



Theoretical aspects of the formation of key elements of the macrophage activation dichotomy concept: Literature review

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Abstract. The aim of this study was to analyse the theoretical aspects of the formation of the macrophage activation dichotomy concept (M1/M2), which, despite the complexity of immune response regulation, reflects the existence of a highly efficient multilevel system controlling macrophage functional states and ensuring the proper course of inflammatory processes. Disruption of this system is associated with the development of pathological conditions, including chronic inflammation and tumour progression. The materials of the study consisted of contemporary publications presenting data from fundamental and experimental research on the mechanisms of macrophage activation and polarisation. The methods used include systematisation, comparative analysis, and generalisation of modern scientific approaches, with emphasis on molecular mechanisms and recent technological advances. The classical model of macrophage polarisation distinguishes between pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes; however, this classification is increasingly considered oversimplified and does not fully reflect macrophage heterogeneity *in vivo*. It was shown that cytokines such as interferon-gamma (IFN- γ), interleukin-4 (IL-4), interleukin-10 (IL-10), and transforming growth factor-beta (TGF- β) play a key role in shaping macrophage phenotypes and regulating their involvement in inflammation, tissue repair, and tumour microenvironment processes. Furthermore, macrophages are capable of simultaneously expressing features of different activation programmes, forming mixed or hybrid phenotypes. Based on the analysis of current data, it was concluded that the M1/M2 dichotomy has limited explanatory capacity and should be replaced by a model that considers macrophage activation as a dynamic continuum dependent on microenvironmental conditions. The results of this study may be useful for researchers and clinicians in immunology and oncology for improving approaches to immunomodulatory therapy and the development of targeted treatment strategies

Keywords: macrophage polarisation; M1/M2; cytokines; immune regulation; inflammation; plasticity; tumour microenvironment

INTRODUCTION

Macrophages are highly specialised cells of the innate immune system that play a key role in maintaining tissue homeostasis, regulating inflammation, and coordinating tissue repair. Due to their pronounced functional plasticity, macrophages can rapidly respond to signals from the

microenvironment and acquire different activation states under physiological and pathological conditions. Interest in macrophage polarisation has significantly increased in recent years because dysregulation of macrophage activation is associated with chronic inflammatory diseases, fibrosis,

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autoimmune disorders, cardiovascular pathology, and cancer progression. Therefore, understanding the mechanisms of macrophage activation is important for the development of modern immunotherapeutic approaches and targeted immune modulation strategies.

Recent studies have substantially expanded current understanding of macrophage heterogeneity and functional specialisation. Authors S. Pérez & S. Rius-Pérez (2022), investigating macrophage polarisation during acute inflammation, demonstrated that redox signalling pathways critically regulate macrophage reprogramming. According to their findings, oxidative stress promotes the pro-inflammatory M1 phenotype, whereas antioxidant mechanisms support M2-associated tissue repair responses. The authors also reported that M1 and M2 macrophages possess distinct metabolic profiles regulated by redox-dependent mechanisms. J. Cornice *et al.* (2024) analysed the role of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signalling in tumour-associated macrophages and showed that NF- κ B transcription factors function as major regulators of macrophage activation in cancer. Their study demonstrated that activation of the NF- κ B pathway contributes to polarisation toward an M2-like immunosuppressive phenotype, thereby promoting tumour progression and suppressing anti-tumour immunity. Additional insight into metabolic regulation of macrophage polarisation was provided by H. Guo *et al.* (2025), who investigated the relationship between lactylation and macrophage functional reprogramming. The authors demonstrated that lactylation acts as an epigenetic mechanism regulating gene expression associated with macrophage polarisation. Increased lactylation was shown to promote M2 polarisation and contribute to tumour progression and inflammatory dysregulation.

The role of macrophage polarisation in fibrotic diseases was investigated by L. Xie *et al.* (2023). The authors demonstrated that activation of G protein-coupled oestrogen receptor 1 (GPER1) inhibited both classically activated macrophages (M1) and alternatively activated macrophages (M2) polarisation and reduced inflammatory and fibrotic lesions in kidney tissues. They additionally reported that suppression of mitogen-activated protein kinase signalling pathways contributed to decreased macrophage-mediated tissue injury. Macrophage polarisation has also been

actively studied in autoimmune diseases. N. Ze-roouk *et al.* (2024), using computational modelling in rheumatoid arthritis research, reported that the balance between classically activated macrophages (M1) and alternatively activated macrophages (M2) plays a crucial role in chronic inflammation. The authors identified nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), Janus kinase 1/Janus kinase 2, and extracellular signal-regulated kinase 1/Notch homolog 1 signalling pathways as potential therapeutic targets capable of selectively suppressing pro-inflammatory macrophage activity.

The dynamic nature of macrophage activation was emphasised by A. Marrufo & A. Flores-Mireles (2024). The authors described macrophages as highly plastic immune cells capable of polarising along a continuum between M1-like and M2-like phenotypes depending on tissue microenvironmental signals. According to their analysis, dysregulated macrophage activation may contribute to persistent inflammatory responses and unfavourable clinical outcomes. An important contribution to understanding macrophage behaviour in the tumour microenvironment was made by M. Bruch-Oms *et al.* (2023). Investigating interactions between cancer-associated fibroblasts and macrophages, the authors demonstrated that activated fibroblasts promote macrophage polarisation toward immunosuppressive phenotypes. Their findings showed that stromal components of the tumour microenvironment significantly influence macrophage functional programming and tumour immune evasion. Similar observations were reported by S. Pisano *et al.* (2025), who analysed interactions between ovarian cancer cells and macrophage populations using organotypic spheroid models. The authors demonstrated that anti-inflammatory macrophages promoted epithelial-to-mesenchymal transition and contributed to metastatic progression through paracrine signalling mechanisms. Collectively, contemporary studies indicate that the traditional M1/M2 dichotomy does not fully reflect the diversity of macrophage phenotypes observed *in vivo*. Current evidence suggests that macrophage activation is regulated through complex interactions between cytokines, stromal cells, metabolic pathways, and tissue-specific environmental signals. Consequently, macrophage activation is increasingly interpreted as a dynamic continuum of functional



states rather than a strict binary classification.

The aim of this study was to analyse current theoretical approaches to macrophage activation and evaluate the evolution of the macrophage polarisation concept from the classical M1/M2 dichotomy toward a continuum-based model of macrophage functional states. The literature review for this study was conducted using the PubMed and Google Scholar databases. Publications published between 2020 and 2026 were analysed to identify recent advances related to macrophage activation, polarisation, tissue heterogeneity, fibrosis, autoimmune disorders, and tumour-associated macrophages. The search strategy included the keywords “macrophage polarisation”, “M1 macrophages”, “M2 macrophages”, “macrophage plasticity”, “tumour microenvironment”, and “macrophage heterogeneity”. Priority was given to peer-reviewed English-language articles indexed in international scientific databases. Both original experimental studies and review articles were included if they addressed theoretical or functional aspects of macrophage activation. Studies published before 2020 or papers lacking relevance to macrophage polarisation mechanisms were excluded from the analysis. In this study, the author systematised and critically analysed current data on the concept of macrophage activation dichotomy.

Origin, ontogeny, and tissue heterogeneity of macrophages

In mammalian organisms, macrophages develop from bone marrow stem cells. In humans, the bone marrow contains resident macrophages, as well as their progenitor cells: monocytes, promonocytes,

and monoblasts, which represent successive stages of mononuclear phagocyte differentiation. E. Kvedaraite *et al.* (2024) demonstrated that monocytes and neutrophils share a common myeloid precursor, highlighting the close developmental relationship between these innate immune cell lineages. The monoblast represents the least differentiated stage of the mononuclear phagocyte system. Through mitotic division, monoblasts give rise to promonocytes, which subsequently differentiate into circulating monocytes. B. Corleis *et al.* (2023) showed that monocytes exit the bone marrow and enter peripheral blood, where they circulate for a limited period before migrating into tissues under the influence of chemotactic signals.

Historically, it was assumed that tissue-resident macrophages are predominantly derived from circulating monocytes. However, E. Mass *et al.* (2023) provided evidence that a substantial proportion of tissue macrophages originate from embryonic precursors and can be maintained locally with minimal contribution from monocyte recruitment. This finding revised the traditional concept of macrophage ontogeny and emphasised their dual origin. Nevertheless, tissue macrophages represent a highly dynamic and adaptable cell population. Their differentiation from monocytes into fully functional macrophages is not a terminal state but rather a continuous process of functional adaptation shaped by cytokines and microenvironmental signals. This plasticity is essential for their dual role in initiating inflammatory responses and promoting tissue repair. The ultrastructural characteristics of macrophages under physiological and infectious conditions are summarised in Figure 1.

