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REVIEW

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Heterogeneous macrophages: Supersensors of exogenous inducing factors

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Abstract

As heterogeneous immune cells, macrophages mount effective responses to various internal and external changes during disease progression. Macrophage polarization, rather than macrophage heterogenization, is often used to describe the functional differences between macrophages. While macrophage polarization partially contributes to heterogeneity, it does not completely explain the concept of macrophage heterogeneity. At the same time, there are abundant and sophisticated endogenous and exogenous substances that can affect macrophage heterogeneity. While the research on endogenous factors has been systematically reviewed, the findings on exogenous factors have not been well summarized. Hence, we reviewed the characteristics and inducing factors of heterogeneous macrophages to reveal their functional plasticity as well as their targeting manoeuvreability. In the process of constructing and analysing a network organized by disease-related cells and molecules, paying more attention to heterogeneous macrophages as mediators of this network may help to explore a novel entry point for early prevention of and intervention in disease.

Caiyun Qian and Zehui Yun contributed equally to this study and should be considered joint first author.

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1 | INTRODUCTION

Macrophages are white blood cells located in tissue whose main functions are phagocytosis of cell debris and pathogens and activation of lymphocytes or other immune cells. Thus, macrophages play an important role in the immune system. Macrophages are diverse in their sources and are widely distributed and functionally heterogeneous. They constitute a large, decentralized and self-balancing system with their dynamic changes throughout the life of the organism related to the pathophysiological processes of a variety of diseases.[1]

Macrophage heterogeneity refers to variations in the differentiation of macrophage morphologies, phenotypes, biochemical characteristics and functions under the influence of internal and external factors.[2] The most well-known research on macrophage heterogeneity is in the study of macrophage polarization. Macrophages can be heterogeneously stimulated by lipopolysaccharide (LPS) and interferon-gamma (IFN-γ) into classically activated macrophages (CAMs or M_1) or stimulated by interleukin-4 (IL-4) and interleukin-13 (IL-13) into alternative activated macrophage (AAMs or M_2).[3] In a variety of physiological and pathological conditions, the former cells show strong pro-inflammatory and antigen-presenting ability, while the latter cells show anti-inflammatory activity and promote damage repair.[4] The term macrophage polarization is often used instead of macrophage heterogeneity to describe functional differences between macrophages; however, M_1 and M_2 macrophages may represent the two most extreme manifestations of macrophage heterogeneity, but they do not represent the most common type of macrophage heterogeneity. There may also be a large number of functional intermediate transition states and alternative heterogeneous macrophage populations that differ from these two extreme cell types.[5] Macrophages are widely distributed in the body and are brought together by external factors and the internal environment, and they respond to environmental changes in a heterogeneous manner to affect physiological and pathological processes. Therefore, a systematic and comprehensive understanding of macrophage heterogeneity and the broad and diverse array of exogenous heterogeneity-inducing factors will provide theoretical guidance for the application of these features as targeted factors in the diagnosis and treatment of clinical diseases.

2 | MACROPHAGE HETEROGENEITY

Macrophages are a multidifferentiated derivative of blood cells. Historically, monocytes formed by differentiation of precursor cells in the bone marrow were considered to be the most important source of macrophages. However, today researchers have found that the majority of resident macrophages have an embryonic origin in most tissues.[6] During embryonic organogenesis, macrophages derived from yolk sac and foetal liver precursors are seeded throughout tissues, persisting in the adulthood as resident and self-maintaining populations. After birth, bone marrow–derived monocytes can replenish tissue-resident macrophages following injury, infection and inflammation.[7] Macrophages are widely distributed in various tissues and organs in the human body, and the macrophages found in different tissues and organs have different names, for example peritoneal macrophages, alveolar macrophages, tissue cells in connective tissue, Langerhans cells in the skin, osteoclasts in the bone, liver Kupffer cells, microglia in the nervous system and fat tissue macrophages, among others.[8] Macrophages exhibit robust heterogeneity in their biological properties and functions due to differences in their origin and distribution and changes in their resident microenvironment. The various processes leading to the heterogeneity influenced by spatial and temporal differences in the microenvironment exhibit plasticity that depends on a variety of different stimuli. This plasticity leads to the possibility of manual intervention.

The functional heterogeneity of macrophages and their different subtypes in different body parts have been studied in the most depth. Different subpopulations of macrophages perform their duties and have different phenotypes and functions.[9] Noelia A-Gonzalez et al found in an engineered mouse model that there are significant differences in the expression levels of phagocytosis-related genes in macrophages from different tissues. For example, LXRα expression is particularly high in the bone marrow, liver and spleen macrophages, and annexin A1, Bcl-2 and PPARγ are mostly expressed in alveolar macrophages; furthermore, Timd4 is predominantly expressed in the liver. The phagocytic activity, phagocytosis frequency and rate of the macrophages are also different in different tissue types.[10] With the increasing availability of tools for classifying cells based on cell size, density, phenotype and molecular sequencing, the division of macrophage subpopulations within the same tissue is becoming more and more refined. This division provides a clearer understanding of the macrophage subpopulations. Cochain et al extracted $CD45^+$ white blood cells from the aortas of mice modelling schizophrenia (regular feeding) and atherosclerosis (11-week high-fat diet), and it was found that macrophages represent the largest cell population in the aortic atherosclerotic lesions, accounting for 28.9% of the total $CD45^+$ cells. The macrophage population can be further divided into three subgroups: inflammatory, Res-like and $TREM2^{hi}$ cells, each having distinct gene expression profiles and different gene enrichments. Inflammatory macrophages overexpress atherosclerosis genes, including CCL3, IL-1β, IL-1α, NLRP3, CEBPB, EGR1 and PHLDA1, as well as several macrophage activation inhibitors: NFKBIZ, NFKBID and IER3. Res-like macrophages express the F13A1, LYVE1, CCL9, CCL24

