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Polarization of Tumor-Associated Macrophages by Chinese Medicine Intervention: Mechanisms and Applications

Yuanjun Lu, Hor Yue Tan, Ning Wang and Yibin Feng

Abstract

Macrophage polarization is a spectrum of phenotypes and generally can be classified into two states: (1) classically activated or M1 macrophages, which can be driven by lipopolysaccharide (LPS) alone or in association with Th1 cytokines and produce pro-inflammatory cytokines such as TNF- α , IL-6 and, IL-12, and (2) alternatively activated M2 macrophages, which can be promoted by Th2 mediators IL-4 and IL-13 and produce anti-inflammatory cytokines such as TGF- β and IL-10. Current studies have found that the phenotypic switch between M1 and M2 macrophages governs the fate of an organ in inflammation or injury. The imbalance of M1/M2 polarization is closely involved in various pathological processes and is becoming a potential target for therapeutic strategies. Traditional Chinese medicine is an integrated healthcare system composed of many practices and is characterized by multi-target, multi-level, and coordinated intervention effects. Chinese medicines nowadays are applied to regulate phenotype polarization of macrophages to improve the microenvironment, thus ameliorating or even eliminating the symptoms. In this chapter, we will discuss the molecular mechanisms of macrophage polarization, their roles in health and disease, and the intervention with Chinese medicines to modulate the polarization of macrophages in tumor microenvironment (TME) for therapeutic purpose.

Keywords: tumor microenvironment, tumor-associated macrophage, polarization, Chinese medicine

1. Introduction

Primary and metastatic tumors are generally known as a complex ecosystem containing tumor cells and the surrounding environment, called tumor microenvironment (TME). Apart from autonomous changes by genetic alteration of tumor cells, the dynamic changes of TME progress the tumor progression [1]. TME is a multifaceted pool that consists of various cell types including neoplastic cells, stromal cells, and immune cells that interact with one another via numerous secreted cytokines, growth factors, and chemokines. Tumor-associated macrophages (TAMs) take up a large portion of recruited immune cells and constitute up

to 50% of the tumor mass. It was reported that the high level of TAMs is associated with poor prognosis and decreasing overall survival in many cancers, such as liver, breast, gastric, and thyroid cancers, suggesting that TAMs certainly play essential roles during tumor development [2–6].

TAM recruitment and accumulation are regulated by various cytokines and chemokines, such as CCL2, CCL5, CCL7, CXCL12, etc., and growth factors including VEGF, PDGF, and CSF1, as well as other factors such as fibronectin and fibrinogen [7–10]. CSF1 is the major regulator for monocyte proliferation and differentiation. CCL2 is a dominant attractant in many tumors. Since monocytes highly expressed the receptor of CCL2 (CCR2), most of tumors produced a high level of CCL2 that can intensely attract monocytes migrating toward CCL2-CCR2 axis [11–17]. However, CCL2 inhibition studies show that it could not completely suppress TAM accumulation, indicating that other factors affect this process [7, 17–21]. The CCL12-CXCR4 axis is reported to promote TAM regional accumulation under therapeutic treatments. In mice model, breast cancer highly expressed CCL20 and CCL5; Either inhibited CCL20 expression or treated with CCR5 antagonist, the number of TAMs was significantly reduced within tumors. These studies have shown that in breast cancer, CCL20-CCR6 and CCL5-CCR5 axes contribute to TAM accumulation. Another chemokine CCL11 can be induced under hypoxia condition and subsequently recruit TAMs to the hypoxic region.

In turn, TAMs can produce different molecules to remodel TME and influence fundamental aspects of tumor pathology. For instance, TAMs secrete endothelial growth factor (EGF) to increase neoplastic proliferation directly [22]; TAMs release vascular endothelial growth factors (VEGF) [23], angiogenic factor thymidine phosphorylase, and other chemokines including CCL2 and CXCL8 to enhance angiogenesis; TAMs produce metalloproteases (MMPs) to change TME matrix architecture for tumor metastasis [24]; and TAMs express immune regulatory molecules such as arginase-1 (ARG1), IL-10, and IL12 to modulate immune response [2]. The role of TAMs is accomplished by their phenotypic plasticity, either pro-inflammatory or anti-inflammatory phenotype, in response to the complex stimuli in TME. The double-edged sword feature of TAM polarization makes them as a novel and potent target for cancer prevention and treatments.

