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Review

Macrophages and Tissue Homeostasis: From Physiological Functions to Disease Onset

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Abstract

The role of macrophages has transcended the traditional binary framework of M1/M2 polarization, emerging as "tissue microenvironment engineers" that dynamically govern organismal homeostasis and disease progression. Under physiological conditions, they maintain balance through phagocytic clearance, metabolic regulation (e.g., lipid and iron metabolism), and tissue-specific functions (such as hepatic detoxification by Kupffer cells and intestinal microbiota sensing), all meticulously orchestrated by epigenetic mechanisms and neuro-immune crosstalk. In pathological states, their functional aberrations precipitate chronic inflammation, fibrosis, metabolic disorders, and neurodegenerative diseases. Notably, this plasticity is most pronounced within the tumor microenvironment (TME): tumor-associated macrophages (TAMs) polarize toward a protumoral phenotype under conditions of low pH and high reactive oxygen species (ROS). They promote angiogenesis via vascular endothelial growth factor (VEGF), suppress immunity through interleukin-10 (IL-10)/programmed death-ligand 1 (PD-L1), and facilitate tumor invasion by degrading the extracellular matrix, ultimately fostering an immune-evasive niche. Novel intervention strategies targeting TAMs in the TME have shown remarkable efficacy: CRISPR-Cas9 spatiotemporal editing corrects aberrant gene expression; pH/ROS-responsive nanoparticles reprogram TAMs to an antitumoral phenotype; chimeric antigen receptor-macrophage (CAR-M) 2.0 enhances antitumor immunity through programmed death-1 (PD-1) blockade and IL-12 secretion; and microbial metabolites like butyrate induce polarization toward an antitumor phenotype. Despite persisting challenges—including the functional compensation mechanisms between tissue-resident and monocyte-derived macrophages, and obstacles to clinical translation—the macrophage-centered strategy of "microenvironmental regulation via cellular engineering" still holds revolutionary promise for the treatment of tumors and other diseases.

Keywords: macrophages; cell polarity; tumor microenvironment; epigenetics; immunotherapy; receptors; chimeric antigen; microbiome; inflammation; fibrosis

1. Introduction

1.1 New Perspectives on Macrophages

As a key member of the innate immune system, macrophages have long been regarded as the "first line of defense" for the body to resist pathogen invasion. Classical immunology theories emphasize their phagocytic and bactericidal functions in the inflammatory response, and classify macrophages into two polarization states: pro-inflammatory (M1) and anti-inflammatory (M2) [1–6]. However, with the rapid development of single-cell sequencing, spatial transcriptomics, and *in vivo* imaging technologies, the functional complexity of macrophages has been gradually revealed [7–9]. The latest research shows that macrophages are not only the executors of the immune response but also "tissue niche engineers". Through the secretion of metabolites and direct cell-cell contact, they dynamically regulate the homeostasis of the tissue microenvironment [7,10–12].

1.2 Controversy Over the Origin of Macrophages

The origin of macrophages has always been a research hotspot in the field of immunology. The early view was that macrophages in adult tissues mainly originated from monocytes differentiated from bone marrow hematopoietic stem cells [13–15]. However, in recent years, single-cell sequencing technology has revealed the long-term self-maintenance ability of embryonic-derived macrophages in adulthood. For example, in the heart, CX_3CR1 macrophages can be traced back to the progenitor cells derived from the yolk sac in the embryonic period. They maintain a stable number through local proliferation in adulthood, independent of the bone marrow monocyte replenishment pathway [16,17]. The discovery of these embryonic-origin macrophages has subverted the traditional understanding and provided a new perspective for understanding the tissue-specific functions of macrophages.

1.3 Macrophages as the Core Role in Homeostasis Regulation

Macrophages play a core role in the regulation of tissue homeostasis [11,18–20] (Table 1, Ref. [11,21–87]). On the one hand, their functional plasticity endows them with the ability to respond to complex environmental changes. For example, the phenomenon of "trained immunity" shows that macrophages can, through epigenetic memory and metabolic reprogramming, produce a stronger response to a secondary stimulus after the first exposure to a pathogen or inflammatory stimulus [88,89]. This plasticity is particularly prominent in the tumor microenvironment, where tumor-associated macrophages (TAMs) undergo phenotypic switching according to signals from the tumor microenvironment, transforming from an anti-tumor active state to a phenotype that promotes tumor growth to adapt to the needs of tumor development [90,91]. On the other hand, macrophages participate in the regulation of systemic homeostasis by constructing a cross-tissue network. Taking the gut-brain axis as an example, gut macrophages sense signals from the microbiota, secrete cytokines to regulate the permeability of the blood-brain barrier and the activity of microglia, and affect the functions of the nervous system [92–96]. In the tumor microenvironment, macrophages also form intricate networks with other cells. They interact with tumor cells, vascular endothelial cells, fibroblasts, and more, and regulate the homeostasis of the tumor microenvironment through the secretion of cytokines, growth factors, and other substances, thereby influencing tumor growth, invasion, and metastasis. For example, vascular endothelial growth factor (VEGF) secreted by TAMs can promote tumor angiogenesis, providing nutrients and oxygen for tumor cells while also serving as a channel for tumor cell metastasis. Additionally, TAMs can secrete immunosuppressive factors such as interleukin-10 (IL-10), which inhibit the activity of immune cells, create an immunosuppressive microenvironment conducive to tumor cell growth, and disrupt the immune homeostasis of the body [97–100].

In response to the abnormal regulation of macrophages in the tumor microenvironment, a variety of innovative intervention strategies have been developed to reshape homeostasis. In terms of precision targeting technologies, spatiotemporally specific gene editing technology can correct the abnormal gene expression of TAMs through the CRISPR-Cas9 system, reactivating their anti-tumor activity [101,102]; pH/reactive oxygen species (ROS) dual-sensitive nanocarriers can respond to the characteristics of the tumor microenvironment to release loaded substances, inducing the reprogramming of TAMs into tumor-suppressive phenotypes [103–105]. In cell engineering therapies, chimeric antigen receptor-macrophage (CAR-M) 2.0 is equipped with dual functional modules of programmed death-1 (PD-1) blockade and Interleukin-12 (IL-12) secretion, enabling precise recognition of tumor antigens, alleviation of immunosuppression, and activation of the immune system [106]; induced pluripotent stem cell (iPSC)-CAR macrophage technology utilizes the properties of induced pluripotent stem cells to generate large quantities of macrophages with specific antigen recognition capabilities, addressing the issue of limited sources of traditional macrophages [107,108]. In microbiome intervention strategies, microbiota metabolites such as butyrate can promote the polarization of macrophages toward anti-tumor phenotypes by regulating gene expression; phage-directed editing technology can precisely eliminate abnormal macrophages infected with pathogens and restore their normal functions [109]. These intervention strategies target macrophages in the tumor microenvironment from different perspectives, aiming to break the imbalanced state of tumor immune escape and restore the body's immune surveillance homeostasis against tumors.

2. The Role of Macrophages in Physiological Tissue Homeostasis

Macrophages are pivotal immune cells in maintaining organismal homeostasis, exhibiting multifaceted functions including phagocytic clearance, immunomodulation, and tissue repair. They orchestrate inflammatory responses, metabolic equilibrium, and tissue-specific regulation (e.g., hepatic detoxification, intestinal microbiota balance, cardiac regeneration, and neuroprotection), while being precisely modulated by epigenetic mechanisms and neural signaling pathways. These sophisticated capabilities establish macrophages as central players in immune defense, tissue regeneration, and therapeutic intervention (Fig. 1).

2.1 Immune Surveillance, Defense, and Tissue Repair and Regeneration

2.1.1 "Scavenger" Function

Macrophages, as the "scavengers" of the body, maintain tissue homeostasis by phagocytosing pathogens, senescent cells, and apoptotic debris [21–24]. In the field of tumor immunology, the phagocytic function of macrophages is recognized as a crucial mechanism for suppressing tumor growth [25–30]. With the rapid advancement of research technologies and the deepening of studies, numerous novel discoveries have been made regarding the "scavenger" function of macrophages in tumors (Fig. 2).

During the phase of recognizing tumor cells, macrophages primarily rely on pattern recognition receptors, such as Toll-like receptors and scavenger receptors, to identify abnormal molecules on the surface of tumor cells. These molecules arise from genetic mutations, metabolic abnormalities, and other factors, including exposed phosphatidylserine (PS) and heat shock proteins (HSPs). They constitute the key "signals" for macrophages to initiate phagocytic behavior. Once recognition is completed, macrophages promptly trigger the endocytic process, enclosing the tumor cells to form phagosomes.

