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Advances in the Regulation of the Role of Myeloid-derived Suppressor Cells in the Tumor Microenvironment by Tumor-derived Exosomes

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Abstract: In the progression of malignancies, myeloid-derived suppressor cells (MDSCs) play a crucial role in modulating tumor immunology within the tumor microenvironment (TME), which is often characterized by the extensive infiltration of immune cells. These cells are abnormally activated and demonstrate strong immunosuppressive properties under pathological conditions such as cancer. Recent research highlights the importance of tumor-derived exosomes (TEXs) as key mediators of this immunosuppressive activity. TEXs, small extracellular vesicles released by tumor cells, carry a diverse array of bioactive molecules such as proteins, lipids, and RNA, which modulate the behavior of recipient cells within the TME. The assembly and release of TEXs are tightly regulated by the TME, and accumulating evidence suggests that TEXs facilitate MDSC activation, expansion, and enhancement of their immunosuppressive functions. This study aims to investigate the role of TEXs in mediating intercellular communication between tumor cells and MDSCs. By understanding these mechanisms, it is possible to develop strategies to regulate MDSC behavior, including promoting their differentiation into mature myeloid cells, reducing their expansion and accumulation, and impairing their suppressive activity. Ultimately, these insights will provide a foundation for targeting MDSCs as a therapeutic approach to inhibit tumor growth, invasion, and metastasis, offering promising directions for future clinical applications.

Keywords: Tumor-derived exosomes, myeloid-derived suppressor cells, tumor microenvironment, immunosuppression

1. Introduction

Exosomes released by tumor cells are referred to as TEXs, and they are frequently detected in cancer patients' bodily fluids and tumor tissues. Although the proportion of TEXs to exosomes originating from normal cells varies in cancer patients' plasma, TEXs typically make up the majority of all exosomes in patients with advanced cancers. TEXs play a role in the TME by facilitating intercellular communication and transferring information from the parent tumor cell to recipient cells, such as MDSC. MDSC are specialized cells consisting of a number of immature heterogeneous cells derived from myeloid lineage cells and they play significant roles in tumor immunomodulation.The assembly and release of TEXs can be regulated by TME, and the current study suggests that TEXs can modulate

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the cell biological properties of MDSC, including promoting their activation, facilitating expansion and enhancing immunosuppressive functions.

It has gradually become clear that MDSCs are an important modulator of anti-tumor immune responses. Furthermore, numerous clinical investigations have found that MDSCs can be useful predictive markers of the course of cancer, and significant efforts are being undertaken to create medicines that specifically target MDSCs. These all demonstrate how MDSCs in the TME contribute to the development of cancer.

As previously stated, the TME is a novel regulator of MDSC cell biology that can control the production and release of exosomes from cancer cells. This study emphasizes new developments in the function of TEXs, which are crucial in cell biology for controlling MDSCs in the TME.

2. TEX formation and release

Following their release into the extracellular space, exosomes use membrane fusion, endocytosis, and binding to target cell surface receptors to help move information to and from target cells. It is now becoming more and more clear that exosomes contribute significantly to illnesses, especially cancers, by encouraging recipient cells to undergo reprogramming [1].

Tumor tissues and cancer patients' bodily fluids frequently contain TEXs, which are exosomes produced by tumor cells. Exosome production by cancer cells is thought to be substantially higher than that of non-cancerous cells, according to a number of studies. For anti-tumor therapy, exosomes are therefore a desirable target.TME conditions (such as hypoxia) and cell-intrinsic mechanisms can influence TEX formation and release [2].

2.1. Insufficient oxygen

An imbalance between the supply and consumption of oxygen by tumor cells results in hypoxia, a crucial feature of the tumor microenvironment [3]. The increased release of exosomes from hypoxic tumor cells may result in enhanced tumor invasion and progression under hypoxia, given the role exosomes play in tumor growth. Exosomes produced from hypoxic tumor cells have several pro-angiogenic components that allow them to stimulate angiogenesis and endothelial cell activation in addition to the effects of increased exosome abundance [2,4].

2.2. Extracellular acidity

Lactate and H+ accumulation leads to extracellular acidity, which is a characteristic of TME. The release of TEX is suggested to be increased by extracellular acidity in TME.In a study by Isabella Parolini et al, exosomes isolated from the culture medium of metastatic melanoma cells were labeled with the lipid fluorescent probe R18 and examined using confocal microscopy and fluorescence spectrophotometry. Exosome absorption and release were found to be greater at low pH than in buffered settings.According to the results, exosome uptake by melanoma cells occurs through fusion. This suggests that the acidic microenvironment is a crucial factor in increasing exosome release and uptake into melanoma cells, and that the acidic microenvironment may be favorable for the fusion of exosomes with cells under both normal and pathological conditions [5,6].