Traditional Chinese medicine is an integrated healthcare system composed of many practices that were rooted in China for over 5000 years. Due to its multi-target, multi-level, and coordinated intervention effects, Chinese medicine is widely used for therapeutic strategies. Recent studies reported that some of the Chinese herbal medicines have beneficial effects on cancer therapy via modulating TAM polarization, indicating a new mechanism for Chinese medicine treatment. In this chapter, we will explore the molecular mechanisms of TAM polarization and their roles in health and disease, and we will review the intervention by some of the Chinese herbal medicines on TAM polarization.

2. TAM polarization and molecular mechanisms

2.1 TAM polarization

It is widely accepted that the majority of TAMs are derived from circulating monocytes via cytokine recruitment and then differentiate to macrophages. And those at the metastatic sites are called metastatic-associated macrophages (MAMs) according to their location [25]. While recent studies have shown that the tissue-resident macrophages also contribute to TAM population [26, 27], these

progenitors, also called embryonic macrophages, are derived from the yolk sac or fetal liver-derived progenitors, and they can maintain themselves by local proliferation in a hematopoietic system-independent way [28]. The selective depletion studies found that only the tissue-resident macrophages support the established tumor growth. Therefore, TAMs are heterogeneous cell populations from both tissue-resident macrophages and monocyte-derived macrophages and assist TME remodeling.

Besides their heterogeneity, TAMs are also characterized by high plasticity. In the general regard, macrophages can be overgeneralized to two extreme subsets based on the stimuli, surface markers, and secreted molecules, as well as functional properties: the classically activated M1 and alternatively activated M2 macrophages. The M1 phenotype is induced by the Th1 cytokine interferon- γ (IFN- γ), bacterial moieties such as lipopolysaccharide (LPS), and Toll-like receptor (TLR) agonists. The M1 macrophages are characterized by their capacity to produce inflammatory cytokines (e.g., IL-6, IL-1, IL-12, IL-23, and TNF- α) and stimulate immune response, express reactive oxygen species (ROS) and inducible nitric oxide synthase (iNOS), and have a cytotoxic effect toward neoplastic cells and phagocytic microorganisms [29–34]. Generally, the M1-like macrophages act as sentries and display tumoricidal function, antimicrobial activity, and tissue destruction effect [33, 35].

In contrast, the M2 phenotype is promoted by Th2 mediators and produces immunosuppressive factors (e.g., IL-10, TGF- β) and growth factors (e.g., VEGF) and exerts anti-inflammatory and pro-tumorigenic activities [34, 36, 37]. Moreover, the M2-like macrophages can be further subdivided into three categories, M2a, M2b, and M2c, based on the type of stimuli. The M2a macrophages are driven by type II cytokines including IL4 and IL13 and expressed a high level of arginase-1; M2b macrophages are activated by immune complexes/TLR, while M2c macrophages by anti-inflammatory cytokines (e.g., IL-10) and glucocorticoids [38]. The M2-like macrophages promote angiogenesis, wound repair, and tumor growth, as well as resistance to parasitic infection. Many studies reported that TAMs mostly represent M2-like macrophages and play pro-tumoral roles.

