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Macrophage Polarization by Nutrients: Helps Many Diseases Condition

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Abstract

Macrophages are phagocytic cells, digest the cellular debris, foreign substances, and microbes. They are equally important for tissue development and homeostasis. Macrophages are generally of two types, one is M1-type, involved in inflammation, aggravating the pathological events, including cardiovascular diseases, diabetes, and neurological disorders. The other one is M2- type, and known for their anti-inflammatory function. The tumor micro-environment (TME) generally loaded with M2-type, and causes the cancer metastasis. The impact of nutrients on immune system, especially on macrophage plasticity is a point of growing research interest. Recent researchers have found pro- and anti-inflammatory properties of some nutrients/diet patterns, which can be used for low-grade inflammatory status correction. In this regard, the assessment of potential effects of nutrition on macrophage differentiation, proliferation, and functioning in health and disease is highly warranted. In this review, we discuss with current data the effects of nutrition on the macrophage functioning in relation to various disease control.

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Abbreviations

TME	Tumor Microenvironment
CAR-M	Chimeric Antigen Receptor Macrophage
PAMPs	Pathogen-Associated Molecular Patterns
MAPK	Mitogen-Activated Protein Kinase

DAMPs	Damage-Associated Molecular Patterns (or Danger-Associated Molecular Patterns)
NF-κB	Nuclear Factor Kappa B (Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells)
IFN-γ	Interferon-Gamma
p65	Protein Transcription Factor p65 (RelA Subunit of NF-κB)
LPS	Lipopolysaccharide
ALI	Acute Lung Injury
NO	Nitric Oxide
ARDS	Acute Respiratory Distress Syndrome
CCL2, CCL3, CCL5	CC Chemokine Ligand 2, 3, and 5
IL-12, IL-6, IL-1β, IL-23	Interleukin-12, Interleukin-6, Interleukin-1 Beta, and Interleukin-23
STAT	Signal Transducer and Activator of Transcription
TNF-α	Tumor Necrosis Factor-Alpha
CXCL8, CXCL9, CXCL10, CXCL11, CXCL16	C-X-C Motif Chemokine Ligand 8, 9, 10, 11, and 16
NOS	Nitric Oxide Synthase (or Nitric Oxide Synthases)
ROS	Reactive Oxygen Species
MHC II	Major Histocompatibility Complex Class II
SOCS	Suppressor of Cytokine Signaling (not Security Operations Center in this biological context)
TLR	Toll-Like Receptor
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
IRF	Interferon Regulatory Factor
IRF5	Interferon Regulatory Factor 5
IRF4	Interferon Regulatory Factor 4

Introduction

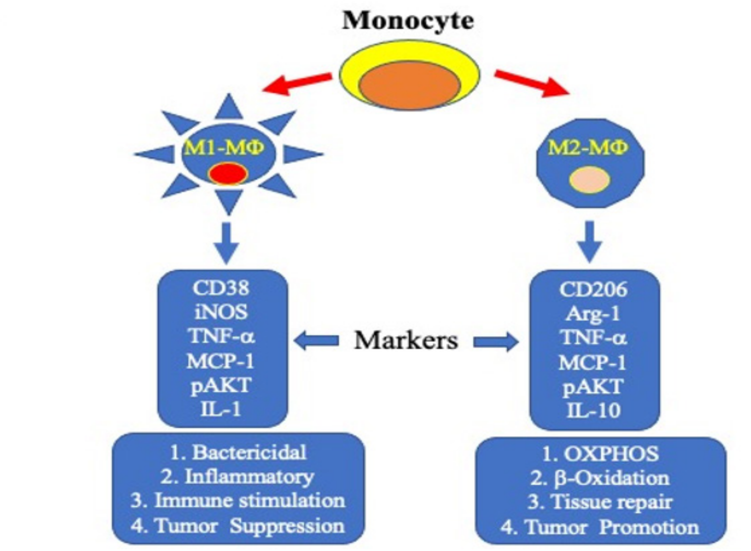
Macrophages are terminally differentiated phagocytic cells including dendritic cells, circulating blood monocytes, myeloid progenitor cells in the bone marrow, and also the microglia in the brain and central nervous system. Based on developmental origins, macrophages are categorized as tissue-resident macrophages and monocyte-derived macrophages, which collectively involved in host defense. These are activated in response to various signals, like Pathogen Associated Molecular Patterns (PAMPs) present on most microbes, and Danger Associated Molecular Patterns (DAMPs) developed in the presence of dead or infected host cells. Notably, the functional states of macrophages exist along a continuum between the classical pro-inflammatory (M1) and anti-inflammatory/reparative (M2) dichotomy [1].