genes (similar to the resident aortic macrophages) and genes related to M_2-type macrophages, such as FOLR2, CBR2 and MRC13. Trem2^{hi} macrophages exhibit specific gene expression profiles, which include genes encoding osteogenic proteins (CD9, SPP1, HVCN1) and several cathepsins (CTSD, CTSB, CTSC). The authors also identified a potential functional heterogeneity among these three macrophage subpopulations based on GO (Gene Ontology) analysis and the related phenotypes and various effects during the different stages of atherosclerosis. M_1-type macrophages may play a pro-inflammatory role, and Res-like macrophages produce a sclerosis-like effect similar to that of M_2-type macrophages, which together mediate the development of atherosclerosis. Trem2^{hi} macrophages have been found to carry out specific functions not found in the other two macrophage subpopulations, such as organic matter and cellular catabolism, lipid metabolism, and cholesterol efflux and oxidative stress regulation (breathing outbreak and oxidative stress).[11]

3 | RELATIONSHIPS BETWEEN MACROPHAGE HETEROGENEITY AND DISEASE

Macrophages not only participate in various physiological processes, such as immune regulation, wound healing and tissue homeostasis but also play indispensable roles in developmental processes and the progression of a variety of diseases (Table 1), including infectious diseases, metabolic diseases, autoimmune diseases, atherosclerosis and tumours.

Jobe et al found that monocyte-derived macrophages (MDMs) can be divided into two distinct subsets when studied in relation to HIV-1 infection: CD14$^+$/Siglec-1^{hi}/CD4$^+$ non-adherent MDMs and CD14$^+$/Siglec-1^{lo}/CD4$^-$ adherent MDMs. There are significant differences in the proportions of the two cell types in different patient specimens, and the two macrophage subsets exhibit different gene expression profiles and have significant differences in their responses to HIV-1 infection.[48] Studies by Li et al have found that macrophages from different sources have different polarization phenotypes and that resident macrophages have a significant role in regulating nutrient homeostasis depending on alternations in their activation state. Thus, promoting the polarization of macrophages to alternative activation states may be a strategy for the treatment of type 2 diabetes.[49] Giles et al[50] found that in multiple sclerosis (MS) and engineered autoimmune encephalomyelitis (EAE) animal models, molecular phenotypic changes occur in the main infiltrating myeloid cells and microglia in the central nervous system (CNS), including differences in the expression levels of pro-inflammatory markers (iNOS) and noninflammatory markers (CD206 and Arg1), during the progression from the EAE activity period to the remission period. Based on these observations, the research team believes that accelerating the transformation of CNS myeloid cells from a pro-inflammatory phenotype to a noninflammatory phenotype could be a central strategy for improving the disease status of MS patients in future. Rogier et al immunostained 110 renal aortic plaques and systematically analysed their specific macrophage subtypes and their activation markers and found heterogeneous macrophage subgroups in the early atherosclerotic plaques. Among this cell population, the cells were divided into several subpopulations with varying abundance: CD68$^+$/iNOS$^+$/CD163$^-$ cells (25%), CD68$^+$/iNOS$^-$/CD163$^+$ cells (13%) and three positive CD68$^+$/iNOS$^+$/CD163$^+$ cell subpopulations (17%), with the remainder consisting of a population of CD68$^+$ cells. As the plaques changed during disease progression, the proportions of each subpopulation also changed accordingly. Therefore, the research team believes that the macrophage heterogeneity far exceeds people's expectations and that the close relationship between macrophage heterogeneity and atherosclerosis is clearer than was previously thought.[20] Hung et al designed a prospective experiment to compare the percentages of circulating macrophages in breast cancer patients and healthy individuals by flow cytometry and found that (a) the percentage of circulating macrophages was significantly higher in the breast cancer patients than in the healthy controls; (b) the percentage of M_1 macrophages (CCR7$^+$/CD86$^+$) was significantly lower in the breast cancer patients than in the healthy controls, while the percentage of M_2 macrophages (CCR7$^-$/CXCR1$^+$, CCR7$^-$/CD86$^+$ and CCR7$^-$/CCR2$^+$) was significantly higher in the breast cancer patients than in the healthy controls; and (c) the percentage of M_{2c}-like macrophages (CCR7$^-$/CCR2$^+$) was significantly higher in advanced (stage II and III) breast cancer cases. These findings indicate that macrophages are highly heterogeneous in breast cancer and are associated with its progression, suggesting that they may provide new molecular markers and potential targets for the diagnosis and treatment of breast cancer.[51] Actually, there are plenty of examples about interfering with diseases by affecting the heterogeneity of macrophages such as the use of specific reagents to repolarize macrophages and the use of adoptively transferred pre-activated cells for effective experimental disease regulation. Cappetta et al[52] provide evidence of renoprotection by DPP4 inhibition in a nondiabetic hypertension–induced model of chronic cardiorenal syndrome. In this case, kidney macrophages expressed GLP-1R, and DPP4 inhibition promoted macrophage polarization towards the anti-inflammatory M2 phenotype. During Wang Chao's study of CVB3-induced viral myocarditis, mice with adoptive transfer of M2 macrophages exhibited less cardiac inflammation and attenuated myocarditis, suggesting the protective role of M2 macrophage in viral myocarditis.[53] In short, macrophage heterogeneity is closely related to diseases, not only participates in the development of various diseases, but also is an important part for disease treatment strategies.

