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Hot to Cold Tumors: Regulations of MEX-3 Family Proteins

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In recent years, along with many advances in cancer immunotherapy, immune checkpoints, a class of immunomodulatory proteins involved in the negative regulation of the immune system, have attracted increasing attention[1]. The blockade of immune checkpoints to target immune checkpoint molecules has become one of the most promising methods for cancer immunotherapy. However, some patients do not respond effectively to immunotherapy, and understanding the molecular mechanism of immunotherapy resistance is crucial for identifying new strategies to overcome immunotherapy resistance[2,3].

In patients with solid tumors, those who respond well to ICB treatment often exhibit an active immune characteristic called the "hot" phenotype (Figure 1). On the other hand, unresponsive patients may show a unique "cold" phenotype[4]. In general, the main difference between hot and cold tumors is the infiltration of immune cells and the response to immunotherapy. Hot tumors are more sensitive to immunotherapy because of the high infiltration of immune cells, whereas cold tumors respond slowly to immunotherapy because of poor infiltration of immune cells or a

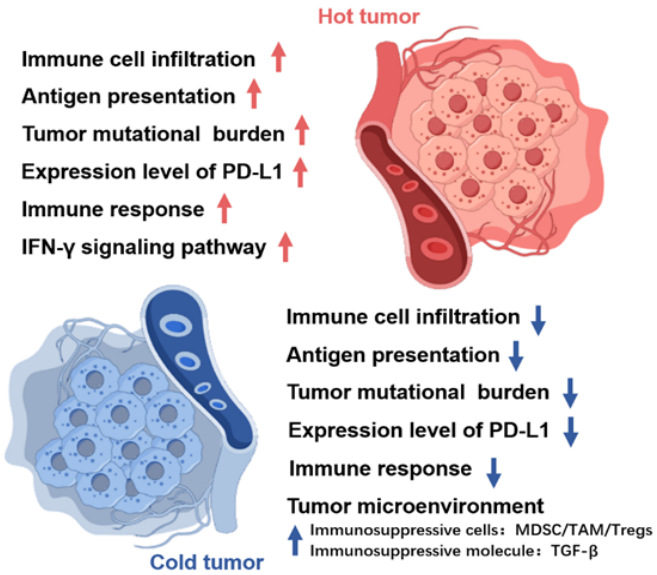

Figure 1: Main immune features of hot and cold tumors. The primary immune features of hot and cold tumors were compared, including immune cell infiltration, antigen presentation, tumor mutational burden, PD-L1 expression, and the immune response. The red arrow indicates upregulation, and the blue arrow indicates downregulation.

lack of infiltration[5]. So, activating the immune cells will be a key point in transforming the cold tumor into a hot tumor and enhancing the efficiency of immunotherapy.

Immune escape by tumors is one of the leading causes of resistance to immunotherapy. Immune escape allows tumor cells to evade surveillance and attack the immune system, reducing the effectiveness of immunotherapy and thus transforming hot tumors that respond well to immunotherapy into cold tumors that respond poorly to immunotherapy. Understanding the mechanism of tumor immune escape will help us develop new tumor treatment strategies to improve tumor immunotherapy's response rate and therapeutic effect and provide a scientific basis for developing new therapeutic approaches and drugs.

There are many mechanisms of immune escape of tumor cells, and some studies define it as the "3C" model[6], that is, camouflage, which hides tumor cells from recognition by immune cells; coercion, direct or indirect interference with immune cells; and cytoprotection, which is the protection of tumor cells from immune cytotoxicity. These mechanisms mainly include defects in tumor antigen expression or presentation: tumor cells may lose or alter the expression of their surface antigens, making it impossible for T cells to recognize and attack them; recruitment of immunosuppressive cells: various immunosuppressive cells (such as regulatory T cells, myeloid suppressor cells, etc.) may be recruited to the tumor microenvironment, which can directly inhibit the function of effector T cells; and cytokine secretion: tumor cells can secrete some immunosuppressive cytokines (such as IL-10, TGF-β, etc.) to inhibit the immune response and promote tumor growth; and changes in the tumor microenvironment: tumor cells can alter the microenvironment to make it more conducive to tumor growth and inhibit antitumor immune responses. These mechanisms often overlap, allowing tumors to evade immune system surveillance effectively.