Macrophages are considered as plastic cells, activation and its polarization to its different types have a functional significance in homeostasis and diseases, like, systemic metabolism, hematopoiesis, vasculogenesis, apoptosis, malignancy, and reproduction, etc. These states are dynamically shaped by spatio-temporally heterogeneous micro-environmental signals and coordinated through intricate molecular networks. The classical (M1) and alternative (M2) activation depend on the type of cytokines and also the micro-environmental signals, that the macrophages encounter [2-4].

M1 Macrophages (Classically Activated)

The classical or M1 activated macrophages have positive effects on inflammation, and formed as a result of classical activation of Toll-like Receptors through interferon-gamma (IFN-γ) or lipopolysaccharide (LPS), and kill invading pathogens through the production of inflammatory mediators, like nitric oxide (NO) and other cytokines (Figure 1) [5].

Fig. 1:



In short, the pro-inflammatory macrophages (M1-type) eliminate infections caused by bacteria, viruses, or fungi, and also kill tumor cells.

Biomarkers Specific for M1-Macrophage Activation [6,7]:

- **Cytokines :** IL-12, TNF-α, IL- 6, IL-1β, IL-23
- **Chemokines:** CXCL8, CXCL9, CXCL10, CXCL11, CXCL16, CCL2, CCL3, CCL5
- **Co-stimulatory molecules:** CD80, CD86
- **Surface markers:** MHCII and TLR2/4
- Inflammatory mediators like nitric oxide synthases (NOS) and reactive oxygen species (ROS)

M2-Macrophages (Alternatively Activated)

M2-macrophages are formed on exposure to cytokines like, IL-4, IL-10, or IL-13, and inhibit inflammation. These macrophages produce polyamines and proline, which induce proliferation and collagen production, hence regulates the immune response towards parasites, allergy, wound healing, and tissue remodeling. Further, the anti-inflammatory macrophages (M2-type) can induce differentiation of regulatory T-lymphocytes. It should be mentioned here that different stimuli can further activate the M2-type into its various sub-types, like M2a (wound-healing) induced by IL-4 and IL-13, M2b (alternative inflammation) triggered by immune complexes in the presence of FcγR/TLR ligand, and M2c by anti-inflammatory stimuli such as glucocorticoids, IL-10, TGF-β [8, 9].

Biomarkers Specific for M2-Macrophage Activation

Arginase-1, Chitinase-3 like protein or Ym1, CD206 and CD163, FIZZ1, DC-SIGN or CD209, MGL-1 and Dectin-1 (CLEC- 7A), cytokines such as IL-10 and IL-1ra, chemokines like CCL17, CD200R, or CD23 are the known makers for M2-macrophages [10].

Transcription Factors for Polarization of Macrophages

Nuclear Factor κB (NF-κB) transcription factor activates the macrophage to its M1-type in response to inflammatory cytokines and stress signals. Activated Protein 1 (AP-1), a group of basic leucine zipper pro-inflammatory transcription factor mediates gene regulation in response to physiological and pathological stimuli. Interferon

Regulatory Factors (IFN) such as IRF5 and IRF4 are important for M1 and M2 differentiation. Hypoxia-Inducible Factors (HIF-1α) activity, regulated by Th1 cytokines, causes M1-macrophage polarization, which promotes the production of Nitric oxide, whereas HIF-2α activity is regulated by Th2 cytokines and causes M2-macrophage polarization. Signal Transducers and Activators of Transcription (STAT1, STAT2) are associated with M1-macrophage polarization, and M2-macrophage polarization, respectively [11-13].

Macrophage Polarization and the Control of Different Diseases

The dynamic balance—typically conceptualized as pro-inflammatory M1 and anti-inflammatory/tissue-repairing M2, are the priming factors for physiological status of the body. Dysregulated macrophage and microglial polarization—a persistent, pathological imbalance between the pro-inflammatory (M1) and anti-inflammatory/tissue-repairing (M2) phenotypes—causes chronic inflammatory, autoimmune, and metabolic conditions, as well as severe fibrotic diseases and invasive carcinoma.