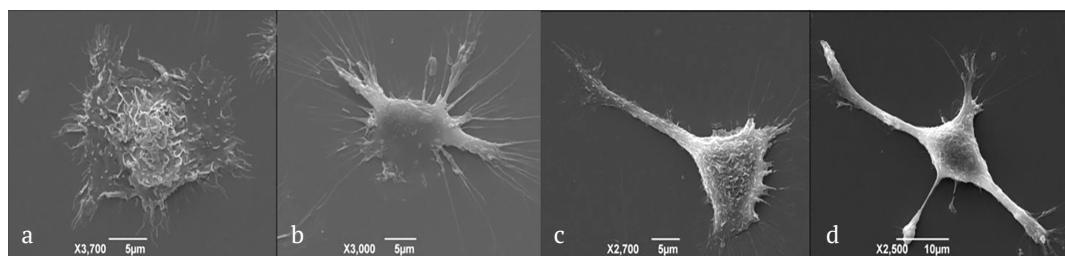


Figure 1. Morphological differences between non-infected and *Trypanosoma cruzi*-infected macrophages
Note: infected macrophages exhibit a more elongated and stellate morphology compared to non-infected cells. Scanning electron microscopy images show peritoneal macrophages from BALB/c mice cultured on polystyrene surfaces, 2D biofilms, and 3D matrices. Non-infected cells are presented in panels (A, C), while infected cells are shown in panels (B, D). Infection was performed using metacyclic trypomastigotes (clone Dm28c) at a 1:1 parasite-to-cell ratio, and images were obtained 48 hours post-infection
Source: J. Logullo *et al.* (2023)

The fate of senescent macrophages remains incompletely understood. D. Guan *et al.* (2025) reported that macrophages are capable of migrating from peripheral tissues to lymphoid organs, where they undergo apoptosis or participate in

antigen presentation. This supports the concept of dynamic turnover and systemic integration of macrophage populations. The distribution and specialisation of mononuclear phagocytes across different tissues are summarised in Table 1.

Table 1. Mononuclear phagocytes in the human body

Location	Organ/tissue	Mononuclear phagocyte
Bone marrow		Monoblasts, promonocytes, monocytes, macrophages
Peripheral blood		Monocytes
Organs	Liver Lungs Spleen Lymph nodes Thymus Bones Synovium Gastrointestinal tract Urogenital tract Endocrine system Central nervous system Skin	Kupffer cells Alveolar macrophages Macrophages of the red pulp Macrophages Macrophages Osteoclasts Type a cells Macrophages Macrophages Macrophages Microglia Langerhans cells
Serous cavities		Pleural macrophages, peritoneal macrophages
Sites of inflammation		Epithelioid cells, exudate macrophages, multinucleated giant cells

Source: developed by the author

During acute inflammatory responses, circulating monocytes are actively recruited to affected tissues, where they differentiate into inflammatory macrophages. R. Britt *et al.* (2023) demonstrated that these recruited cells actively contribute to immune cell infiltration and the production of pro-inflammatory cytokines, thereby amplifying local inflammatory responses.

Metabolic reprogramming and plasticity of macrophages

Macrophage metabolism represents a highly dynamic and tightly regulated system that undergoes profound changes during the transition from circulating monocytes to differentiated tissue macrophages. This process is accompanied by extensive metabolic reprogramming that enables macrophages to adapt to diverse microenvironmental conditions and functional demands. As demonstrated by O. Kolliniati *et al.* (2022), macrophage activation is closely linked to shifts in core metabolic pathways, including glycolysis, oxidative phosphorylation, and fatty acid metabolism. Similarly, S. Wculek *et al.* (2022) emphasised that tissue-resident macrophages display remarkable metabolic heterogeneity, which reflects both their

developmental origin and local environmental cues. Recent findings by A. Wong *et al.* (2025) further highlight that macrophage energy metabolism plays a critical role in maintaining cellular function under both physiological and pathological conditions, particularly in cardiometabolic diseases. During differentiation, macrophages exhibit an increase in mitochondrial biogenesis and enhanced oxidative capacity, which supports their functional specialisation. At the same time, glycolytic pathways remain essential, particularly under inflammatory conditions. L. Wang *et al.* (2023) demonstrated that immunometabolic reprogramming is a central mechanism regulating macrophage polarisation, especially in acute inflammatory states such as lung injury. In addition, X. Chen *et al.* (2025) showed that metabolic intermediates themselves can act as signalling molecules, modulating inflammatory responses and contributing to the phenomenon of meta-inflammation observed in obesity and diabetes. These findings indicate that metabolism is not merely a source of energy but also a key regulatory system controlling macrophage behaviour.

Adenosine triphosphate generated through metabolic pathways is essential for supporting



energy-intensive processes such as phagocytosis, migration, and cytokine secretion. According to B. Wang *et al.* (2021), lipid metabolism pathways, including arachidonic acid metabolism, play a crucial role in shaping inflammatory responses and determining macrophage functional states. Furthermore, it was demonstrated that interactions with mesenchymal stem cells can induce metabolic reprogramming in macrophages, thereby altering their phenotype and functional activity. These observations underscore the importance of metabolic plasticity as a fundamental property of macrophages. Macrophages are capable of maintaining functional activity under a wide range of environmental conditions, including hypoxia. This adaptability is particularly important in pathological contexts such as tumours, chronic inflammation, and ischemic tissues. As shown by N. Tran & E. Mills (2024), redox regulation is a key component of macrophage metabolism, linking cellular metabolic state with reactive oxygen species production and signalling pathways. The generation of reactive oxygen intermediates plays a critical role in antimicrobial defence but must be tightly controlled to prevent tissue damage. In this context, T. Liu *et al.* (2025) highlighted the importance of metabolic enzymes in regulating inflammatory and pathological processes, particularly in liver diseases and cancer.

In addition to classical metabolic pathways, recent studies have identified novel regulatory mechanisms involving transcriptional and post-transcriptional control. For example, J. Fernandes *et al.* (2024) demonstrated that microRNA-mediated regulation of polyamine metabolism significantly influences macrophage activation and pathogen response. Similarly, J. Galley *et al.* (2021) reported that systemic metabolic changes, including alterations in tryptophan metabolism, can indirectly affect macrophage function through host-microbiome interactions. These findings suggest that macrophage metabolism is integrated into broader systemic metabolic networks. Importantly, macrophage metabolic states are closely linked to their functional phenotypes. Pro-inflammatory macrophages are typically associated with increased glycolysis and disrupted mitochondrial respiration, whereas anti-inflammatory or tissue-repair phenotypes rely more on oxidative metabolism and lipid

utilisation. M. Klichinsky *et al.* (2020) demonstrated that targeted metabolic reprogramming can enhance macrophage anti-tumour activity, opening new perspectives for immunotherapy. Moreover, F. Guan *et al.* (2025) emphasised that macrophage heterogeneity and metabolic diversity are critical determinants of disease progression and therapeutic response. Thus, macrophage metabolism should be considered not only as a supportive system for cellular energy supply but as a central regulatory hub integrating environmental signals, intracellular pathways, and functional outcomes. The ability of macrophages to dynamically reprogram their metabolism in response to changing conditions represents a key mechanism underlying their plasticity and versatility in both health and disease.