TABLE 1 Diseases related to heterogeneous macrophage. The table shows diseases in different systems have a close relationship with heterogeneous macrophages. The macrophages involved in each reference and the heterogeneous types of macrophages are marked behind the disease

System name	Disease name	Relevant cells	Related phenotype	References
Motor system	Cervical compressive myelopathy	Mice microglia	Arg-1, CD206, iNOS, CD16/32	12
	Myasthenia gravis	Human serum samples	IL-15, VEGF, IL-4	13
	Rheumatoid arthritis	Human THP-1 cells	IL-10, CXCL10	14
	Osteoporosis	Mice osteoblasts and bone marrow cells	IL-6, IL-11, LIF	15
Nervous system	Epileptogenesis	Mice microglia	Arg-1, CD163	16
	Meningoencephalitis, Myelitis	Mice microglia	CD11b, CD74, CD52, CD68, IFN-γ, IL-12, MKC	17
	Alzheimer's disease	Rat microglia	NO, ROS, TNF-α	18
	Brain ischaemia	Mice microglia	Arg-1, IL-1β	19
Circulatory system	Atherosclerosis	Human perirenal aortic plaques macrophages	CD68, iNOS, CD163	20
	Heart failure	Mice myocardium macrophages	IL-1β, Ym-1, VEGF, TNF-α, TGFβ1, Mrc-1	21
	Hypertension	Mice circulating macrophages	IL1β, IL-6, IL-18	22
	Cardiomyopathy	Mice circulating macrophages	IL-1, IL-6, TNF-α	23
Haematologic system	Immune thrombocytopenia (ITP)	Human spleens macrophages	CD68, iNOS, IL-12 p70, TNF-α	24
	Haemolytic diseases	Raw264.7 cells and mice bone marrow–derived macrophage	MHC-II, TNF-α, CD86, CD14, IL-6, IL-1β, CD206, IL-10, Arg-1	25
	Myelodysplastic syndrome (MDS)	Human peripheral blood macrophage	CD206, SIRP, iNOS	26
	Haemophilia	Mice macrophages in blood, spleen, synovium, and knee lavage	MHCI, MHC-II, CD86, CD163	27
Respiratory system	Viral pneumonia	Human peripheral blood monocyte-derived macrophages	CCL2, CXCL10, IL-8, CCL17, CXCR1, IL-10, CD163, Arg-1	28
	Chronic obstructive pulmonary disease (COPD)	Mice alveolar macrophage	Mmp9, Mmp12, Mmp28, CXCL1	29
	Tuberculosis	Human peripheral blood monocyte-derived macrophages	IL-6, IL-12, TNF-α, IL-10, CXCL10, CXCL1	30
	Asthma	Human peripheral blood monocyte-derived macrophages	IL-4	31
Digestive system	cholestasis	Mice hepatic macrophages	IL-1β, TNF-α, IL-6	32
	Liver cirrhosis	RAW264.7 murine macrophages	TGFβ1, iNOS, IL-1β, Arg-1, Mrc1, Ym-1	33
	Crohn's disease (CD) and Intestinal tuberculosis (ITB)	Human Colonic mucosal macrophages	iNOS, CD68	34
	Gastritis	Murine bone marrow–derived macrophages	CCL2, CCL3, CCL4, CCL5, CXCL1, CXCL2, CXCL10, IL-17, TNF-α	35

(Continues)

TABLE 1 (Continued)

System name	Disease name	Relevant cells	Related phenotype	References
Urinary system	Glomerulonephritis	Rats bone marrow-derived macrophages	IL-6, iNOS, TNF-α, IL-1β, IL-10	36
	Nephrotic syndrome	Rats renal macrophage	TNF-α	37
	Tubulointerstitial kidney diseases	Mice bone marrow–derived macrophage	IL-10, CCL5	38
	Acute kidney injury	Mice renal macrophage	Mannose receptor, Arg-1	39
Reproductive system	Prostatitis	Raw 264.7 macrophages	Ym-1, CD206	40
	Trichomonas vaginitis	Human monocyte–derived macrophages	IL-1, IL-6, TNF- α, NO	41
	Pelvic inflammatory disease	Human monocyte–derived macrophages	IL-6, TNF-α, GRP-α, MIP-1α, RANTES	42
	Testicular inflammation	Rats testicular macrophages	MHC-II, CD80, CD86	43
Endocrine system	Diabetes Mellitus	Human peripheral blood monocyte–derived cells	CD16, IL-6, iNOS, TNF-α, CD36	44
	Gaucher disease	Human peripheral blood monocyte–derived cells	IL-10, IL-6, IL-18, IL-12α, IL-12β	45
	Thyroid dysfunction	Rats monocyte–derived macrophages	ROS, MIP-1α, IL-1β	46
	Gout	Human THP-1 cells	CXCL10, CXCL2, CXCL4	47

