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Progress of SPP1 Involved in Tumor Immune Escape in Lung Cancer

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Abstract: SPP1 (Secreted Phosphoprotein 1), alternatively named Osteopontin (OPN), is a multifunctional secreted glycoprotein capable of binding with integrins that promotes tumor cells to evade the surveillance and attack of the immune system by influencing infiltration of immune cells, function, and pathways in the tumor microenvironment (TME). However, the specific mechanism has not yet been clearly expressed. Based on the function of SPP1 in the TME and the changes in the formation of the lung cancer (LC) TME, this study delves into the mechanism of the high expression of SPP1 in LC tumors, and potential LC therapeutic options targeting SPP1 in the future. Therefore, the research theme of this paper is the progress of SPP1 involved in the immune escape of LC tumors. The data collection and organization enabled profound discussions on the factors that activate SPP1 to help tumor cells for immune escape, how SPP1 regulates the TME for immune escape, and the prospect of SPP1-targeted therapy. SPP1 may become a potential target for immunotherapy of LC, which can be directed to inhibit the expansion of LC cells through the preparation of monoclonal antibodies and other means.

Keywords: SPP1, M2 macrophages, lung cancer, immune escape, targeted therapy.

1. Introduction

Lung cancer (LC) is the deadliest type of malignant tumor worldwide, with both incidence and mortality rates on the rise. The TME plays a critical role in the progression of LC. This environment includes a diverse range of immune cells including T-cells, B-cells and macrophages, along with cytokines like IL-6 and TNF-α, all of which influence tumor growth and metastasis. The TME is fundamental to tumorigenesis, development, and metastasis. Research has identified SPP1 (Secreted Phosphoprotein 1), otherwise called Osteopontin (OPN), as a versatile secreted protein which functions to facilitate the growth and metastasis of tumor cells.SPP1 affects immune cell infiltration, function, and the pathways within the TME, primarily through activating the CD44/PI3K/AKT pathway. This pathway supports M2 polarization, which facilitates tumor cells in evading immune detection. Specifically, bone-bridging proteins bind to the CD44 receptor, activating the PI3K/AKT pathway. That pathway is critically important in respect of a wide range of biological phenomena including cell growth, survival, metabolism, movement and angiogenesis. The activation of it is associated with the evolution of diverse diseases such as cancer, diabetes and cardiovascular conditions. Additionally, AKT activates the NF-κB pathway, which is crucial for regulating immune responses, inflammatory factor release, and apoptosis, thereby contributing to tumor development

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and aiding tumor cells in evading immune attacks. Numerous studies have demonstrated that SPP1 helps tumor cells escape immune surveillance by impacting immune cell infiltration and function and modulating pathways in the TME. However, the precise mechanisms through which SPP1 operates remain poorly understood.

This paper will directly analyze the role of SPP1 in the TME, particularly focusing on the infiltration of M2 macrophages. This paper will also explore the mechanisms underlying the elevated expression of SPP1 in LC tumors and discuss potential therapeutic options targeting SPP1 in the future. Therefore, the main theme of this paper is the role of SPP1 in facilitating immune escape in LC tumors.

2. SPP1 function in the TME

2.1. Regulation of immune cell function

SPP1 accelerates the progression of idiopathic pulmonary fibrosis (IPF) by promoting the polarization of M2 macrophages through the JAK2/STAT3 pathway. JAK2 (Janus kinase 2) and STAT3 (signal transducer and activator of transcription 3) are key molecules involved in intracellular signaling [1]. When cell surface receptors are activated, JAK2 phosphorylates STAT3, leading to the dimerization and translocation of STAT3 to the nucleus. This process allows STAT3 to regulate the expression of specific genes, thereby influencing cell behavior. By activating the JAK2/STAT3 pathway, SPP1 gives impetus to the polarization of M2-type macrophages. When SPP1 binds to receptors on the surface of macrophages, it activates JAK2, which then phosphorylates STAT3. This signaling activates specific gene expression patterns in M2-type macrophages, further promoting M2 polarization. M2 macrophages may exacerbate fibrosis in IPF by producing anti-inflammatory cytokines and facilitating tissue repair. Therefore, inhibiting SPP1 expression or blocking its pathway may reduce M2 macrophage polarization, potentially slowing the progression of IPF. Suggesting a promising therapeutic approach for IPF, the targeting of SPP1 in macrophages is proposed by these findings.