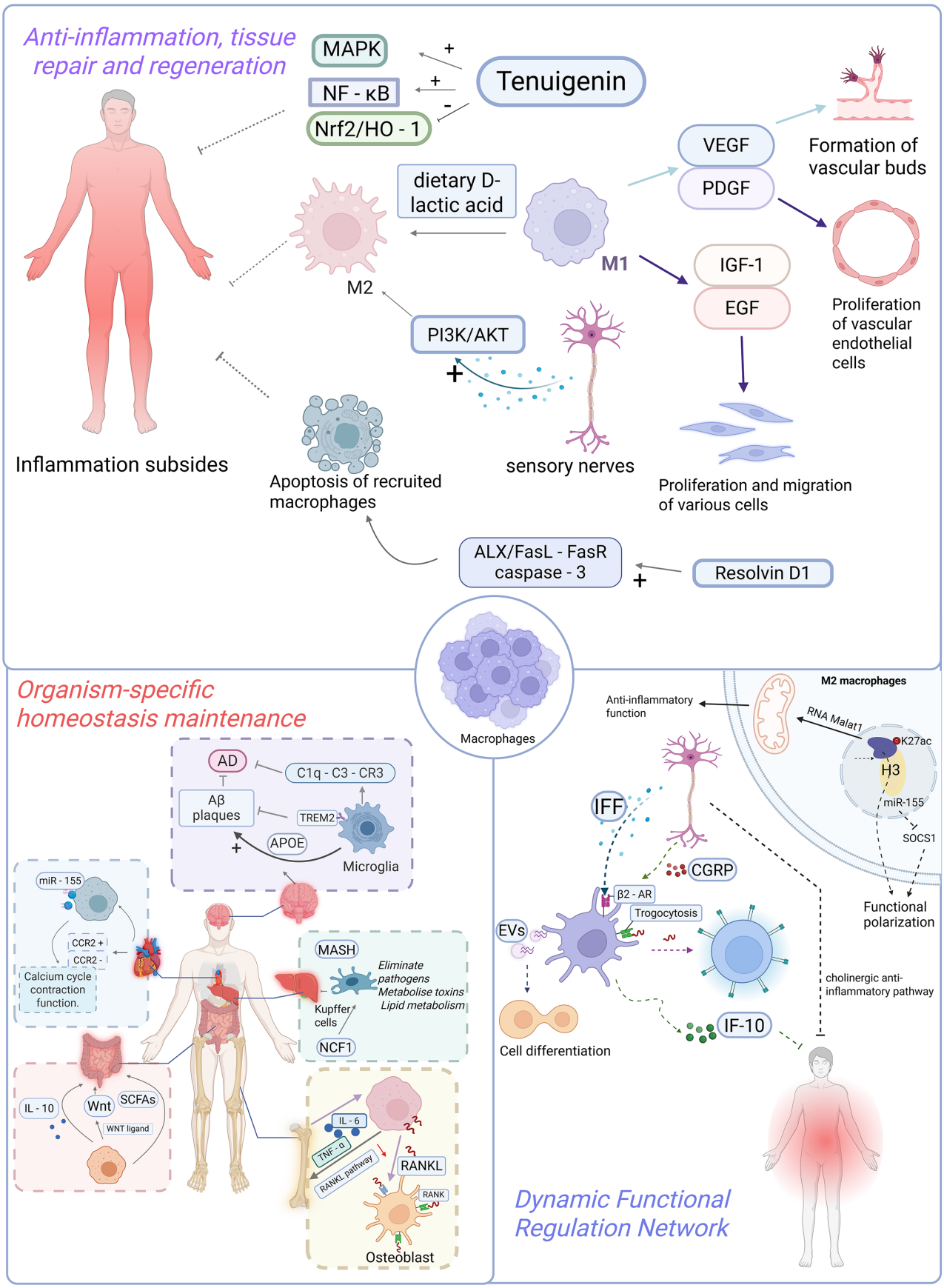
Anti-inflammation, tissue repair and regeneration
MAPK
NF - κB
Nrf2/HO - 1
+
+
-
Tenuigenin
VEGF
PDGF
Formation of vascular buds
dietary D-lactic acid
M2
M1
IGF-1
EGF
Proliferation of vascular endothelial cells
PI3K/AKT
+
Inflammation subsides
Apoptosis of recruited macrophages
sensory nerves
Proliferation and migration of various cells
ALX/FasL - FasR caspase - 3
+
Resolvin D1
Macrophages
Organism-specific homeostasis maintenance
AD
C1q - C3 - CR3
Aβ plaques
TREM2
APOE
+
Microglia
miR - 155
CCR2 +
CCR2 -
Calcium cycle contraction function.
MASH
Eliminate pathogens
Metabolise toxins
Lipid metabolism
Kupffer cells
NCF1
IL - 10
Wnt
SCFAs
WNT ligand
IL - 6
TNF - α
RANKL pathway
RANKL
RANK
Osteoblast
M2 macrophages
Anti-inflammatory function
RNA Malat1
K27ac
H3
miR-155
SOCS1
Functional polarization
IFF
CGRP
β2 - AR
Trogocytosis
EVs
cholinergic anti-inflammatory pathway
IF-10
Cell differentiation
Dynamic Functional Regulation Network

Fig. 1. The role of macrophages in physiological tissue homeostasis. (1) Anti-inflammation, tissue repair and regeneration: Macrophages are pivotal in the resolution of inflammation as well as tissue repair and regeneration: in terms of inflammatory resolution, they terminate inflammation and facilitate repair by secreting anti-inflammatory cytokines and lipid mediators. Moreover, substances such as tenuigenin, dietary D-lactic acid, calcitonin gene-related peptide (CGRP) released by sensory nerves, and resolvin D1 (Rv-D1) accelerate inflammatory resolution through mechanisms including inhibiting or activating relevant signaling pathways, regulating macrophage polarization, or promoting their apoptosis. In the context of tissue repair and regeneration, macrophages secrete pro-angiogenic factors like vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) to participate in angiogenesis, thereby supplying energy to damaged tissues. They also secrete cytokines such as insulin-like growth factor-1 (IGF-1) and epidermal growth factor (EGF), which promote the proliferation and migration of cells including fibroblasts and keratinocytes, thus expediting tissue repair. (2) Organism-specific homeostasis maintenance: Kupffer cells in the liver are involved in pathogen clearance, toxin metabolism, and lipid metabolism regulation, while the protein encoded by the *NCF1* gene can modulate their susceptibility to ferroptosis. Intestinal macrophages maintain the stability of intestinal flora by secreting IL-10, promote the repair of intestinal epithelial barriers via secreting WNT ligands, and are also capable of sensing microbial metabolites to regulate their own functions, thereby preserving intestinal immune homeostasis. Cardiac macrophages are categorized into $CCR2^{+}$ monocyte-derived and $CCR2^{-}$ resident subsets; the resident macrophages can regulate calcium cycling and contractile function of cardiomyocytes, and the exosomes carrying miR-155 secreted by them are able to improve cardiac function. Macrophages in the skeletal system (osteoclast precursors) facilitate osteoclast differentiation and activation by expressing RANKL, thereby driving bone resorption; their aberrant activation is associated with osteoporosis, and the cytokines they secrete can balance the activities of osteoblasts and osteoclasts. Microglia in the central nervous system mediate synaptic pruning during early neurodevelopment; in Alzheimer's disease, the TREM2 receptor on their surface can clear Aβ plaques, and *APOE* influences their clearance capacity, with the *APOE4* isoform in particular exacerbating neural damage. (3) Dynamic Functional Regulation Network: In epigenetic regulation, histone modifications (e.g., H3K27ac) mediate enhancer reprogramming to determine the reparative phenotype; non-coding RNAs (e.g., long-chain Malat1, miR-155) influence anti-inflammatory functions and polarization by regulating related genes (e.g., miR-155 suppresses *SOCS1* to promote M1 phenotype). In neuro-immune interactions, macrophages respond to norepinephrine from sympathetic nerves (activating β2-AR), CGRP from sensory neurons (inducing IL-10), and the cholinergic anti-inflammatory pathway of the vagus nerve, exerting anti-inflammatory effects or maintaining homeostasis. In terms of new technologies for intercellular communication, spatial multi-omics deciphers cell-cell interactions; macrophages transfer antigens through synapse-like structures (e.g., trogocytosis); extracellular vesicles (EVs) carry substances such as proteins and nucleic acids (e.g., miRNAs) to regulate the functions of recipient cells (e.g., stem cell differentiation, tissue repair). CCR2, C-C Chemokine Receptor Type 2; miR-155, MicroRNA-155; *SOCS1*, Suppressor of Cytokine Signaling 1; M1, M1 Phenotype (Classically Activated Macrophage); β2-AR, Beta-2 Adrenergic Receptor; CGRP, Calcitonin Gene-Related Peptide; IL-10, Interleukin-10; EVs, Extracellular Vesicles; H3K27ac, Histone H3 Lysine 27 Acetylation; Malat1, Metastasis-Associated Lung Adenocarcinoma Transcript 1; ncRNAs, Non-Coding RNAs; RANKL, Receptor Activator of Nuclear Factor κB Ligand; TREM2, Triggering Receptor Expressed on Myeloid Cells 2; Aβ, Amyloid Beta; *APOE*, Apolipoprotein E; *NCF1*, Neutrophil Cytosolic Factor 1; MASH, Macrophage Apoptosis-Associated Sphingolipid Hydrolase; VEGF, Vascular Endothelial Growth Factor; IGF-1, Insulin-Like Growth Factor 1; EGF, Epidermal Growth Factor; AD, Alzheimer's Disease. Created in BioRender. https://BioRender.com/ritqdp8.

Subsequently, the phagosomes fuse with lysosomes to form phagolysosomes, where tumor cells are gradually degraded and eliminated under the action of lysosomal enzymes, such as proteases and nucleases. This process not only directly reduces the number of tumor cells but also holds profound significance for immune activation. After phagocytosing tumor cells, macrophages, through antigen presentation, present tumor antigens to $CD4^{+}$ T cells using major histocompatibility complex (MHC) class II molecules. Meanwhile, they secrete cytokines like IL-12 to activate the activation and proliferation of $CD8^{+}$ T cells, thereby triggering and enhancing adaptive immune responses to continuously combat tumors [30,110–112].