Macrophage receptors: Structure, diversity, and functional roles in activation and signalling

To perform their diverse functions in the body, macrophages possess a wide array of receptors responsible for regulating processes such as growth, differentiation, activation, ligand recognition, endocytosis, phagocytosis, migration, and secretion. As emphasised by M. Wang *et al.* (2021), macrophage populations exhibit substantial heterogeneity in receptor expression depending on tissue localisation and developmental origin, which directly affects their functional specialisation. The complexity of macrophage receptor systems reflects their central role in both innate and adaptive immunity, as well as in maintaining tissue homeostasis. Among the first described macrophage receptors are Fc receptors, which are receptors for the Fc fragment of Immunoglobulin G (IgG) and receptors for components of the complement system. According to H. Bauer-Smith *et al.* (2023), Fc receptor-mediated signalling plays a crucial role in determining the threshold of immune activation and coordinating downstream effector responses. In addition, A. Petty *et al.* (2022) demonstrated that alterations in Fc receptor expression are associated with pro-inflammatory states, further highlighting their regulatory importance. Ligand binding to Fc receptors activates a wide variety of processes in macrophages, ranging from endocytosis and cytoskeletal rearrangement to phagocytosis and the secretion of molecules





necessary for the antibacterial response. The Fc receptor family includes the high-affinity receptor cluster of differentiation 64 (CD64), as well as the low-affinity receptors CD32 and CD16. Stimulation of macrophages with IL-4 activates the expression of another low-affinity Fc receptor, CD23, a low-affinity Fc receptor that binds Immunoglobulin E (IgE), linking Fc receptor signalling to alternative activation pathways, as also supported by N. Kern *et al.* (2021). In parallel with Fc receptors, macrophages express receptors for components of the complement system, including complement receptors CR1, CR3, and CR4. These receptors are responsible for the recognition, binding, and internalisation of opsonised particles. A. Lokki *et al.* (2021) demonstrated that functional alterations in complement receptors, particularly CR3 and CR4, can significantly affect immune responses and are associated with pathological conditions such as pre-eclampsia. The coordinated action of Fc and complement receptors ensures efficient pathogen clearance and modulation of inflammatory responses.

Macrophages also express a large number of receptors for cytokines and growth factors. Cytokine receptors are subdivided into families depending on homology to one of the following receptors: IL-2R (interleukin-2 receptor), IL-3R (interleukin-3 receptor), IL-4R (interleukin-4 receptor), GM-CSFR (granulocyte-macrophage colony-stimulating factor receptor), immunoglobulin-like receptor, TNFR (tumour necrosis factor receptor) and TGF- β R (transforming growth factor- β

receptor). The signalling systems activated by these receptors often use kinase activity as the first stage of signal transduction. This is followed by the activation of various transcription factors, among which it is worth noting NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells), activated in response to TNF- α (tumour necrosis factor alpha) and IFN- γ (interferon-gamma), transcription regulators of the STAT proteins (signal transducers and activators of transcription), and Smad family members (proteins homologous to *Caenorhabditis elegans* Sma and *Drosophila* Mad). As demonstrated by C. Li *et al.* (2024), interferon-gamma (IFN- γ) signalling is a key driver of macrophage-mediated inflammatory responses, particularly in respiratory pathologies. Exposure to specific cytokines or their combinations can profoundly alter macrophage function. For example, IL-4 (interleukin-4) and IL-13 (interleukin-13) promote alternative activation and increase expression of the mannose receptor, whereas IFN- γ enhances oxidative and bactericidal activity. In addition, H. Jo *et al.* (2026) showed that extracellular signals, such as platelet-derived factors, can reprogram macrophage responses through receptor-mediated mechanisms, further emphasising the plasticity of these cells. Given the diversity of ligands and signalling pathways involved, macrophage receptor systems can be broadly categorised according to their functional roles. A structured overview of the major receptor classes expressed by monocytes and macrophages, along with their corresponding ligands, is presented in Table 2.

Table 2. Monocyte and macrophage receptors

Receptor	Ligands
Fc receptors	Immunoglobulin (Ig)G, A, E
Complement receptors	Complement component (C3)b, d, anaphylatoxin, complement component 1q, Inactivated complement component 3b (iC3b)
Cytokine receptors	MIF ¹ , MAF ² , LIF ³ , CF ⁴ , MFF ⁵ , Interleukin (IL)-1, -2, -3, -4, -6, -7, -10, -13, -17, Interferon (IFN)- α , β , γ , GM-CSF ⁶ , CSF1 ⁷
Chemokine receptors	MIP-1 α , -1 β ⁸ , RANTES ⁹ , MCP-1, -2, -3, -4 ¹⁰ , IL-8 ¹¹ , SDF-1 ¹²
Hormone receptors	Insulin, glucocorticosteroids, angiotensin
Transferrin & lactoferrin receptors	Transferrin, lactoferrin
Lipoprotein & lipid receptors	Low-density lipoproteins (LDL), prostaglandin E ₂ , leukotriene B ₄ , leukotriene D ₄ , apolipoproteins B and E
Peptide & small molecule receptors	1,25-dihydroxyvitamin D ₃ , endorphins, substance P, vasopressin
Coagulation & anticoagulation factor receptors	Fibrinogen/fibrin, coagulation factor VII, heparin
Fibronectin receptors	Fibronectin
AGE receptors	Advanced glycation end-products (AGEs)





Table 2. Continued

Receptor	Ligands
Lectin-like receptors	Fucose, mannose, galactose, sialic acid
Toll-like receptors (TLRs)	Pathogen-specific molecular patterns (lipopolysaccharide, unmethylated cytosine-phosphate-guanine DNA motifs (CpG oligonucleotides))

Note: MIF – macrophage migration inhibitory factor; MAF – macrophage activating factor; LIF – leukaemia inhibitory factor; CF – chemotactic factor; MFF – macrophage fusion factor; GM-CSF – granulocyte-macrophage colony-stimulating factor; CSF-1 – colony-stimulating factor 1 (macrophage CSF, M-CSF); MIP-1 α / MIP-1 β – macrophage inflammatory protein-1 alpha/beta; RANTES – regulated upon activation, normal T cell expressed and secreted (CCL5); MCP-1, -2, -3, -4 – monocyte chemoattractant proteins (CCL2, CCL8, CCL7, CCL13); IL-8 – interleukin-8 (CXCL8); SDF-1 – stromal cell-derived factor 1 (CXCL12)

Source: developed by the author

In addition to a wide spectrum of cytokine receptors, a large number of various chemokine receptors, macrophages express a large number of various chemokine receptors that regulate their migration and positioning within tissues. As shown by N. Zhang *et al.* (2022), receptors such as CXCR4 (C-X-C chemokine receptor type 4) play a critical role in macrophage-mediated intercellular communication and tissue remodelling, particularly in cardiovascular diseases. Representatives of the CC (chemokine ligand family with two adjacent cysteines), CXC (chemokine ligand family with one amino acid separating two cysteines), and CX3C (chemokine ligand family with three amino acids between two cysteines) receptor families, including CCR1 (CC chemokine receptor 1), CCR2 (CC chemokine receptor 2), CCR5 (CC chemokine receptor 5), CXCR1 (CXC chemokine receptor 1), CXCR2 (CXC chemokine receptor 2), CXCR4 (CXC chemokine receptor 4), and CX3CR1 (CX3C chemokine receptor 1), enable macrophages to respond dynamically to chemotactic gradients and adapt to changing physiological conditions. Furthermore,

H. Piao *et al.* (2022) demonstrated that chemokine receptor signalling contributes to the interaction between tumour-associated macrophages and cancer cells, promoting disease progression. Morphological differences between macrophage phenotypes under various culture conditions are illustrated in Figure 2. A special place among macrophage receptors is occupied by lipoprotein receptors. These receptors enable macrophages to bind, internalise, and break down cholesterol-containing lipoproteins and low-density lipoproteins (LDL). According to Z. You *et al.* (2023), dysregulation of lipid receptor pathways can lead to pathological processes such as ferroptosis and contribute to the development of atherosclerosis. This is further supported by Y. Liu *et al.* (2026), who highlighted the role of macrophage receptor-mediated lipid uptake in disease progression and therapeutic targeting. Scavenger receptors, in particular, play a dual role: under physiological conditions they contribute to the clearance of modified lipoproteins, while under pathological conditions they promote intracellular lipid accumulation and foam cell formation.