2.2. Interaction with multiple immune cells

There is a positive relationship between the interaction of SPP1 indication and various immune cells and the infiltration levels of CD4+ T cells, CD8+ T cells, macrophages, neutrophils, and dendritic cells. This implies that SPP1 could have a function in controlling the infiltration of various immune cells inside the TME [2]. Immunohistochemical methods were utilized in the study to authenticate the presence magnitudes of SPP1 and CD8 in the samples taken from ovarian cancer patients.This process involved several steps: deparaffinization of tissue sections, hydration, antigen repair, blocking of endogenous peroxidase activity, and incubation with primary and secondary antibodies, followed by DAB color development. After analyzing the data and making a comparison of the clinical differences between the two groups, it was observed that SPP1 expression was positively correlated with the levels of several kinds of immune cells. Notably, the correlations were particularly significant with neutrophils ($r = 0.473$, $p = 4.28e\text{-}28$) and dendritic cells ($r = 0.355$, $p = 1.05e\text{-}15$).

During neuroinflammation, SPP1 detects and controls acute and chronic neuroinflammation by employing glial cells and immune cells and relying on neuronal ligand-receptor interactions [3]. These results emphasize the diverse and complex functions of SPP1 within the tumor microenvironment, not only influencing immune cell function but also potentially participating in the regulation of neuroinflammation.

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2.3. Interaction with the TME

Increased expression of SPP1 was associated with the aggregation of M2-like tumor-associated macrophages (TAM) in esophageal squamous cell carcinoma (ESCC), and they both predicted poor prognosis. It was found that when SPP1 was knocked down, the infiltration of M2 TAM in xenograft tumors was significantly inhibited. Experiments of in vivo mouse modeling demonstrated that the process of macrophage education, which is mediated by SPP1, has a crucial role in the development of esophageal squamous carcinoma [4]. From a mechanistic perspective, SPP1 recruits macrophages and promotes M2 polarization through CD44/PI3K/AKT signaling activation, then induces VEGFA and IL6 excretion aimed at maintain ESCC progression. Ultimately, the use of RNA aptamers to block SPP1 led to a significant inhibition of tumor growth and the infiltration of M2 TAM in a xenograft mouse model. In colorectal cancer (CRC), the interaction of SPP1+ macrophages with FAP+ fibroblasts forms a “wall”-like extracellular matrix barrier that blocks cytotoxic T lymphocytes (CTLs) from infiltrating the tumor core, thus suggesting a new mechanism of tumor immunotherapy tolerance. In hepatocellular carcinoma (HCC), there is a greater quantity of SPP1+ TAMs. Moreover, the SPP1 receptor CD44 shows high expression levels in both T cells and tumor cells. When the SPP1-CD44 axis is targeted, T cell function can be restored and the tumor burden can be substantially decreased. This implies that the SPP1-CD44 axis represents a potential target for attaining a more beneficial immune response during HCC treatment [5].

In summary, within the tumor microenvironment (TME), SPP1 is capable of regulating immune cells. It promotes M2 macrophage polarization via the Jak2/Stat3 pathway. Through its interaction with diverse immune cells, it not only impacts the function of immune cells but also might be engaged in the modulation of neuroinflammation. Additionally, in the TME, the knockdown of SPP1 notably restrained the intrusion of M2 tumor-associated macrophages (TAMs) in tumors, which indicates that SPP1 is a prospective objective for immunotherapy.