The "scavenger" function of macrophages is also reflected in their efficient clearance of apoptotic tumor cell debris and abnormal extracellular matrix components in the tumor microenvironment. During the proliferation of tumor cells, a large number of apoptotic debris are generated due to factors such as hypoxia and nutrient deficiency. If these debris are not cleared in a timely manner, they may release pro-inflammatory factors and even promote tumor cell metastasis. Macrophages can rapidly phagocytose these apoptotic debris, effectively avoiding their negative impact on the tumor microenvironment. Additionally, the excessive deposition of extracellular matrix components in the tumor microenvironment, such as collagen and fibronectin, can hinder the infiltration of immune cells. Macrophages, however, can degrade these components by secreting matrix metalloproteinases (MMPs) and other substances, improving the permeability of the tumor microenvironment

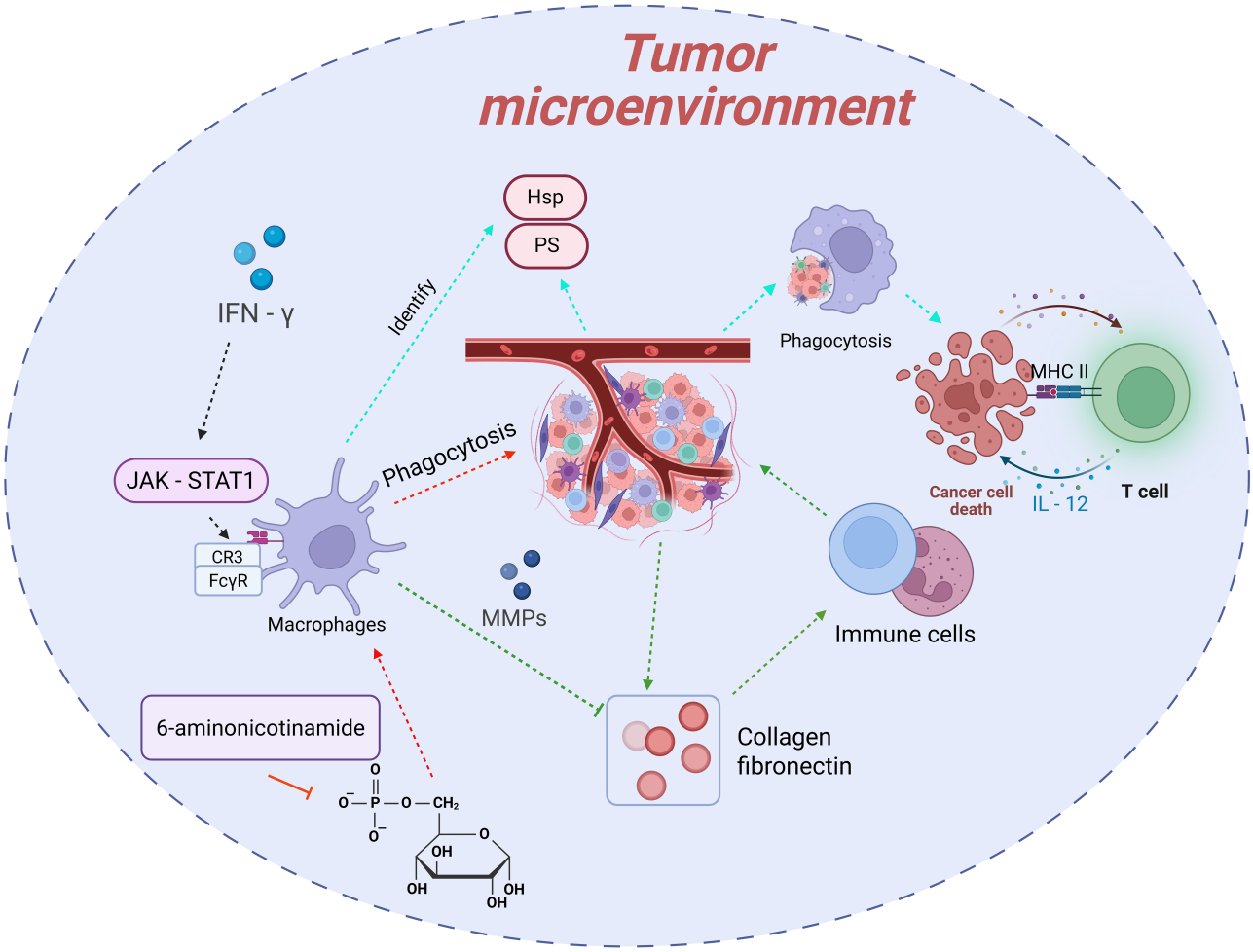

Fig. 2. The "scavenger" function of macrophages in tumors and its regulatory mechanisms. Macrophages recognize and phagocytose abnormal molecules on the surface of tumor cells through pattern recognition receptors, followed by degradation. They activate T cells via antigen presentation and cytokine secretion to trigger adaptive immune responses. Additionally, macrophages can clear apoptotic debris and degrade extracellular matrix components to improve the tumor microenvironment. Their "scavenger" function is regulated by mechanisms such as metabolic reprogramming (e.g., inhibition of the pentose phosphate pathway, PPP) and cytokines in the tumor microenvironment (e.g., enhancement by interferon-γ, IFN-γ; inhibition by transforming growth factor-β, TGF-β and interleukin-10, IL-10). PS, Phosphatidylserine; HSPs, Heat Shock Proteins; MHC, Major Histocompatibility Complex; IL-12, Interleukin-12; PPP, Pentose Phosphate Pathway; NADPH, Nicotinamide Adenine Dinucleotide Phosphate; ROS, Reactive Oxygen Species; IFN-γ, Interferon-γ; TGF-β, Transforming Growth Factor-β; IL-10, Interleukin-10; JAK-STAT1, Janus Kinase-Signal Transducer and Activator of Transcription 1; FcγR, Fc gamma Receptor; CR3, Complement Receptor 3; SMAD, Mothers Against Decapentaplegic Homolog; MMPs, Matrix Metalloproteinases. Created in BioRender. https://BioRender.com/np1tsea.

and creating favorable conditions for other immune cells to function [31,113].

Recent studies have achieved significant breakthroughs in understanding the regulatory mechanisms underlying the "scavenger" function of macrophages. Metabolic reprogramming has been confirmed as a key link in regulating this function. For example, studies have revealed that inhibiting the pentose phosphate pathway (PPP) in macrophages can enhance their ability to phagocytose and clear lymphoma cells. As an important intracellular metabolic pathway, PPP is mainly responsible for generating NADPH and ribose-5-phosphate, providing raw materials and reducing power for biosynthesis. When PPP is inhibited, the level of NADPH in macrophages decreases, and the production of reactive oxygen species (ROS) increases, which in turn activates downstream signaling pathways, upregulates the expression of phagocytosis-related genes, and ultimately enhances phagocytic function [31].

Cytokines and signaling molecules in the tumor microenvironment also exert a significant influence on the "scavenger" function of macrophages. Interferon-γ (IFN-γ) can upregulate the expression of phagocytic receptors on

Table 1. Functional features of macrophages in physiological homeostasis vs. disease.

Category	Physiological role	Disease association	Key molecules/pathways	Intervention strategies	Recourse
Immune surveillance	Pathogen/apoptotic cell clearance	Chronic inflammation, tumor immune evasion	TNF-α/IL-1β, CSF1R	CAR-M, anti-cytokine targeting	[21–53]
Metabolic regulation	Lipid/iron homeostasis	Atherosclerosis, NAFLD	oxLDL, FABP4, TfR1	Metabolic reprogramming drugs	[11,53–56]
Tissue repair	Angiogenesis, ECM remodeling	Fibrosis (lung/liver/kidney)	TGF-β, PDGF, YAP	Targeting pro-fibrotic subsets	[53,57–74]
Neural regulation	Synaptic pruning (microglia)	Alzheimer's, Parkinson's	TREM2, *APOE4*, mtDNA-STING	TREM2 agonists, mitophagy modulators	[53,75–83]
Aging-Related	Tissue renewal	Senile pulmonary fibrosis, chronic inflammation	p16INK4A, DNA methylation dysregulation	Senolytics, epigenetic modulators	[84–87]

TNF-α, tumor necrosis factor-α; CSF1R, Colony-Stimulating Factor 1 Receptor; CAR-M, Chimeric Antigen Receptor-Macrophage; NAFLD, Non-Alcoholic Fatty Liver Disease; oxLDL, Oxidized Low-Density Lipoprotein; FABP4, Fatty Acid-Binding Protein 4; TfR1, Transferrin Receptor 1; TGF-β, Transforming Growth Factor-beta; PDGF, Platelet-Derived Growth Factor; YAP, Yes-Associated Protein; TREM2, Triggering Receptor Expressed on Myeloid Cells 2; *APOE*, Apolipoprotein E.

Table 2. Tissue-resident macrophages: types, key functions, and mechanisms.