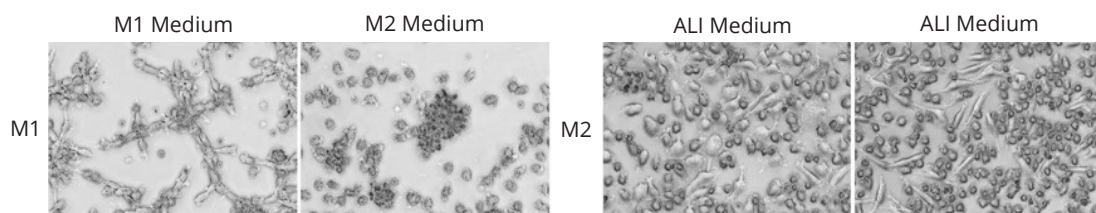


Figure 2. Morphology of M1, and M2 macrophages after 72 hours of culture

Note: macrophages of different activation states (M0, M1, and M2) were cultured either in their respective differentiation media or in air-liquid interface (ALI) medium, under monoculture conditions or in co-culture with human bronchial epithelial cells (HBECs); morphological characteristics were assessed using white light microscopy after 72 hours of culture

Source: N. Ronaghan *et al.* (2022)





Lectin-like receptors represent another important class of macrophage receptors that recognise carbohydrate structures on the pathogen surfaces. These receptors, including the mannose receptor, bind oligosaccharides containing terminal residues of mannose, fucose, galactose, and sialic acid. Their activation allows macrophages to recognise and internalise non-opsonised pathogens. This mechanism is essential for early innate immune responses and can function independently of Fc or complement receptor pathways. In addition to lectin-like receptors, macrophages express Toll-like receptors (TLRs), which are key pattern recognition receptors involved in detecting pathogen-associated molecular patterns. Among them, TLR2, TLR4, and TLR9 play a particularly important role. A. Mansouri *et al.* (2025) demonstrated that activation of TLR2/1 and TLR4 induces the production of pro-inflammatory cytokines such as interferon-gamma (IFN- γ) and tumour necrosis factor-alpha (TNF- α), highlighting their central role in innate immune activation. The broad ligand specificity and high sensitivity of TLRs enable macrophages to detect a wide range of pathogens and mount an appropriate immune response without the need for prior sensitisation.

Effector functions of macrophages in host defence and tissue homeostasis

Mononuclear phagocytes provide the first line of defence against invading pathogens such as bacteria, viruses, fungi, and protozoa. Macrophages are capable of actively migrating to the site of pathogen invasion by orienting themselves along the gradient of molecules produced by the pathogen. During recognition, several receptor systems can participate simultaneously, including complement receptors, Fc receptors, lectin-like receptors, and scavenger receptors, ensuring efficient detection and response to pathogens; disruption of this process significantly impairs macrophage infiltration and function (Ikebukuro *et al.*, 2023; Mvubu, 2025).

The processes of pathogen recognition and internalisation typically initiate the mechanism for its destruction. Following the formation of the phagosome, it fuses with lysosomes, releasing lysosomal enzymes necessary for destroying the pathogen. Furthermore, upon activation of macrophages induces the generation of reactive oxygen species, contributing to microbial killing

but also influencing intracellular signalling pathways (Mangiaterra *et al.*, 2024). Despite the high efficacy of macrophages in destroying pathogens, some microorganisms have developed protective mechanisms that allow them not only to avoid destruction but also to replicate inside macrophages. The most prominent example of a bacterium utilising this survival strategy is *Mycobacterium tuberculosis*, which produces sulpholipids that prevent phagosome-lysosome fusion, thereby avoiding degradation (Saha *et al.*, 2021; Bo *et al.*, 2023). The capture and destruction of a pathogen provide macrophages with the opportunity to activate the acquired immune system for more effective protection of the organism. After destroying the pathogen in the phagosome, pathogen-specific antigens are processed inside the cell, forming peptides that are presented on the macrophage surface in complex with major histocompatibility complex class II (MHC class II) molecules, allowing interaction with T lymphocytes and initiation of antigen-specific immune responses. However, the efficiency of macrophages in activating T cells remains context-dependent and may vary depending on the microenvironment. In addition to their antimicrobial functions, macrophages play a central role in maintaining immune homeostasis through the secretion of a wide range of bioactive molecules. These include enzymes, cytokines, chemokines, soluble receptors, coagulation factors, complement components, and extracellular matrix proteins. Protein secretion in macrophages involves synthesis in the rough endoplasmic reticulum, processing in the Golgi apparatus, and transport via vesicles to the plasma membrane. Some mediators are released through classical exocytosis, while others require more complex regulatory mechanisms. For example, TNF is initially synthesised as a transmembrane precursor, and its release depends on cleavage by the metalloproteinase ADAM17 (a disintegrin and metalloproteinase 17) (Gnosa *et al.*, 2022; Aljohmani *et al.*, 2026). Similarly, interleukin-1 β (IL-1 β) is produced as an inactive precursor in the cytoplasm and requires proteolytic activation by caspases, particularly caspase-1, as well as non-canonical pathways involving caspase-4/5/11 (Chaintreuil *et al.*, 2022; Pollock *et al.*, 2023). The mechanisms regulating the extracellular release of the mature cytokine remain an active area of research.



The secretory products of macrophages regulate numerous physiological processes, including immune cell recruitment, inflammation, tissue remodelling, and angiogenesis. Dysregulation of these processes may lead to pathological conditions such as chronic inflammation, autoimmune diseases, fibrosis, and impaired immune responses. Given the diversity of macrophage functions and their central role in maintaining physiological

balance, dysfunction of these cells can lead to a wide range of diseases. These pathological alterations may affect different stages of macrophage activity, including pathogen recognition, phagocytosis, cytokine production, antigen presentation, and tissue remodelling. To summarise these relationships, the key mechanisms of macrophage dysfunction and their associated pathological conditions are presented in Table 3.

Table 3. Examples of macrophage dysfunction and associated diseases

Dysfunction	Mechanism	Disease
Avoidance of phagolysosome fusion	Sulpholipids produced by <i>Mycobacterium tuberculosis</i>	Tuberculosis
Excessive proinflammatory cytokine secretion	Dysregulation of TNF, interleukin (IL)-1, -6 synthesis	Rheumatoid arthritis, psoriasis, atherosclerosis
Impaired antigen presentation	Reduced MHC class II ¹ (human leukocyte antigen (HLA)-DR, -DP, -DQ isotypes) expression	Chronic infections, immunodeficiencies
Tumour immune evasion	Suppression of macrophage activity in the tumour microenvironment	Cancer progression, metastasis
Defective pathogen recognition / phagocytosis	Mutations in scavenger receptors, Fc receptors, or complement system	Recurrent bacterial infections, autoimmunelike disorders
Aberrant tissue remodelling / fibrosis	Overproduction of growth factors (TGF- β^2 , PDGF) and matrix enzymes	Organ fibrosis (pulmonary, hepatic), sarcoidosis

Note: MHC class II – major histocompatibility complex class II; TGF- β – transforming growth factor; PDGF – platelet-derived growth factor; TNF – tumour necrosis factor

Source: developed by the author

In addition to maintaining homeostasis, timely detection, and destruction of bacteria, the functions of macrophages in the body include controlling the emergence of tumour cells. Macrophages can directly lyse tumour cells through cytotoxic mechanisms and contribute to the activation of anti-tumour immune responses involving cytotoxic lymphocytes (Yu *et al.*, 2026). Experimental studies have demonstrated that activation of macrophages enhances their ability to eliminate tumour cells. This effect is mediated both by soluble factors and by direct cell-to-cell interactions. Among soluble mediators, cytokines such as TNF and interleukins play a critical role in suppressing tumour cell proliferation and modulating the tumour microenvironment (Mortezaee & Majidpoor, 2022). In addition to cytokine-mediated effects, macrophages exhibit cytotoxic activity upon direct contact with tumour cells. Antibody-dependent cellular cytotoxicity represents another important mechanism, in which macrophages recognise antibody-coated tumour cells and induce their destruction

(Wilhelm *et al.*, 2025). However, under conditions of immunosuppression, tumour cells can evade macrophage-mediated immune responses. In such cases, tumours not only escape immune surveillance but may also exploit macrophages to promote tumour progression, invasion, and metastasis.

Concept of macrophage activation dichotomy

As mentioned earlier, during differentiation, macrophages acquire a phenotype characteristic of the physiological state of the tissue. This process is accompanied by profound metabolic and functional reprogramming that defines their role in immune responses (Yan *et al.*, 2024). For a long time, it was believed that in a healthy organism, macrophages reside in a state awaiting activation by exogenous or endogenous factors. The main factors activating macrophages were considered to be bacterial products and interferon gamma (IFN- γ), which induced strong antimicrobial and pro-inflammatory responses. However, subsequent studies demonstrated that macrophage activation is not

limited to this pathway. Under the influence of interleukin-4 (IL-4), macrophages not only lose part of their bactericidal activity but also acquire distinct functional properties associated with tissue repair and immunoregulation. These findings led to the introduction of the concept of alternative macrophage activation and significantly expanded the understanding of macrophage functional diversity (Wei *et al.*, 2021). The development of this

concept was closely linked to the established type 1 T helper (Th1) and type 2 T helper (Th2) paradigm of T helper cell differentiation, which provided a theoretical framework for classifying macrophage activation states. To illustrate this analogy and the functional relationship between T helper cell subsets and macrophage activation pathways, Figure 3 presents the polarisation of T helper cells and their associated immune responses.