4 | EXOGENOUS INDUCERS OF MACROPHAGE HETEROGENEITY

Macrophages adapt to internal and external changes in the body via induction of heterogeneity to promote homeostasis. There have been many studies on endogenous factors that stimulate macrophage heterogeneity. However, the effects of exogenous factors on macrophage heterogeneity have not been well organized or summarized. To this end, this review summarizes the exogenous factors (Figure 1) that induce macrophage heterogeneity to increase their notoriety within the research community and to provide a basis for the use of exogenous factors to regulate macrophage heterogeneity and their functional phenotypes in disease treatment.

4.1 | Physical factors

Physical influencing factors include noise, radiation, oxygen pressure and electrical stimulation. Most of these factors are derived from the external physical environment, and some of them are also widely used as physical interventions in the treatment of human diseases. As "all-arounders" with multiple functions, macrophages naturally become one of the main performers during the responses of the body to these physical factors.

4.1.1 | Noise

With the modern development and scientific progress, noise has an increasing influence in human life and health. Research has demonstrated that mice exposed to noise pressure had lower TNF-α and IL-1α production by peritoneal and alveolar macrophages, which reduced the capacity of the animals to clear pathogens and limited wound healing in these tissues.[54] However, not every macrophage-dependent inflammatory response can be reduced by noise. As the first cells to experience noise, cochlea basement macrophages can differentiate into a MCH-II^{hi} subtype to promote a local inflammatory reaction during noise stimulation, and this process can cause cochlea injury and delay recovery.[55]

4.1.2 | Radiation

In a study of melanoma in young rats, it was found that Ly6^{low}/MHCII^{hi} macrophages were found in the skin following exposure to ultraviolet light after macrophage infiltration. Such cells can be abundantly present in the skin of young rats exposed to ultraviolet light where they can induce and accelerate the formation of melanoma.[56] Radiotherapy has been widely used in the treatment of diseases, but different doses of radiotherapy have different therapeutic effects. Clinical studies have shown that localized low-dose gamma-ray irradiation can induce an iNOS^{+}macrophage population in pancreatic cancer microenvironments that can mediate an antitumour immune response to eliminate tumour cells.[57] The effect of high-dose radiation is the opposite. Oh et al[58] also found in a study that localized high-dose radiotherapy for colon cancer–induced macrophages to express MMP9, inhibit tumour immunity and to indirectly promote tumour pulmonary metastasis.

