major cell types in the immune system and are closely related to tumor development, which can be polarized into M1 type with anti-tumor activity or M2 type with pro-tumor activity. The infiltration of more macrophages into tumor predicts poorer prognosis due to their more exhibition of M2 phenotype under the influence of many factors in the tumor microenvironment (TME). Therefore, reverse of M2 macrophage polarization in TME is conducive to the suppression of tumor deterioration and understanding the influencing factors of macrophage polarization is helpful to provide new ideas for the subsequent targeting macrophages for tumor therapy.

Purpose: This review summarizes the effects of TME on macrophage polarization and natural products against M2 macrophage polarization, which may provide some directions for tumor therapy.

Methods: The search of relevant literature was conducted using the PubMed, Science Direct, CNKI and Web of Science databases with the search terms “macrophage”, “tumor microenvironment”, “natural product” and “tumor”.

Results: The mutual transformation of M1 and M2 phenotypes in macrophages is influenced by many factors. Tumor cells affect the polarization of macrophages by regulating the expression of genes and proteins and the secretion of cytokines. The expression of some genes or proteins in macrophages is also related to their own polarization. Many natural products can reverse M2 polarization of macrophages which

has been summarized in this review.

Conclusion: Regulation of macrophage polarization in TME can inhibit tumor development, and natural products have the potential to impede tumor development by regulating macrophage polarization.

Key words: Natural product; Macrophage; Polarization; Tumor microenvironment; Immune

Abbreviations: AIE, Aggregation-induced emission; ALOX5AP, Arachidonate 5-Lipoxygenase activating protein; ARCR, *Astragalus mongholicus* Bunge-Curcuma aromatica *Salisb*. extract; ASO, Antisense oligo nucleotide; CAFs, Cancer-associated fibroblasts; CTHRC1, Collagen triple helix repeat containing 1; C5aR, Complement 5a receptor; DCLK1, Doublecortin-like kinase 1; DC-SIGN, DC-specific ICAM-3-grabbing non-integrin; DHA, Dihydroartemisinin; DLBCL, Diffuse large B-cell lymphoma; EAT, Ethyl acetate fraction of Adenophoratriphyllavar.japonica; ESCC, Esophageal squamous cell carcinoma; FGL2, Fibrinogen-like protein 2; FoxQ1, Forkhead box Q1; GBC, Gallbladder cancer; GBM, Glioblastoma multiforme; GLSP, G. lucidum spore polysaccharide; Gpr132, G protein-coupled receptor 132; HNSCC, Head and neck squamous cell carcinoma; HMGA2, High-mobility gene group A2; HPV, Human papilloma virus; ICAM-1, Intercellular cell adhesion molecule-1; IL-10, Interleukin-10; IFN-γ, Interferon gamma; IL1RL10, Interleukin-1 receptor like 1; ISG15, Interferon-stimulated gene 15; NF-κB, Nuclear factor kappa-B; NPC, Nasopharyngeal carcinoma; NSCLC, Non-small cell lung cancer; MEMA, Methylene chloride extract of Morus alba L; MK2, MAPK-activated protein kinase 2; MIF,

Migration inhibitory factor; MMP, Matrix metalloproteinases; MMR, Macrophage mannose receptor; M-CSF, macrophage colony-stimulating factor; ObR, leptin receptor; PAI-1, Plasminogen activator inhibitor-1; PINK1, PTEN-induced kinase 1; PTX, Paclitaxel; PDA, Pancreatic ductal adenocarcinoma; PGE2, Prostaglandin E2; PTEN, Phosphatase and tensin homolog deleted on chromosome 10; PPARc, Peroxisome proliferator-activated receptor-c; Prxs, Peroxiredoxins; RKIP, Raf kinase inhibitory protein; ROS, Reactive oxygen species; SI-CLP, Stabilin-1 interacting chitinase-like protein; SLC2A, Solute carrier 2A; SMS2, Sphingomyelin synthase 2; SPON2, Spondin-2; SUCNR1, Succinic acid receptor; STAT, Signal transducer and activator of transcription; SYK, Spleen tyrosine kinase; S100A9, S100 calcium-binding protein A9; TAMs, Tumor-associated macrophages; TDO2, Tryptophan 2,3-dioxygnease 2; TFEB, Transcription factor EB; TGF-β, Transforming growth factor-β; TME, Tumor microenvironment; TLR7, Toll-like receptor 7; TNBC, Triple-negativebreast cancer; TNFSF15, Tumor necrosis factor superfamily-15; VEGF, Vascular endothelial growth factor; YPF, Yu-Ping-Feng

Introduction

Tumor microenvironment (TME) plays an important role in tumor metastasis, immunosuppression and chemotherapy resistance, which mainly includes tumor cells, infiltrating immune cells (macrophages, lymphocytes, dendritic cells, etc.) and infiltrating stromal cells (cancer-associated fibroblasts, endothelial cells, etc.) (Kenny et al., 2007; Mao et al., 2021). Macrophages as the most widely infiltrating immune cells in TME provide support for the development of tumors(Qian and Pollard, 2010). Tumor-associated macrophages (TAMs) recruit endothelial cells by secreting a variety of cytokines such as vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMP), thereby inducing angiogenesis in tumor sites which is the main reason for tumor growth and invasion(Cendrowicz et al., 2021). TAMs also inhibit the cytotoxic activity of T lymphocytes and NK cells by releasing immunoregulatory factors such as prostaglandin E2 (PGE2), interleukin-10 (IL-10) and transforming growth factor-β (TGF-β) to exert immunosuppressive effect(Li et al., 2011), indicating that TAMs are a potential target for tumor therapy. Plasticity is one of the key features of macrophages, which can make their phenotypes and functions adapt to the needs of the surrounding environment to promote tumor deterioration.

As shown in Figure 1, macrophages can be divided into classically activated macrophages (M1 type) and alternatively activated macrophages (M2 type)(Liu and Wang, 2020). Interferon gamma (IFN-γ) induces the polarization of macrophages into M1, promoting T helper (Th) 1 immune response and anti-tumor activity(Locati et al.,

2013), while IL-4/IL-13 elicits their polarization into M2, increasing anti-inflammatory Th2 immune response and pro-tumor activity. In addition, M2 macrophages can be further subdivided into M2a, M2b, M2c and M2d under different stimuli. M2a and M2b play an immune regulatory role and drive Th2 response, while M2c plays a leading role in inhibiting immune response and promoting tissue remodeling. M2d, also known as tumor associated macrophages (TAMs), is closely associated with tumor progression(Li et al., 2011).

Macrophages are one of the main immune cells in the immune system, which can regulate homeostasis, resist pathogens and promote wound healing(Wang et al., 2021a). In TME, most macrophages show M2 phenotype with tumor promoting effects due to the influence of the surrounding environment. Nevertheless, a small number of macrophages still display M1 phenotype with anti-tumor ability. Therefore, understanding the regulatory factors related to the differentiation and function of macrophages is conducive to the development of drugs targeting macrophages further. This review summarizes the regulatory mechanism of macrophage polarization in TME and natural products against M2 polarization, so as to provide directions for tumor therapy.

Tumor microenvironment facilitates polarization and recruitment of macrophages

Regulation of macrophage polarization and recruitment

Macrophages exhibit different phenotypes due to the influence of surrounding environment, which is related to the expression of proteins or genes in macrophages. Therefore, the effects of genes or proteins in macrophages on their functions are summarized below to provide some idea for regulating macrophages in TME. It is well known that TAMs exhibit various functions in TME, such as promoting angiogenesis, mediating immune escape and accelerating tumor cell migration. In addition, TAMs still maintain phagocytic function and present anti-tumor activity under appropriate re-education which is regulated by protein or gene in macrophages (Lecoultre et al., 2020). VentX, a master regulator of macrophage plasticity is associated with the phagocytic activity of macrophages, which is significantly decreased in TAMs in the pancreatic ductal adenocarcinoma (PDA) microenvironment. The recovery of VentX expression in TAMs promotes phagocytosis, but the mechanism remains unclear(Le et al., 2020). The metabolism is also related to macrophage phenotypes and functions(Zhang et al., 2021a). As mentioned above, macrophages can exhibit M1 and M2 phenotypes, which have different metabolic patterns due to their different functions. M1 macrophages are characterized by aerobic glycolysis, while M2 by oxidative phosphorylation. IL-33/ST2 axis was reported to be associated with oxidative phosphorylation and glycolysis in macrophages, which enhances mitophagy through the activation of mTOR and then

increase the expression of genes related to M2 polarization, promoting M2 polarization further (Xu et al., 2021b). Integrin is a cell adhesion and signal protein which plays an important role in the biological function of cells(Slack et al., 2022). The overexpression of integrin β3 on the surface of TAMs *in vivo* and *in vitro* accelerates M2 polarization through activating peroxisome proliferator-activated receptor-c (PPARc)(Shu et al., 2020). Collagen triple helix repeat containing 1 (CTHRC1), a secreted ECM protein, promotes the recruitment of TAMs through integrin β3/PI3K/Akt/CX3CR1 signaling pathway(Li et al., 2019) and promotes M2 polarization through the activation of pSTAT6(Bai et al., 2020). SPON2 in macrophages activates RhoA and Rac1 by acting on α4β1 integrin, promotes F-actin reorganization and further increases M1-like macrophage recruitment(Zhang et al., 2018b). However, SPON2 has been reported to be associated with a poor prognosis in colorectal cancer and promote macrophage M2 polarization through activating integrinβ1/PYK2 axis(Huang et al., 2021a). ROS is involved in a plethora of processes in cells and plays an important role in macrophage-mediated immunity(Herb and Schramm, 2021). Isoprenaline facilitates the M2 polarization of breast cancer macrophages through inhibiting autophagy probably by regulation of ROS/ERK and mTOR signaling pathways, indicating that repression of autophagy may be a possible treatment for cancer (Shan et al., 2017). M2 macrophages modulated the secretion of IL-1β by regulating fatty acid oxidation in ROS and NLRP3 dependent manner, thus promoting the development of cancer(Zhang et al., 2018a). Peroxiredoxins (Prxs) are a family of antioxidant enzymes that possess the ability of removing H_2O_2 and peroxynitrite. When the lung carcinoma cells with or without

knockdown of Prx5 are injected to WT or Prx5-/- mice, the volume of the tumor is related to the expression of Prx5 in the mice and but not in the cancer cells injected, indicating that tumor growth is uncorrelated with the expression of Prx5 in tumor cells. The deficiency of Prx5 in macrophages induces ROS accumulation, promoting their own M2-like phenotype (Seong et al., 2021).

