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Research on the Effect of Exosomes on the Polarization of Macrophages

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Abstract: *Exosomes, as key tools of cellular communication, are involved in both physiological processes and pathological development of the organism.Macrophages are an important component of the body's intrinsic immunity and play an important role in the regulation of inflammation, maintenance of intra-tissue stability, and promotion of tissue repair and regeneration.Under the regulation of exosomal signaling, macrophages can polarize into M1-type pro-inflammatory and anti-tumor subtypes and M2-type anti-inflammatory and pro-tumor subtypes, which play a double-edged role in the development and progression of disease.This paper discusses the ways and pathways of exosomal micro-molecular long-stranded non-coding RNAs and miRNAs of different cellular origins affecting macrophage polarization and phenotype in three areas: tumor, neurological diseases, and cardiovascular diseases, aiming to provide new ideas and methods for research in this field.*

Keywords: *Exosome, Tumor-associated Macrophages, Polarization*

1. Introduction

Exosomes were first discovered in 1983 by Johnstone and his colleagues while culturing reticulocytes and were named "exosome" in 1987 [1]. Initially, scholars thought that exosomes were just a common carrier used to detoxify intracellular waste products [2]. As the research progressed, it was found that exosomes of different cell sources could selectively carry bioactive substances similar to parental cells, such as lipids, proteins, nucleic acids (mRNA, microRNA, long-stranded non-coding RNA) [3-5], and play different roles, which has become a hot topic of research in recent years. As a kind of bilayer phospholipid extracellular vesicles, exosomes shuttle between different cells and tissues of the organism, participate in cell signaling and exchange of substances, and play a key role in inflammatory response, tissue regeneration, organ development, and immune regulation of the organism [6-8], while the development of tumors is also closely related to them.

Macrophages are a class of natural immunomodulatory cells with highly heterogeneous phenotype and function in the organism, and as the first barrier of the organism, they play an important function in normal physiological processes and pathological processes of the organism. Macrophages can be classified into classically activated M1 type and alternatively activated M2 type according to their different activation states and functions [9], and M2 type can be further classified into M2a, M2b, and M2c types depending on the inducing factors. It was found that M1-type macrophages have the ability to kill bacteria, resist tumors, and secrete a variety of pro-inflammatory cytokines, while M2-type macrophages have anti-inflammatory, infection clearance, and tissue repair functions. The current research on macrophage-related studies mainly focuses on the conversion of M1 and M2 macrophage phenotypes. When the microenvironment of the body is changed or regulated by different cytokines and stimulated by different factors, macrophages will switch from one cell phenotype to another and thus play the corresponding roles.

Based on the basis that exosomes are involved in signaling functions and macrophage phenotypic alterations regulate the pathophysiology of the body, this paper focuses on the mechanisms of exosomal long-stranded non-coding RNA (lncRNA) and microRNA (miRNA) regulating macrophage phenotypic alterations from three aspects: tumor, neurological diseases and cardiovascular diseases.

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2. The Regulation of Macrophage Polarization by Exosomes is Involved in Tumorigenesis and Development

It is well known that the tumor microenvironment plays a crucial role in tumor development. As important components of the tumor microenvironment, exosomes and tumor-associated macrophage (TAM) [10] play an important role in regulating infiltration depth, lymphatic metastasis, promoting tumor growth, tissue remodeling, promoting angiogenesis, suppressing acquired immunity, influencing patient prognosis and chemotherapy resistance, etc. The performance of this role is closely related to the microenvironment This role is closely related to the effective transmission of signals from the microenvironment.