Tissue/organ	Macrophage type	Key functions	Representative mechanisms/molecules	Recourse
Liver	Kupffer cells	Maintain hepatic homeostasis (pathogen clearance, toxin/lipid metabolism); Modulate NASH inflammation and fibrosis	*NCF1*, MASH, ferroptosis	[57–68,123,124]
Intestine	Intestinal macrophages	Sustain microbiota homeostasis (IL-10-mediated anti-pathogen); Promote epithelial repair (WNT ligands); Regulate immunity via SCFA sensing	IL-10, Wnt ligands, SCFA sensing	[59–73,125,126]
Heart	$CCR2^-$ resident macrophages; $CCR2^+$ monocyte - derived macrophages	Preserve myocardial contraction (calcium cycling); Mediate infarct repair (M1: necrotic clearance; M2: scar formation); Protect cardiomyocytes via exosomal miR-155	miR-155 exosomes, M1/M2 polarization	[74,127–132,145]
Skeletal system	Osteoclast precursors	Drive osteoclast differentiation (RANKL-RANK pathway); Balance bone metabolism (cytokine-mediated osteoblast/osteoclast regulation)	RANKL-RANK signaling, TNF-α, IL-6	[133–140,146,147]
CNS	Microglia	Support neurodevelopment (complement-mediated synaptic pruning); Clear Aβ plaques in AD (TREM2-dependent); *APOE4*-associated neurodamage promotion	C1q-C3-CR3, TREM2, *APOE4*	[74–83,141–144]

NCF1, Neutrophil Cytosolic Factor 1; MASH, Macrophage Apoptosis-Associated Sphingolipid Hydrolase; RANKL, Receptor Activator of Nuclear Factor κB Ligand.

the surface of macrophages, such as Fc gamma Receptor (FcγR) and Complement Receptor 3 (CR3), by activating the Janus kinase-signal transducer and activator of transcription 1 (JAK-STAT1) signaling pathway, thereby significantly enhancing their ability to recognize and phagocytose tumor cells [114,115]. Conversely, immunosuppressive cytokines secreted by tumor cells, such as transforming growth factor-β (TGF-β) and interleukin-10 (IL-10), can inhibit the phagocytic function of macrophages. TGF-β can downregulate the expression of phagocytosis-related genes by activating the mothers against decapentaplegic homolog (SMAD) signaling pathway, while IL-10 suppresses the activation of macrophages and reduces their phagocytic activity [116–118].

2.1.2 Anti-Inflammation, Tissue Repair and Regeneration

Macrophages play a key role in the resolution of inflammation. By secreting anti-inflammatory cytokines and lipid mediators, they terminate the inflammatory response and promote tissue repair [32]. Tenuigenin, a natural flavonoid compound, can exert anti-inflammatory activity by inhibiting the MAPK and NF-κB signaling pathways and simultaneously inducing the Nrf2/HO-1 signaling pathway in macrophages [33]. In addition, the intake of dietary D-lactic acid can regulate the polarization of macrophages, promote the transformation from the M1 to the M2 phenotype, and accelerate the resolution of inflammation. Sensory nerves release calcitonin gene-related peptide (CGRP), which activates the PI3K/AKT signaling pathway in macrophages and promotes their transformation into the M2 phenotype, playing an essential role in the resolution of corneal inflammation [34]. In the late stage of inflammation, Resolving D1 (Rv-D1) promotes the apoptosis of recruited macrophages through the ALX/FasL-FasR/caspase-3 signaling pathway, thereby accelerating the resolution of inflammation [35].

Macrophages promote the proliferation and migration of vascular endothelial cells by secreting pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), thereby participating in the process of angiogenesis [119]. In wound healing models, VEGF released by macrophages induces the formation of vascular sprouts, supplying oxygen and nutrients to the damaged tissue and facilitating repair [120]. Additionally, macrophages can accelerate tissue repair by secreting cytokines such as insulin-like growth factor-1 (IGF-1) and epidermal growth factor (EGF), which promote the proliferation and migration of various cells, including fibroblasts and keratinocytes [121,122].

2.2 Maintenance of Tissue-Specific Homeostasis

Tissue-resident macrophages play essential roles in preserving the physiological equilibrium of diverse organs, exhibiting remarkable functional specialization shaped by local cues. Across systems such as the liver, intestine, heart, skeletal tissue, and central nervous system, macrophages act as sentinels and regulators of homeostasis (Table 2, Ref. [57–83,123–147]).

2.2.1 Liver

As the metabolic hub of the body, the liver harbors a large population of macrophages known as Kupffer cells [123,124]. Kupffer cells play multifaceted roles in maintaining hepatic homeostasis, including pathogen clearance, toxin metabolism, and lipid metabolism regulation. Studies have shown that the reactive oxygen regulatory protein encoded by neutrophil cytosolic factor 1 (*NCF1*) modulates the susceptibility of Kupffer cells to macrophage apoptosis-associated sphingolipid hydrolase (MASH)-mediated ferroptosis. In non-alcoholic steatohepatitis (NASH) models, overactivation of Kupffer cells leads to increased release of inflammatory factors, exacerbating liver fibrosis. Targeted modulation of Kupffer cell function may offer novel therapeutic strategies for NASH [58].

2.2.2 Intestine

As the largest immune organ in the human body, intestinal homeostasis relies on the interaction between macrophages and the gut microbiota [125,126]. Macrophages maintain microbial diversity and stability by secreting IL-10, preventing pathogen invasion [59]. In intestinal injury models, macrophages secrete WNT ligands to activate the Wnt signaling pathway in intestinal stem cells, promoting epithelial barrier repair [60,71]. Additionally, intestinal macrophages sense microbial metabolites (e.g., short-chain fatty acids, SCFAs) to modulate their own functions, thereby regulating intestinal immune homeostasis [72,73].

2.2.3 Heart

Cardiac macrophages can be classified into $CCR2^{+}$ monocyte-derived macrophages and $CCR2^{-}$ resident macrophages [74,127]. Resident macrophages play a pivotal role in maintaining cardiac homeostasis by regulating cardiomyocyte calcium cycling and preserving contractile function [13]. In myocardial infarction models, macrophage polarization significantly influences cardiac repair. Early recruitment of M1 macrophages clears necrotic tissue, but excessive inflammation exacerbates myocardial injury. In contrast, later polarization toward M2 macrophages promotes tissue repair and scar formation [128–130]. Studies indicate that macrophage-derived exosomes carrying miR-155 can enhance cardiomyocyte survival and improve cardiac function by targeting specific cardiomyocyte genes [131,132].

2.2.4 Skeletal System

Macrophages in the skeletal system, known as osteoclast precursors, play a critical role in bone remodeling [133–135]. By expressing receptor activator of nuclear fac-

tor κB ligand (RANKL), macrophages interact with RANK receptors on osteoblasts to promote osteoclast differentiation and activation, facilitating bone resorption. In osteoporosis models, aberrant macrophage activation enhances bone resorption and reduces bone mass. Therapeutic strategies targeting macrophage function, such as inhibiting the RANKL signaling pathway, may offer new avenues for osteoporosis treatment [136–138]. Moreover, macrophages secrete cytokines (e.g., TNF-α, IL-6) to balance osteoblast and osteoclast activity, maintaining skeletal homeostasis [136,139,140,148].

2.2.5 Central Nervous System

Macrophages in the central nervous system, termed microglia, are indispensable for neural development and homeostasis [75,76]. During early neurodevelopment, microglia mediate synaptic pruning via the complement pathway (C1q-C3-CR3), eliminating redundant synapses to refine neural circuits [77–80]. In neurodegenerative diseases such as Alzheimer's disease (AD), microglial dysfunction is closely linked to disease progression. Triggering receptor expressed on myeloid cells 2 (TREM2), a key receptor on microglia, recognizes Aβ plaques and facilitates their clearance, exerting neuroprotective effects [81,82]. Loss-of-function mutations in TREM2 are associated with increased AD risk [83]. Furthermore, apolipoprotein E (*APOE*), a major genetic risk factor for AD, influences microglial Aβ clearance capacity, particularly the *APOE4* isoform, exacerbating neuroinflammation and neuronal damage [141–144].

2.3 Dynamic Functional Regulation Network

2.3.1 Epigenetic Regulation

The functional plasticity of macrophages is primarily governed by epigenetic regulatory mechanisms [149–151]. Histone modifications, a key mode of epigenetic regulation, modulate gene expression by altering chromatin structure [152–154]. Studies demonstrate that H3K27ac-mediated enhancer reprogramming determines the reparative phenotype of macrophages, guiding their functional polarization after tissue injury [155]. Additionally, non-coding RNAs (ncRNAs) play pivotal roles in macrophage regulation. The long non-coding RNA Malat1 influences the anti-inflammatory functions of macrophages by regulating mitochondrial metabolism-related genes [156–158]. MicroRNAs (miRNAs) fine-tune macrophage polarization and function through mRNA targeting [159,160]. For instance, miR-155 promotes M1 polarization by suppressing *SOCS1* expression [161–164].

2.3.2 Neuro-Immune Interaction

Macrophages serve as critical hubs in the extensive and intricate network bridging the nervous and immune systems, modulating their functions in response to neural signals [165–167]. Sympathetic nerves release norepinephrine to activate β2-adrenergic receptors (β2-AR) on macrophages, suppressing inflammatory responses in adipose tissue macrophages and contributing to metabolic homeostasis [163,168]. Sensory neurons release calcitonin gene-related peptide (CGRP) to induce IL-10 secretion by macrophages, exerting anti-inflammatory effects [169–173]. Furthermore, the vagus nerve regulates macrophage-mediated inflammation via the cholinergic anti-inflammatory pathway, playing a key role in systemic inflammatory diseases [173].

2.3.3 New Technologies for Intercellular Communication

Technology advancementshave provided novel tools to dissect macrophage regulatory mechanisms [10,11,174,175]. Spatial multi-omics technologies now enable single-cell-resolution analysis of spatial interactions between macrophages and other cell types [176–178]. Research reveals that macrophages can directly transfer antigens to T cells through synapse-like structures (e.g., trogocytosis), enhancing antigen presentation and immune responses [179,180]. Extracellular vesicles (EVs), as essential carriers of intercellular communication, deliver bioactive molecules (e.g., proteins, nucleic acids, lipids) to modulate recipient cell functions [181–184]. Macrophage-derived EVs, for example, regulate stem cell differentiation and tissue repair via miRNA transfer [185,186].

3. Disease Onset: From Mechanisms to Targets

Macrophages serve as pivotal regulators in the pathogenesis of diverse diseases. Their aberrant activation contributes to tissue damage, promotes fibrotic matrix deposition, induces metabolic dysregulation, facilitates tumor immune evasion, exacerbates neurodegenerative processes, and perpetuates chronic inflammatory states during aging, rendering macrophage-targeted interventions a promising therapeutic avenue (Fig. 3).