Cytokines promote tumor development and interleukin-10 (IL-10) is known as an anti-inflammatory and immunomodulatory cytokine which has been proved to suppress inflammatory response through inhibiting the activation of macrophages(Kim et al., 2020). The expression and secretion of IL-10 in TAMs are closely related to their functions. OVOL2 expression is higher in M1 macrophages than in M2. The overexpression of OVOL2 decreases M2 polarization of macrophages by inhibiting the transcription of IL-10(Wu et al., 2022). The overexpression of nuclear factor of activated T cells 1 (NFATc1) in macrophages is associated with tumor growth. The tumor volume in mice subcutaneously inoculated with sh-NFATc1 TAM + SiHa is lower than that with shNC TAM + SiHa, revealing the important role of NFATc1 in the tumor growth. Mechanically, the overexpression of NFATc1 in macrophages facilitates M2 polarization by regulating c-myc/PKM2 pathway to enhance IL-10 secretion(Tan et al., 2022). Chemokines are chemotactic cytokines which can cause the targeted migration of leukocytes. Most cells in TME secrete a series of chemokines that affect TME by recruiting stromal cells and stimulating angiogenesis(Balkwill, 2004). According to the number and spacing of the first two cysteine residues in the amino-terminal part of the protein, chemokines are divided into four groups, i.e. C, CC, CXC

and CX3C(Slettenaar and Wilson, 2006). Macrophages in TME can recruit more from other sites and induce their polarization by secreting chemokines. PTEN (phosphatase and tensin homolog deleted on chromosome 10) is regarded as a new tumor suppressor regulated by NHERF-1, whose deficiency drives M2-like polarization of macrophages in TME by increasing CCL2 and VEGF-A (Li et al., 2015). CCL2 and IL-6 recruit monocytes to TME and increases their polarization into M2 macrophages by inhibiting caspase-8 cleavage and enhancing autophagy in macrophages(Roca et al., 2009). S100 calcium-binding protein A9 (S100A9) is an inflammatory microenvironment-related secretory protein up-regulated in TAMs and acts on tumor cells through AGER/NF-κB axis, thereby facilitating the transcription of CCL2, which accelerates the expression of S100A9 in macrophages in return(Wei et al., 2021). The deficiency of MAPK-activated protein kinase 2 (MK2) in macrophages inhibits tumor angiogenesis by regulating the secretion of CXCL-12/SDF-1, suggesting that MK2 inhibitor may be a potential treatment for cancer(Suarez-Lopez et al., 2020). Chemokine receptors also play an important role in the polarization of macrophages. The up-regulation of CX3CR1 in TAMs is related to the poor prognosis of cancer. The knockout of CX3CR1inhibits tumor angiogenesis and liver metastasis in mice and the mechanism needs further investigation (Zheng et al., 2013).

The aberrant expression of proteins or genes in macrophages can induce macrophage polarization to promote their recruitment from other sites. Therefore, understanding the proteins or genes related to the polarization and function of macrophages is instrumental in provide an idea for the subsequent therapy targeting

macrophages. The regulation of polarization and recruitment of macrophages is shown in Table 1.

Effects of tumor cells on polarization of macrophages

Macrophages can exhibit specific phenotypes when affected by the surrounding environment. The communication between tumor cells and macrophages in TME plays a key role in mediating the function of macrophages. Signals from tumor cells can induce the additional functions of macrophages(Jiang et al., 2021; Pan et al., 2020). Ovarian cancer stem cells promote macrophage M2 polarization by activating the PPARγ and inhibiting NF-κB pathway(Deng et al., 2015). The M2 polarization and PD-L1 expression of macrophages are also facilitated by hemangiosarcoma cells(Gulay et al., 2022). Exosomes from metastatic osteosarcoma cells regulated TAMs signaling to enhance M2 phenotype, thereby eliciting an immunosuppression of tumor-promoting microenvironment by producing TGFB2(Wolf-Dennen et al., 2020). As shown in Figure 2, the communication between different types of cells can be mediated by exosomes. The aberrant expression of some RNAs in tumor cells affects macrophage function by packaging these RNAs in exosomes. miRNAs in exosomes derived from bladder cancer cells induce macrophage polarization into immunosuppressive phenotype by activating the PTEN/AKT/STAT3/6 pathway(Jiang et al., 2021). miR-21-5p is up-regulated in exosomes of esophageal cancer cells, which converts M0 macrophages into M2 through activation of the PTEN/AKT/STAT6 pathway(Song et al., 2021a). cir_0001142 is highly expressed in breast cancer and

endoplasmic reticulum stress promotes the release of exosomes encapsulating circ_0001142 in breast cancer cells, which interferes with the process of autophagy and polarization of macrophages(Lu et al., 2022). Overexpression of Linc00514 in breast cancer cells enhances the phosphorylation of STAT3 and then activates Jagged1-mediated Notch signaling pathway to accelerates the polarization of co-cultured macrophages into M2(Tao et al., 2020). In addition, mutations of genes in tumor cells can result in the changes in macrophage function. The mutation of CREBBP/EP300 in B-lymphoma patient-derived tumor xenografted mice increases M2 polarization of TAMs through FBXW7-NOTCH-CCL2/CSF1 axis(Huang et al., 2021c). KRAS is the most frequently mutated oncogene in human neoplasia. Oxidative stress induced KRAS mutation in pancreatic cancer cells and mutated KRAS packaged into exosomes are then taken up by macrophages through an AGER-dependent mechanism, which causes macrophages switch to an M2-like pro-tumor phenotype via STAT3-dependent fatty acid oxidation(Dai et al., 2020). Macrophages cultured in p53 mutant tumor cell medium reduces M1 markers and inhibit phagocytosis, indicating that p53 mutation facilitates M2 polarization of macrophages(Xu et al., 2022).

As displayed in Figure 3, some metabolites such as succinic acid and lactic acid in TME are closely related to the deterioration of tumors(Zhao et al., 2017). The level of succinate and succinic acid receptor (SUCNR1) in the serum of patients with lung cancer is higher than that of healthy people. Mechanically, succinic acid released by cancer cells activates the succinic acid receptor (SUCNR1) signal on macrophages,

248 which is polarized into TAMs through the PI3K- HIF-1α axis, thus promoting the
249 development of tumors(Wu et al., 2020). Lactic acid, a key metabolite of tumors in
250 TME, is 40 times higher in tumor cells than in normal cells, which is closely associated
251 with the deterioration of tumors. Lactic acid drives tumor progression by inhibiting
252 anti-tumor immunity, increasing tumor angiogenesis and regulating tumor
253 microenvironment(Feng et al., 2017; Végran et al., 2011). Lactic acid in TME is also
254 closely relevant to the function of macrophages. Gastric cancer cell produced lactic
255 acid accelerates M2 polarization of macrophages(Zhang and Li, 2020). Breast cancer
256 derived lactate acid increases macrophage M2 polarization by activating the
257 ERK/STAT3 signaling pathway(Mu et al., 2018) while lactic acid from cancer cells
258 induces M2 polarization by activating Gpr132 in macrophages(Chen et al., 2017). M2
259 polarization of macrophages is facilitated by transitional bladder carcinoma cells
260 secreted lactic acid(Zhao et al., 2015). The abnormal expression of some proteins in
261 tumor cells is also associated with lactate secretion. SLC2A3 overexpression in gastric
262 cancer cells promotes the release of lactic acid, thereby increasing the polarization and
263 infiltration of M2 macrophages(Yao et al., 2020). The expression of some proteins or
264 genes in tumor cells can induce the recruitment and polarization of macrophages by
265 regulating the secretion of chemokines, further promoting the deterioration of tumors
266 (Figure 4). FoxQ1, also known as HFH1, is a member of the forkhead transcription
267 factor family, which is related to the poor prognosis of many tumors. The expression
268 of FoxQ1 in hepatocellular carcinoma cells accelerates the recruitment of macrophage
269 infiltration through CCL2 secretion, which in turn drives hepatocellular carcinoma