Recent studies have shown that long-stranded non-coding RNAs (Lnc RNAs) in different cellular exosomes are a class of key regulators of TAM and initiators of cancer development, which can promote tumor development by activating and regulating macrophage M2-type polarization through multiple pathways. For example, gastric cancer cell-derived exosomes as well as lnc RNA in exosomes can not only inhibit Toll receptor 4 (TLR4) expression and nuclear factor (NF-) phosphorylation, but also promote M2-type macrophage polarization by activating the extracellular regulatory protein kinase/signal transducer and activator of transcription 3 (ERK/STAT3) signaling pathway, producing results that promote gastric cancer development [11, 12]. Lin Xin [13] found, among others, that the gastric cancer cell-derived exosomes (GCCs) lncRNA HCG18 increased KLF4 expression by suppressing miR-875-3p expression in macrophages to achieve the effect of promoting M2-type macrophage polarization, which in turn accelerated gastric carcinogenesis development. In addition, in breast cancer development, long-stranded non-coding RNAs can also promote tumor development through macrophage M2-type polarization. lncRNA GNAS-AS1 was highly expressed in breast cancer tissues, cell lines and M2-type macrophages, and overexpression of GNAS-AS1 positively regulated the downstream target GATA3 pathway, which significantly increased the proportion of M2-type polarized macrophages, thus significantly accelerated the proliferation, migration and invasion of breast cancer cells [14], suggesting that exosomes could accelerate the development of breast cancer through the GNAS-AS1/miR-433-3p/GATA3 axis. Yiran Liang et al [15] found that overexpression of exosomal LncRNA BCRT1 promoted the polarization of M2-type macrophages and increased the migration rate of breast cancer, and the mechanism may be related to the lncRNA BCRT1/miR-1303 axis and the inhibition of miR-1303 response by BCRT1 overexpression. Meanwhile, TBP3, as a promoter of breast cancer, the competitive binding of lncRNA BCRT1 to miR-1303 prevented the degradation of PTBP3 and also promoted the development of breast cancer. It was concluded that lncRNA BCRT1 could be used as a potential biomarker and therapeutic target for breast cancer. Zong Shoukai [16] found that lncRNA SNHG1, a regulator of M2-type macrophage polarization, could affect tumor development by regulating tumor growth and angiogenesis. reduced SNHG1 expression not only inhibited M2-type macrophage polarization by inhibiting STAT6 phosphorylation, but also significantly attenuated MCF-7 cell migration and human umbilical vein endothelial cell (HUVEC) formation, preventing the cellular mixture of MCF-7 cells and macrophages from promoting tumor growth and angiogenesis. In summary, inhibition of STAT6 phosphorylation and NF-phosphorylation, as well as activation of the STAT3 signaling pathway, under the regulation of exosomal long-chain noncoding RNAs, can promote M2-type macrophage polarization and thus inhibit tumor development and transformation.

Long-stranded non-coding RNAs in exosomes of different cellular origin can also promote M1-type polarization of macrophages to achieve pro-inflammatory and tumor suppressive effects. Study[17] found that reducing LincRNA-p21 expression promoted macrophage polarization to pro-inflammatory M1-type macrophages in the tumor microenvironment, induced apoptosis, inhibited cell migration and invasion in cancer cells, and the mechanism may be related to the proteasome-dependent degradation triggered by MDM2 to p53, activated NF- and STAT3 pathways. It was found [18] that long-stranded non-coding RNA GAS5 is a key suppressor in human glioma. Based on this, a study by Xiaowen Chi[19] further found that polarization of macrophages by human monocyte-derived exosomal lncRNA GAS5 may be achieved through inhibition of the AK2/STAT3 pathway.

A large number of experiments have found that long-stranded non-coding RNAs can not only induce M1-type macrophage polarization, but also inhibit M2-type polarization. Ji Cao[20] found that LncRNA-MM2P could act as a regulator of M2-type macrophage polarization, and its low expression not only blocked the polarization of M2-type macrophages, but also inhibited STAT6 phosphorylation to impair angiogenesis. Tsai Tsao[21] found that exosomes entering glioma cells SHG449 induced cell morphological transformation in polarized macrophages and decreased expression of M2-type macrophage activation markers Arginase, CD206, CCL22, TGF- and increased expression of M1-type

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activation markers iNOS, CD68, IL-1, TNF-, suggesting that human bone marrow mesenchymal cells secreting exosomes can inhibit the conversion of tumor-associated macrophages to the M2 phenotype and induce their conversion to the M1 phenotype, regulating the tumor immune microenvironment and thus achieving cancer suppression.

By analyzing the above literature, long-stranded noncoding regulates macrophage polarization mainly through the lncRNA-miRNA-mRNA axis. A large number of animal experiments and clinical trials have confirmed that M2 polarization occurs more frequently and the mechanism of action is more complex than M1 in cancer development and progression. Therefore, it is particularly important to study the specific pathways of macrophage polarization, and inhibiting the aggregation, intervention, and polarization of M2-type macrophages in the tumor microenvironment has become a hot issue in the field of tumor therapy.