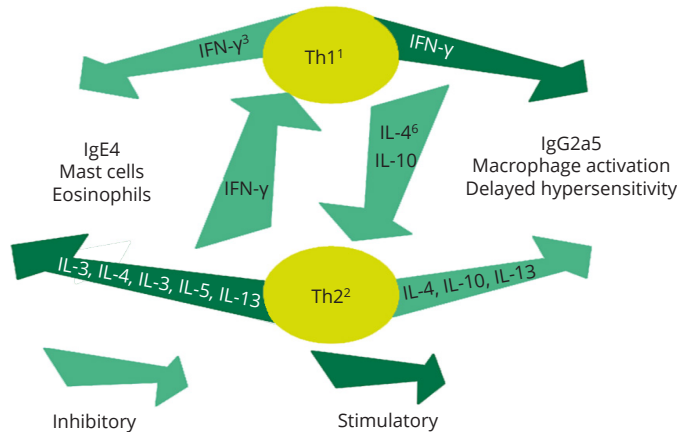


Figure 3. Functional polarisation of T helper cells in immune responses

Note: Th1 – T helper 1 cells; Th2 – T helper 2 cells; IFN-γ – interferon-gamma; IgE – immunoglobulin E; IgG2a – immunoglobulin G2a; IL – interleukin

Source: developed by the author

According to this framework, classical macrophage activation corresponds to stimulation by Th1-associated cytokines, primarily interferon-gamma (IFN-γ), whereas alternative activation is driven by Th2-associated cytokines such as interleukin 4 and interleukin 13. This analogy led to the introduction of the M1/M2 terminology, which became widely used to describe macrophage activation states (Shoeran & Anand, 2025). By the late 1990s, the dichotomous model of macrophage activation had taken its final form. M1 macrophages were defined as pro-inflammatory cells induced by IFN-γ or bacterial components such as lipopolysaccharide, whereas M2 macrophages were associated with anti-inflammatory responses and tissue repair, being induced by cytokines such as interleukin 4, interleukin 10, and transforming growth factor beta (TGF-β). Despite its conceptual usefulness, this model has significant limitations. Increasing evidence indicates that macrophage activation is

highly context-dependent and cannot be fully explained by a binary classification.

In response to the limitations of the dichotomy, the scientific community is proposing new, more flexible classification systems. For example, it has been proposed to consider macrophages through the prism of their main functions in a specific context: inflammation, clearance (efferocytosis), tissue repair, or immunoregulation (Kumar Jha *et al.*, 2024). Another approach is to define disease-specific signatures. Thus, the study of tumour-associated macrophages has identified dozens of unique subpopulations that are not M1 or M2 analogues but have prognostic significance for cancer progression and response to immunotherapy (Ferrarini *et al.*, 2023; Pavlov *et al.*, 2026). Thus, the current emphasis is shifting from labelling to understanding the causal relationships between the microenvironment, transcriptomic profile, and functional outcome. Furthermore, studies in cancer biology demonstrate that macrophage



behaviour is strongly influenced by the tumour microenvironment, including hypoxia and stromal interactions, which shape their immunosuppressive or pro-tumorigenic functions (Nazon *et al.*, 2022; Carlson *et al.*, 2025). Thus, modern research by R. Li *et al.* (2024) increasingly shifts the focus from rigid classification toward understanding the

dynamic relationships between the microenvironment, transcriptional programmes, and functional outcomes of macrophage activation. To systematise the classical view of macrophage activation and highlight the key molecular and functional differences between M1 and M2 phenotypes, these characteristics are summarised in Table 4.

Table 4. Molecular and functional features of type 1 and type 2 activated macrophages

Type 1 activation (M1)	Type 2 activation (M2)
Tumour necrosis factor (TNF) Interleukin 1 (IL-1) Interleukin 6 (IL-6) Interleukin 12 (IL-12)	Interleukin 10 (IL-10) Interleukin 4 (IL-4) Interleukin-1 receptor antagonist (IL-Ira) Alternative macrophage activation-associated C-chemokine-1 (AMAC-1) C-C motif chemokine ligand 18 (CCL18)
Fc gamma receptor I (FcγRI) Fc gamma receptor II (FcγRII) Fc gamma receptor III (FcγRIII) Oxidative burst Bactericidal activity	Mannose receptor (CD206) β-glucan receptor (Dectin-1) Scavenger receptors class A (SR-A/CD204) Haemoglobin scavenger receptor (CD163) Endocytosis of degradation products

Source: developed by the author

Type 1 activated macrophages (M1) are relatively well characterised and are defined by the production of pro-inflammatory cytokines, including TNF (tumour necrosis factor), IL-1 (interleukin-1), IL-6 (interleukin-6), and IL-12 (interleukin-12), as well as high bactericidal activity and the capacity to generate an oxidative burst. These properties make them critical for host defence against intracellular pathogens. In contrast, type 2 activated macrophages (M2) exhibit a broader and more heterogeneous range of functions. They are primarily associated with anti-inflammatory responses, tissue remodelling, and repair processes. M2 macrophages produce cytokines such as IL-10 (interleukin-10) and express receptors involved in endocytosis and clearance of cellular debris, including lectin-like and scavenger receptors (Bongartz *et al.*, 2024; D. Guan *et al.*, 2025). At the same time, M2 macrophages demonstrate reduced bactericidal activity compared to M1 macrophages and are often involved in resolving inflammation and restoring tissue homeostasis. Recent advances in high-throughput technologies, including single-cell transcriptomics and multi-omics analysis, have further challenged the dichotomous model. These approaches reveal that macrophages frequently express gene signatures characteristic of both M1 and M2 phenotypes simultaneously, forming hybrid activation states (Yan *et al.*, 2024). Such

hybrid phenotypes are highly dynamic and can rapidly change in response to local environmental signals. This plasticity highlights the limitations of the M1/M2 classification and supports the concept of macrophage activation as a continuum rather than discrete states (Kumar Jha *et al.*, 2024).

In summary, the understanding of macrophage activation has evolved from a simplified dichotomous M1/M2 framework toward a more dynamic and context-dependent model. Although the M1/M2 classification remains useful for describing general pro-inflammatory and anti-inflammatory tendencies, accumulating evidence demonstrates that macrophages exhibit substantial phenotypic plasticity and often adopt hybrid activation states shaped by local microenvironmental cues. Therefore, contemporary research increasingly focuses not on rigid categorisation but on identifying the molecular mechanisms and functional programmes that determine macrophage behaviour in specific physiological and pathological contexts.

CONCLUSIONS

When describing M2 macrophages, emphasis is often placed on the shared functional outcomes induced by different stimuli, while the underlying molecular differences receive less attention. Although cytokines such as interleukin 4 and





interleukin 13 produce similar effects due to activation of a common receptor complex and downstream signalling pathway, other mediators, including interleukin 10, operate through distinct signalling mechanisms. As a result, macrophages activated by these factors exhibit significant molecular and functional differences despite being grouped within the same category. Comparable variability is observed when contrasting cytokine-induced activation with hormone-mediated effects. For instance, macrophages stimulated by interleukin 4 differ substantially from those activated by glucocorticoids in terms of receptor expression and functional capabilities. These differences highlight that grouping such activation states under a single classification does not adequately reflect their biological diversity. Taken together, these observations indicate that the classical dichotomous model of macrophage activation has limited explanatory power. It does not fully account for the diversity of phenotypes that arise in response to specific cytokines, hormones, and microenvironmental signals. A more refined framework is therefore required, one that considers the distinct activation programmes and their regulatory mechanisms.