3.1 Tumor Immune Microenvironment

In the tumor immune microenvironment, macrophages play an extremely complex and crucial role, profoundly affecting the occurrence and development of tumors as well as the tissue homeostasis of the body [187–189]. Macrophages exhibit high plasticity and can differentiate into various polarized phenotypes in response to different signaling stimuli within the tumor microenvironment. Among these, M2-polarized macrophages are closely associated with the malignant progression of tumors.

M2-polarized macrophages act like "accomplices" in the tumor microenvironment, promoting tumor progression through multiple pathways. They secrete vascular endothelial growth factor (VEGF), which directly acts on vascular endothelial cells surrounding the tumor, stimulating their proliferation, migration, and lumen formation, thereby fa-

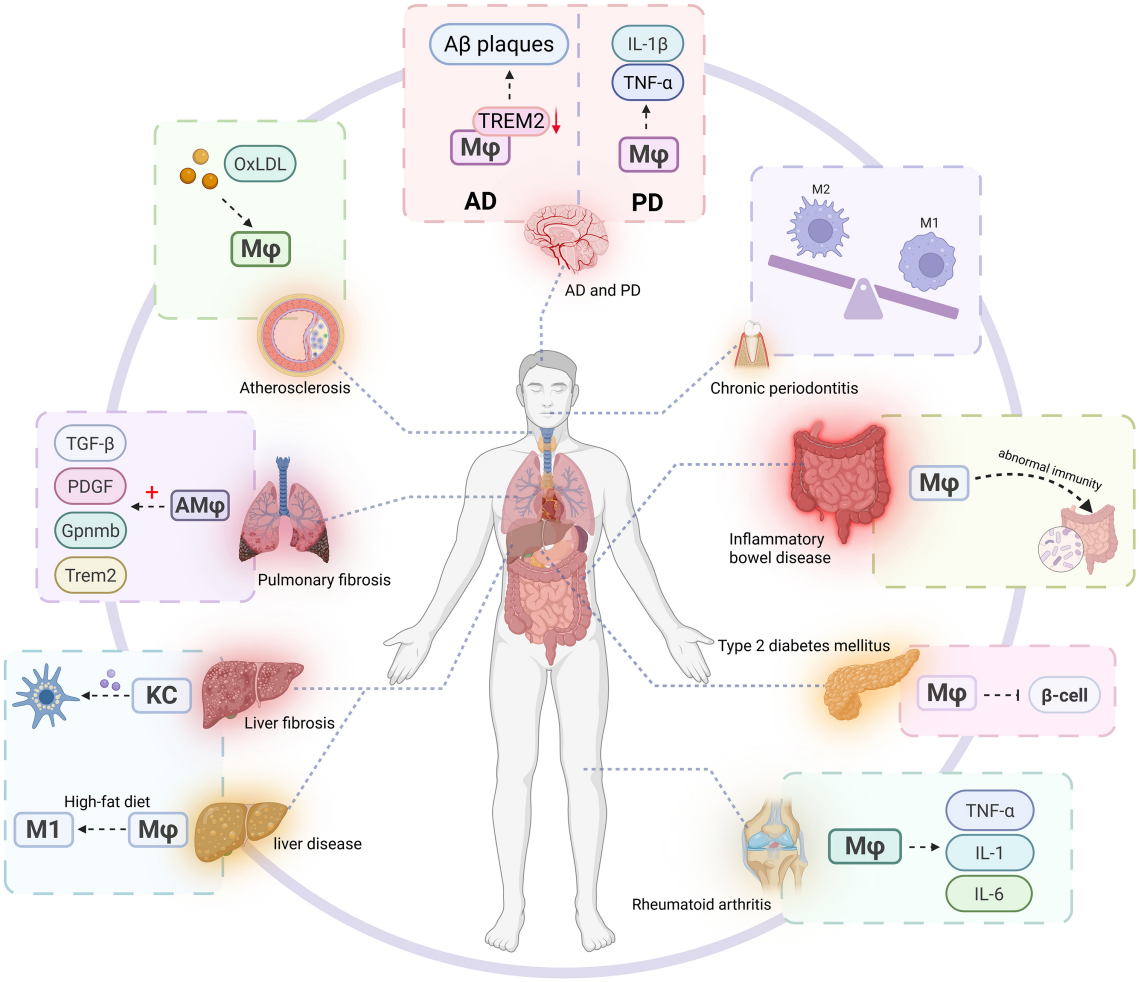

Fig. 3. Macrophages play a key role in various diseases. In chronic inflammatory diseases (such as rheumatoid arthritis, inflammatory bowel disease, and chronic periodontitis), the continuous activation or polarization imbalance of macrophages leads to the release of pro-inflammatory cytokines (such as TNF-α, IL-1, IL-6) and abnormal immune responses to the microbiota, which induce tissue damage. In fibrotic diseases (such as pulmonary fibrosis and liver fibrosis), macrophages promote fibrosis by secreting profibrotic factors (such as TGF-β and PDGF) and upregulating the expression of *Gpnmb* and *Trem2* genes. In metabolic diseases (NAFLD, type 2 diabetes, and atherosclerosis), macrophages promote disease progression through pro-inflammatory polarization (M1 type), destruction of β-cell function, or formation of foam cells. In neurodegenerative diseases (AD and PD), microglia (the macrophages of the central nervous system) cause neuronal damage through abnormal responses to Aβ plaques or inflammatory mediators (TNF-α, IL-1β), and the TREM2 receptor influences disease progression. A deeper understanding of the mechanisms by which macrophages act in these diseases will provide a theoretical basis for developimg new therapeutic targets and intervention measures. TNF-α, Tumor Necrosis Factor-alpha; IL-1, Interleukin-1; IL-6, Interleukin-6; IL-1β, Interleukin-1β; TGF-β, Transforming Growth Factor-beta; PDGF, Platelet-Derived Growth Factor; *Gpnmb*, Glycoprotein Non-Metastatic Melanoma Protein B; *Trem2*, Triggering Receptor Expressed on Myeloid Cells 2; NAFLD, Non-Alcoholic Fatty Liver Disease; AD, Alzheimer's Disease; PD, Parkinson's Disease. Created in BioRender. https://BioRender.com/0wxd4ml.

cilitating tumor angiogenesis. These newly formed blood vessels not only provide sufficient oxygen and nutrients for the rapid proliferation of tumor cells but also establish "channels" for distant metastasis of tumor cells, enabling them to spread to other parts of the body via the bloodstream or lymphatic system.

Meanwhile, interleukin-10 (IL-10) secreted by M2 macrophages is a potent immunosuppressive factor. It can inhibit the activation, proliferation, and cytotoxic functions of immune cells such as T cells and natural killer (NK) cells, reducing the body's immune surveillance and killing capacity against tumor cells. Furthermore, M2 macrophages highly express programmed death ligand 1 (PD-L1) on their surface, which specifically binds to programmed death receptor 1 (PD-1) on T cells, triggering the immunosuppressive signaling pathway in T cells. This renders T cells un-

able to effectively recognize and attack tumor cells, as if placing "shackles" on T cells, creating a microenvironment conducive to the growth, survival, and immune escape of tumor cells, and severely disrupting the tissue homeostasis of tumor immune balance [55,190]. In addition, M2 macrophages can secrete substances such as matrix metalloproteinases, which degrade the extracellular matrix surrounding the tumor, creating favorable conditions for the invasion and metastasis of tumor cells [188,191].

The emerging CAR-M therapy has brought groundbreaking hope for tumor treatment, representing a significant innovation in the field of tumor immunotherapy. Taking CD19-CAR macrophages as an example, chimeric antigen receptors (CARs) capable of specifically recognizing certain antigens (e.g., CD19) on the surface of tumor cells are introduced into macrophages through advanced genetic engineering techniques. A CAR consists of an antigen-recognition domain, a hinge region, a transmembrane domain, and an intracellular signaling domain. Among these, the antigen-recognition domain, typically derived from the variable region of a monoclonal antibody, can precisely match the "lock"—specific antigen—on the surface of tumor cells like a "key", thereby endowing macrophages with the ability to specifically recognize and target tumor cells for killing.

Genetically modified CAR-M macrophages can penetrate physical barriers such as the fibrotic envelope surrounding tumor tissues and infiltrate into the interior of tumor tissues by virtue of their migratory capacity. They phagocytose and degrade tumor cells through their strong phagocytic ability; meanwhile, they secrete cytotoxic substances such as tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) to directly induce apoptosis of tumor cells. More importantly, CAR-M macrophages can reshape the tumor immune microenvironment. They can eliminate immunosuppressive cells and factors in the tumor microenvironment, such as reducing the number of M2-type macrophages and the levels of inhibitory cytokines like IL-10. Simultaneously, they release chemokines to recruit other immune cells such as T cells and NK cells to the tumor site, activate their anti-tumor activity, and form a synergistic anti-tumor immune network. This helps restore tissue homeostasis disrupted by tumors, enabling the body's immune system to reinitiate effective attacks against tumor cells. For instance, in a B-cell lymphoma model, CD19-CAR macrophages can precisely recognize and eliminate CD19-positive lymphoma cells, significantly reducing tumor volume and prolonging the survival of model animals. During the treatment process, the number of infiltrating T cells in the tumor microenvironment increases significantly, with their activity also enhanced remarkably [192–196].