metastasis(Xia et al., 2014). The number of TAMs and the volume of tumor decrease in PYK2 knockout mice. Mechanically, PYK2 interferes with the polarization of M2 macrophages by reducing the expression of NI1ICD, which drives the secretion of CCL2 in breast cancer cells to increase the angiogenesis and tumor-promoting phenotypes in macrophage through IL4Rα/pSTAT6 axis. (Muller et al., 2022). The expression of SI-CLP (Stabilin-1 interacting chitinase-like protein) in mouse TS/A cells impedes tumor growth through suppressing the recruitment of macrophages by inhibition of the secretion of CCL2 in breast cancer cells(Yin et al., 2020). The high-mobility gene group A2 (HMGA2), an oncoprotein, is aberrantly overexpressed in colorectal cancer cells. It is bound directly to STAT3 promoter to activate the transcription, which induces the secretion of CCL2, thereby promoting macrophage recruitment(Wang et al., 2022). Overexpression of Spi-B is associated with poor prognosis of patients with lung cancer, which facilitates TAM recruitment by up-regulating CCL4 expression(Huang et al., 2021b). The expression of Twist1 in tumor cells drives macrophage recruitment and tumor angiogenesis by secreting CCL2(Low-Marchelli et al., 2013). The expression of RKIP is correlated with the expression of CCL5 in breast cancer and the overexpression of RKIP in breast cancer cells inhibits macrophage infiltration to tumor sites through the decrease of CCL5 expression(Datar et al., 2015). The overexpression of BRD4 is associated with poor prognosis in gastrointestinal stromal tumor which enhances the expression of CCL2 in cancer cells by activation of the NF-κB signaling pathway, thereby promoting macrophage recruitment to tumor sites(Mu et al., 2019). Table 2 exhibits the effects of exosomes

from tumor cells on macrophage polarization and recruitment.

Effects of other cells on polarization of macrophages

The communication between macrophages and other cells in TME also modulates the function of macrophages. In pancreatic ductal adenocarcinoma (PDAC), CAFs induce monocytes to transform into tumor-promoting TAM phenotype by secreting macrophage colony-stimulating factor (M-CSF) and enhancing ROS production in monocytes (Zhang et al., 2017). Mesenchymal stromal cells injected into paracarcinoma could secrete IFN-γ, leading to the polarization of macrophages into M1 phenotype(Relation et al., 2018). Interestingly, salt extracellular environment induces an anti-inflammatory M2 macrophage phenotype(Amara et al., 2016) and higher matrix stiffness strengthens the polarization of M2 macrophages through the integrin β5-FAK-MEK1/2-ERK1/2 pathway(Xing et al., 2021). In addition, supplements of some nutrients can prevent macrophage M2 polarization. Dietary protein or amino acid inhibit M2 polarization of macrophages through ROS/mTOR, thus restoring tumor immune response(Orillion et al., 2018). Ocoxin® oral solution (OOS) is a nutritional supplement, which can impede the M2 protumoral polarization of macrophages(Hernandez-SanMiguel et al., 2019).

Bacteria regulate polarization of macrophages

The function of macrophages is not only affected by various cells in TME, but is also related to microorganisms. Bacterial infection plays a dual role in the development

of cancer. On the one hand, it activates the immune system, which not only has antibacterial effect but also possesses antitumor activity, and the competition of essential nutrients between bacteria and tumor cells in TME also exert anti-tumor effects(Azevedo et al., 2020; Yasunaga and Matsuoka, 2018). On the other hand, bacterial infection can also promote the occurrence of cancer. Globally, 15% of cancers are caused by carcinogenic pathogens, such as HPV infection for cervical cancer, *Helicobacter pylori* for gastric cancer, *Candida albicans* for oral squamous cell carcinoma and *Streptococcus hemoglobin* for bladder cancer(Sawant et al., 2020), indicating that the occurrence of tumors can be induced by bacterial infection. Besides, bacterial infection can also affect macrophage polarization. *Fusobacterium nucleatum* enhances the infiltration and M2 polarization of macrophages by activating CCL20 to promote tumor growth(Xu et al., 2021a). *Listeria infection* drives TAM to exhibit the function of M1 macrophages, with the ability of phagocytic function and tumoricidal activation to exert antitumor effect(Rai et al., 2012). *Akkermansia muciniphila* impede the development of colon cancer by inducing TLR2/NLRP3-mediated M1-like TAM activation(Fan et al., 2021). In addition, some microbial metabolites are also associated with the polarization of macrophages. Pullulan is a non-ionic, non-immunogenic and edible polysaccharide produced by *Aureobasidium pullulan*. Spermine modified pullulan (PS) activates Akt-, Erk-, and JNK-mediated signaling pathways and NF-κB signaling pathway by up-regulation of TLR1, TLR3, and TLR4, resulting in the polarization of M2 macrophages into M1 phenotype, which alleviates the immunosuppressive TME and restores the function of T cells(Xie et al., 2019).

Natural products targeting macrophages in TME

Macrophages are crucial to tumor development and at present, some compounds with the ability of regulating macrophage polarization and recruitment to tumor sites have been found(Saeedifar et al., 2021). Many extracts of traditional Chinese medicine have been reported to have anti-tumor effects, some of which can regulate the polarization of macrophages. KSG-002, an extract of radices *Astragalus membranaceus* and *Angelica gigas* with the ratio of 3:1, inhibits macrophage infiltration through increase of NF-κB-mediated TNFα production with no toxicity to rat intestinal epithelial (RIE) cells(Woo et al., 2013). *Astragalus mongholicus* Bunge-*Curcuma aromatica* Salisb. (ARCR) is a typical mixture of medication which can treat a variety of malignancies through impeding M2 polarization of macrophages by regulating the Sp1/ZFAS1/miR-153-3p/CCR5 axis, thereby preventing the development of colon cancer. ARCR at the dose of 6 $g/kg/d^{-1}$ has no obvious toxicity and adverse reactions in orthotopic transplantation colon cancer model mice (Gu et al., 2022; Liu et al., 2022a). The extract of *Cordyceps sinensis* accelerates M1 polarization of macrophages by activating the NF-κB signaling pathway(Li et al., 2020). *Cordyceps sinensis* has been considered to be a medicinal plant and health food. However, its long-term intake may lead to health risks due to the content of As and the related products(Liu et al., 2022b). Some polysaccharides extracted from natural products can also regulate the phenotype of macrophages. Oligo-Fucoidan, a sulfated polysaccharide isolated from the brown seaweed, induces monocyte differentiation into M1-like macrophages

and repolarization of M2 macrophages into M1 phenotype(Chen et al., 2020a). G. lucidum spore polysaccharide (GLSP) increases M1 polarization of macrophages but does not repress the activity on macrophage growth (Song et al., 2021b). Homogeneous polyporus polysaccharide facilitates M1 polarization of macrophages of bladder cancer. But its toxicity is still unclear(Jia et al., 2021).

Chinese medicine formula is characterized by multiple components and multiple targets, some of which have been reported to regulate the polarization of macrophages. Aiduqing formula increases M1 polarization by inhibiting CXCL1 secretion in macrophages without noticeable hepatotoxicity, nephrotoxicity, or hematotoxicity observed *in vivo* (Li et al., 2021). Yu-Ping-Feng (YPF), an ancient Chinese herbal decoction, induces M1 polarization of macrophages by promoting phosphorylation of STAT1 but does not affect the osmotic pressure of the medium and the activity of LLC cells and macrophages within 24 h up to the dose of 1 mg/mL (Wang et al., 2019).

In addition, some natural compounds isolated from Chinese medicines can also affect the development of tumors by regulating macrophages. Astragaloside IV is a natural compound from Chinese herb *Radix Astragali* and fulfills pleiotropic function in several cancers. It hinders the development of ovarian cancer by inhibiting HMGB1/TLR4 pathway in macrophages with little cytotoxicity within experimental doses (Wang et al., 2021b) and also promotes M1 polarization of macrophages in colorectal cancer without toxicity observed in the test concentration (Liu et al., 2020). Resveratrol isolated from *Polygonum cuspidatum* increases M1 polarization of macrophages and the ratio of M1/M2(Cheuk et al., 2022). But the low bioavailability

is its main limitation, which is extensively metabolized in the liver and intestines (Robertson et al., 2022). In addition, resveratrol analogue HS-1793 induces TAMs differentiation into anti-tumor phenotype by enhancement of IFN-γ production(Jeong et al., 2014). Dihydroartemisinin (DHA), the active metabolite of artemisinin, is one of the most important and effective antimalarial drugs, which is able to regulate various aspects of immune response (Xiao et al., 2022). Dihydroartemisinin increases M1 polarization of macrophages in TME of Lewis lung carcinoma via AKT/mTOR pathway without obvious cytotoxicity observed in mice and cells at the experimental doses (Xiao et al., 2022) and suppresses M2 polarization by inhibiting STAT3 activation in head and neck squamous cell carcinoma (HNSCC) (Chen et al., 2020b). Natural products associated with macrophage polarization and recruitment are shown in Table 3.