The modern understanding of macrophage biology increasingly shifts from a binary classification toward a continuum-based and context-dependent model. This conceptual transition has important therapeutic implications. Rather than attempting to broadly shift macrophages from one generalised state to another, current strategies focus on the precise modulation of specific functional programmes within defined tissue environments. In particular, enhancing targeted processes such as the clearance of apoptotic cells represents a promising direction for therapeutic intervention. Clinical observations further underscore the importance of this approach. In the

context of implant integration, excessive accumulation of macrophages and elevated levels of pro-inflammatory mediators are associated with adverse outcomes, including implant failure. At the same time, successful tissue remodelling depends on a coordinated sequence of macrophage activation states, where early pro-inflammatory responses are followed by reparative processes that support regeneration. These findings suggest that effective biomaterial design should prioritise immunomodulation rather than simple suppression of immune responses. Materials capable of directing macrophage activation toward beneficial functional programmes may improve tissue integration while minimising chronic inflammation and foreign body reactions. Similarly, controlling macrophage-driven fibrotic responses may offer therapeutic benefits in chronic inflammatory conditions. Future research integrating single-cell analysis, spatial transcriptomics, and functional studies will provide a more detailed understanding of macrophage heterogeneity in pathological settings. This will enable the development of targeted strategies for precise regulation of macrophage activity in clinical practice.

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CONFLICT OF INTEREST

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REFERENCES

- [1] Aljohmani, A., *et al.* (2026). Leukocytic ADAM10 and ADAM17 modulate disease severity and systemic outcome in bacterial and viral pneumonia. *European Respiratory Journal*, 67(2), article number 2402060. doi: [10.1183/13993003.02060-2024](https://doi.org/10.1183/13993003.02060-2024).
- [2] Bauer-Smith, H., Sudol, A.S.L., Beers, S.A., & Crispin, M. (2023). Serum immunoglobulin and the threshold of Fc receptor-mediated immune activation. *Biochimica et Biophysica Acta – General Subjects*, 1867(11), article number 130448. doi: [10.1016/j.bbagen.2023.130448](https://doi.org/10.1016/j.bbagen.2023.130448).
- [3] Bo, H., Moure, U.A.E., Yang, Y., Pan, J., Li, L., Wang, M., Ke, X., & Cui, H. (2023). *Mycobacterium tuberculosis*-macrophage interaction: Molecular updates. *Frontiers in Cellular and Infection Microbiology*, 13, article number 1062963. doi: [10.3389/fcimb.2023.1062963](https://doi.org/10.3389/fcimb.2023.1062963).



- [4] Bongartz, H., Bradfield, C., Gross, J., Fraser, I.D.C., Nita-Lazar, A., & Meier-Schellersheim, M. (2024). IL-10 dependent adaptation allows macrophages to adjust inflammatory responses to TLR4 stimulation history. *Biorxiv*. doi: [10.1101/2024.03.28.587272](https://doi.org/10.1101/2024.03.28.587272).
- [5] Britt, R.D., Ruwanpathirana, A., Ford, M.L., & Lewis, B.W. (2023). Macrophages orchestrate airway inflammation, remodeling, and resolution in asthma. *International Journal of Molecular Sciences*, 24(13), article number 10451. doi: [10.3390/ijms241310451](https://doi.org/10.3390/ijms241310451).
- [6] Bruch-Oms, M., Olivera-Salguero, R., Mazzolini, R., del Valle-Pérez, B., Mayo-González, P., Beteta, Á., Peña, R., & García de Herreros, A. (2023). Analyzing the role of cancer-associated fibroblast activation on macrophage polarization. *Molecular Oncology*, 17(8), 1492-1513. doi: [10.1002/1878-0261.13454](https://doi.org/10.1002/1878-0261.13454).
- [7] Carlson, E.G., Lopez, J.C., Yamaguchi, Y., Gibson, J., Priceman, S.J., & LaBarge, M.A. (2025). CD105⁺ fibroblasts support an immunosuppressive niche in women at high risk of breast cancer initiation. *Breast Cancer Research*, 27, article number 81. doi: [10.1186/s13058-025-02040-7](https://doi.org/10.1186/s13058-025-02040-7).
- [8] Chaintreuil, P., et al. (2022). Reprogramming monocyte-derived macrophages through caspase inhibition. *Oncoimmunology*, 11(1), article number 2015859. doi: [10.1080/2162402X.2021.2015859](https://doi.org/10.1080/2162402X.2021.2015859).
- [9] Chen, X., et al. (2025). FFAR4-mediated IL-6 release from islet macrophages promotes insulin secretion and is compromised in type-2 diabetes. *Nature Communications*, 16, article number 3422. doi: [10.1038/s41467-025-58706-5](https://doi.org/10.1038/s41467-025-58706-5).
- [10] Corleis, B., et al. (2023). Tobacco smoke exposure recruits inflammatory airspace monocytes that establish permissive lung niches for *Mycobacterium tuberculosis*. *Science Translational Medicine*, 15(725), article number eadg3451. doi: [10.1126/scitranslmed.adg3451](https://doi.org/10.1126/scitranslmed.adg3451).
- [11] Cornice, J., Verzella, D., Arboretto, P., Vecchiotti, D., Capece, D., Zazzeroni, F., & Franzoso, G. (2024). NF- κ B: Governing macrophages in cancer. *Genes*, 15(2), article number 197. doi: [10.3390/genes15020197](https://doi.org/10.3390/genes15020197).
- [12] Fernandes, J.C.R., Muxel, S.M., López-González, M.A., Barbas, C., & Floeter-Winter, L.M. (2024). Early *Leishmania* infectivity depends on miR-372/373/520d family-mediated reprogramming of polyamines metabolism in THP-1-derived macrophages. *Scientific Reports*, 14, article number 996. doi: [10.1038/s41598-024-51511-y](https://doi.org/10.1038/s41598-024-51511-y).
- [13] Ferrarini, I., Bernardelli, A., Lovato, E., Schena, A., Krampera, M., & Visco, C. (2023). An updated portrait of monocyte-macrophages in classical Hodgkin lymphoma. *Frontiers in Oncology*, 13, article number 1149616. doi: [10.3389/fonc.2023.1149616](https://doi.org/10.3389/fonc.2023.1149616).
- [14] Galley, J.D., Chen, H.J., Antonson, A.M., & Gur, T.L. (2021). Prenatal stress-induced disruptions in microbial and host tryptophan metabolism and transport. *Behavioural Brain Research*, 414, article number 113471. doi: [10.1016/j.bbr.2021.113471](https://doi.org/10.1016/j.bbr.2021.113471).
- [15] Gnosa, S.P., Blasco, L.P., Piotrowski, K.B., Freiberg, M.L., Savickas, S., Madsen, D.H., auf dem Keller, U., Kronqvist, P., & Kveiborg, M. (2022). ADAM17-mediated EGFR ligand shedding directs macrophage-promoted cancer cell invasion. *JCI Insight*, 7(18), article number e155296. doi: [10.1172/jci.insight.155296](https://doi.org/10.1172/jci.insight.155296).
- [16] Guan, D., et al. (2025). Deficiency of myeloid NPC1 exacerbates liver injury and fibrosis by impairing macrophage efferocytosis. *Journal of Advanced Research*, 72, 213-227. doi: [10.1016/j.jare.2024.11.020](https://doi.org/10.1016/j.jare.2024.11.020).
- [17] Guan, F., Wang, R., Yi, Z., Luo, P., Liu, W., Xie, Y., Liu, Z., Xia, Z., Zhang, H., & Cheng, Q. (2025). Tissue macrophages: Origin, heterogeneity, biological functions, diseases and therapeutic targets. *Signal Transduction and Targeted Therapy*, 10, article number 93. doi: [10.1038/s41392-025-02124-y](https://doi.org/10.1038/s41392-025-02124-y).
- [18] Guo, H., Luan, N., Gao, J., Pang, X., Bi, J., & Zhu, L. (2025). Exploring the mechanisms of mutual influence between lactylation and macrophage polarization in the context of disease. *Clinical and Translational Medicine*, 15(11), article number e70499. doi: [10.1002/ctm2.70499](https://doi.org/10.1002/ctm2.70499).
- [19] Ikebukuro, T., Arima, T., Kasamatsu, M., Nakano, Y., Tobita, Y., Uchiyama, M., Terashima, Y., Toda, E., Shimizu, A., & Takahashi, H. (2023). Disulfiram ophthalmic solution inhibited macrophage infiltration by suppressing macrophage pseudopodia formation in a rat corneal alkali burn model. *International Journal of Molecular Sciences*, 24(1), article number 735. doi: [10.3390/ijms24010735](https://doi.org/10.3390/ijms24010735).
- [20] Jo, H.Y., Kim, M.K., Kim, K.T., Choi, C., & Rhee, W.J. (2026). Extracellular vesicles for macrophage reprogramming: An emerging paradigm in immunomodulatory therapeutics. *Journal of Biological Engineering*, 20, article number 13. doi: [10.1186/s13036-025-00594-w](https://doi.org/10.1186/s13036-025-00594-w).