Metabolic checkpoints have shown great potential in tumor immunotherapy, providing new ideas and strategies for cancer treatment. To meet the needs of rapid growth and unlimited proliferation, tumor cells exhibit significant differences in metabolic patterns compared with normal cells, with unique metabolic characteristics. Among them, the growth and survival of tumor cells are highly dependent on arginine, a semi-essential amino acid that plays a crucial role in cell proliferation, differentiation, and other processes. Tumor cells often lack the key enzymes required for arginine synthesis, so they need to uptake large amounts of arginine from the tumor microenvironment to maintain their metabolic demands.

Based on this characteristic, arginine deprivation combined with anti-PD-1 therapy has become a highly promising combined treatment strategy. Arginine deprivation can degrade arginine in the tumor microenvironment through the use of drugs such as arginase or arginine deiminase, causing tumor cells to fail to proliferate normally or even undergo apoptosis due to arginine deficiency. Meanwhile, arginine deficiency can also affect the function of immunosuppressive cells, such as reducing the number and activity of regulatory T cells (Tregs) and enhancing the function of effector T cells. In contrast, anti-PD-1 therapy can block the binding of PD-L1 to PD-1, relieve the immunosuppression of T cells, and restore the anti-tumor activity of T cells. When used in combination, they can produce a synergistic effect, not only directly inhibiting the growth of tumor cells but also enhancing the body's anti-tumor immune response, thereby improving the efficacy of tumor treatment. In various tumor models such as melanoma and non-small cell lung cancer, this combined treatment strategy has shown more significant anti-tumor effects than single treatment, effectively delaying tumor progression and prolonging the survival of model animals [197–199].

3.2 Chronic Inflammatory Diseases

The pathogenesis of chronic inflammatory diseases—including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and chronic periodontitis—is closely linked to sustained macrophage activation [36,37,200,201]. In RA, activated macrophages release proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which drive synovial cell proliferation, pannus formation, and cartilage destruction [38–40]. Targeting macrophage surface receptors (e.g., colony-stimulating factor 1 receptor [CSF1R]) can suppress macrophage activation and proliferation, alleviating joint inflammation [41]. In IBD, aberrant immune responses of intestinal macrophages to microbiota compromise barrier function and perpetuate chronic inflammation [42,43]. Single-cell sequencing reveals heightened heterogeneity in intestinal macrophages from IBD patients, with specific subsets overexpressing proinflammatory genes that exacerbate disease progression [44,202]. In chronic periodontitis, imbalanced macrophage polarization (M1-dominant) promotes osteoclast recruitment and alveolar bone resorption [45,203]. Deciphering

macrophage mechanisms in these diseases may yield novel therapeutic targets.

3.3 Fibrotic Diseases

Fibrotic diseases such as pulmonary, hepatic, and renal fibrosis are characterized by excessive extracellular matrix deposition leading to organ dysfunction [46,47,204–206]. Macrophages play a pivotal role in fibrotic disease development.

In pulmonary fibrosis, alveolar and monocyte-derived macrophages exhibit high heterogeneity and dynamic changes in pro-fibrotic gene expression during disease progression [48,49,207]. Research indicates that macrophage-specific upregulation of *Gpnmb* and *Trem2* gene levels correlates with fibrosis progression, suggesting their regulatory importance [48,50]. Additionally, macrophage-secreted pro-fibrotic factors like transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF) promote fibroblast proliferation and activation, accelerating pulmonary fibrosis [51,52,208].

In hepatic fibrosis, activated Kupffer cells secrete inflammatory mediators and pro-fibrotic factors that induce hepatic stellate cell activation, transforming them into myofibroblasts that synthesize abundant extracellular matrix, ultimately causing liver fibrosis [61,209]. Therapeutic strategies targeting macrophages, such as inhibiting macrophage recruitment/activation or modulating their polarization state, may offer new directions for treating fibrotic diseases [210,211].

Macrophage mechanosensing also significantly influences fibrosis. The Piezo1 channel on macrophage surfaces mediates their response to tissue stiffness. When tissue hardness changes due to fibrosis, macrophage Piezo1 channels activate, triggering intracellular signaling cascades that initiate Yes-associated protein (YAP)-dependent fibrotic responses [212]. As a critical transcriptional coactivator, activated YAP promotes expression of fibrosis-related genes, markedly increasing extracellular matrix synthesis and exacerbating fibrosis progression. This reveals an important pathway through which mechanical forces influence tissue fibrosis via macrophages [213].

3.4 Metabolic Diseases

Macrophage function is intricately regulated by metabolic pathways, including lipid processing, iron handling, and mitochondrial dynamics. These metabolic features not only shape macrophage polarization and plasticity, but also directly contribute to the pathogenesis of metabolic disorders such as non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, and atherosclerosis [214,215].

Lipid metabolism critically affects macrophage phenotype and inflammatory status. For instance, 25-hydroxycholesterol (25-HC) induces immunosuppressive programming via lysosomal AMPK signaling [216,217]. In atherosclerosis, excessive uptake of oxidized low-density lipoprotein (oxLDL) leads to foam cell formation and plaque buildup. Targeting lipid-handling molecules such as FABP4 has been shown to reduce foam cell formation and attenuate disease progression [218].

Iron metabolism is another essential regulatory axis. Macrophages express ferritin and heme oxygenase-1 (HO-1) to mediate iron storage and recycling. Under inflammatory stress, iron overload increases reactive oxygen species (ROS) production, amplifying tissue injury. Genes such as transferrin receptor 1 (*TfR1*) modulate iron uptake and may be leveraged to regulate inflammatory output [54,219,220].

Mitochondrial dynamics, including fusion, fission, and mitophagy, are tightly linked to macrophage activity. Mitochondrial DNA (mtDNA) release can activate STING-dependent type I interferon signaling, while mitophagy via the PINK1/Parkin pathway maintains mitochondrial quality and anti-inflammatory capacity. Disruption of these processes impairs macrophage resolution functions and tissue repair [221,222].

These metabolic features directly impact disease outcomes. In NAFLD, high-fat diets drive adipose macrophage accumulation and M1 polarization, promoting hepatic insulin resistance and steatosis. Scavenger receptor A1 (SR-A1) on macrophages plays a protective role, and its deficiency worsens inflammation and fibrosis [190,223]. In type 2 diabetes, macrophage infiltration into pancreatic islets disrupts β-cell function and reduces insulin secretion [224–226]. In atherosclerosis, lipid-loaded macrophages form foam cells that exacerbate vascular plaque development [227,228]. Therapeutic strategies that reprogram macrophage metabolism—by modulating lipid uptake, oxidative stress, or mitochondrial homeostasis—represent promising avenues to combat these metabolic diseases [107,229–231].

3.5 Neurodegenerative Diseases

In neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), the dysfunction of microglia (macrophages in the central nervous system) is closely related to the disease progression [232,233]. In AD, the abnormal response of microglia to Aβ plaques leads to an increase in the release of inflammatory factors, enhanced neurotoxicity, and accelerated neuronal death [234–236]. TREM2, as a key receptor on the surface of microglia, its loss-of-function mutations are associated with an increased risk of AD. TREM2 can affect the disease process by regulating the ability of microglia to clear Aβ [237,238]. In PD, after microglia are activated, they release inflammatory mediators such as TNF-α and IL-1β, leading to the damage of dopaminergic neurons [239]. In addition, mitochondrial dysfunction plays a vital role in microglia-mediated neuroinflammation. By regulating mitophagy, the function of microglia can be improved, and neuroinflammation can be alleviated [240,241]. In-depth research on the mechanism of the role of microglia in neurodegenerative diseases will

provide new targets for developing neuroprotective therapeutic strategies.

3.6 Aging-Related Diseases

As the body ages, macrophages gradually enter a senescent state. Among them, senescent macrophages with the characteristic of p16INK4a$^+$ play a negative role in senile pulmonary fibrosis. The accumulation of these cells interferes with the normal physiological functions of the lungs. They may secrete substances such as inflammatory factors and matrix metalloproteinases, disrupting the balance of the extracellular matrix of the lung tissue, activating fibrosis-related signaling pathways, causing the lung tissue to become fibrotic and gradually impairing the gas exchange function. Using Senolytic targets to eliminate p16INK4a$^+$ senescent macrophages can effectively reduce the secretion of harmful factors, restore the homeostasis of the lung tissue microenvironment, and provide new ideas for improving senile pulmonary fibrosis [84,242].

4. Intervention Strategies Focusing on the Tumor Microenvironment: Technological Innovation Driving a Therapeutic Revolution

4.1 Precision Targeting Technology

4.1.1 Spatiotemporal Specific Gene Editing

Precision targeting technology shows excellent potential in the treatment of macrophage-related diseases. Spatiotemporal specific gene editing technology, such as the CRISPR-Cas9 liposome targeted delivery system, uses liposomes as carriers. By precisely modifying the liposomes, they can specifically recognize and bind to specific receptors on the surface of target macrophages [85–87]. This targeted delivery method equips the CRISPR-Cas9 system with an accurate navigation system, efficiently transporting it to specific tissues or cells. After reaching the destination, the CRISPR-Cas9 system can precisely edit the genes related to diseases in macrophages [243]. For example, in tumor treatment, macrophages in the tumor microenvironment are often "domesticated" by tumor cells and transformed into a phenotype that promotes tumor growth. Through spatiotemporal specific gene editing, the abnormal gene expression of these macrophages can be corrected, their anti-tumor activity can be reactivated, and their killing function against tumor cells can be restored, breaking the barrier of tumor immune escape [244].