Discussion

At present, the treatments of tumors mainly include surgical resection, chemotherapy and radiotherapy, all of which have side effects related to macrophages. Surgical resection removes in situ tumors, but tumor metastasis is the major reason for cancer deterioration. Circulating tumor cells play a key role in tumor metastasis which can combine with TAMs in peripheral blood to promote tumor metastasis(Adams et al., 2014; Salmaninejad et al., 2019). As a major cancer treatment, chemotherapy causes many side effects and drug resistance, which is also associated with macrophages. For example, sorafenib, a well-known targeted anti-tumor drug, can promote TAMs

infiltration in tumor tissue and further leads to immunosuppressive microenvironment in patients with hepatocellular carcinoma(Zhang et al., 2021b). Radiotherapy can directly elicit the death of tumor cells, but also damages immunogenic cells to promote tumor immunity. Moreover, macrophages are also the most radiation-resistant cells, which can produce a large number of antioxidant molecules, thus limiting the effect of radiotherapy(Prenen and Mazzone, 2019). Therefore, targeting macrophages can alleviate some limitations of current tumor treatment, which is expected to become an adjuvant therapy in the future.

Immunotherapy has become a hot topic in cancer treatment recently and activation of immune system can combat cancer cells(Johdi and Sukor, 2020). Restoration of the normal immune function in TME can enhance the clearance of cancer cells without damaging normal cells. Macrophages, as one of the main cells in the immune system, possess the function of clearing antigen. However, macrophages in TME mainly play a role in promoting tumor development due to the influence of the surrounding environment. Furthermore, the overexpression of CD47 on the surface of many cancer cells transmit the “don’t eat me” signal by interaction with SIRPα protein on macrophages, which inhibits the phagocytosis of macrophages(Chen et al., 2019; Qiu et al., 2018). Therefore, suppressing CD47 expression on tumor cells can promote macrophage phagocytosis and hinder tumor deteriorate. There are a large number of macrophages in tumor microenvironment. Once these are transformed into anti-tumor cells, the expression of “don’t eat me” signal on tumor cell surface will be inhibited, thus preventing the development of tumors. As displayed in Figure 5, the polarization

of macrophages can be regulated by knockout or overexpression of some genes or proteins in TME, which could provide an idea for tumor treatment by targeting macrophages. But the adverse effect remains unclear, which needs to be investigated further.

As mentioned above, some natural products inhibit macrophage polarization and recruitment. However, due to unclear target and off-target toxicity, it is particularly important to design some drug delivery systems improving the targetability and toxicity of compounds. Nanotechnology provides great opportunities for targeted regulation of macrophages polarization, which could improve cancer immunotherapy(Ding et al., 2021). Immunostimulation usually starts from the interaction between nanocarriers and innate immune cells such as macrophages(Andon et al., 2017). Therefore, one of the most critical issues for nanomedicine to strengthen immunotherapy is the intrinsic effect of drug-free liposomes on activation and polarization of macrophages through cell interaction. The synthesized drug-free mannosylated liposomes enhance anti-tumor immunity by inhibiting macrophage polarization from M2 to M1(Ye et al., 2019). Therefore, the preparation of some natural products with definite efficacy into nanomedicine is helpful to improve efficacy and reduce toxicity. Macrophage mannose receptor (MMR or CD206) expressed in TAMs is a key promoter of tumor progression and a major opponent for cancer therapy (De Vlaeminck et al., 2019). Therefore, it is possible to improve the targeting of drugs by designing a vector targeting MMR. Besides, exosomes also play an important role in TME. Can a drug-coating exosome be designed to target macrophages? Bacterial infection can activate the immune system.

Maybe a vaccine can be designed to activate the immune function in TME, thus hindering tumor development.

Macrophages play a prominent role in the development of tumors, and M2 macrophages drive tumor invasion, growth and angiogenesis. Therefore, understanding the factors of affecting macrophage polarization is helpful for subsequent tumor therapy targeting macrophages. The cells in TME induce macrophage polarization by regulating the expression of proteins and genes in macrophages, thus driving the development of tumors, and natural products can reverse the undesired polarization. This review provides new ideas for the development of anti-tumor drugs targeting macrophages.

Author contributions

HZ and XL contributed to the conception of the manuscript. QPL and YYC wrote the draft. QPL and PA drew the graphs. HZ and KR revised the manuscript.

Declaration of competing interest

The authors have declared that there is no conflict of interests.

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Legends

Figure 1 Classification of macrophages. Macrophages can be divided into M1 type and M2 type. IFN-γ induces the polarization of macrophages into M1 with anti-tumor activity, while IL-4/IL-13 promotes the polarization of macrophages into M2 with pro-tumor activity. In addition, M2 macrophages can be subdivided into M2a, M2b, M2c and M2d under different stimuli. M2a and M2b play an immune regulatory role and drive Th2 response, M2c inhibits immune response and promotes tissue remodeling, while M2d facilitates tumor progression.

Figure 2 Effects of exosomes from cancer cells on polarization of macrophages. Cancer cells promote M2 polarization by secreting exosomes to activate several signaling pathways in macrophages.

Figure 3 Metabolites from cancer cells enhance the polarization of macrophages. Succinic acid and lactic acid from tumor cells promote M2 polarization of macrophages.

Figure 4 Chemokines secreted by cancer cells enhance the recruitment of macrophages. Tumor cells secrete a series of cytokines that encourage the recruitment of macrophages to the tumor site.

Figure 5 The regulative mechanism of macrophage M2 polarization.

Table 1 Regulation of macrophage polarization and recruitment

Table 2 Effects of tumor cells on macrophage polarization and recruitment

Table 3 Natural products and drugs targeting macrophages in TME

Table 1 Regulation of macrophage polarization and recruitment

Cancer	Protein	Target	Effect	Model	Refs
PDA	VentX	-	Promoting phagocytosis of TAMs	*In vitro*	(Le et al., 2020)
Breast cancer	integrin b3	PPARc	Promoting M2 polarization	*In vivo* and *in vitro*	(Shu et al., 2020)
Hepatocellular carcinoma	SPON2	SPON2/α4β1 integrin	Promoting M1 recruitment	*In vivo* and *in vitro*	(Zhang et al., 2018b)
Lung cancer	Prx5	ROS	Inhibiting M2 polarization	*In vivo* and *in vitro*	(Seong et al., 2021)
Colon cancer	MK2	CXCL-12/SDF-1	Promoting angiogenesis	*In vivo* and *in vitro*	(Suarez-Lopez et al., 2020)
Colon cancer	CX3CR1	-	Promoting TAMs apoptosis	*In vivo* and *in vitro*	(Zheng et al., 2013)
Breast cancer	PTEN	CCL2	Inhibiting M2 polarization	*In vitro*	(Li et al., 2015)
-	CCL2 and IL-6	caspase-8	Promoting M2 polarization	*In vitro*	(Roca et al., 2009)
Breast cancer	OVOL2	IL-10	Inhibiting M2 polarization	*In vivo*	(Wu et al., 2022)
Lewis lung cancer	DC-SIGN	-	Promoting M2 polarization	*In vitro*	(Yan et al., 2016)
Serous ovarian cancer	ALOX5AP	-	Promoting M2 polarization and recruitment	*In vitro*	(Ye et al., 2021)
Colon cancer	ICAM-1	PI3K/AKT	Promoting M2 polarization	*In vivo* and *in vitro*	(Yang et al., 2015)
Renal carcinoma	AIM2	Inflammasome signaling	Enhancing TAMs polarization switch from anti-inflammatory M2 to pro-inflammatory M1	*In vivo* and *in vitro*	(Chai et al., 2021)
Triple-negative breast cancer	SMS2	-	Promoting M2 polarization	*In vivo* and *in vitro*	(Deng et al., 2021b)
Breast cancer	KLF14	RhoA/Rock/STAT3	Inhibiting M2 polarization	*In vivo* and *in vitro*	(Chu et al., 2022)
Colorectal cancer	-	TLR-4/MyD88/NF-κB	prompting M1 polarization	*In vivo* and *in vitro*	(Andreuzzi et al., 2022)
Endometrial cancer	CTHRC1	CTHRC1-integrinβ3-Akt	Promoting M2 recruitment	*In vitro*	(Li et al., 2019)
Ovarian Cancer	CTHRC1	STAT6	Promoting M2 polarization	*In vitro*	(Bai et al., 2020)
Colon cancer	C5aR	NF-Kb	Promoting M2 polarization and infiltration	*In vivo* and *in vitro*	(Piao et al., 2018)