3. The Involvement of Exosome Regulation of Macrophage Polarization in the Development and Progression of Neurological Diseases

Microglia, as brain macrophages, play a key role in regulating brain development, maintaining neuronal networks and injury repair, and their functions are strictly regulated by the microenvironment of the central nervous system[22]. Exosomes in the microenvironment, as the body's own components, are expected to be one of the most effective approaches for clinical treatment because of their many advantages in the treatment of neurological diseases such as the ability to evade the immune system, free penetration of the blood-brain barrier, long circulating half-life, low toxicity, and high targeting.

Currently, spinal cord injury (SCI) is a serious neurological disorder that can lead to permanent loss of physical and sensory abilities[23, 24]. The inflammatory response plays a key role because it can worsen secondary injuries and also lead to the formation of glial scars. Numerous studies both nationally and internationally have shown that exosomes of different cellular origin may inhibit the inflammatory response attenuating neurological damage mediated through miRNA-mRNA networks.

In spinal cord ischemia-reperfusion injury and acute ischemic stroke, exosomal microRNA-124-3p derived from bone marrow MSCs not only promoted the polarization of anti-inflammatory M2-type macrophages, but overexpression of microRNA-124-3p inhibited apoptosis, which in turn attenuated neurological injury and tissue damage in spinal cord ischemia-reperfusion[25]. It was found[26] that the oncogene PTEN may act as a target gene for exosomal microRNA-181c from bone marrow mesenchymal stem cells to reactivate NF-κB phosphorylation inhibited by microRNA-181c, inhibit pro-inflammatory M1-type polarization, and reduce apoptosis, thereby attenuating spinal cord injury. Compared to studies in the field of oncology[27, 28], the mechanism of PTEN action in the nervous system has been less studied. It was found that overexpression of exosomal miR-216a-5p from MSCs under hypoxic conditions inhibited the TLR4/NF-κB signaling pathway, which in turn activated the PI3K/AKT signaling pathway, mediated the conversion of microglia to M2 type, and promoted the recovery of functional behavior after spinal cord injury[29]. It is suggested that exosomes can regulate microglia to attenuate spinal cord injury through signaling cascade responses. Another study found[30] that Interferon Regulatory Factor 5 (IRF5), a target gene of miR-22-3p, and overexpression of miR-22-3p not only negatively regulated IRF5 to attenuate inflammation in tissues, but also promoted M2-type macrophage polarization to enhance blockage of repair, inhibit inflammation, and attenuate spinal cord injury by ischemia-reperfusion. Furthermore, Zhang qing[31] verified from the opposite direction that knockdown of the bone marrow MSC-derived exosome miR-125a increased the expression of IRF5 in the spinal cord tissue of SCI rats, and IRF5 promoted M1-type macrophage polarization and inflammatory factor secretion, which in turn attenuated the neuroprotective effect of bone marrow MSC-derived exosome on SCI, suggesting that regulatory factors also play a key role in mediating macrophage polarization-regulated signaling pathways to attenuate inflammation in spinal cord injury.

4. Exosome Regulation of Macrophage Polarization is Involved in the Development and Progression of Cardiovascular Diseases

Deaths from cardiovascular diseases account for the first cause of total deaths in both urban and rural areas in China, 46.66% in rural areas and 43.81% in urban areas, and the prevalence of cardiovascular diseases in China is in a continuous rise[32]. Due to the low survival rate and low local reperfusion rate of cardiovascular diseases and the inability to perform myocardial repair although

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traditional treatments (drug therapy, intervention) can significantly reduce mortality, making cardiovascular diseases one of the major factors endangering people's life and health, it is urgent to find better treatments. Recent studies have found that in terms of molecular biological mechanisms, stem cells can protect cardiomyocytes and reduce myocardial infarction and myocardial injury through paracrine exosomal miRNAs, regulation of target genes and regulatory factors that affect the direction of macrophage polarization, respectively, by inhibiting inflammatory response and apoptosis, inhibiting myocardial autophagy and myocardial fibrosis.