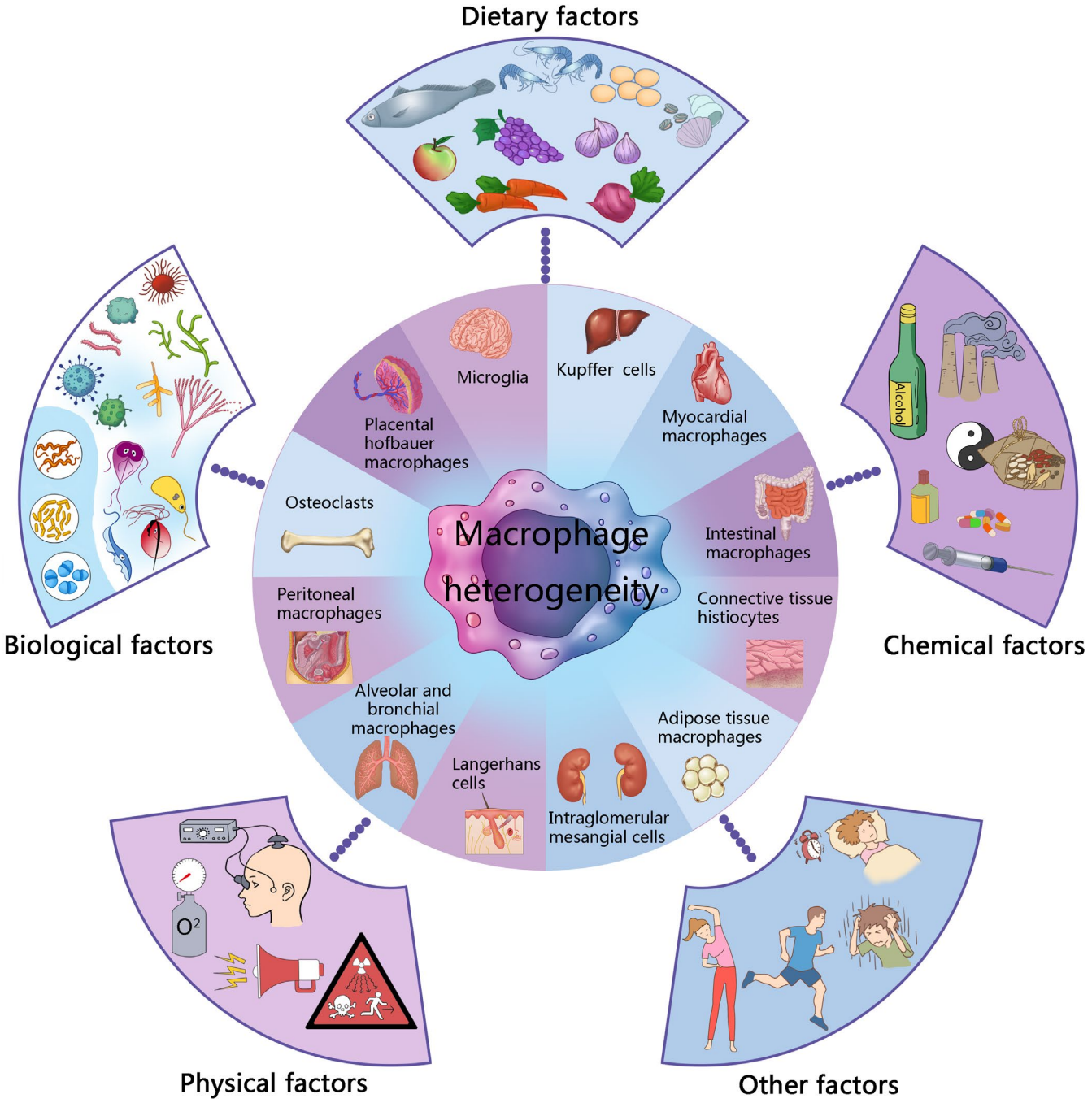

FIGURE 1 Exogenous inducers affecting macrophage heterogeneity. This figure shows a variety of exogenous factors affecting macrophage heterogeneity, including physical factors, chemical fators, food-borne factors, biological factors, and other factors. The special name of macrophages in different tissues and organs also has been shown

4.1.3 | Oxygen pressure

A large number of experimental studies have shown that changing the oxygen pressure in the body can greatly affect macrophage function.[59] Hyperbaric oxygen therapy (HBOT), which is widely used, is the most representative example. Studies from Geng[60] and others using a rabbit spinal cord injury model found that HBOT can reduce the blood concentrations of TNF-α and IFN-γ, increase the concentrations of IL-4 and IL-13 and significantly reduce the numbers of $iNOS^+$ and $CD16/32^+$ macrophages, while increasing the numbers of Arg^+ and $CD206^+$ macrophages; these effects promoted axonal growth and myelin retention. When mice were quickly moved from a high-oxygen pressure environment to a hypoxic environment, the rapid decompression of the lung tissue caused a rapid increase in the blood TNF-α concentration. The number of $CD16/32^+$ macrophages increased significantly and the number of $CD206^+$ macrophages

decreased. Thus, macrophages play an important role in the process of decompression sickness and lung injury.[61]

4.1.4 | Electrical stimulation

A number of experimental studies have shown that macrophages stimulated by moderate currents can induce benign effects on tissue repair and cell regeneration.[62] An experimental study on muscle atrophy induced by chronic kidney disease (CKD), in which mouse muscles were stimulated by low-frequency current (LFES), revealed that macrophages begin to express IL-1β during the acute reaction, thus promoting the release of pro-inflammatory factors such as IFN-γ and IL-6. However, after 2 days of LFES stimulation, the expression of arginase-1 (Arg-1) was significantly increased, accompanied by an increase in the IGF-1 content in the tissue. These results showed that LFES can upregulate the insulin-like growth factor (IGF-1) signalling pathway to alleviate the skeletal muscle atrophy induced by CKD via activation of M_2 macrophages, thereby improving muscle protein metabolism and promoting muscle production.[63]

4.2 | Chemical factors

People often encounter chemical factors in their work and living environments. Whether they come from drug-derived substances in chemotherapy, daily alcohol intake or smoke in the surrounding environment, chemical factors can act on macrophages and modifying their physiological functions, thereby altering the body's immunity.

4.2.1 | Dust

Small particles, including those comprising dust and smoke, can be present in the air in large quantities. Some particles, such as PM2.5, are small in diameter and are not easily visible to the naked eye. Some dust particles are large and can, at high concentrations, form smoke, such as cement dust during construction work. Both large and small particles can be inhaled into the lungs and have negative impacts on the body. It was found that the alveolar macrophages in mice that inhaled PM2.5 changed significantly and that a large number of macrophages with high IL-1 and CCL2 expression accumulated in the alveoli where they led to obvious inflammation.[64] Particles with large diameters, such as silicon dust and lime dust, are important causes of occupational injuries. In studies of workers who were forced to inhale silicon and lime dust for a long time, it was shown that both of these types of dust can induce macrophages to shift to a state in which they highly express IL-1β, TNF-α and IL-6. Moreover, this transformation is not limited to alveolar macrophages but also occurs in the peripheral macrophages. Therefore, the harm caused by these particles is not limited to the lungs, as it can also cause damage to the cardiovascular system by inducing inflammation.[65] In addition, the relationship between macrophage heterogeneity and gold particles is worthy of attention. In the research of Taratummarat et al[66], gold nanoparticles alter cytokine production of bone marrow–derived macrophages including reduced TNF-α, IL-6 and IL-1β and induce macrophage polarization towards anti-inflammatory responses as presented by increasing Arg1 and PPARγ with decreasing Nos2 in vitro.