- [21] Kern, N., Dong, R., Douglas, S.M., Vale, R.D., & Morrissey, M.A. (2021). Tight nanoscale clustering of Fcγ receptors using DNA origami promotes phagocytosis. *eLife*, 10, article number e68311. [doi: 10.7554/eLife.68311](https://doi.org/10.7554/eLife.68311).
- [22] Klichinsky, M., *et al.* (2020). Human chimeric antigen receptor macrophages for cancer immunotherapy. *Nature Biotechnology*, 38, 947-953. [doi: 10.1038/s41587-020-0462-y](https://doi.org/10.1038/s41587-020-0462-y).
- [23] Kolliniati, O., Ieronymaki, E., Vergadi, E., & Tsatsanis, C. (2022). Metabolic regulation of macrophage activation. *Journal of Innate Immunity*, 14(1), 51-68. [doi: 10.1159/000516780](https://doi.org/10.1159/000516780).
- [24] Kumar Jha, P., Aikawa, M., & Aikawa, E. (2024). Macrophage heterogeneity and efferocytosis: Beyond the M1/M2 dichotomy. *Circulation Research*, 134(2), 186-188. [doi: 10.1161/CIRCRESAHA.123.324011](https://doi.org/10.1161/CIRCRESAHA.123.324011).
- [25] Kvedaraite, E., *et al.* (2024). Intestinal stroma guides monocyte differentiation to macrophages through GM-CSF. *Nature Communications*, 15, article number 1752. [doi: 10.1038/s41467-024-46076-3](https://doi.org/10.1038/s41467-024-46076-3).
- [26] Li, C., *et al.* (2024). Comparative single-cell analysis reveals IFN-γ as a driver of respiratory sequelae after acute COVID-19. *Science Translational Medicine*, 16(756), article number eadn0136. [doi: 10.1126/scitranslmed.adn0136](https://doi.org/10.1126/scitranslmed.adn0136).
- [27] Li, R., Huang, J., Wei, Y., Wang, Y., Lu, C., Liu, J., & Ma, X. (2024). Nanotherapeutics for macrophage network modulation in tumor microenvironments: Targets and tools. *International Journal of Nanomedicine*, 19, 13615-13651. [doi: 10.2147/IJN.S491573](https://doi.org/10.2147/IJN.S491573).
- [28] Liu, T., Zhang, F.Y., Feng, Y., Han, P.S., & Gao, Y.H. (2025). Alcohol-metabolizing enzymes, liver diseases and cancer. *Seminars in Liver Disease*, 45(1), 99-113. [doi: 10.1055/a-2551-3320](https://doi.org/10.1055/a-2551-3320).
- [29] Liu, Y., *et al.* (2026). Recent advances in nanodelivery systems based on extracellular and intracellular reprogramming strategies for enhanced therapy of atherosclerosis. *International Journal of Nanomedicine*, 21, article number 541504. [doi: 10.2147/IJN.S541504](https://doi.org/10.2147/IJN.S541504).
- [30] Logullo, J., *et al.* (2023). Increased *Trypanosoma cruzi* growth during infection of macrophages cultured on collagen I matrix. *Life*, 13(4), article number 1063. [doi: 10.3390/life13041063](https://doi.org/10.3390/life13041063).
- [31] Lokki, A., *et al.* (2021). Dysfunction of complement receptors CR3 (CD11b/18) and CR4 (CD11c/18) in pre-eclampsia: A genetic and functional study. *BJOG: An International Journal of Obstetrics and Gynaecology*, 128(8), 1282-1291. [doi: 10.1111/1471-0528.16660](https://doi.org/10.1111/1471-0528.16660).
- [32] Mangiaterra, S., Gavazza, A., Biagini, L., & Rossi, G. (2024). Study of macrophage activity in cats with FIP and naturally FCoV-shedding healthy cats. *Pathogens*, 13(6), article number 437. [doi: 10.3390/pathogens13060437](https://doi.org/10.3390/pathogens13060437).
- [33] Mansouri, A., Akthar, I., & Miyamoto, A. (2025). TLR2 and TLR4 bridge physiological and pathological inflammation in the reproductive system. *Communications Biology*, 8, article number 1008. [doi: 10.1038/s42003-025-08424-x](https://doi.org/10.1038/s42003-025-08424-x).
- [34] Marrufo, A.M., & Flores-Mireles, A.L. (2024). Macrophage fate: To kill or not to kill? *Infection and Immunity*, 92(9), article number e00476-23. [doi: 10.1128/iai.00476-23](https://doi.org/10.1128/iai.00476-23).
- [35] Mass, E., Nimmerjahn, F., Kierdorf, K., & Schlitzer, A. (2023). Tissue-specific macrophages: How they develop and choreograph tissue biology. *Nature Reviews Immunology*, 23, 563-579. [doi: 10.1038/s41577-023-00848-y](https://doi.org/10.1038/s41577-023-00848-y).
- [36] Mortezaee, K., & Majidpoor, J. (2022). Roles for macrophage-polarizing interleukins in cancer immunity and immunotherapy. *Cellular Oncology*, 45, 333-353. [doi: 10.1007/s13402-022-00667-8](https://doi.org/10.1007/s13402-022-00667-8).
- [37] Mvubu, N.E. (2025). Innate immune recognition of *Mycobacterium tuberculosis*: Receptor engagement and inflammatory outcomes at the site of infection. *The Cell Surface*, 14, article number 100150. [doi: 10.1016/j.tcs.2025.100150](https://doi.org/10.1016/j.tcs.2025.100150).
- [38] Nazon, C., *et al.* (2022). Together intra-tumor hypoxia and macrophagic immunity are driven worst outcome in pediatric high-grade osteosarcomas. *Cancers*, 14(6), article number 1482. [doi: 10.3390/cancers14061482](https://doi.org/10.3390/cancers14061482).
- [39] Pavlov, S., Ali, E., Ambrozkiwicz, F., Ye, W., Rajtmajerová, M., Liška, V., Hemminki, K., & Trailin, A. (2026). Macrophages in colorectal cancer: From normal mucosa to distant metastasis: Beyond the M1/M2 paradigm. *Journal of Cancer*, 17(1), 157-176. [doi: 10.7150/jca.126772](https://doi.org/10.7150/jca.126772).
- [40] Pérez, S., & Rius-Pérez, S. (2022). Macrophage polarization and reprogramming in acute inflammation: A redox perspective. *Antioxidants*, 11(7), article number 1394. [doi: 10.3390/antiox11071394](https://doi.org/10.3390/antiox11071394).