Table 2 Effects of tumor cells on macrophage polarization and recruitment

Cancer	Exosome	Target	Effect	Model	Refs
Breast cancer	Gpr132	-	Promoting M2 polarization	*In vivo* and *in vitro*	(Chen et al., 2017)
Gastric cancer	SLC2A3	-	Promoting M2 polarization and infiltration	*In vivo* and *in vitro*	(Yao et al., 2020)
Breast cancer	miR-375	SREBP2	Regulating metabolism of macrophages	*In vivo* and *in vitro*	(Frank et al., 2021)
Gallbladder cancer	Leptin	STAT3	Promoting M2 polarization	*In vitro*	(Zhao et al., 2022b)
Breast cancer	Leptin	Ob/ObR	Promoting recruitment of TAMs	*In vivo* and *in vitro*	(Gelsomino et al., 2020)
Bladder cancer	miRNA	PTEN/AKT/STAT3/6	Inducing macrophage polarization into immunosuppressive phenotype	*In vivo* and *in vitro*	(Jiang et al., 2021)
Esophageal cancer	miR-21-5p	PTEN/AKT/STAT6	Promoting M2 polarization	*In vitro*	(Song et al., 2021a)
Breast cancer	circ_0001142	circ_0001142/miR-361–3p/PIK3CB	Promoting M2 polarization	*In vitro*	(Lu et al., 2022)
Breast cancer	Linc00514	NOTCH	Promoting M2 polarization	*In vivo* and *in vitro*	(Tao et al., 2020)
Hepatocellular carcinoma	FoxQ1	VersicanV1/CCL2	Promoting recruitment of macrophages	*In vivo* and *in vitro*	(Xia et al., 2014)
Breast cancer	PYK2	Notch1	Regulating monocyte recruitment, macrophage polarization and tumor angiogenesis	*In vivo* and *in vitro*	(Muller et al., 2022)
Breast cancer	SI-CLP	-	Inhibiting recruitment of macrophages	*In vivo* and *in vitro*	(Yin et al., 2020)
Lung cancer	Spi-B	-	Promoting TAM recruitment to TEM	*In vivo* and *in vitro*	(Huang et al., 2021b)
Colorectal cancer	HMGA2	STAT3	Promoting recruitment of macrophages	*In vivo* and *in vitro*	(Wang et al., 2022)

Breast cancer	Twist1	-	Promoting recruitment of macrophages	*In vivo* and *in vitro*	(Low-Marchelli et al., 2013)
Breast cancer	RKIP	-	Inhibiting macrophage infiltration into tumor site	*In vivo* and *in vitro*	(Datar et al., 2015)
Triple-negative breast cancer	RKIP	-	Inhibiting TAMs infiltration into tumor site	*In vivo* and *in vitro*	(Frankenberger et al., 2015)
Nasopharyngeal carcinoma	ISG15	LFA-1-SRC-CCL18	Promoting M2 polarization	*In vitro*	(Chen et al., 2020c)
Gastrointestinal stromal tumor	BRD4	NF-κB	Promoting recruitment of M2 macrophages	*In vitro*	(Mu et al., 2019)
Breast cancer	CITED2	-	Promoting recruitment of macrophages	*In vivo* and *in vitro*	(Jayaraman et al., 2018)
Glioblastoma	FGL2	CD16/SyK/PI3K/HIF1α	Inducing macrophages to secrete chemokines	*In vitro*	(Yan et al., 2021)
Colorectal cancer	SPON2	SPON2/integrin β1/PYK2	Promoting TAMs infiltration and M2 polarization	*In vivo* and *in vitro*	(Huang et al., 2021a)
DLBCL	CREBBP/EP300	FBXW7-NOTCH-CCL2/CSF1	Promoting M2 polarization	*In vivo* and *in vitro*	(Huang et al., 2021c)
PDA	KRAS	Ferroptosis	Promoting M2 polarization	*In vitro*	(Dai et al., 2020)
Lung cancer	p53	-	Promoting M2 polarization	*In vivo* and *in vitro*	(Xu et al., 2022a)
Breast cancer	Annexin 1	FPR2	Promoting M2 polarization	*In vivo* and *in vitro*	(Moraes et al., 2017)
Lewis lung cancer	TNFSF15	STAT1, STAT3 and STAT6	Promoting M1 infiltration and polarization	*In vivo* and *in vitro*	(Zhao et al., 2022a)
Hemangiosarcoma	-	-	Promoting M2 polarization	*In vivo* and *in vitro*	(Gulay et al., 2022)
Gastric cancer	PINK1	-	Promoting M2 polarization	*In vivo* and *in vitro*	(Xu et al., 2022b)
-	PAI-1	p38MAPK and NF-kB	Promoting M2 polarization	*In vivo* and *in vitro*	(Kubala et al., 2018)

Melanoma	Osteopontin	ERK and p38	Promoting macrophage infiltration	*In vivo* and *in vitro*	(Kale et al., 2014)
esophageal squamous cell carcinoma	TDO2	AKT/GSK3b/IL-8	Promoting M2 polarization and recruitment	*In vivo* and *in vitro*	(Zhao et al., 2021)
Nasopharyngeal carcinoma	MIF	-	Inhibiting ferroptosis of macrophages	*In vivo* and *in vitro*	(Chen et al., 2021)
Glioblastoma	MSI1	-	Promoting M2 polarization	*In vivo* and *in vitro*	(Yang et al., 2021b)
Lung cancer	succinic acid	PI3K/HIF-1α	Promoting polarization of macrophages to TAMs	*In vivo* and *in vitro*	(Wu et al., 2020b)
Melanoma	SCOD	-	Promoting M1 polarization of TAMs	*In vivo* and *in vitro*	(Sun et al., 2022)
Glioblastoma multiforme	FX	ERK1/2 and AKT	Promoting macrophages recruitment and M2 polarization	*In vivo* and *in vitro*	(Zhang et al., 2020)
Pancreatic cancer	ANXA1	-	Promoting M2 polarization	*In vivo* and *in vitro*	(Novizio et al., 2021)
Breast cancer	Fra-1	-	Promoting differentiation of macrophages into M2d	*In vitro*	(Wang et al., 2010)
Lung cancer	IL1RL10	Rab37/ST2	Enhancing ratio of M1/M2	*In vitro*	(Tzeng et al., 2018)
Esophageal squamous cell carcinoma	PTEN	PI3K/AKT	Inducing M2 polarization	*In vitro*	(Yang et al., 2021a)
Melanoma	bcl-2	-	Promoting M2 polarization	*In vivo* and *in vitro*	(Di Martile et al., 2020)
esophageal squamous cell carcinoma	FOXO1	FAK/PI3K/AKT	Promoting M2 polarization	*In vivo* and *in vitro*	(Wang et al., 2020)
PDA	DCLK1	-	Promoting M2 polarization	*In vivo* and *in vitro*	(Chandrakesan et al., 2020)
Breast cancer	TFEB	STAT3	Promoting M2 polarization	*In vivo* and *in vitro*	(Fang et al., 2017)
Ovarian cancer	glutamine	-	Promoting M2 polarization	*In vitro*	(Menga et al., 2021)

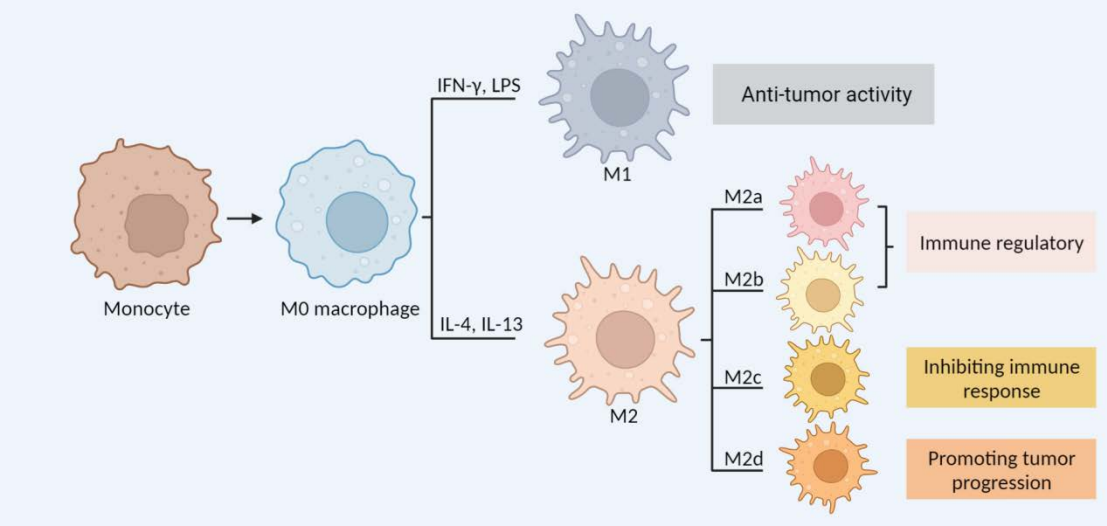
	synthetase				
Breast cancer	SNAIL1	-	Regulating macrophage polarization	*In vivo* and *in vitro*	(Brenot et al., 2018)
esophageal squamous carcinoma	S100A7	-	Promoting M2 polarization and recruitment of macrophages to tumor sites	*In vivo* and *in vitro*	(Lu et al., 2021)
Breast cancer	Kindlin-2	-	Promoting recruitment of macrophages	*In vivo* and *in vitro*	(Sossey-Alaoui et al., 2017)
Non-small cell lung cancer	Angptl2	-	Inducing M2 polarization	*In vivo* and *in vitro*	(Wei et al., 2017)
Ovarian Cancer	-	PPA Rγ/NF-κB	Promoting M2 polarization	*In vitro*	(Deng et al., 2015)
DLBCL	GP130	STAT3	Promoting M2 polarization	*In vitro*	(Ling et al., 2022)
Non-small cell lung cancer	LAMC2	-	Promoting macrophage infiltration	*In vitro*	(Liu et al., 2021)
Breast cancer	Oncostatin M	mTORC2-Akt1	Promoting M2 polarization	*In vivo* and *in vitro*	(Shrivastava et al., 2019)
-	Nodal	-	Promoting M2 polarization	*In vitro*	(Wang et al., 2014)