3. Unraveling the mechanism of SPP1 high expression in lc tumors

3.1. Promotion of M2-type macrophage infiltration

SPP1 emerges in a diverse range of organs. Nevertheless, on the cellular level, its expression is restricted to a handful of cell types including osteoblasts, fibroblasts, macrophages, dendritic cells, lymphoid cells, and monocytes. Additionally, SPP1 is also produced by cancer cells. Increased expression of SPP1 correlates with the accumulation of M2-like TAM in lung adenocarcinomas, and they are both predictive of poor prognosis [6]. SPP1 is expressed through the CD44/PI3K/AKT pathway to promote differentiation into M2-like macrophages. Investigations showed that SPP1+ TAM was identified only among patients having lymph node metastasis when lymph node loci were analyzed, suggesting that SPP1+ tumor-associated macrophages (TAM) facilitate the metastatic spread of colorectal cancer (CRC) cells. Consequently, the inhibition of its function might have a beneficial impact on the treatment of patients with CRLM which may, in turn, affect the progression of LC by promoting angiogenesis and tumor metastasis [7].

3.2. Associated with tumor progression and metastasis

SPP1 upregulation increases the risk of IPF developing into LC through the activation of tumor-promoting macrophages. Crosstalk between SPP1+ macrophages and inflammation-associated cancer-associated fibroblasts promotes the tumorigenic process of IPF. In lung adenocarcinomas (LUADs), the expression level of SPP1 shows a positive correlation with the TNM stage, the emergence of lymph node metastasis, and the extent of infiltration, Moreover, its high expression correlates with unfavorable survival of patients. The reduction in SPP1 expression suppresses the

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motility and penetration of cells in both laboratory in vitro models and living in vivo systems, decreases the presentation of epithelial markers (E-cadherin), and increases the presentation of mesenchymal markers (N-cadherin and waveform protein), thus promoting epithelial-mesenchymal transition (EMT) [6]

3.3. Pathways in the microenvironment affecting tumors

3.3.1. Relevance to the immunosuppressive microenvironment

The expression of SPP1 in the TME correlates with the immunosuppressive microenvironment, which mediates the growth, infiltration, and metastasis of a variety of malignant tumors by interacting with ligands and influencing downstream pathways to keep the TME in a suppressive state.

3.3.2. Influence pathway through CD44 receptor

SPP1 interacts with CD44 receptors on tumor cells to activate downstream pathways and promote tumor progression and immune escape. In HCC, the number of SPP1+ TAMs is higher and the SPP1 receptor CD44 is highly expressed in T cells and tumor cells, Aiming at the SPP1-CD44 axis can revive T cell function and remarkably lessen the tumor load [8].

3.3.3. Influence on intercellular communication

Within the context of lung adenocarcinoma, the ion channel gene GJB2 exerts an influence on intercellular communication through the up-regulation of the SPP1 pathway, and hub genes associated with GJB2 have an impact on intercellular communication by means of the SPP1 pathway, which may affect cellular interactions in the TME [9].

3.3.4. Engagement with diverse cell types within the TME

SPP1 interacts with a multiplicity of cell types within the TME, such as macrophages, fibroblasts, and epithelial cells. These interactions influence the pathways within this environment, which subsequently affects tumor progression and metastasis.

3.4. Tumor drug resistance-related

Studies have shown that the elevated expression of SPP1 is a marker of poor prognosis in LC and aid in the progression of malignancy and the resistance against cisplatin. The overexpression of SPP1 in LC tumor tissues is triggered through a DNMT1-mediated decrease in the methylation degree of the promoter area, which is a DNA methylase whose activity can affect gene expression. In LC, DNMT1 may increase the repellence of LC cells to cisplatin by decreasing the methylation level of the promoter region of the SPP1 gene, leading to the upregulation of SPP1 gene expression. The high expression of SPP1 makes changes in the TME, which affects the penetration and distribution of chemotherapeutic agents such as cisplatin, and thus its efficacy.