2.2 Molecular mechanisms in regulating TAM polarization

2.2.1 The JNK signaling pathway

The c-Jun N-terminal kinase (JNK) proteins are a group of stress-activated serine threonine protein kinases of the MAPK and can be activated by various external stimuli including inflammatory cytokines, environmental stresses, growth factors, and GPCR agonists. The outside signals can be transduced by small GTPase to MAP3Ks and further activate MKK4/7. The MAP3Ks play key roles in the JNK pathway and affect tremendous downstream transcription factors including AP-1, Smad3, and STAT3, thus controlling many biological processes [39]. The studies on adipose tissue macrophages (ATMs) have demonstrated that the JNK pathway is indispensable in regulating M1/M2 phenotype formation. In HFD-/NAFLD-induced inflammation and obesity, the activated JNK pathway can promote the expression of the M1-associated genes via CCR2 and NF- κ B signaling. The M1-like ATMs are related to the resistance to insulin [40, 41]. Recent studies found that normal adipocytes produce Th2 cytokines, such as IL-13 and IL-4 which can enhance M2-like macrophage polarization via activating STAT6 and PPAR δ/β , as well as ACE to block the JNK pathway-induced M1-like phenotype [42]. Studies also found that vigorous exercise can promote M2 state through decrease phosphor-JNK [43].

2.2.2 The PI3K/Akt signaling pathway

Among different pathways, the PI3K/Akt pathway is playing a central role in regulating polarized phenotype alteration. It can be activated by many stimuli such as TLR4, PRRs, FcRs, and cytokines and modify downstream cytokine production [44–47]. In turn, the PI3K/Akt pathway can affect the expression of stimuli and form a feedback loop. For example, the activated PI3K/Akt pathway can inhibit the transcription factors of TLR4 including TRAF6 and FOXO1 either directly or indirectly to suppress TLR4 stimulation. The PI3K has two transducers PIP2 and PIP3 which exert opposite functions during stimulation. It has been reported that PIP2 can enlarge LPS-induced M1-like macrophage polarization, while PIP3 can target mTORC2 via Akt recruitment and promote M2-like macrophage polarization. Other studies found that PTEN and SHIP play an inhibitory effect on PI3K/Akt transduction by transforming PIP3 to PIP2. The downstream signals mTORC1 and mTORC2 also participate in regulating M1/M2 alteration. Deletion of TSC1 can promote LPS-induced M1 polarization and inhibit IL-4-triggered M2 polarization via inhibiting mTORC1-induced Akt signaling, while the deletion of TSC2 gives an opposite response. Furthermore, the isoforms of Akt also contribute to influence the M1-/M2-polarized phenotype transformation in the opposite way. In knocked out Akt1, the expressions of iNOS and IL-12 were enhanced which is a hallmark of M1-like macrophages, and the transcription factor C/EBP β of M2-related genes was decreased. The deletion of Akt2 led to C/EBP β and M2 markers enhanced, including Arg1, Fizz1, and Ym1 [48].

2.2.3 The JAK/STAT signaling pathway

The JAK/STAT pathway is one of the principle regulators for transducing different signals and affects various gene expressions. The JAK family consists of JAK1–3 and TYK2 and can be recruited and bind to the intracellular domains of activated receptors. JAKs will subsequently become dimers after autophosphorylation and then phosphorylate their downstream STAT family which has seven members including STAT1–4, STAT5A/B, and STAT6. The activated STAT family will translocate to the nucleus and modulate the expression of their target genes [49]. Increasing evidence found that the JAK/STAT pathway is closely related to M1/M2 phenotypic polarization. Among different stimuli of JAK/STAT signaling pathway, the IFN- γ has been known as a strong inducer of M1 phenotype through STAT1 activation [50]. It is controlled by IRF5 and IRF4 which exert promotive and inhibitory effects, respectively [51]. The IL-4 and IL-10 can activate STAT3 and STAT6 to program the M2-like phenotype and also have cross talk with JNK pathway as mentioned in the JNK signaling pathway. The IL-13 can activate both M1- and M2-associated genes through STAT1, STAT3, and STAT6 activation [52]. There are two regulators of JAK/STAT pathway that affect M1/M2 reprogramming, SOCS1 and SOCS3. The SOCS1 exhibits a suppressive function on STAT1, thus leading to the M1-like phenotype inhibition, while activating STAT6 to induce M2 polarization. The SOCS3 can activate STAT1 activity to contribute M1 polarization [53, 54].