4.2.2 | Alcohol

The effects of alcohol on macrophages are induced by a two-way regulation depending on different modes of ingestion. Alcohol intake stimulates pancreatic cells to secrete chemokines to attract circulating monocyte-derived macrophages into the pancreatic tissue, where they differentiate into cells expressing IL-1β and CCL3; therefore, under the stimulation of alcohol, infiltration of inflammatory cells and secretion of inflammatory mediators are induced, thus promoting the development of pancreatitis and the formation of fibrosis.[67] Mouse macrophages that rapidly ingest alcohol over a short time period exhibit endotoxin tolerance. Even in the case of bacterial infection, the expression levels of TNF-α and IL-6 in macrophages are still decreased, and the body mounts either no immune response or a weak immune response to the bacterial invasion.[68] During the wound healing process, the effects of alcohol-induced macrophage differentiation into the M_2 subtype are particularly obvious. Bacterial clearance in wounds is inhibited, and the healing process in the damaged tissue becomes very slow, greatly increasing the risk of infection.[69]

4.2.3 | Drug-derived substance

Drugs are generally divided into Western medicine and traditional Chinese medicine. There are many kinds of Western medications relevant to the study of macrophage heterogeneity, including antitumour drugs, antibiotics and hypoglycaemic agents. In recent years, with the ongoing development of purification technologies in traditional Chinese medicine, research reports on the effects of certain components of Chinese herbal medications on macrophage heterogeneity are not uncommon.

A variety of Western medications affect macrophage heterogeneity via direct or indirect mechanisms. For example, gemcitabine can promote the upregulation of macrophage Arg-1 and TGF-β1 indirectly through PC cells, thereby promoting the growth, migration and invasion of RAW264.7 macrophages.[70] Doxycycline promotes Cox-2, CXCL9 and iNOS expression in macrophages and downregulates the expression levels of Arg-1, Fizz-1, CCL17 and MRC1, thereby inhibiting angiogenesis. This phenomenon can be applied as

an effective treatment strategy for neovascular macular degeneration and even in the treatment of certain cancer types.[71] In an animal model of ischaemic brain injury, metformin can downregulate CD32 and IL-1β expression and upregulate CD206 and Arg-1 expression, thus stimulating the formation of blood vessels in the endothelial cells of the brain via AMPK-dependent mechanisms. These observations suggest that metformin can improve brain ischaemia by regulating macrophage heterogeneity after stroke.[72]

Currently, the research and development of most Chinese herbal extracts mainly focus on two aspects: inflammation and tumours. Most of the extracts used for inhibiting inflammation in traditional Chinese medications have "clearing and detoxifying" effects. Aloe vera extract can downregulate TNF-α, IL-1β and IL-6 expression in macrophages in a mouse model of lipopolysaccharide (LPS)-induced acute lung injury (ALI), thus potentially protecting LPS-induced ALI.[73] Other extracts used in traditional Chinese medicine, such as curcumin,[74] emodin,[75] berberine [76] and grass coumarone,[77] have similar effects. Most of the traditional Chinese medications that inhibit tumours have "promoting blood stasis, reducing swelling and dispersing" effects. For example, paclitaxel derived from yew bark enters the microenvironment of breast cancer via transport by nanocarriers, where it causes $CD204^+$ macrophages, which is the dominant cell type, to transition into $CD80^+$-expressing macrophages, thereby exerting its antitumour effect.[78] Other ingredients in traditional Chinese medication, including scorpion polysaccharide, gambogic acid,[79] triptolide[80] and crocin,[81] have a similar effect. It is worth mentioning that both triptolide[82] and crocin[83] have anti-inflammatory and antitumour effects.

4.3 | Food-borne factors

In light of the particularity of food-borne substances, they are described as an independent factor. Common diets generally consist of animal-derived foods and plant-derived foods, depending on their sources. Many components of the diet can affect human immunity by altering the phenotype of macrophages.

Examples of animal-derived foods include egg mucin, astaxanthin and fish oil. Experimental studies have found that egg mucin extracted from egg white can stimulate macrophages to upregulate CCR7 and inhibit CD206 expression, thereby promoting tissue repair.[84] Astaxanthin is abundant in most crustaceans and carps. Assays have shown that astaxanthin can downregulate CD11C, iNOS, MCP1 and CCR2 expression and upregulate CD163, CD206, IL10, CHI3L3 and MGL1 expression, thereby improving insulin resistance and reducing liver inflammation in adipose tissue.[85] Fish oil is now used as a healthcare product and has been embraced by consumers. Studies have shown that fish oil can induce upregulation of CD86 macrophages and increase the TNF-α, IFN-γ, IL-2 and IL-1β expression levels, thereby reducing inflammation and insulin resistance caused by obesity.[86]

Examples of botanical foods include carotene, onion and vegetable oil. Carotene is present in a variety of vegetables and regulates the immune function of macrophages by upregulating IL-1β, IL-6 and IL-12 p40 expression.[87] Onion A extracted from onions inhibits the expression of CD163 by macrophages in tumour microenvironments, thereby inhibiting tumour growth.[88] Experimental studies have demonstrated that vegetable oil can promote the transformation of macrophages into the IL-1β and TNF-α subtypes, enabling them to exert positive immune killing function.[89] Other food components, such as mung bean seed coat extract,[90] β-cryptoxanthin,[91] Pyropia yezoensis glycoprotein[92] and quercetin,[93] which are abundant in apple, grape and onion, can regulate macrophage heterogeneity to alter immune function in the body.