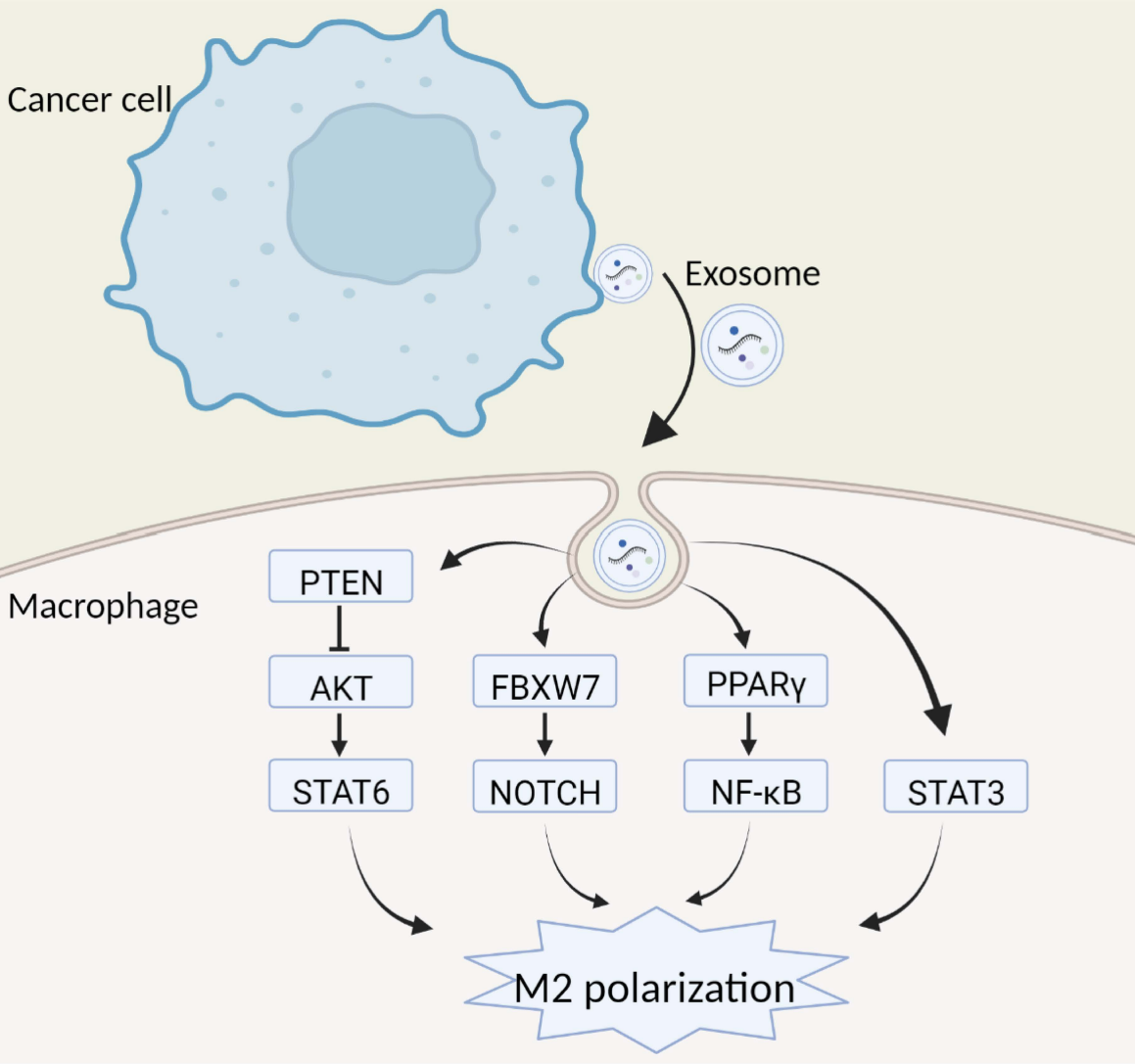
Table 3 Natural products targeting macrophages in TME

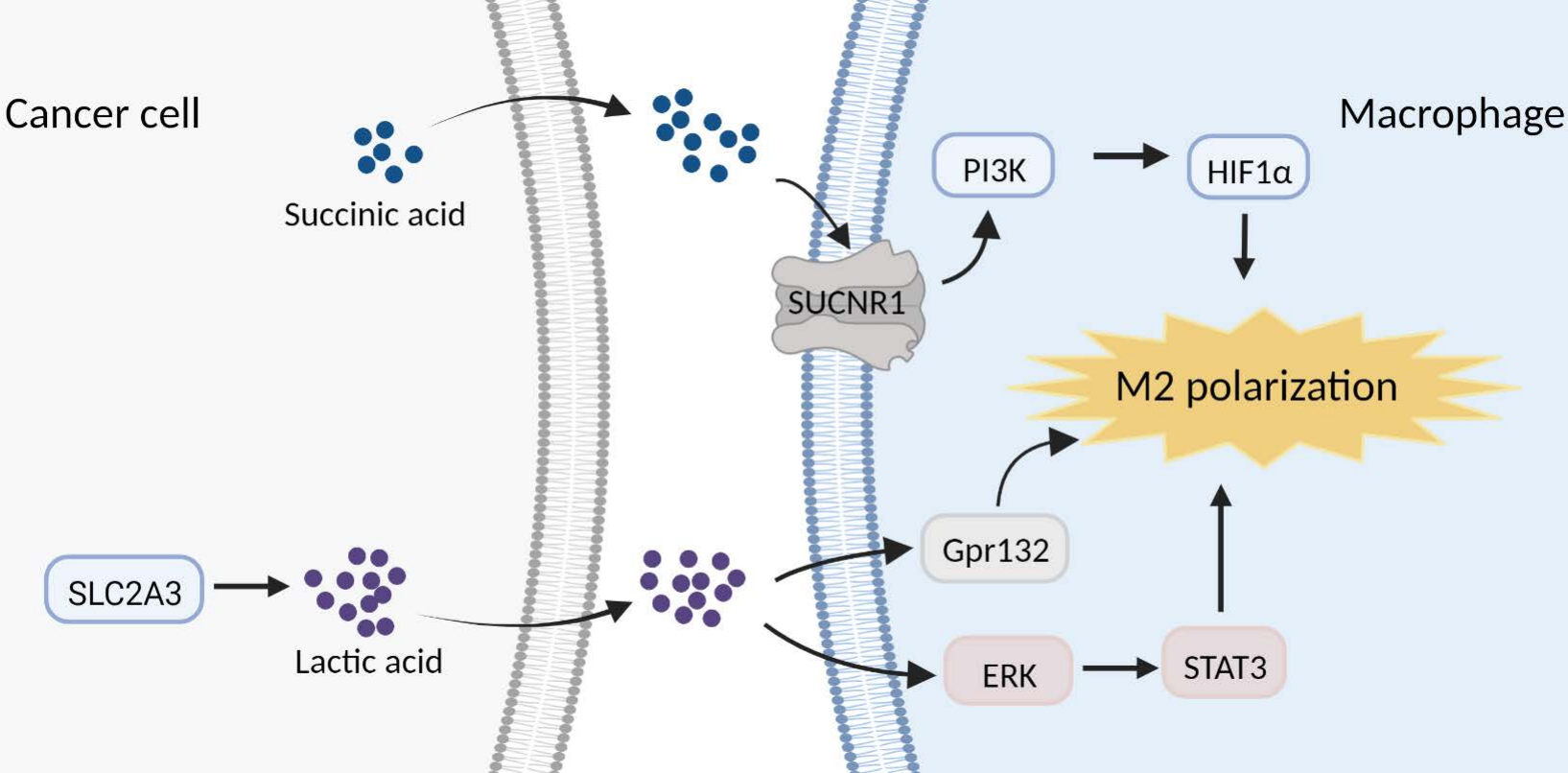
Name	Cancer	Nature	Target	Effect	Model	Dose	Refs
KSG-002	Breast cancer	Extract	NF-κB/ TNFα	Inhibiting M2 polarization	*In vivo* and *in vitro*	500 mg/kg/day in mice; 50, 100, 200, 500 μg/mL in cells	(Woo et al., 2013)
Taraxacum mongolicum	Triple-negative breast cancer	Extract	STAT3 and PD-L1	Inhibiting M2 polarization	*In vitro*	20, 40, 80 μg/mL	(Deng et al., 2021a)
EAT	Lung cancer	Extract	-	Inhibiting M2 polarization	*In vitro*	50, 100, 200 μg/mL	(Park, 2019)
ARCR	Colorectal cancer	Extract	Sp1/ZFAS1/miR-153-3p/CCR5	Inhibiting M2 polarization	*In vivo* and *in vitro*	0.64 g/kg/day in cells; 6 g crude drug/kg/day in mice	(Gu et al., 2022)
Huaier extract	Breast cancer	Extract	-	Inhibiting M2 polarization and recruitment of macrophages	*In vivo* and *in vitro*	4, 8 mg/mL in cells; 75 mg per mouse	(Li et al., 2016)
Cordyceps sinensis	Triple-negative breast cancer	Extract	NF-κB	Promoting M1 polarization	*In vivo* and *in vitro*	100, 200 mg/kg in mice; 0.1, 0.4 mg/mL in cells	(Li et al., 2020)
MEMA	-	Extract	STAT6 and STAT3	Inhibiting M2 polarization and recruitment of macrophages	*In vitro*	25, 50, 10 μg/mL	(Park et al., 2020b)
GLSP	Hepatocellular carcinoma	Polysaccharide	-	Promoting M1 polarization	*In vitro*	200, 400, 800 μg/mL	(Song et al., 2021b)
Oligo-Fucoidan	Colon cancer	Polysaccharide	-	Promoting M1 polarization	*In vivo* and *in vitro*	150 mg/kg in mice; 400 μg/mL in cells	(Chen et al., 2020a)
Aiduqing	Breast cancer	Formula	CXCL1	Promoting polarization of M2 into M1	*In vivo* and *in vitro*	0.7, 1.4 g/kg/day in mice; 20, 40, 80, 100, 200 μg/mL in cells	(Li et al., 2021)
Yu-Ping-Feng	Lewis lung cancer	Decoction	STAT1	Promoting M1 polarization	*In vivo* and *in vitro*	117 mg per mouse; 0.125, 0.25, 0.5, 1 mg/mL in cells	(Wang et al., 2019)
β-carotene	Colon cancer	Compound	IL-6/STAT3	Inhibiting M2 polarization	*In vivo* and *in vitro*	40 μM in cells; 5, 15 mg/kg in mice	(Lee et al., 2020)
Astragaloside IV	Ovarian cancer	Compound	HMGB1/TLR4	Inhibiting M2 polarization	*In vitro*	10 μg/mL	(Wang et al., 2021b)
Astragalosid	Colorectal cancer	Compound	-	Promoting M1 polarization	*In vivo* and *in*	15 mg/kg in mice; 10, 50, 100	(Liu et al., 2020)