There are different strategies to alter the tumor microenvironment, including the regulations of the protein level or mRNA level. The MEX-3 family is a translation suppressor that plays a role in many physiological processes of organisms, including the occurrence and development of tumors and immune escape. In the human MEX-3 family of proteins[7], there are four homologous proteins, namely, MEX3A, MEX3B, MEX3C, and MEX3D. A study by Lu Huang et al. revealed that low MEX3B expression in melanoma patients was closely related to PD-1 antibody immunotherapy. Further studies showed that MEX3B can downregulate the expression of HLA-A on the surface of tumor cells by binding to the 3'UTR of HLA-A mRNA, thus promoting the immune escape of tumors[8]. Our previous studies revealed the specific fragment and molecular mechanism of MEX3B recognition of HLA-A mRNA[9], which is crucial for understanding the function of MEX3B in promoting tumor immune escape.

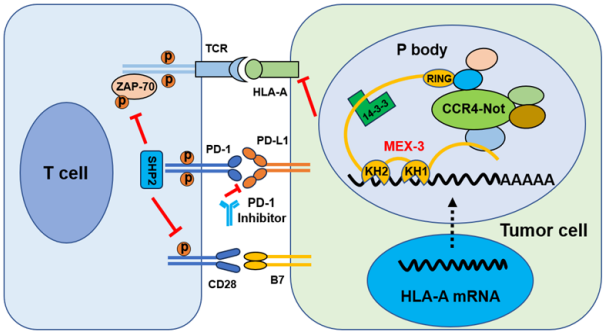

Figure 2: The molecular mechanism by which MEX3B promotes tumor immune escape. The binding of PD-L1 to PD-1 inhibited the activation of T cells. PD-1 antibody immunotherapy promotes T-cell activation by inhibiting the binding of PD-L1 to PD-1. MEX3B binds to HLA-A mRNA and recruits the CCR4-Not complex to downregulate HLA-A expression on the surface of tumor cells, and 14-3-3 proteins regulate this localization process. Owing to the downregulation of HLA-A, antigen presentation is blocked, and T cells cannot effectively recognize and kill tumor cells.

APCs deliver tumor antigens to T-cell receptors (TCRs) through the MHC. When the MHC antigen complex specifically binds to the TCR, it triggers a series of signal transduction pathways, including the phosphatidylinositol signaling pathway and mitogen-activated protein kinase signaling pathway, activating the immune response of effector T cells. When PD-L1 binds to PD-1, tyrosine residues in the ITSM and ITIM domains of the PD-1 cytoplasmic region are phosphorylated, recruiting and activating SHP2[10]. The subsequently recruited SHP-2 mediates the dephosphorylation of TCR-associated CD3 and ZAP70 signaling while inhibiting CD28 costimulatory signals[11]. The interaction of MEX3B with the 14-3-3 protein results in its localization in the P body[12], the leading site of mRNA degradation. MEX3B can recognize the 3'UTR of HLA-A mRNA through the N-terminal KH domain and promote mRNA deadenylation by recruiting the CCR4-Not complex, further leading to mRNA degradation (Figure 2). The degradation of HLA-A mRNA directly downregulated HLA-A protein expression on the surface of tumor cells. As an MHC-I molecule, the downregulation of HLA-A directly affects the recognition of tumor cells by T cells. T cells cannot recognize and kill tumor cells, which further leads to the immune escape of tumor cells. Notably, our recent study revealed that the MEX3B protein can recruit the CCR4-Not complex for its function by interacting with the CNOT9 protein via the N-terminal CBM sequence. The multiple ways RNA-binding proteins are recruited mean they are more efficient at recruiting the CCR4-Not complex. This finding further complements the molecular mechanism by which MEX-3 family proteins inhibit translation.

In addition to directly affecting the recognition of tumor cells by T cells, a growing number of studies have shown that MEX-3 family proteins mediate the immune escape of tumors in a variety of ways (Figure 3). For example, studies have shown that MEX3A mediates the degradation of RIG-I by activating IGF-1R in the CRC tumor microenvironment and inhibits IFN-I-related immune cells, thus promoting the progression of CRC[13]. The MEX3A/circMPP6 complex can promote the degradation of PDE5A mRNA and promote angiogenesis in the tumor microenvironment by increasing cGMP levels, thus triggering the aggressiveness of CRC cells[14]. Clinically, CRC patients with elevated MEX3A expression and decreased PDE5A expression have a worse prognosis. In summary, MEX3A plays an essential role in the TME, which is not only involved in drug resistance and immune escape in tumor cells but also related to the autophagy process and degradation of specific mRNAs, affecting tumor progression and patient prognosis.