4.4 | Biological factors

Viruses, bacteria and parasites survive and multiply within the human body, secrete toxic factors and evoke the body's immune response. When they invade the human body, microbes regulate the host immune system in unique ways. As macrophages perform important immune functions, they can be a target of such regulation. Some more representative articles are selected for a brief summary. This is an area that still needs to be explored and has great potential.

4.4.1 | Bacteria

Experiments show that the β-(1,3)-glucan produced by archaea can stimulate macrophages to upregulate the expression of antigen-presenting molecules, such as CD80, CD86, MHC-I and MHC-II, and promote microbial clearance in vivo by stimulating the release of cytokines, such as TNF-α, IL-6 and IL-1β, from macrophages.[94] Most bacterial invasions lead to enhanced immune function in macrophages, including invasions by *Mycobacterium tuberculosis*,[95] *Salmonella typhi*[96] and *Escherichia*.[97] There are also certain organisms that can escape immune recognition and clearance through special mechanisms. For example, *Shigella* can evade immune detection by changing its LPS composition and downregulating the expression and secretion of IL-1β by macrophages.[98]

4.4.2 | Virus

Hepatitis C virus (HCV) is a well-known virus. Experimental studies have found that HCV can downregulate IL-12 expression and upregulate CD206 and CD163 expression to significantly reduce the immune response in the tissue to provide a suitable growth environment for itself.[99] The virus

is highly invasive, and most of the experimentally studied viruses can inhibit the immune response and even promote the occurrence of cancer via the heterogeneous properties of macrophages. Examples of such viruses include Kaposi's sarcoma-associated herpesvirus (KSHV)[100] and swine influenza virus (SIV).[101] There are also some viruses that significantly enhance the immune function of macrophages, for example Theiler's murine encephalomyelitis virus (TMEV). A study of Terrell mouse myelitis caused by TMEV showed that TMEV can increase the numbers of $CD16^+$ and $CD32^+$ macrophages in the tissue, which further promotes the inflammatory reaction in the tissue and the demyelination of neurons.[102]

4.4.3 | Parasites

Parasites have always been an important culprit in polluting the living environment and endangering human health. The body's immune response to most parasites consists of immune recognition and clearance. For example, when mouse peritoneal macrophages are invaded by *Leishmania*, peritoneal macrophages can be rapidly converted to cells with high TNF-α and IL-6 expression to augment tissue inflammation and rapidly eliminate the pathogens.[103] A similar situation arises with other parasites, including *Plasmodium*[104] and *Echinococcus multilocularis*.[105] A considerable number of parasites can also suppress the macrophage-mediated immune response, with *Toxoplasma gondii* representing a typical example. After phosphatidylserine-expressing *Toxoplasma gondii* invade the body, the resulting secretion of TGF-β1 by mouse peritoneal macrophages significantly reduces NO synthesis, significantly weakening the ability of the tissues to clear the parasites.[106] Interestingly, resistance to Leishmaniasis depends on mouse strain. C57BL/6 (B6) mice are resistant to this parasite and can control infection, whereas Leishmania parasites thrive in BALB/c mice. AS the macrophges from B6 mice are more mature, they can produce more inducible NO synthase (iNOS) and NO in response to *Leishmania braziliensis* parasites. Meanwhile, BALB/c mice developed macrophages express an incomplete M1 phenotype.[107]

4.4.4 | Fungi

Much of the current research on the heterogeneity of fungi and macrophages has focused on *Candida albicans* and *Cryptococcus*. Various in vitro and in vivo experimental studies have shown that, in most cases, *C albicans* and *Cryptococcus* can reduce the production of immune responses through various mechanisms, thereby promoting self-survival and proliferation. Jeanette Wagener demonstrated that *C. albicans* can regulate arginine metabolism to increase Arg-1 expression via cellular exposure to cell wall chitin exposure, thus inducing arginine activation and reducing nitric oxide production to enhance immune evasion.[108] Alison J. Eastman explored the effects of fungi on macrophage heterogeneity by constructing a mouse model of *Cryptococcus* infection. Compared with the uninfected group, the infected group showed a significant upregulation of the expression levels of Arg-1 and CD206 in the infected lesion, which could interfere with the host's defensive immune response.[109]