In a myocardial infarction model, adipose mesenchymal stem cell-derived exosomes could regulate macrophage polarization by activating S1P / SK1 / S1PR1 signaling. activation of S1PR1 not only promoted M2-type macrophage polarization, but also inhibited TGF-β1-induced fibrosis in cardiac fibroblasts and prevented hypoxia-induced apoptosis in H9c2 cells, suggesting that S1P / SK1 / S1PR1 signaling pathway could be an important target for myocardial protection[33]. A study[34] found that lipopolysaccharide (LPS)-directed bone marrow stem cell-derived exosomes (L-Exo) promoted the conversion of the M1 phenotype of macrophages to the M2 phenotype to attenuate post-infarction myocardial inflammation. This is mainly because L-Exo reduces the phosphorylation level of IκB, inhibits the LPS-dependent NF-κB signaling pathway, and reduces the production of pro-inflammatory factors IL-6, TNF-α, and IL-1β. In addition, AKT, an upstream regulator of NF-κB signaling pathway, L-Exoke activates AKT1 phosphorylation to promote M2 macrophage polarization and inhibits AKT2 phosphorylation to reduce M1 macrophage polarization. It suggests that NF-κB signaling pathway is an important pathway for macrophage polarization, and it can be a potential target for myocardial protection.

Inhibition of inflammatory response and oxidative stress is particularly important in myocardial ischemia-reperfusion injury. Jinxuan Zhao[35] found that MSC exosomes could downregulate TLR4/MyD88/NF-icB pathway and upregulate PI3K/ AKT pathway by transporting miR-182, thus promoting the conversion of macrophages from M1 to M2 type, inhibiting myocardial inflammatory response and reducing myocardial ischemia-reperfusion injury, and this mechanism was validated in vitro and in vivo[36]. dafu Shen[37] found that miR-21-5p is an anti-apoptotic gene and that inhibition of miR-21-5p expression of MSC-EXOs promotes LPS-induced polarization of RAW264.7 cells to the M1 phenotype and, while promoting miR-21-5p induces polarization of RAW264.7 cells to the M2 phenotype and reduces the levels of inflammatory factors in culture supernatants. It is suggested that miR-21-5p plays a key role in suppressing myocardial ischemia-reperfusion injury by regulating the inflammatory response after promoting macrophage polarization.

In atherosclerosis models, KLF6 and ERK2 serve as targets of miR-21a-5p. miR-21a-5p-containing bone marrow MSC-derived exosomes not only promote M2 polarization of RAW264.7 cells by inhibiting KLF6 expression, but also inhibit the migration of RAW264.7 cells by suppressing the ERK1/2 signaling pathway, which in turn reduces cell infiltration[38]. The MSC-derived exosome miR-let7 promotes M2 macrophage polarization in plaques via the miR-let7 / HMGA2 / NF- pathway and, also, inhibits macrophage infiltration via the miR-let7 / IGF2BP1 / PTEN pathway, ultimately reducing atherosclerotic plaque area in ApoE mice [39]. From the above analysis, it can be concluded that cell-derived exosomal miRNAs, such as miR-let7, can alleviate atherosclerosis at the molecular level by inhibiting cancer cell infiltration and suppressing inflammation leading to a reduction in atherosclerotic areas through different pathways. Besides, compared to the mechanism of action of NF-signaling pathway in the tumor microenvironment[40], its specific mechanism in the nervous system is not clear and needs to be further explored.

5. Summary and Outlook

Since the first discovery of exosomes, subsequent exosome research has experienced a period of silence and has not received sufficient attention in the past 20 years. However, in recent years, the basic and preclinical research results related to long-stranded non-coding RNAs and miRNAs in exosomes have been increasing and become one of the hot spots in the molecular field.

Combining the results of animal and cellular experiments for exosomes of different cellular sources in recent years at home and abroad, this paper reviews the role of exosomes of different cellular sources with macrophage polarization, focusing on the role of exosomal tiny molecule long-chain non-coding RNAs, miRNAs in three aspects of tumor, neurological diseases and cardiovascular diseases through lncRNA-miRNA-mRNA axis, miRNA- mRNA network mediates the molecular regulatory mechanism of M1/M2 macrophage polarization. In conclusion, exosomes are multi-target and multi-pathway in

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affecting macrophage polarization.

As natural carriers, exosomes can carry a variety of bioactive molecules, which can be used as tumor markers and provide new strategies for disease treatment, but the clinical application of exosomes still faces major difficulties, such as the standardization of exosome classification, dissociation, purification, and how to make the beneficial components of exosomes home to the damaged tissues in a targeted manner. Therefore, with the support of many basic research results, exploring the mechanism of exosome-mediated macrophage polarization in the development of tumors, cardiovascular diseases and neurological diseases through clinical studies has become a great challenge for current research and eventually a key for future exosome research.

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