3. MDSC

The majority of immature myeloid cells (IMCs) make up the heterogeneous group of cells known as MDSC. Under physiological conditions, within bone marrow (BM), IMCs rapidly transform into mature monocytes, dendritic cells (DCs), and granulocytes. However, in a pathological state such as cancer, the obstruction to the differentiation and maturation of these IMCs leads to the expansion of

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MDSCs in a living organism [7]. A substantial amount of substances produced by tumor cells, stromal cells, and activated immune cells initiates MDSC multiplication and immunosuppression in the TME.There are two groups of molecules that are interrelated and can be divided, as shown in Figure 1.

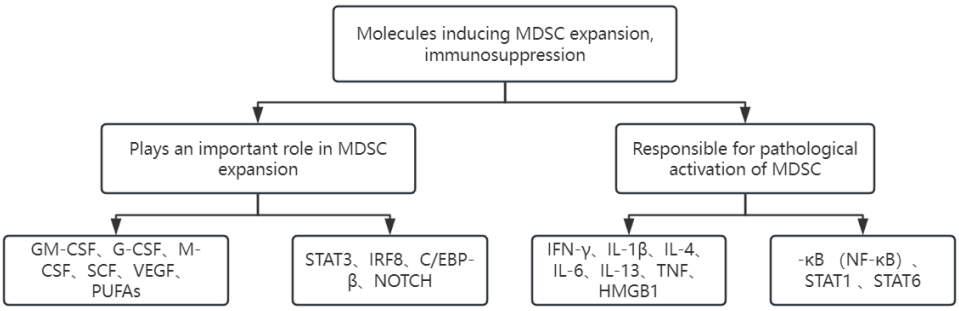

Figure 1: Molecules inducing MDSC expansion, immunosuppression [8-10].

4. TEX induces MDSC amplification and enhances immunosuppression

Tumor cells, stromal cells, and activated immune cells all generate cytokines that lead to the activation, proliferation, and immunosuppression of MDSCs in the TME. It has been proven that exosomes secreted by various tumor cells are highly significant for the growth, survival, and immunosuppression of MDSCs. The expansion of MDSCs is caused by TEXs via numerous mechanisms [11]. Research has indicated that TEXs disrupt the maturation of DCs, impede the activation of natural killer (NK) cells, trigger myeloid-derived suppressor cells, and contribute to the emergence of a tumor-favoring phenotype in macrophages [12]. By raising the anti-apoptotic proteins Bcl-xL and Mcl-1 and activating the STAT3 and STAT1 pathways, exosomes directly enhance the survival of MDSCs [13]. Additionally, in tumor models, TEXs increase the inhibitory function of MDSCs and encourage the synthesis of their inhibitory chemicals [14].TEXs are emphasized as important in MDSC cell biology, and the precise mechanism of TEXs regulation in MDSC is gradually revealed.

4.1. TEX proteins involved in the regulation of MDSC amplification and immunosuppression

4.1.1. PGE2 and TGFβ

Mice injected with TEX were shown by Xiang X and his team to have enlarged spleens with accumulations of CD11b+Gr-1+ MDSCs. The pro-inflammatory cytokine IL-6 and the tumor growth factor VEGF were also secreted by the CD11b+Gr-1+ cells induced by exosomes. The promotion of tumor growth resulted from the simultaneous injection of bone marrow-derived CD11b+Gr-1+ cells and tumor cells. Consequently, it was further determined that PGE2 and TGF-β in tumor exosomes have a role in triggering the accumulation of MDSCs. The accumulation of MDSCs expressing Cox2, IL-6, VEGF, and arginase-1 was led by TEX. The activity of exosomes PGE2 and TGF-β in inducing MDSCs was inhibited by antibodies against them, thus reducing tumor promotion mediated by MDSCs. Exosomes PGE2 and TGF-β were more plentiful in TEX compared to exosomes isolated from cultured tumor cell supernatants (C-exosomes). The tumor microenvironment affected the strength of the induction of MDSCs mediated by TEX through regulating the sorting and amount of exosomes PGE2 and TGF-β [14]. These results are beneficial for the formulation of specific targeted therapeutic approaches that aim to decrease or get rid of the immunosuppression caused by MDSCs, thereby improving the effectiveness of the host's anti-tumor immunotherapy.

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4.1.2. Hsp72 series

In their research, Chalmin F and their colleagues isolated TEXs from a mouse cell line. They showed that the association between Hsp72 associated with TEX and MDSCs dictates the inhibitory potency of MDSCs by activating Stat3. Moreover, tumor-derived soluble factors instigated the expansion of MDSCs by activating Erk. TEX-linked Hsp72 activated Stat3 in MDSCs in a TLR2/MyD88-reliant manner through the autocrine production of IL-6. Utilizing dimethylamiloride to reduce exosome generation improved the in vivo antitumor efficiency of the chemotherapeutic drug cyclophosphamide in three distinct mouse tumor models. The research also confirmed the relevance of this mechanism to cancer patients since TEXs from human tumor cell lines activated human MDSCs and initiated their inhibitory function in an Hsp72/TLR2-dependent manner. Moreover, MDSCs from cancer patients treated with amiloride, a drug for high blood pressure that can also inhibit exosome formation, exhibited a diminished inhibitory capacity. In general, the study findings imply that in both mice and humans, Hsp72 located on the TEX surface suppresses tumor immunosurveillance by enhancing the inhibitory function of MDSCs [15].