Neurodegenerative Diseases: In the central nervous system, the chronic M1 activation of resident immune cells, microglia. causes neurotoxicity. Whereas, a failing or depleted M2 state decreases the brain's ability to clear debris and resolve inflammation [14,15].

- **Alzheimer's Disease (AD):** Characterized by hyperactive M1 microglia responding to amyloid-beta (A) plaques and tau tangles, resulting in progressive synaptic loss.
- **Parkinson's Disease (PD):** Caused by M1-induced oxidative stress and pro-inflammatory cytokines that drives the death of dopaminergic neurons.
- **Amyotrophic Lateral Sclerosis (ALS):** M1-type of macrophages induce neuroinflammation by causing the accumulation of mutated proteins (e.g., SOD-1). This, then, accelerates the motor neuron degeneration.
- **Multiple Sclerosis (MS):** An autoimmune disease, when microglia and macrophages polarize to its M1-phenotype, leading to the breakdown of the blood-brain barrier and the destruction of myelin [14-20].

Autoimmune & Systemic Inflammatory Disorders: An increased M1-to-M2 ratio perpetuates chronic systemic attacks on host tissues:

- **Rheumatoid Arthritis (RA):** M1 macrophages heavily drive synovial inflammation and joint degradation, while defective M2 macrophages fail to properly repair the extracellular matrix.
- **Inflammatory Bowel Disease (IBD):** Crohn's disease and ulcerative colitis are marked by an overabundance of M1 macrophages producing cytokines, which destroy the mucosal lining.
- **Systemic Lupus Erythematosus (SLE):** An abnormal balance of both M1 and M2 states prevents the resolution of inflammation, leading to chronic organ and tissue damage, particularly in the kidneys (lupus nephritis) [14-17].

Metabolic & Cardiovascular Diseases: The polarization state of macrophages dictates a systemic metabolic health and vessel integrity:

- **Obesity & Type 2 Diabetes:** Adipose tissue expansion promotes a shift of macrophages toward the inflammatory M1 phenotype. These M1 cells release cytokines that counteract insulin, ultimately induces insulin resistance [14].
- **Atherosclerosis:** Excess lipids convert arterial macrophages into inflammatory M1-type, which contribute to the formation and rupture of atherosclerotic plaques [14,15].
- **Fibrotic Disorders:** While the M2 phenotype is essential for tissue repair, an unchecked, chronic polarization toward M2 macrophages directly promotes the excessive accumulation of the extracellular matrix (e.g., collagen) [14].
- **Systemic Sclerosis (Scleroderma):** M2a macrophages are recognized as primary drivers of tissue fibrosis, destroying organ architecture.
- Chronic Kidney Disease (CKD): Progressive loss of kidney function driven by chronic M2-induced fibrosis and macrophage-induced oxidative stress [14,15].

Oncology (Tumor-Associated Macrophages - TAMs)
In many tumors, macrophages are polarized into an M2-like state. Instead of fighting the cancer, as M1-type does, these M2 macrophages secrete factors that suppress the immune system, stimulate tumor angiogenesis (growth of blood vessel), and promote metastasis [14,15].

Mechanisms Involved Behind the Roles of M1/M2-Macrophages in Inflammatory Responses

Inflammation is a part of homeostasis where the body recruits' immune cells to destroy the infectious agents, pathogens, and dead cells. The immune cells that include T cells, B cells, NK cells, monocytes, macrophages, dendritic cells, neutrophils, basophils, eosinophils, and mast cells to participate in the process of pathogen recognition and also to activate the signaling cascade of inflammation. An inflammatory response is required by the immune system to recruit more immune cells. Various signaling molecules like IL-2, IL-3, IL-4, IL-12, IFN-γ, and TNF-α, etc. participate in immune cell activation and proliferation. Polarized T cells i.e. Th-1 and Th-2, secrete Th1 cytokines (IL-12, IFN-γ, TNF-β) and Th2 cytokines (IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13), respectively. The Th-1 cytokines influence the M1 polarization and Th-2 cytokines cause M2 macrophages polarization. Among the various other factors, the microenvironment and surrounding cytokines can also polarize M1/M2 macrophages [10,20,21].