2.2.4 The Notch signaling pathway

The Notch pathway is generally known to play a fundamental role in regulating development and assist to govern the fate in response to different stimuli. There are four members of transmembrane receptors including Notch1–4. When the Notch receptors bind to their ligand family, such as Delta-like proteins (DLLs) and Jagged

proteins, the Notch intracellular domain (NICD) receptors will be released into the cell nucleus and binds to RBP-J to form a transcription complex, thus driving the target gene expression [55]. For example, LPS stimulation can upregulate DLL4 which is one of the DLLs in the TLR4/NF- κ B-dependent way. The increased DLL4 can lead to activated Notch signaling and induce pro-inflammatory genes, such as IL-12 and iNOS [56]. Apart from the direct function of RBP-J, it can also positively regulate IRF8 activation to promote pro-inflammatory cytokine production. And this regulation is associated with PI3K/Akt and TLR4/NF- κ B pathways [57].

2.2.5 Other molecular mechanisms

Apart from the signaling pathways mentioned above, there are many other pathways involving in M1/M2 reprogramming. For example, the TLR/NF- κ B pathway is important in regulating the innate immune response. TLRs can sense the microbial components and transduce signals to affect NF- κ B activity. When the NF- κ B is formed as p50/p65, it promotes M1-associated gene expression, while p50/p50 form has beneficial effects on M2-associated gene expression [58, 59]. It is worth noting that the hypoxia-dependent pathway also participates in M1/M2 phenotypic switch. The HIF-1 α is induced under hypoxia condition and serves as a transcription factor to regulate protein production. It has been reported that HIF-1 α promotes M1-like polarization by enhancing iNOS production and HIF-2 α promotes M2 phenotype via increasing Arg-1 expression [60].

3. Roles of TAM polarization and Chinese medicine intervention

The roles of TAMs under physiological and pathological conditions depend on their dichotomic polarization. Generally, when infection of tissue or damage occurs, The first-responding TAMs show M1-like phenotype and secrete pro-inflammatory cytokines to defend against invading pathogens and eliminate necrotic cells. And at the latter stage, the M2-like macrophages have shown as a compensation mechanism to prohibit extensive inflammation and assist in wound healing. In cancers, the M1-like TAMs predominantly exert cytotoxicity effect on cancer cells, while the M2-like TAMs assist in modulating immunosuppressive and pro-tumoral TME for cancer progression. Nowadays, TAMs are becoming promising targets for therapeutic strategies [61, 62]. Many Chinese herbal medicines have been identified to have anti-microbial, anti-inflammatory, immune regulatory, and antitumor effects. It would be interesting to review the intervention of Chinese medicines on TAM polarization in different cancers and diseases. Here, we select some of the Chinese medicines to describe as examples.

3.1 Baicalein

Baicalein (5,6,7-trihydroxyflavone) is isolated from the Chinese herb *Scutellaria baicalensis* root and has many beneficial effects on antitumor, anti-inflammation, anti-fibrosis, and antimicrobial [63, 64]. The treatment of baicalein in breast cancer is the first to explain its effect on TAM regulation. In breast cancer, TAMs showed M2-like phenotype that produced TGF- β 1 and enhanced tumor growth and EMT process via PI3K/Akt signaling pathway. In turn, the tumor cells secreted TGF- β 1 to maintain TAMs in M2-like phenotype. The positive feedback loop between tumor cells and M2-like macrophages was formed and further contributed to tumor metastasis in the lung. Baicalein administration could block TGF- β 1 via inhibiting PI3K/Akt pathway. Besides, instead of altering the population of TAMs, baicalein could

drive M2-like macrophages to M1-like macrophage differentiation, with M1 markers increased. Therefore, the application of baicalein in regulating TAM polarization in breast cancer may provide a new understanding of other cancer treatments [65].