4.1.3. Bcl-xL and Mcl-1

A research led by Wang J and his team found that MDSCs in multiple myeloma (MM) absorb exosomes which come from bone marrow stromal cells (BMSCs), and this absorption leads to their expansion during in vitro experiments. Besides, these exosomes directly improve the survival rate of MDSCs by activating the STAT3 and STAT1 pathways and elevating the amounts of anti-apoptotic proteins Bcl-xL and Mcl-1. The application of inhibitors for the STAT3 and STAT1 pathways remarkably limits the survival of MDSCs that are influenced by BMSC exosomes, thereby verifying the participation of these pathways in exosome-induced cell survival [13].

In summary, the different TEX proteins each have a unique role to play in regulating MDSC amplification and immunosuppression, and they work in concert with each other or on their own to influence the overall picture of tumor development within the body. In the future, a better understanding of how these proteins work may lead to better ways of dealing with problems in tumor therapy.

4.2. TEX nucleic acids involved in the regulation of MDSC amplification and immunosuppression

MiRNAs circulate in a stable, cell-free state in various body fluids such as blood. TEXs are able to directly transfer miRNAs to target receptor cells and take part in the process of intercellular communication. After being delivered to the receptor cells, the exosomal miRNAs are internalized and maintain their functions in these cells. MDSCs are the main receptor cells for TEX nucleic acids.

4.2.1. miRNA-21 and miR-10a

In a study, Guo X and colleagues isolated glioma-derived exosomes (GDEs) that were stimulated by normoxia and hypoxia. They then investigated the ability of these GDEs to induce MDSCs both in vivo and in vitro. The results indicated that hypoxia promotes the secretion of GDEs, and these GDEs are absorbed by mouse MDSCs. Furthermore, GDEs that are stimulated under hypoxic conditions have a stronger ability to trigger MDSCs in contrast to GDEs stimulated under normoxic conditions (N-GDEs). The presence of miR-10a and miR-21 inside GDEs generated under hypoxic circumstances controls the enlargement and activation of MDSCs by focusing on RAR-associated orphan receptor α (RORA) and phosphatase and tensin homologue (PTEN). Mice injected with

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glioma cells in which miR-10a or miR-21 has been knocked out produce a lesser number of MDSCs in comparison to those injected with ordinary glioma cells [16].

4.2.2. miR-155

Chronic lymphocytic leukemia (CLL) of B-cell origin is characterized by immunodeficiency that hinders an effective anti-tumor response. The accumulation of immunosuppressive CD14+ HLA-DR low monocytic MDSCs is connected with advanced-stage disease and an unfavorable prognosis. In a study, Bruns H and colleagues asserted that exosomes from CLL cells triggered a phenotypic and functional transformation of conventional monocytes into MDSCs. Pretreating CLL cells with vitamin D led to the exosomes losing their capacity to stimulate MDSCs. In fact, higher serum concentrations of vitamin 25D were associated with lower quantities of circulating MDSCs in CLL. A considerable number of biologically active molecules, including microRNAs (miRs), are transported by exosomes. miR-155 is plentiful in CLL exosomes, and using antagonists against miR-155 can impede the exosomal induction of MDSCs. Additionally, exosomes from patients with low vitamin D levels contain more copies of miR-155. Thus, the application of vitamin D reduces the production of miR-155 in CLL cells. Generally, the transfer of exosomal miR-155 promotes the development of MDSCs in CLL [17].

These miRNAs play important roles in different types of exosomes, and they are capable of transmitting information across cells, which in turn affects the amplification and immunosuppressive functions of MDSC. By regulating the levels of these miRNAs, it is possible to control the activity of MDSC, which is important for understanding the development of certain diseases and developing new therapeutic approaches. For example, regulating vitamin D levels may help to reduce the number of MDSC in patients with certain types of cancer, thereby enhancing their immune system's ability to recognise and attack tumors.

5. Conclusions

This review underscores the essential significance of TEXs in the cell-to-cell interaction taking place among cancer cells and MDSCs within the TME. Investigating the regulation of MDSCs by TEXs in tumor immunity will aid in overcoming tumor progression, recurrence, metastasis, and drug resistance, offering potential biomarkers and targets for cancer immunotherapy. Nevertheless, current research on the function, mechanism, and contribution of MDSCs in tumor immunity is restricted. The questions of how to apply MDSCs to advanced cancer patients promptly and how to ensure the safety of MDSCs in clinical applications remain popular scientific inquiries that demand urgent exploration. Targeting TEX regulation and MDSC therapy may provide an idea and a new direction for anti-tumor therapy.

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