During a pathogenic encounter, M1-type macrophages are involved in the process of phagocytosis by secreting various cytokines and chemokines, and after pathogen removal the other phenotype, M2-macrophages, clear the apoptotic cells, produce extracellular matrix, blood vessels, secrete chemotactic factors and IL-10, resulting in the process of wound healing, tissue repair, and mitigation of inflammation [22].

Macrophage Polarization Due to Environment

The transformation between M1 and M2 macrophages is also an environment-driven process (Figure 2). Mechanistically, in classical activation of M1 macrophages, induction of NOS2 produces NO, which causes inflammation. In case of M2 macrophages activation, expression of arginase expression gests up-regulated, and convert arginine to ornithine and subsequently into hydroxyproline and polyamines. Those amino acids help in the reconstruction of the damaged extracellular matrix [23].

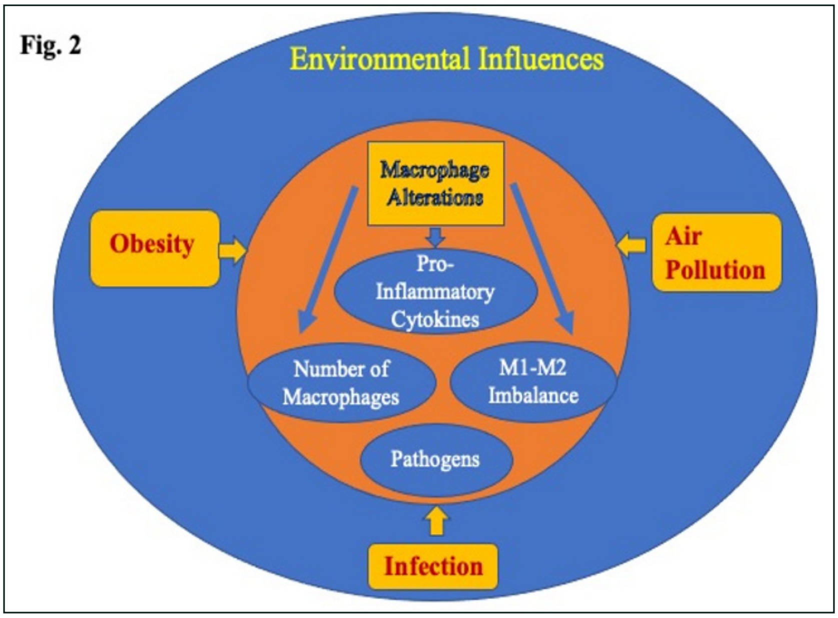


Figure 2: Environmental Influences on Macrophage Polarization

\IFN and TLR induced IRF/STAT signaling, activates M1 macrophages while IL-4 and IL- 13 induced IRF/STAT signaling via STAT 6 induces M2 macrophages**.** Furthermore, SOCS, a family of proteins can inhibit cytokine-mediated signal transduction. The knock-out study of SOCS led to the observation that the ratio of SOCS1: SOCS3 is high in M2 macrophages, but low in M1 macrophages**.** Therefore, it is considered that the expression of SOCS also can affect the M1- M2 macrophage polarization [24,25].

Some Patho-Physiological Conditions can Change the Macrophage Phenotype

An early phase of bacterial infection M1-macrophages induces an inflammatory response, whereas during the late phase of infection macrophages polarize into M2-type to protect the host from excessive injuries and to undergo wound healing. However, in the case of viral infections like influenza, HIV, and SARS, M2-macrophages dominate these pathological conditions. The formation of new blood vessels is a characteristic of M1-mediated inflammatory conditions, as observed in atherosclerosis and tumor, whereas M2 dominated phase is involved during angiogenesis, which is required for cells recruitment and wound healing, and also tumor growth. However, Jetten, et al. recently reported the pro-angiogenesis role of M2 macrophages but not for the M1 macrophages. Much research is required to decide the presence of specific ratio of M1/M2 population in any pathological condition [26-30].