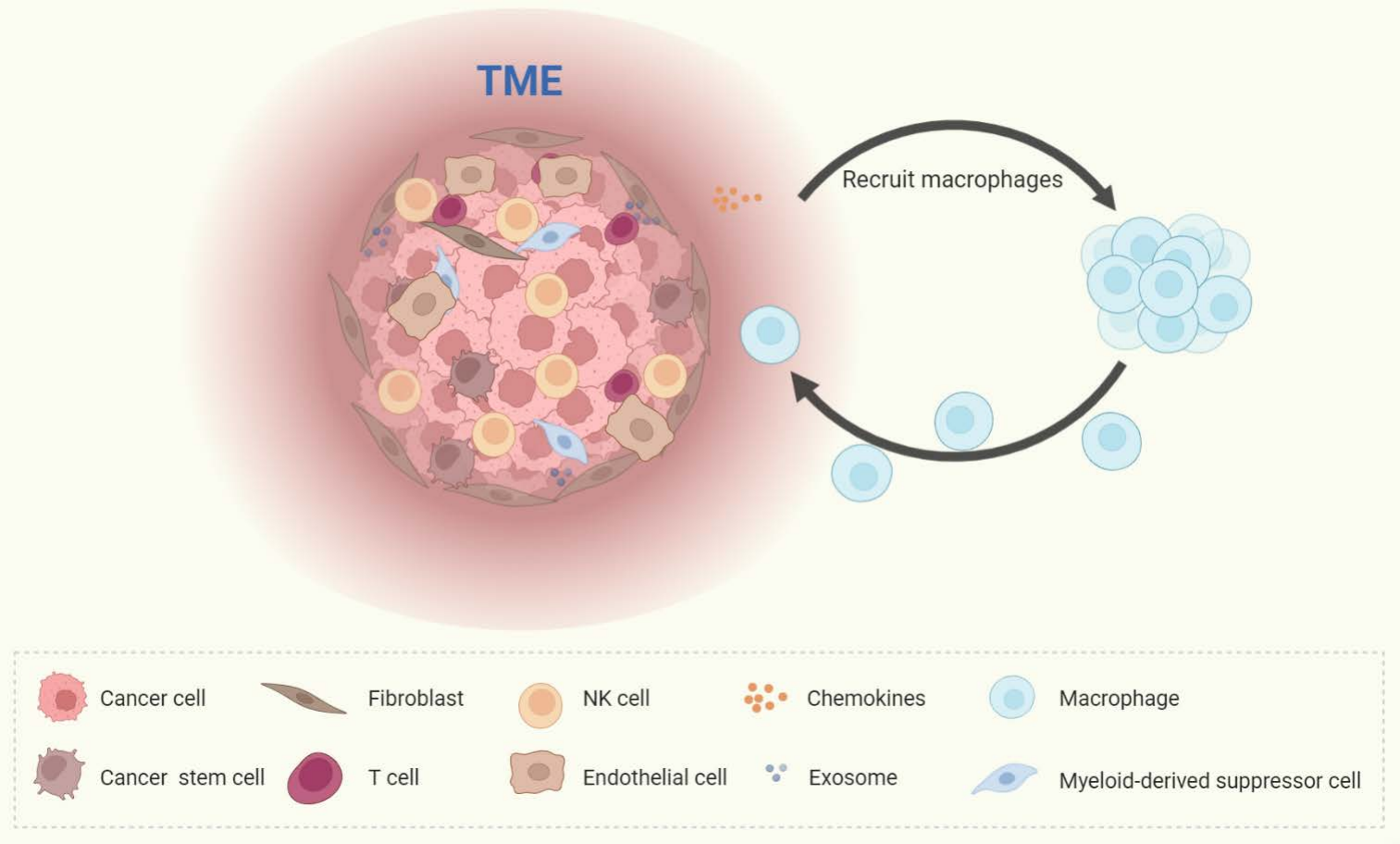
e IV					*vitro*	nM in cells	
Berberine	DLBCL	Compound	c-myc	Promoting macrophage phagocytosis	*In vivo* and *in vitro*	100 mg/kg in mice; 15, 30, 60 μM in cells	(Ren et al., 2021)
Xanthoangelol	osteosarcoma	Compound	STAT	Inhibiting M2 polarization	*In vivo* and *in vitro*	25 and 50 mg/kg in mice; 5, 10, 25, 50 μM in cells	(Sumiyoshi et al., 2015)
4-hydroxyderricin	osteosarcoma	Compound	-	Inhibiting macrophage activation	*In vivo* and *in vitro*	25, 50 mg/kg in mice; 5, 10, 25, 50 μM in cells	(Sumiyoshi et al., 2015)
Resveratrol	Breast cancer	Compound	IL-6/STAT3	Promoting M1 polarization	*In vitro*	40 mg/kg in mice; 5, 10, 25 μM in cells	(Cheuk et al., 2022)
Resveratrol analog	Breast cancer	Compound analog	-	Promoting TAM differentiation into antitumor phenotype	*In vivo* and *in vitro*	1.5 mg/kg in mice; 1.25, 2.5, 5 μM in cells	(Jeong et al., 2014)
Polyporus polysaccharide	Bladder cancer	Polysaccharide	-	Inhibiting M2 polarization	*In vitro*	1, 10, 100 μg/mL	(Jia et al., 2021a)
Cucurbitacin B	Colorectal cancer	Compound	JAK-2/STAT3	Inhibiting M2 polarization	*In vivo* and *in vitro*	0.5, 1 mg/kg in mice; 0.4, 0.8 μM in cells	(Zhang et al., 2022)
Curcumin	Lung cancer	Compound	p53	Promoting M1 polarization	*In vivo* and *in vitro*	5, 10, 20 μM	(Xu et al., 2022a)
Dihydroartemisinin	HNSCC	Compound	STAT3	Inhibiting M2 polarization	*In vitro*	50 μM	(Chen et al., 2020b)
Dihydroartemisinin	Lewis Lung carcinoma	Compound	AKT/mTOR	Promoting M1 polarization	*In vivo* and *in vitro*	12.5 mg/kg in mice; 0.5 ,1,5 ,10 μM in cells	(Xiao et al., 2022)
Luteolin	Lewis lung carcinoma	Compound	-	Inhibiting secretion in TAMs	*In vitro*	1, 5, 10 μM	(Choi et al., 2016)
Epigallocatechin gallate \	Breast cancer	Compound	miR-16	Inhibiting macrophage infiltration and M2 polarization	*In vivo* and *in vitro*	10 mg/kg in mice; 100 μM in cells	(Jang et al., 2013)
Lupeol	Lewis lung carcinoma	Compound	-	Inhibiting M2 polarization and recruitment of macrophages	*In vitro*	10, 20, 50, 100 μM	(Park et al., 2020a)
2-methylpyridine-1-ium-1-sulfonate	Colorectal cancer	Compound	-	Promoting M1 polarization	*In vitro*	2, 4, 6 μM	(Rastegari-Pouyani et al., 2022)
Triptolide	Ovarian cancer	Compound	PI3K/Akt/NF-kB	Inhibiting M2 polarization	*In vivo* and *in*	0.15 mg/kg/d in mice; 6.25,	(Le et al., 2021)