Studies have shown that MEX3B can upregulate the expression of CXCL2, and our recent study revealed this phenomenon. CXCL2 plays a crucial role in the tumor microenvironment. For example, in bladder cancer, tumor cells induce the accumulation and expansion of myeloid suppressor cells (MDSCs) in the tumor microenvironment through CXCL2/MIF-CXCR2 signaling, which is positively correlated with the degree of tumor invasion[15]. These findings suggest that MEX3B may be involved in the immune escape process of tumors by influencing the tumor cell microenvironment. In addition, MEX3B-overexpressing tumor cells could significantly reduce IFN-γ secretion when cocultured with tumor-infiltrating lymphocytes (TILs). IFN-γ is an important cytokine vital in regulating the immune response and antitumor activity. MEX3B may indirectly regulate the immune response in the tumor microenvironment by influencing the secretion of IFN-γ[8].

High MEX3C expression is associated with increased bone marrow-derived suppressor cells (MDSCs) expression. MDSCs can promote the differentiation of regulatory T cells and form an immunosuppressive microenvironment around tumors[16]. This immunosuppressive microenvironment helps tumor cells escape immune attack. MEX3C gene analysis revealed that MEX3C is enriched in the TGF-β signaling pathway, which plays a crucial role in fibrosis and immune regulation in the HCC microenvironment[17]. TGF-β signaling can be used by tumor cells to reshape the immune microenvironment and promote the development of immune escape. In summary, MEX3C may play a role in tumor immune escape through a variety of mechanisms, including affecting the expression of immune checkpoints, modulating the activity of immunosuppressive cells, and participating in the TGF-β signaling pathway, thereby promoting tumor cell evasion of immune system attack. These findings provide potential targets for the development of new immunotherapy strategies.

Studies have shown that the MEX3D expression level in cervical cancer tissues is more significant than that in normal cervical tissues and that its high expression is related to the progression of cervical cancer. MEX3D,

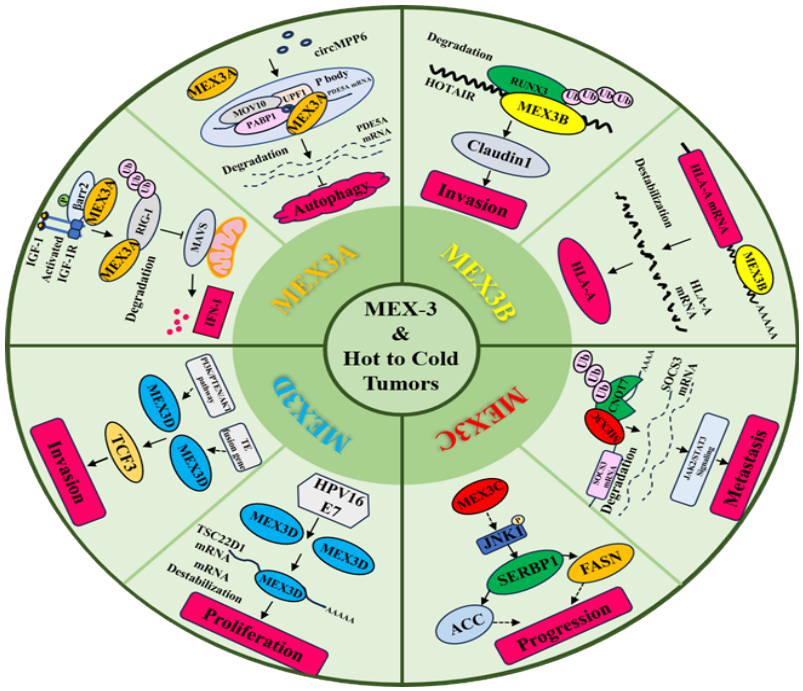

Figure 3: MEX-3 family proteins facilitate the transformation of hot tumors into cold tumors via multiple pathways. MEX-3 family proteins are directly or indirectly involved in the proliferation, metastasis and immune escape of tumor cells through various pathways. This causes the tumor to exhibit a cold phenotype resistant to immunotherapy.

an RNA-binding protein, can promote cervical cancer oncogenesis by affecting the stability of TSC22D1 mRNA. TSC22D1 is a tumor suppressor. MEX3D may promote the malignant phenotype of cervical cancer cells by reducing the stability of TSC22D1 mRNA, which is closely related to the regulation of gene expression in the tumor microenvironment[18].