3.2 *Panax notoginseng*

The root of *Panax notoginseng* (PN) (Burk.) F.H. Chen is one of the popular Chinese herbs also known as sanqi, tianqi, or sanchi in Asia [66]. It has been widely used in many disorders for over 400 years due to its anticancer, anti-inflammatory, antiatherosclerotic, and hemostatic properties [67, 68]. Recent studies have shown that PN not only has cytotoxicity on cancer cells but also can redirect TAM polarization. It is commonly known that M2-like macrophages exert pro-tumorigenic effects on cancer, and to redirect M2 phenotype to antitumor M1 phenotype would be one of the promising strategies in cancer treatment. In many lung cancer studies, it has been reported that high doses of PN administration have direct cytotoxic effects on cancer cells, while the lower dose of PN still have inhibitory effects on tumor growth, suggesting there are other regulatory mechanisms. The in vitro study found that a lower dose of PN did not affect cancer cells, but it could reeducate M2-like macrophages toward M1 phenotypic differentiation [69]. It would help to better explain the pharmacological mechanism of PN.

3.3 Osthole

Osthole [7-methoxy-8-(3-methyl-2-butenyl)-2H-1-benzopyran-2-one] is isolated from *Cnidium monnieri* (*Fructus Cnidii*) and belongs to coumarin family, which is a benzopyrone and used as tumor-target drug carrier [70]. Osthole not only has cytotoxicity to cancer cells, such as breast cancer, lung cancer, HCC, and nasopharyngeal cancer (NPC) [71–73], but also has immunomodulatory effects on different tumors. In pancreatic tumors, osthole decreased M2-like macrophage population both in tumor site and spleen. But it did not affect M1-like macrophages. An in vitro study found that osthole could significantly inhibit STAT6 pathway and p-ERK1/2-C/EBP β signal, thus further inhibiting the M2-like macrophage polarization [74].

3.4 Emodin

Emodin (1,3,8-trihydroxy-6-methylantraquinone) is a natural anthraquinone derivative from many Chinese herbs, and it has multiple pharmacological effects [75]. One study focused on the effects of emodin on macrophage polarization has shown that it could bidirectionally regulate both M1 and M2 phenotype programs via different signaling pathways, as well as participated in the epigenetic modification. It seems like that emodin can restrain excessive M1- or M2-like macrophages and assist in maintaining homeostasis in different pathologies. For example, in breast cancer, emodin decreased TAM infiltration and inhibited M2-polarized phenotype by suppressing STAT6 and C/EBP β signaling pathway. Moreover, it could increase H3K27m3 to downregulate M2-related genes.

3.5 Other Chinese medicine

Many other Chinese medicines have protective functions on different diseases through regulating M1/M2 phenotypic switch (as shown in **Table 1**). For example, curcumin can promote macrophages toward M2-like phenotype to ameliorate liver fibrosis, and it also assists wound healing [76]. Smiglaside A and Ginsenoside Rb3 have protective functions against acute lung injury via inducing M2-like

Chinese medicine	M1/M2 phenotype switch	Disease	Reference
<i>Angelica sinensis</i>	M2	Cardiac fibrosis	[79]
Baicalein	M1	Breast cancer	[65]
Berberine	M2	Colitis; insulin resistance	[80, 81]
Bergenin	M2	Colitis	[82]
Celastrol	M2	Diet-induced obesity; acute ischemic stroke	[83, 84]
Corilagin	M1	Schistosome egg-induced hepatic fibrosis	[85]
Crocin	M2	Atherosclerosis	[86]
Curcumin	M2	Liver fibrosis; wound healing	[76, 87]
Dioscin	M1	Melanoma	[88]
Diosgenin glucoside	M2	Neuroinflammatory diseases	[89]
Emodin	M1	Breast cancer	[90]
<i>Ganoderma lucidum</i> Karst	M1	Inflammation	[91]
Gastrodin	M2	Cerebral palsy	[92]
Ginkgolide B	M2	Ischemic stroke	[93]
Ginsenoside Rb1	M2	Atherosclerosis	[94]
Ginsenoside Rb3	M2	Acute lung injury	[78]
Isoliquiritigenin	M2	Acute kidney injury	[95]
Kumatakenin	M1	Ovarian cancer	[96]
Magnesium lithospermate B	M2	Neuronal injury	[97]
<i>Mylabris phalerata</i>	M1	Lung carcinoma	[98]
Osthole	M1	Pancreatic cancer	[74]
Paeoniflorin	M2	Neuronal injury	[99]
<i>Panax notoginseng</i>	M1	Lung carcinoma; influenza A virus infection	[69, 100]
Pentacyclic triterpene Lupeol	M2	Inflammatory bowel disease	[101]
Pterostilbene	M1	Lung cancer	[102]
Punicalagin	M2	Inflammation	[103]
Saponin	M2	Intestinal polyps	[104]
Smiglaside A	M2	Acute lung injury	[77]
Tanshinone IIA	M2	Acute kidney injury Inflammation	[105]
Timosaponin AIII	M2	Colitis	[106]
<i>Trichosanthes Kirilowii</i> lectin	M2	Streptozocin-induced kidney injury	[107]