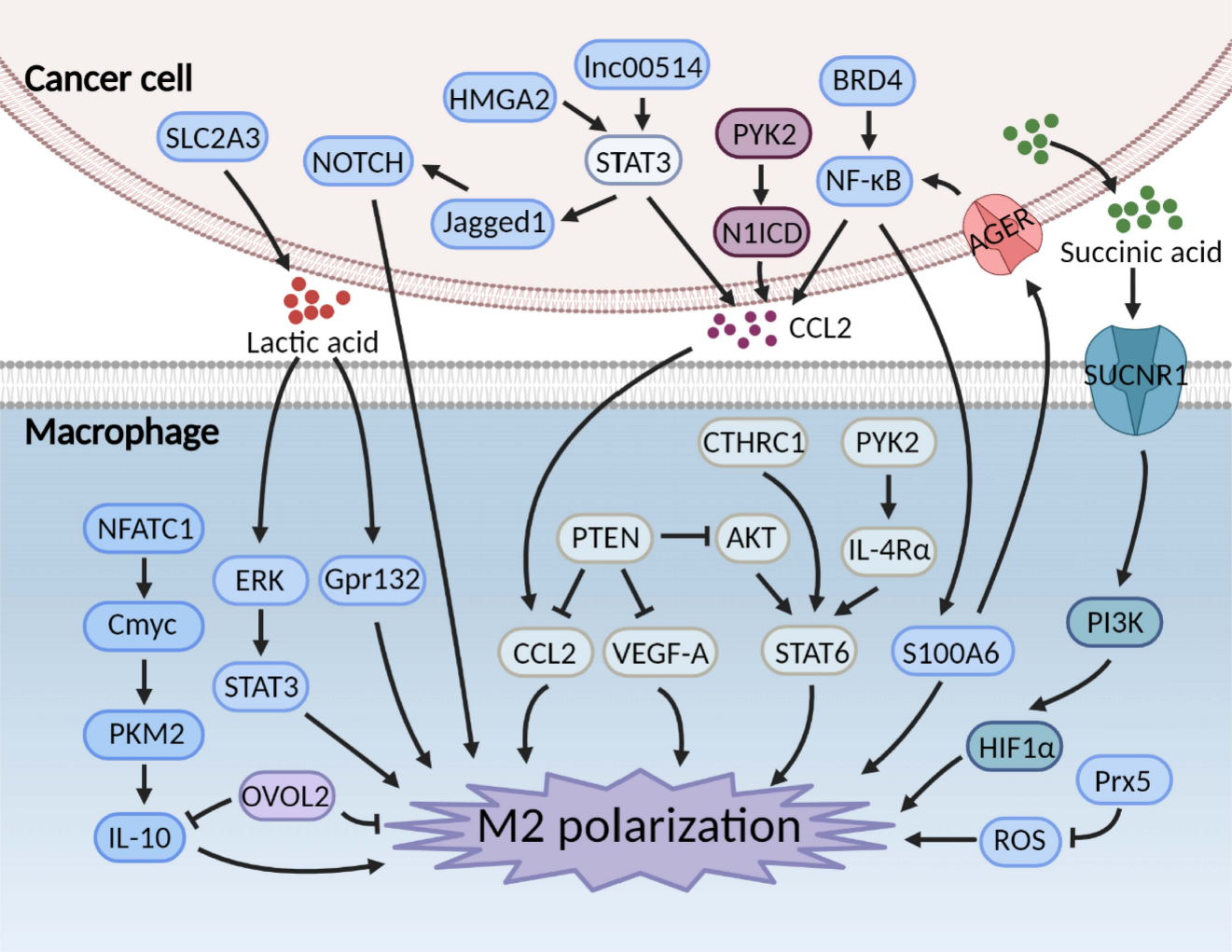
					vitro	12.5, 25, 50, 100 nM in cells	
Corosolic acid	-	Compound	STAT3	Inhibiting M2 polarization	*In vivo* and *in vitro*	17.5 mg/kg in mice; 10, 20, 30 μM in cells	(Fujiwara et al., 2014)
Oleanolic acid	-	Compound	STAT3	Inhibiting M2 polarization	*In vitro*	10, 20, 30 μM in cells	(Fujiwara et al., 2014)
Ovatodiolide	Bladder cancer	Compound	-	Reducing expression of tumor promoting factors in TAM exosomes and inhibiting M2 polarization	*In vivo* and *in vitro*	5 mg/kg in mice	(Wu et al., 2020a)

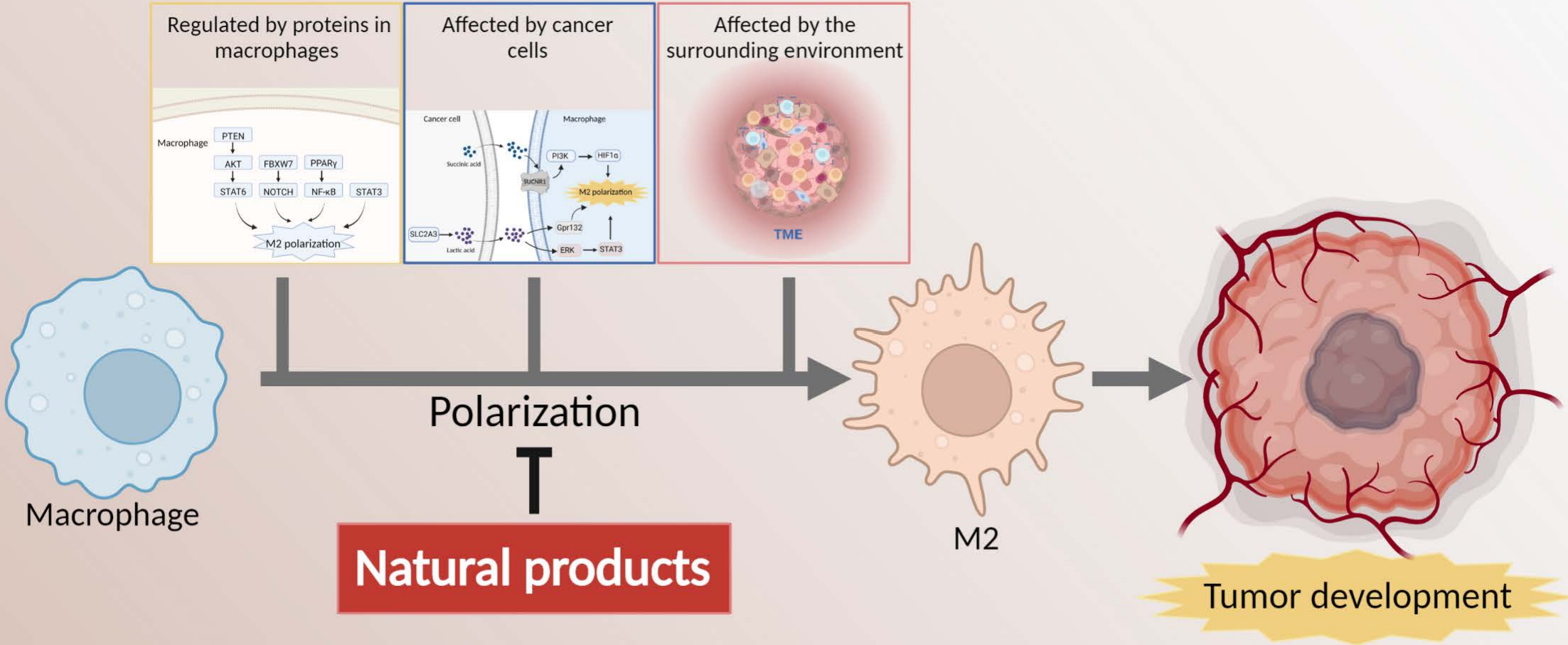

Monocyte
M0 macrophage
IFN-γ, LPS
IL-4, IL-13
M1
M2
M2a
M2b
M2c
M2d
Anti-tumor activity
Immune regulatory
Inhibiting immune response
Promoting tumor progression


Cancer cell
Exosome
Macrophage
PTEN
AKT
STAT6
FBXW7
NOTCH
PPARγ
NF-κB
STAT3
M2 polarization


Cancer cell
Macrophage
Succinic acid
SUCNR1
PI3K
HIF1α
M2 polarization
SLC2A3
Lactic acid
Gpr132
ERK
STAT3


TME
Recruit macrophages
Cancer cell
Fibroblast
NK cell
Chemokines
Macrophage
Cancer stem cell
T cell
Endothelial cell
Exosome
Myeloid-derived suppressor cell


Cancer cell
SLC2A3
NOTCH
HMGA2
lnc00514
STAT3
Jagged1
PYK2
N1ICD
BRD4
NF-κB
AGER
Succinic acid
Lactic acid
CCL2
SUCNR1
Macrophage
NFATC1
Cmyc
PKM2
IL-10
OVOL2
ERK
Gpr132
STAT3
PTEN
AKT
CTHRC1
PYK2
IL-4Rα
CCL2
VEGF-A
STAT6
S100A6
PI3K
HIF1α
Prx5
ROS
M2 polarization


Regulated by proteins in macrophages
Affected by cancer cells
Affected by the surrounding environment
Macrophage
PTEN
AKT
FBXW7
PPARγ
STAT6
NOTCH
NF-κB
STAT3
M2 polarization
Cancer cell
Macrophage
Succinic acid
SUCNR1
PI3K
HIF1α
M2 polarization
SLC2A3
Lactic acid
Gpr132
ERK
STAT3
TME
Macrophage
Polarization
Natural products
M2
Tumor development