Key Signaling Pathways Guide Polarization Directions

Metabolic pathways like, glycolysis, pentose phosphate pathways while can do M1 polarization, the oxidative phosphorylation and fatty acid oxidation favor M2 polarization. Furthermore, epigenetic mechanisms, like DNA methylation, histone modifications, and non-coding RNAs, contribute to stabilizing polarized phenotypes with functional diversity [31,32].

Psychological conditions can also polarize macrophage phenotype. The Stress can activate the brain macrophages (microglia) and attain the M1 macrophage phenotype, which is related to inflammatory mechanisms leading to neurodegeneration. Treatment with plant-derived natural compounds polarize the M1-microglia towards the M2-type, and prevent the inflammatory responses and thus protect the neurons [14,33].

Therefore, the technology of M1 to M2 phenotype polarization may hold clinical promise in several inflammatory diseases. Pharmacological interventions using small molecules and metabolic modulators to reprogram cell phenotypes, CAR-M macrophages or exosome-mediated reprogramming to remodel immune micro-environments, along with gene editing or epigenetic modifications are the present adopted methods for therapeutic macrophage polarization. However, obstacles are there in advancing the field as the clinical translation faces the challenges like off-target effects, inefficient delivery, micro-environmental dependency [34-36].

Nutrition/Diet-Based Macrophage Polarization and the Control of Different Diseases

There are many studies on plant-derived natural products which reported to show macrophage polarization.

- Dietary-compounds, like polyphenols have potent natural anti-oxidative properties. Within this group of polyphenols, curcumin (isolated from bright-yellow Indian spice, turmeric) has been shown to suppress macrophage inflammatory responses, polarize/repolarize macrophages toward the M2 phenotype. Curcumin significantly reduces co-stimulatory molecules and also inhibits MAPK activation and the translocation of NF-κB p65. Curcumin-treated macrophages are highly efficient in antigen capture and endocytosis via the mannose receptor, as well as it is therapeutically potential for the inflammation-related diseases. However, their precise effects on polarization and immune-stimulatory functions are still remain unknown [37-45].
- Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) is a pulmonary inflammatory disease with high mortality. During the development of ALI/ARDS, macrophages usually polarize toward M1 pro-inflammatory type and aggravate the lung tissue damage. Natural compounds, like flavonoid, brevilin A, and tetrahydropalmatine with anti-inflammatory response showed an excellent result in the treatment of ALI/ARDS through macrophage polarization. Therefore, the in-depth exploration of the regulatory mechanism of macrophages can establish the foundation for the application of flavonoids in alleviating the inflammation-related lung injury [46].
- How Foods Polarize Macrophages: Foods and their components can directly influence macrophage polarization — the process by which macrophages adopt distinct functional states — through specific nutrients, bioactive compounds, and dietary patterns.

Diets can change the macrophage phenotype by altering their metabolic state and signaling pathways. For example:

- Cholesterol-rich diets can promote pro-inflammatory (M1-like) macrophage activation, contributing to chronic inflammation [47].
- Protein deficiency has been linked to altered macrophage function, potentially skewing toward inflammatory states [47].
- Vitamin B6 deficiency can impair immune

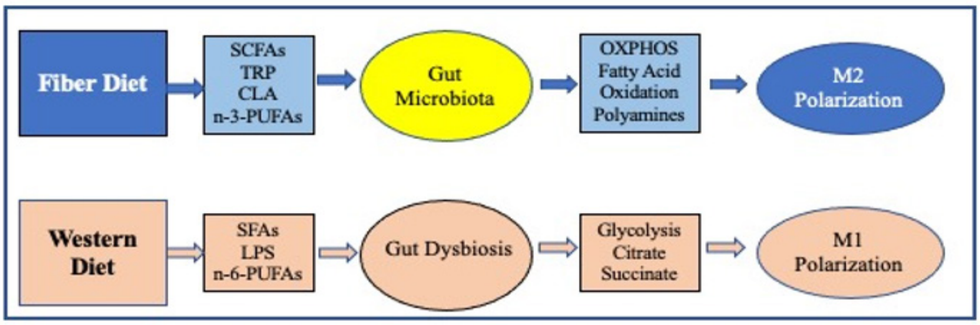
regulation, affecting macrophage polarization [47].
- Anti-inflammatory diets rich in polyphenols, omega-3 fatty acids, and fiber tend to favor M2-like (anti-inflammatory/reparative) macrophages, supporting tissue repair and immune homeostasis [47].