Table 1.
The intervention of Chinese medicine on M1/M2 switch in different diseases.

macrophage polarization [77, 78]. These findings may throw a new light for the regulatory mechanisms of Chinese medicines and promote their applications in health and diseases.

4. Conclusions

Current studies have described the heterogeneity and adaptive plasticity of TAMs in the intrinsic and dynamic TME. They are composed of both tissue-resident macrophages and monocyte-derived macrophages and interplay with TME. The latter one is attracted and recruited to the tumor site via various signals in TME, while TAMs can produce different molecules to remodel TME. In response to different stimuli, TAMs can differentiate into either classically activated/M1 macrophages or alternatively activated/M2 macrophage which involves multiple signaling pathways. The role of TAMs depends on their dichotomic polarization in health and disease. Therefore, they are becoming potential targets for many therapeutic strategies. Chinese medicine has been widely used in a long history of Asia and shows multiple effects on different diseases. Knowing the intervention of Chinese medicine on TAMs polarization may help to better understand the principle of Chinese medicine and contribute to the comprehensive applications in many diseases.

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Conflict of interest

The authors have no conflict of interest.

Abbreviations

AP-1	activator protein 1
ARG1	arginase-1
ATM	adipose tissue macrophage
CCR	C-C motif chemokine receptors
CSF1	colony stimulating factor
DLL	Delta-like protein
EGF	endothelial growth factor
FcR	Fc receptor
FOXO1	Forkhead Box O1
GPCR	G-protein-coupled receptors
HFD	high-fat diet
HIF	hypoxia inducible factor
IFN	interferon
IL	interleukin
iNOS	inducible nitric oxide synthase
IRF	interferon regulatory factor
JAK	Janus kinase
JNK	c-Jun N-terminal kinase
LPS	lipopolysaccharide

MAM	metastatic-associated macrophage
MAPK	mitogen-activated protein kinase
MMP	metalloprotease
mTOR	mammalian target of rapamycin
NAFLD	nonalcoholic fatty liver disease
NICD	intracellular domain of notch receptor
NPC	nasopharyngeal cancer
PDGF	platelet-derived growth factor
PI3K	phosphoinositide-3-kinase
PIP2	phosphatidylinositol 4,5-bisphosphate
PIP3	phosphatidylinositol 3,4,5-trisphosphate
PN	<i>Panax notoginseng</i>
PPAR	peroxisome proliferator-activated receptor
PRR	pattern recognition receptor
RBP-J	recombination signal binding protein for immunoglobulin Kappa J region
ROS	reactive oxygen species
Smad3	SMAD family member 3
SOCS	suppressor of cytokine signaling
STAT	signal transducer and activator of transcription
TAM	tumor-associated macrophages
TGF	transforming growth factor
Th1	type 1 T helper
Th2	type 2 T helper
TLR	Toll-like receptor
TME	tumor microenvironment
TRAF	TNF receptor-associated factor
VEGF	vascular endothelial growth factor
Ym1	chitinase-like 3


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