4.5 | Other factors

In addition to the above factors, there are some additional factors that can affect macrophage heterogeneity that are closely connected to people's work and life that are also worthy of attention. For example, an experimental study by Shogo Sato showed that the sleep-related circadian clock Rev-ErbA can disrupt cell adhesion and migration during inflammation by directly inhibiting Ccl2 expression and blocking CCL2 activation signals (ERK and p38), thereby regulating the inflammatory function of macrophages.[110] In a mouse model of aerobic exercise training (AET) constructed by Pinto PR, it was observed that the expression levels of MCP-1, PPARγ, LOX-1, TNF and IL-10 were significantly downregulated in aortic macrophages from mice with AET, while ABCA-1, SR-BI and IL-6 were all upregulated. These data suggest that exercise training can reduce the uptake of low-density lipoprotein (LDL) by arterial wall macrophages by altering the phenotypes of the macrophages.[111]

Recently, the effects of stress on human immune function have drawn some attention. Yi WJ et al found in a mouse stress model that during stress, the serum levels of IL-1β and IL-6 increased significantly, and the level of IL-10 decreased significantly. At the same time, the NOS2a and CD40 expression levels were significantly increased in Kupffer cells and peritoneal macrophages, and the Arg-1 expression level was significantly decreased.[112] Paik IH recruited 42 college students and drew blood samples on the same day they took a stress test and after 4 weeks. The results showed that under mental stress, the levels of IL-1β, IL-6 and IL-10 in the blood increased significantly, while the IFN-γ level decreased significantly. This finding suggests that stress can likely enhance Th2 cell–mediated humoral immunity and macrophage activity and attenuate Th1 cell–mediated cellular immunity. It was concluded that the inflammatory response to stressful conditions can seriously affect people's physical and mental health.[113]

5 | DISCUSSION

In summary, macrophages are widely distributed and can produce integrated adaptive responses to various internal and external factors, immunoregulate the microenvironments of various tissues and organs through heterogeneous methods and participate in various pathophysiological processes.

Towards the goal of developing a comprehensive and in-depth understanding of the heterogeneous characteristics of macrophages and their exogenous inducing factors, two key areas of necessary research are clear: on the one hand, researchers should pay more attention to the study of heterogeneous macrophages in the construction and analysis of disease-associated cell and molecular cross-linking networks; on the other hand, the plasticity of macrophage heterogeneity and the operability of the pathological processes that target its regulation could provide an entry point for clinical advancements in disease prevention and treatment. There are clearly still some issues worthy of discussion in the field of macrophage heterogeneity research.

5.1 | Classification and identification of heterogeneous macrophage communities and analysis of subpopulation distribution ratios

Identification of heterogeneous macrophages often relies on the detection of their molecular markers. However, the existing markers for assessing macrophage heterogeneity are lacking. On the one hand, there are no specific criteria for molecular markers to type different heterogeneous macrophage communities and for their rigorous detection and qualitative methods, which results in differences between research groups in how respective molecular markers are used to characterize heterogeneous macrophage colonies. The experimental conclusions are more difficult for others to cross-verify. Therefore, the application of a unified set of molecular markers for heterogeneous macrophages is imperative. On the other hand, due to the presence of different heterogeneous macrophage colonies within a lesion, the study of a single macrophage community often fails to fully reflect the dynamic changes in the complete macrophage community in the microenvironment. To overcome this challenge in the study of macrophage heterogeneity, should the focus be transferred from studying a single subpopulation of macrophages to analysing the distribution ratios of macrophages in different subpopulations?

5.2 | Research on endogenous cellular metabolites that induce macrophage heterogeneity

It is well known that a variety of endogenous intercellular signalling molecules in the tissue microenvironment, such as colony-stimulating factors, chemokines and cytokines, can affect macrophage heterogeneity.[114] It is worth mentioning that some in vivo cellular metabolites can also affect macrophage heterogeneity. Carmona-Fontaine et al[115] discovered through the construction of a tumour experimental model that hypoxia and lactic acid in the tumour microenvironment can induce tumour-associated macrophages (TAM) to differentiate into cell subsets expressing arginase 1 (ARG1) and the mannose receptor (MRC1) via the MAPK signalling pathway. Phenotypic and functional changes in these macrophage subpopulations trigger the formation of tube-like structures by the adjacent endothelial cells, helping to restore blood perfusion in the ischaemic area. Therefore, in addition to traditional cytokines, is it possible to target various metabolites in the microenvironment that induce macrophage heterogeneity as a strategy for clinical intervention?

5.3 | Research on how heterogeneous macrophages mediate the regulation of immune function by human symbiotic colonies

The body's surface, intestines, respiratory tract, genitourinary tract and other parts that are in close contact with the external environment contain massive bacterial communities. It can be demonstrated that the "organ" formed by the commensal flora not only continuously produces and supplies nutrients such as vitamins, trace elements and essential amino acids to the body but also affects the body's immune function by regulating its heterogeneity via its metabolites that act on local or circulating macrophages. According to Yun-Gi Kim et al, antibiotic (Abx) treatment can cause excessive growth of various species of the Candida symbiotic fungus. Subsequently, the expression of Arg1, Chi3l3 and Retnla by macrophages in the distal lung is significantly upregulated via increased concentrations of related factors in the blood. These effects lead to allergic airway inflammation.[116] Is it possible that studies on macrophage heterogeneity in local microenvironments, which are reminiscent of symbiotic colonies, more clearly reveal the pathogenesis and physiology of human symbiotic colonies?

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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