It is widely believed that immunotherapy, represented by PD-1/PD-L1 inhibitors, can effectively improve the prognosis of cancer patients by enhancing the immunosuppressive TME and restoring the recognition and killing effects of immune killer cells on cancer cells. However, ICB therapy has a good effect on hot tumors but a very limited effect on cold tumors. It needs to be combined with other treatments to enhance the infiltration of immune cells into tumor tissue and transform cold tumors into hot tumors.

In the context of tumor immunotherapy, the role of MEX-3 proteins in regulating the tumor immune microenvironment and influencing tumor transformation underscores their significant clinical potential. Aberrant expression of MEX-3 proteins in various tumor types indicates that they could serve as promising biomarkers for early cancer detection[19,20]. By measuring MEX-3 protein levels in blood or tissue samples, clinicians can identify tumors at earlier stages, allowing for timely therapeutic interventions. Additionally, the expression levels of MEX-3 proteins may reflect tumor aggressiveness, providing valuable insights for prognostic assessment. MEX-3 proteins play critical roles in tumor immune evasion, cell proliferation, and migration, positioning them as attractive therapeutic targets[21,22]. Targeting MEX-3 proteins with strategies such as RNA interference, monoclonal antibodies, or small molecule inhibitors may effectively reduce tumor cell proliferation and metastasis, thereby enhancing the effectiveness of immunotherapy.

Many studies have shown that MEX-3 family proteins are highly expressed in many tumor tissues[20], often associated with poor prognosis. Therefore, combining targeted therapy with immune checkpoint inhibitors based on the MEX-3 protein is particularly important. Studies have reported that anti-MEX3B oligonucleotide therapy can inhibit neutrophil allergic airway inflammation[23]. As previously reported, some melanoma patients with high MEX3B expression have a poor response to PD-1 antibody immunotherapy, so can the above anti-MEX3B oligonucleotide therapy be combined with them? Could this significantly improve resistance to checkpoint-blocking therapy in some patients to improve treatment and patient outcomes? This requires further research. In addition, MEX3C may also be a promising therapeutic target, and the combination of MEX3C knockdown with Lenvatinib (a multitarget tyrosine kinase inhibitor) may provide a new therapeutic avenue for HCC treatment[24]. This combination therapy may enhance the immune response to tumors by affecting immunosuppressive cells and modulating the immune microenvironment, which could overcome the limitations of monotherapy.

MEX-3 proteins may promote immune evasion in the tumor microenvironment by modulating the expression of immune-related genes, including immunosuppressive factors and cytokines [9]. This modulation can facilitate the transition from “hot” tumors to “cold” tumors, characterized by reduced immune cell infiltration and an impaired immune response[25]. Consequently, inhibiting the expression or function of MEX-3 proteins may enhance immune cell infiltration into tumors, improving tumor immunotherapy’s efficacy. Such inhibition could also promote the transformation of “cold” tumors to “hot” tumors, ultimately boosting the immune system’s ability to recognize and eliminate malignancy cells[20].

Immune checkpoint inhibitor combination therapy is a revolutionary change in the field of cancer treatment, opening a new path for multiple cancer therapies. This combination therapy involves not only combining different immune checkpoint inhibitors but also combining them with traditional treatment methods such as chemotherapy and radiotherapy, as well as emerging immunotherapy methods, aiming to improve clinical efficacy through synergistic effects. In general, combination therapy is a future direction. Still, the regimen, dose, sequence and duration of combination therapy need to be further explored, with particular attention given to reducing adverse effects and improving economic applicability. With the development of increasing clinical research in the field of immunotherapy, the application of immunotherapy in patients is expected to expand, providing the most appropriate combination therapy program, accurately evaluating the therapeutic effect, and achieving the best therapeutic effect with minimal toxic damage.

In summary, MEX-3 family proteins play essential roles in regulating the response of hot tumors to cold tumors. They participate in the proliferation and survival of tumor cells and may affect the immune response in the tumor microenvironment, thus becoming new biological biomarkers and potential new targets for tumor diagnosis and treatment. Further investigations are required to clarify the specific mechanisms through which MEX-3 family proteins operate within the tumor immune microenvironment and to evaluate their clinical applicability, establishing a robust theoretical framework for the advancement of innovative cancer therapies.

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Conflict of Interest

All of the authors declare that they have no conflict of interest

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