Bioactive Food Compounds Certain food-derived molecules can directly modulate macrophage polarization:
- Polyphenols (e.g., from berries, tea, and dark chocolate) suppress NF-κB signaling, reducing pro-inflammatory cytokine production and promoting M2 polarization [47].
- Omega-3 fatty acids (from fatty fish, flaxseeds, walnuts) generate anti-inflammatory lipid mediators (e.g., resolvins) that shift macrophages toward M2 phenotypes [47].
- Fiber and prebiotics (e.g., in whole grains, legumes, and vegetables) modulate gut microbiota, which in turn influence intestinal macrophage polarization toward anti-inflammatory states [47].

Mechanisms of Polarization Foods influence macrophage polarization via:
- Metabolic reprogramming: M1 polarization is linked to glycolysis and the pentose phosphate pathway, while M2 polarization favors oxidative phosphorylation and fatty acid oxidation [48]. Nutrients in food can shift these metabolic pathways.
- Epigenetic regulation: Dietary components can alter DNA methylation, histone modifications, and non-coding RNA expression, stabilizing polarized phenotypes [48].
- Cytokine modulation: Food-derived compounds can influence local cytokine environments, guiding macrophages toward M1 or M2 states.

Functional Outcomes:
- Pro-inflammatory foods (high in saturated fats, refined sugars, processed foods) often increase M1 macrophage activity, exacerbating chronic inflammation and tissue damage.
- Anti-inflammatory foods (whole plant foods, healthy fats, fermented foods) tend to promote M2 macrophage activity, aiding in inflammation resolution and tissue repair [49].
- The influence of some diet patterns on Macrophage polarization are shown as a cartoon figure. (Figure: 3)

Fig. 3 **Influence of Some Diets on Macrophage Polarization**



Conclusion

Macrophages adopt a long functional spectrum, driven by mainly two mutually transformable phenotypes, M1 and M2. M1-type while known as the pro-inflammatory, which is essential for eliminating pathogens but can cause tissue damage, if overactive. Glycolysis, a metabolic pathway can drive to M1-type. The other type M2 (Anti-inflammatory/Repair), can be driven by Fatty Acid Oxidation (FAO) and Oxidative Phosphorylation (OXPHOS), and that normalizes the inflammation and promotes the tissue repair.

Macrophage polarization—a process by which immune cells adapt distinct functional states—is tightly connected with systemic nutrient availability and their cellular metabolism. By modulating the MQ phenotypes, nutrients and diet-plan can control inflammatory, autoimmune, and metabolic diseases in humans. Some amino acids like Arginine, Glutamine, and Tryptophan influence the functional states of the macrophages, modulate the immune system, and alter the severity of autoimmune diseases. Saturated fatty acids from high-fat diets often promote the inflammatory M1-like polarization, and thus result the meta-inflammation. Conversely, Omega-3 fatty acids and conjugated linoleic acids (CLAs) promote the M2-like phenotype. Plant-derived antioxidants (polyphenols) exert anti-inflammatory effects by encouraging a shift from M1 to M2-type.

Imbalances in macrophage polarization dictate the onset and progression of several major human conditions, like: High-fat diets trigger M1 infiltration in adipose and hepatic tissues, result chronic inflammation and insulin resistance. While shifting to an M2-like phenotype restores insulin sensitivity and helps the hyperglycemia. Lipid dys-homeostasis and oxidative stress promote pro-inflammatory M1-type MQ, while nutraceuticals and dietary polyphenols can shift M1- to an anti-inflammatory, protective M2-type. Elevated M1/M2 ratios are tied to rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis; whereas a high M2/M1 macrophage ratio is closely linked to tumor progression, chronic fibrotic conditions. Modulating metabolism with targeted amino acids or nutrients helps to correct this immune imbalance.

In summary, Foods polarize macrophages by providing specific nutrients and bioactive compounds that alter their metabolism, signaling, and epigenetic state, thereby shifting them toward pro- or anti-inflammatory phenotypes. This makes diet a powerful tool for modulating macrophage function in health and disease. Future research must integrate multi-omics data to develop individualized therapies, and investigate the stability/plasticity of polarization states. Advanced model systems are required to advance precision immune-therapeutics.

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Conflict of interest

I declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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