4.1.2 Smart Responsive Nanoparticles

Smart responsive nanoparticles are also an essential breakthrough in precision targeting technology. Take the pH/ROS dual-sensitive nanocarrier as an example. The tumor microenvironment has the unique characteristics of a low pH value and a high level of reactive oxygen species (ROS) [244]. The nanocarrier remains stable in the blood circulation. When it reaches the vicinity of the tumor tissue, the low pH value and high ROS level in the tumor microenvironment will trigger a structural change in the nanocarrier, just like unlocking it, causing it to release the pre-loaded drugs or bioactive molecules [245]. These molecules can precisely act on tumor-associated macrophages (TAMs), inducing the reprogramming of TAMs. The originally tumor-promoting TAMs can be transformed into a tumor-inhibiting phenotype after reprogramming, significantly enhancing the phagocytic and killing abilities of macrophages against tumor cells, providing a precise and efficient new strategy for tumor treatment.

4.2 Cell Engineering Therapy

4.2.1 Chimeric Antigen Receptor-Macrophage (CAR-M) 2.0

Cell engineering therapy brings new vitality to macrophage therapy. CAR-M 2.0 technology is an essential upgrade of the traditional CAR-M cell therapy. Although the conventional CAR-M cell therapy has shown some potential in tumor treatment, it faces many challenges in the complex tumor microenvironment. CAR-M 2.0 is equipped with a dual-functional module of PD-1 blockade and IL-12 secretion [195]. On the one hand, it can precisely recognize the antigens on the surface of tumor cells through CAR; on the other hand, the PD-1 blockade function can effectively relieve the immunosuppressive state in the tumor microenvironment, allowing the immune system to play its role fully [246]. At the same time, the secretion of IL-12 further activates the immune system, not only enhancing the killing activity of macrophages against tumor cells themselves but also recruiting and activating other immune cells to participate in the anti-tumor battle together, significantly improving the treatment effect in solid tumors and bringing new hope for cancer treatment [247].

4.2.2 Synthetic Biology Modification

Synthetic biology modification technology provides an effective means for precisely regulating the polarization of macrophages. Constructing a light-controlled gene circuit is an essential progress in this field. Through careful design, light-sensitive elements are connected to key genes that regulate the polarization of macrophages, forming a gene circuit that can be precisely regulated by light [247]. When light of a specific wavelength and intensity irradiates, the gene circuit is activated, thereby precisely regulating the polarization of macrophages towards one particular functional phenotype [175]. In inflammatory diseases, the light instruction can prompt macrophages to polarize towards an anti-inflammatory phenotype, alleviating the inflammatory response and promoting tissue repair; in tumor treatment, it can also make macrophages polarize towards an anti-tumor phenotype, enhancing the body's anti-tumor immune response, providing a flexible and precise strategy for the treatment of different types of diseases [2,248].

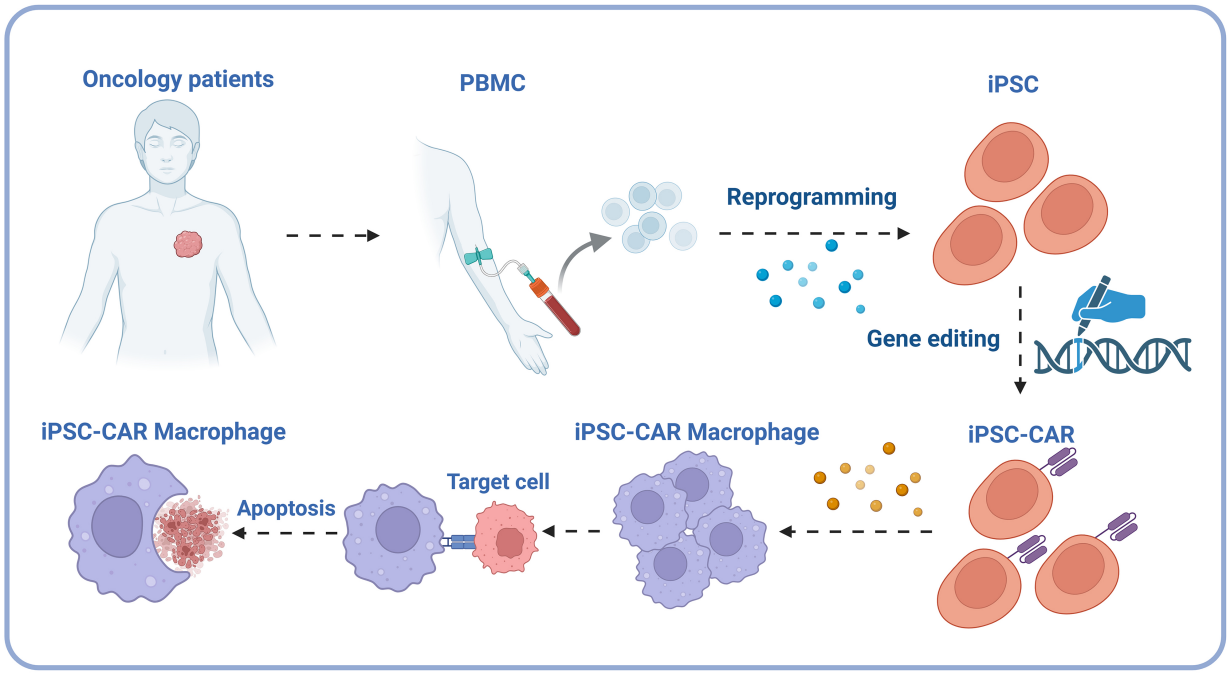

Fig. 4. iPSC-CAR macrophage technical flowchart. The process involves extracting peripheral blood mononuclear cells (PBMC) from oncology patients, reprogramming them into induced pluripotent stem cells (iPSC), introducing chimeric antigen receptors (CAR) through gene editing, and ultimately differentiating them into iPSC-CAR macrophages capable of identifying and inducing apoptosis in cancer cells. PBMC, peripheral blood mononuclear cells; iPSC, induced pluripotent stem cells; CAR, chimeric antigen receptors. Created in BioRender. https://BioRender.com/nglah6m.

4.2.3 iPSC-CAR Macrophage Technology

The iPSC-CAR macrophage technology cleverly utilizes induced pluripotent stem cells (iPSCs) characteristics. iPSCs have the potential for unlimited proliferation and multi-directional differentiation [193]. This technology first reprograms somatic cells from patients into iPSCs, restoring them to a pluripotent state. It then induces iPSCs to differentiate into macrophages and makes them express chimeric antigen receptors (CAR) [192]. After this series of operations, a large number of macrophages with specific antigen recognition ability can be prepared, solving the problem of limited sources of traditional macrophages [192] (Fig. 4). The recognition and killing abilities of these modified macrophages against specific targets are significantly enhanced, and they have broad application prospects in tumor immunotherapy and the treatment of other macrophage-related diseases. They are expected to become one of the core strategies of a new generation of cell therapy [249,250].

4.3 Microbiome Intervention

Microbiome intervention provides a new perspective for the treatment of macrophage-related diseases. Research on regulating of microbiota metabolites has found that butyrate, as a critical microbiota metabolite, plays a key role in regulating the functions of macrophages [72,251]. Butyrate can affect macrophages' gene expression and functional state by inhibiting histone deacetylase 3 (HDAC3) [252]. In tumor treatment, butyrate can regulate the functions of immune cells such as macrophages, promote the polarization of macrophages towards an anti-tumor phenotype, and enhance their phagocytic and killing activities against tumor cells [253]. At the same time, butyrate can also regulate the functions of other immune cells in the tumor microenvironment, reshape the tumor immune microenvironment, and activate the body's own anti-tumor immune response, opening up a new strategy for tumor treatment based on microbiota metabolites [254–257].

5. Future Directions: Disruptive Technologies and Unsolved Mysteries

5.1 Directions of Technological Innovation

Traditional research methods are challenging in capturing individual macrophages' unique behaviors and dynamic changes, and can only obtain population average information. However, real-time dynamic monitoring of single-cell multi-omics (*in vivo* imaging combined with scRNA-seq) has opened up a new way to explore the mysteries of macrophages [258]. *In vivo* imaging can track the migration, and proliferation of macrophages in the body and their interactions with other cells in real time without disrupting the organism's physiological state. scRNA-seq can reveal the gene expression profiles of individual macrophages at different time points, and clarify their func-

tional states and molecular characteristics. The combination of the two enables researchers to dynamically analyze the changes in the molecular regulation network of macrophages during the maintenance of tissue homeostasis and the occurrence and development of diseases at the single-cell level, accurately identify key cell subsets and functional conversion nodes, and provide a theoretical basis for targeted treatment strategies [259,260].

The functions of macrophages are jointly affected by various factors in their microenvironment. The integrated organoid-immune chip model provides a powerful research tool for this [7,18]. Organoids can highly reproduce the tissue-specific microenvironment, and the immune chip can accurately detect the dynamic changes of various immune molecules. The model that integrates the two can produce the interactions between macrophages and other cells and microenvironmental factors *in vitro*. For example, in tumor research, this model can be used to explore the coordinated regulation of tumor cells, stromal cells, immune cells, and metabolites in the tumor microenvironment on the polarization and functions of macrophages, deeply understand the mechanism of tumor immune escape, and provide an experimental platform for tumor immunotherapy [7].

The regulatory network of macrophages is highly complex. With the help of AI-driven target prediction, graph neural networks can be used to integrate and analyze massive biological data to accurately diagnose this regulatory network [261,262]. Graph neural networks construct complex network models by taking the information of genes, proteins, metabolites, etc., of macrophages as nodes and their interactions as edges. By learning and analyzing this model, potential drug targets and therapeutic intervention sites can be predicted, accelerating the research and development process of drugs for macrophage-related diseases and providing more targeted strategies for clinical treatment. These cutting-edge technologies assist macrophage research from different aspects and are expected to promote breakthroughs in related fields [260].