- [41] Petty, A., Glass, L.J., Rothmond, D.A., Purves-Tyson, T., Sweeney, A., Kondo, Y., Kubo, S., Matsumoto, M., & Weickert, C.S. (2022). Increased levels of a pro-inflammatory IgG receptor in the midbrain of people with schizophrenia. *Journal of Neuroinflammation*, 19, article number 188. doi: [10.1186/s12974-022-02541-8](https://doi.org/10.1186/s12974-022-02541-8).
- [42] Piao, H., Fu, L., Wang, Y., Liu, Y., Wang, Y., Meng, X., Yang, D., Xiao, X., & Zhang, J. (2022). A positive feedback loop between gastric cancer cells and tumor-associated macrophage induces malignancy progression. *Journal of Experimental & Clinical Cancer Research*, 41, article number 174. doi: [10.1186/s13046-022-02366-6](https://doi.org/10.1186/s13046-022-02366-6).
- [43] Pisano, S., Jimenez, Y.S., Rees, P., Xiao, J., Gonzalez, D., Conlan, R.S., & Corradetti, B. (2025). Insights into spheroid formation: Interaction of ovarian cancer cells with macrophage populations in the tumor microenvironment. *Journal of Translational Medicine*, 23, article number 1192. doi: [10.1186/s12967-025-07162-2](https://doi.org/10.1186/s12967-025-07162-2).
- [44] Pollock, T.Y., Vázquez Marrero, V.R., Brodsky, I.E., & Shin, S. (2023). TNF licenses macrophages to undergo rapid caspase-1, -11, and -8-mediated cell death that restricts *Legionella pneumophila* infection. *Plos Pathogens*, 19(6), article number e1010767. doi: [10.1371/journal.ppat.1010767](https://doi.org/10.1371/journal.ppat.1010767).
- [45] Ronaghan, N.J., Soo, M., Pena, U., Tellis, M., Duan, W., Tabatabaei-Zavareh, N., Kramer, P., Hou, J., & Moraes, T.J. (2022). M1-like, but not M0- or M2-like, macrophages, reduce RSV infection of primary bronchial epithelial cells in a media-dependent fashion. *Plos One*, 17(10), article number e0276013. doi: [10.1371/journal.pone.0276013](https://doi.org/10.1371/journal.pone.0276013).
- [46] Saha, S., Hazra, A., Ghatak, D., Singh, A.V., Roy, S., & Dasgupta, S.B. (2021). A bumpy ride of mycobacterial phagosome maturation: Roleplay of coronin1 through cofilin1 and cAMP. *Frontiers in Immunology*, 12, article number 687044. doi: [10.3389/fimmu.2021.687044](https://doi.org/10.3389/fimmu.2021.687044).
- [47] Shoeran, G., & Anand, N. (2025). Interplay of autophagy and Th1/Th2-mediated macrophage polarization in host-pathogen dynamics. *Frontiers in Cellular and Infection Microbiology*, 15, article number 1679514. doi: [10.3389/fcimb.2025.1679514](https://doi.org/10.3389/fcimb.2025.1679514).
- [48] Tran, N., & Mills, E.L. (2024). Redox regulation of macrophages. *Redox Biology*, 72, article number 103123. doi: [10.1016/j.redox.2024.103123](https://doi.org/10.1016/j.redox.2024.103123).
- [49] Wang, B., Wu, L., Chen, J., Dong, L., Chen, C., Wen, Z., Hu, J., Fleming, I., & Wang, D.W. (2021). Metabolism pathways of arachidonic acids: Mechanisms and potential therapeutic targets. *Signal Transduction and Targeted Therapy*, 6, article number 94. doi: [10.1038/s41392-020-00443-w](https://doi.org/10.1038/s41392-020-00443-w).
- [50] Wang, L., Wang, D., Zhang, T., Ma, Y., Tong, X., & Fan, H. (2023). The role of immunometabolism in macrophage polarization and its impact on acute lung injury/acute respiratory distress syndrome. *Frontiers in Immunology*, 14, article number 1117548. doi: [10.3389/fimmu.2023.1117548](https://doi.org/10.3389/fimmu.2023.1117548).
- [51] Wang, M., et al. (2021). Two populations of self-maintaining monocyte-independent macrophages exist in adult epididymis and testis. *Proceedings of the National Academy of Sciences of the United States of America*, 118(1), article number e2013686117. doi: [10.1073/pnas.2013686117](https://doi.org/10.1073/pnas.2013686117).
- [52] Wculek, S.K., Dunphy, G., Heras-Murillo, I., Mastrangelo, A., & Sancho, D. (2022). Metabolism of tissue macrophages in homeostasis and pathology. *Cellular & Molecular Immunology*, 19, 384-408. doi: [10.1038/s41423-021-00791-9](https://doi.org/10.1038/s41423-021-00791-9).
- [53] Wei, Y., Wang, M., Ma, Y., Que, Z., & Yao, D. (2021). Classical dichotomy of macrophages and alternative activation models proposed with technological progress. *BioMed Research International*, 2021, article number 9910596. doi: [10.1155/2021/9910596](https://doi.org/10.1155/2021/9910596).
- [54] Wilhelm, O., et al. (2025). Afucosylated broadly neutralizing antibodies targeting the HIV envelope elicit enhanced NK-cell-mediated cytotoxicity against HIV-infected CD4⁺ T-cell and macrophage targets. *Journal of Leukocyte Biology*, 117(5), article number qiaf033. doi: [10.1093/jleuko/qiaf033](https://doi.org/10.1093/jleuko/qiaf033).
- [55] Wong, A., Sun, Q., Latif, I.I., & Karwi, Q.G. (2025). Macrophage energy metabolism in cardiometabolic disease. *Molecular and Cellular Biochemistry*, 480, 1763-1783. doi: [10.1007/s11010-024-05099-6](https://doi.org/10.1007/s11010-024-05099-6).
- [56] Xie, L., et al. (2023). Activation of GPER1 in macrophages ameliorates UUO-induced renal fibrosis. *Cell Death & Disease*, 14, article number 818. doi: [10.1038/s41419-023-06338-2](https://doi.org/10.1038/s41419-023-06338-2).



- [57] Yan, L., Wang, J., Cai, X., Liou, Y.-C., Shen, H.-M., Hao, J., Huang, C., Luo, G., & He, W. (2024). Macrophage plasticity: Signaling pathways, tissue repair, and regeneration. *MedComm*, 5(8), article number e658. doi: [10.1002/mco2.658](https://doi.org/10.1002/mco2.658).
- [58] You, Z., Ye, X., Jiang, M., Gu, N., & Liang, C. (2023). Inc-MRGPRF-6:1 promotes ox-LDL-induced macrophage ferroptosis via suppressing GPX4. *Mediators of Inflammation*, article number 5513245. doi: [10.1155/2023/5513245](https://doi.org/10.1155/2023/5513245).
- [59] Yu, L., et al. (2026). Reinforced immunotherapy of M1 macrophage-derived exosomes with CEL on TNBC via regulating macrophage functions. *Journal of Advanced Research*, 82, 1163-1178. doi: [10.1016/j.jare.2025.07.024](https://doi.org/10.1016/j.jare.2025.07.024).
- [60] Zerrouk, N., Alcraft, R., Hall, B.A., Augé, F., & Niarakis, A. (2024). Large-scale computational modelling of the M1 and M2 synovial macrophages in rheumatoid arthritis. *NPJ Systems Biology and Applications*, 10, article number 10. doi: [10.1038/s41540-024-00337-5](https://doi.org/10.1038/s41540-024-00337-5).
- [61] Zhang, N., Ma, Q., You, Y., Xia, X., Xie, C., Huang, Y., Wang, Z., Ye, F., Yu, Z., & Xie, X. (2022). CXCR4-dependent macrophage-to-fibroblast signaling contributes to cardiac diastolic dysfunction in heart failure with preserved ejection fraction. *International Journal of Biological Sciences*, 18(3), 1271-1287. doi: [10.7150/ijbs.65802](https://doi.org/10.7150/ijbs.65802).

Теоретичні аспекти формування ключових елементів концепції дихотомії активації макрофагів: огляд літератури

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Анотація. Метою цього дослідження був аналіз теоретичних аспектів формування концепції дихотомії активації макрофагів (M1/M2), яка, незважаючи на складність регуляції імунної відповіді, відображає існування вискоєфективної багаторівневої системи контролю функціональних станів макрофагів і забезпечує належний перебіг запальних процесів. Порушення цієї системи пов'язане з розвитком патологічних станів, зокрема хронічного запалення та прогресії пухлин. Матеріали дослідження охопили сучасні публікації, що містять дані фундаментальних та експериментальних досліджень механізмів активації та поляризації макрофагів. Використані методи включали систематизацію, порівняльний аналіз і узагальнення сучасних наукових підходів з акцентом на молекулярні механізми та новітні технологічні досягнення. Класична модель поляризації макрофагів розрізняє прозапальні (M1) та протизапальні (M2) фенотипи; однак така класифікація дедалі частіше розглядається як спрощена і не повністю відображає гетерогенність макрофагів *in vivo*. Показано, що такі цитокіни, як інтерферон- γ (IFN- γ), інтерлейкін-4 (IL-4), інтерлейкін-10 (IL-10) та трансформувальний фактор росту- β (TGF- β), відіграють ключову роль у формуванні фенотипів макрофагів і регуляції їх участі в запаленні, відновленні тканин і процесах пухлинного мікрооточення. Крім того, макрофаги здатні одночасно проявляти ознаки різних програм активації, формуючи змішані або гібридні фенотипи. На основі аналізу сучасних даних зроблено висновок, що дихотомія M1/M2 має обмежену пояснювальну здатність і повинна бути замінена моделлю, яка розглядає активацію макрофагів як динамічний континуум, залежний від умов мікрооточення. Результати дослідження можуть бути корисними для науковців і клініцистів у галузях імунології та онкології з метою вдосконалення підходів до імуномодулювальної терапії та розроблення таргетних стратегій лікування.

Ключові слова: поляризація макрофагів; M1/M2; цитокіни; імунна регуляція; запалення; пластичність; пухлинне мікрооточення