5.2 Key Scientific Issues

Macrophages are key in maintaining the body's immune balance and tissue homeostasis. Among them, the functional compensation mechanisms of tissue-resident and monocyte-derived macrophages, the encoding of spatially specific immune responses by metabolite gradients, and the analysis of the conservation and heterogeneity of macrophage functions across species are all key areas of current research [263,264]. Tissue-resident macrophages have been colonized in various tissues and organs since the early stage of embryonic development and play a fundamental role in maintaining tissue homeostasis. Monocyte-derived macrophages are recruited from the blood circulation to tissues under stress conditions such as inflammation. Currently, these issues are still unclear for the functional compensation mechanisms of the two under different physiological and pathological states, such as when tissue-resident macrophages dominate during tissue damage repair, when monocyte-derived macrophages play a significant role, and how they coordinate and compensate. Answering these questions will help to deeply understand the complex mechanisms of macrophages in maintaining tissue homeostasis and disease repair, and provide theoretical guidance for treating related diseases [264,265].

How the concentration gradients of various metabolites in the tissue microenvironment affect the functional polarization of macrophages and encode spatially specific immune responses is a key issue that needs to be solved urgently. For example, in the tumor microenvironment, the metabolite gradients in hypoxic and oxygen-rich regions prompt macrophages to exhibit different polarization directions, affecting tumor growth and metastasis. Analyzing this mechanism will help to reveal the spatial heterogeneity of the occurrence and development of diseases and provide a basis for precise treatment strategies based on microenvironmental metabolic regulation [266,267].

Macrophages are widely present in different species and are crucial for maintaining the body's immune balance and tissue homeostasis. The functions of macrophages among different species have both conservation, such as possibly having similar phagocytic and bactericidal functions when resisting pathogen infections, and evident heterogeneity, with significant differences in the repair response to self-tissue damage and the synergistic effect with the adaptive immune system. In-depth analysis of their conservation and heterogeneity is conducive to the rational selection of animal models for macrophage-related research and promoting the better transformation and application of basic research results to treat human diseases [268,269].

5.3 Challenges in Clinical Translation

The clinical translation of macrophage-related research faces many challenges. First, the safety and effectiveness of drugs or therapies that precisely target macrophages in clinical trials still need to be further verified. Optimizing the treatment plan and reducing adverse reactions are key to clinical translation [270,271]. Second, cell engineering treatment strategies, such as CAR-M technology, face problems such as complex cell preparation processes and high costs. Achieving large-scale production and clinical promotion is an urgent problem to be solved [215]. In addition, the standardization and individualization of microbiome intervention are also one of the challenges in clinical application. Formulating personalized microbiome intervention plans according to patients' specific conditions and improving the treatment effect is the direction of future research. Finally, establishing effective clinical monitoring indicators to evaluate the efficacy and safety of macrophage-related treatments is also an important issue that needs to be solved in the process of clinical translation [196,270,271].

6. Conclusion

As a core component of the innate immune system, macrophages have expanded their functional scope from the traditional M1/M2 polarization model to "tissue microenvironment engineers", exerting diverse roles in maintaining physiological homeostasis and driving disease progression. Their characteristics and regulatory mechanisms in the tumor microenvironment are particularly representative.

Under physiological conditions, macrophages perform phagocytic functions as "scavengers" to engulf pathogens and apoptotic debris. They secrete anti-inflammatory factors to terminate inflammation and promote tissue repair, regulate lipid, iron, and mitochondrial metabolism to maintain metabolic balance, and execute tissue-specific homeostatic functions in organs such as the liver, intestines, and heart. For instance, hepatic Kupffer cells participate in toxin metabolism, intestinal macrophages sense microbiota signals to regulate immunity, and cardiac resident macrophages maintain myocardial contractile function. Meanwhile, epigenetic regulation (e.g., histone modifications, non-coding RNAs) and neuroimmune crosstalk (e.g., sympathetic nerve-derived norepinephrine) precisely modulate their functions, forming a complex dynamic network.

In disease states, macrophage dysfunction is widely involved in processes such as chronic inflammation, fibrosis, metabolic diseases, and neurodegenerative disorders: in rheumatoid arthritis, they release pro-inflammatory factors to exacerbate joint damage; in pulmonary fibrosis, they secrete TGF-β to activate fibroblasts; in non-alcoholic fatty liver disease, M1 polarization triggers insulin resistance; in Alzheimer's disease, abnormal responses of microglia to Aβ plaques accelerate neuronal death.

The tumor microenvironment represents a concentrated manifestation of macrophage functional plasticity. Tumor-associated macrophages (TAMs) polarize toward the M2 phenotype in a microenvironment characterized by low pH and high ROS. They promote angiogenesis by secreting VEGF, inhibit immune cell activity via IL-10 and PD-L1 release, and degrade the extracellular matrix to facilitate tumor invasion and metastasis, thereby establishing an immunosuppressive microenvironment. In response, strategies such as precision targeting technologies (e.g., spatiotemporal editing via CRISPR-Cas9 to correct abnormal gene expression in TAMs, pH/ROS-sensitive nanocarriers for targeted drug delivery), cell engineering therapies (e.g., CAR-M 2.0 with PD-1 blockade and IL-12 secretion modules to enhance anti-tumor activity; iPSC-CAR macrophage technology to address source limitations), and microbiome interventions (e.g., butyrate-mediated regulation of TAM polarization) have demonstrated potential in reshaping the tumor microenvironment and activating immune responses.

Despite significant research progress, challenges remain: the functional compensation mechanisms between tissue-resident and monocyte-derived macrophages, as well as the spatial coding of metabolite gradients on immune responses, remain unclear; technologies such as single-cell multi-omics real-time monitoring and organoid model construction require optimization; issues including targeting precision, large-scale production, and individualized regimens in clinical translation urgently need resolution. In the future, integrating cutting-edge technologies to decode the dynamic regulatory network of macrophages will advance their transition from basic research to clinical applications in cancer and other diseases, laying the foundation for a therapeutic paradigm of "regulating the microenvironment through cells".

Abbreviations

25-HC, 25-Hydroxycholesterol; Aβ, Amyloid Beta; *APOE*, Apolipoprotein E; AMPK, Adenosine Monophosphate-Activated Protein Kinase; CAR-M, Chimeric Antigen Receptor-Macrophage; CCR2, C-C Chemokine Receptor Type 2; CR3, Complement Receptor 3; CGRP, Calcitonin Gene-Related Peptide; CSF1R, Colony-Stimulating Factor 1 Receptor; EVs, Extracellular Vesicles; EGF, Epidermal Growth Factor; FABP4, Fatty Acid-Binding Protein 4; FcγR, Fc Gamma Receptor; HDAC3, Histone Deacetylase 3; HO-1, Heme Oxygenase-1; H3K27ac, Histone H3 Lysine 27 Acetylation; IFN-γ, Interferon-γ; IGF-1, Insulin-Like Growth Factor 1; IBD, Inflammatory Bowel Disease; IL-10, Interleukin-10; IL-12, Interleukin-12; iPSC, Induced Pluripotent Stem Cell; JAK-STAT1, Janus Kinase-Signal Transducer and Activator of Transcription 1; M1, M1 Phenotype (Classically Activated Macrophage); M2, M2 Phenotype (Alternatively Activated Macrophage); Malat1, Metastasis-Associated Lung Adenocarcinoma Transcript 1; MAPK, Mitogen-Activated Protein Kinase; MASH, Macrophage Apoptosis-Associated Sphingolipid Hydrolase; MMPs, Matrix Metalloproteinases; mtDNA, Mitochondrial DNA; ncRNAs, Non-Coding RNAs; NASH, Non-Alcoholic Steatohepatitis; NF-κB, Nuclear Factor-Kappa B; *NCF1*, Neutrophil Cytosolic Factor 1; Nrf2, Nuclear Factor Erythroid 2-Related Factor 2; oxLDL, Oxidized Low-Density Lipoprotein; PD-1, Programmed Death-1; PD-L1, Programmed Death-Ligand 1; PI3K/AKT, Phosphatidylinositol 3-Kinase/Protein Kinase B; Piezo1, Piezo Type Mechanosensitive Ion Channel 1; PINK1, PTEN-Induced Kinase 1; p16INK4a, Cyclin-Dependent Kinase Inhibitor 2A; PBMC, Peripheral Blood Mononuclear Cell; RANKL, Receptor Activator of Nuclear Factor κB Ligand; Rv-D1, Resolvin D1; RA, Rheumatoid Arthritis; ROS, Reactive Oxygen Species; SR-A1, Scavenger Receptor A1; SMAD, Mothers Against Decapentaplegic Homolog; *SOCS1*, Suppressor of Cytokine Signaling 1; scRNA-seq, Single-Cell RNA Sequencing; STING, Stimulator of Interferon Genes; *TfR1*, Transferrin Receptor 1; TREM2, Triggering Receptor Expressed on Myeloid Cells 2; VEGF, Vascular

Endothelial Growth Factor; YAP, Yes-Associated Protein; *Gpnmb*, Glycoprotein Non-Metastatic Melanoma Protein B; miR-155, MicroRNA-155; β2-AR, Beta-2 Adrenergic Receptor.

Author Contributions

YHL, HHC and SAZ contributed to the study design; YHL and HHC wrote the manuscript. All authors reviewed drafts and approved the final version of the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity. All authors contributed to editorial changes in the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the writing phase of this manuscript, the authors utilized DeepSeek to perform text spell-checking, grammatical corrections, and language refinement. All generated content was personally reviewed and revised by the authors, who assume full responsibility for the ultimately published text. The specific application scope of the artificial intelligence technology has been accurately documented.

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