3.5. Other Immune cell interactions in the TME of LC

SPP1 expression was positively correlated with the infiltration level of multiple immune cell types such as macrophages, dendritic cells, neutrophils, and CD8+ T cells. Studies have shown that in non-small cell LC (NSCLC), a significant positive correlation is manifested between SPP1 expression and the level of T-cell infiltration, thereby suggesting that SPP1 exerts a regulatory function in modulating the infiltration of T-cells within the tumor microenvironment [2,10]. Through an exploration of the linkage regarding SPP1 expression and the infiltration level of specific immune cell subtypes with

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the utilization of the TIMER database, it was discovered that SPP1 expression bore a significant and positive correlation with the immune infiltration level of cancer-associated fibroblasts (CAFs) in both lung squamous cell carcinoma (LUSC) and lung adenocarcinoma (LUAD). This implies that increased expression levels of SPP1 are associated with increased infiltration of CAFs in the TME. In light of a direct positive link between SPP1 and CAF infiltration and taking into account the potential impact of CAFs on T cell infiltration within the TME, it is reasonable to hypothesize that SPP1 might have an indirect effect on T cell infiltration through modulating the behavior of CAFs. CAFs can secrete a variety of cytokines and chemokines, which can attract T cells into the TME, thus affecting the T cell infiltration Levels.

From the above, the mechanism by which SPP1 is highly expressed in the tumor environment of LC is that it facilitates the polarization of M2-type macrophages through the CD44/PI3K/AKT channel, affecting the downstream pathways in the TME, indirectly affecting the intercellular communication, and interact with a variety of cell types, which in turn affects the progression and metastasis of tumors, and at the same time, the high degree of expression of SPP1 makes the alteration of the TME, thus affecting the penetration and spreading pattern of chemotherapeutic substances such as cisplatin, and thus its efficacy.

4. Potential future LC treatment options targeting SPP1

4.1. Gene therapy targeting SPP1

Direct knockout or silencing of the SPP1 gene by gene editing techniques such as CRISPR/Cas9 may be an effective therapeutic strategy [11]. The CRISPR-Cas9 system is based on the adaptive immune defense mechanism found in bacteria, which helps them combat invading viruses and foreign DNA. In gene editing, researchers design a single-stranded RNA guide molecule (sgRNA) that is complementary to the target DNA sequence. This sgRNA is then introduced into the target cell along with the Cas9 protein complex. The sgRNA directs Cas9 to the specific DNA sequence, enabling it to cleave the double-stranded DNA at that precise location. Z. Regarding LC treatment, the upregulation of the SPP1 gene is tied to a bad prognostic indication and contributes to the advancement of cancer and resistance to cisplatin, a common chemotherapeutic. Therefore, directly knocking down or silencing the SPP1 gene using CRISPR/Cas9 technology may serve as an effective therapeutic strategy. Research has demonstrated that SPP1 knockdown significantly reduces the propagation, translocation and invasive capability of prostate cancer cells [12]. These findings disclose that SPP1 plays an important role in prostate cancer progression and imply that SPP1 could be a potential target for treating prostate cancer bone metastasis.

4.2. Small molecule inhibitors targeting the SPP1 pathway

The development of small molecule drugs that can inhibit the downstream pathways of SPP1, such as inhibitors targeting the PI3K/AKT and ERK1/2 pathways, may aid in suppressing the growth and dissemination of tumor cells as well as the emergence of drug resistance, which has the ability to reduce tumor cell propagation and metastasis through the inhibition of the activity of these pathways, and at the same time, it may increase the sensitivity of the tumor cells to the chemotherapeutic drugs, thus inhibiting the drug resistance Development [13]. The therapeutic potential of this strategy lies in the fact that by precisely inhibiting specific pathways within the tumor cells, the impact on normal cells can be reduced, thus potentially reducing side effects. Additionally, this treatment approach can be combined with other therapies, namely chemotherapy, radiotherapy, or immunotherapy, for the purpose of enhancing the therapeutic effect. It has been shown that the use of chemotherapeutic agents in combination with inhibitors of the PI3K-Akt pathway significantly enhances the effect of chemotherapeutic agents and reduces the IC50 value.

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4.3. Monoclonal antibodies (mAbs) targeting SPP1

The development of mAbs targeting SPP1 can block the interaction of SPP1 with its receptor, thereby inhibiting the migration and invasion of tumor cells [14]. Several studies have presented evidence that the SPP1/CD44 axis contributes to cancer chemoresistance within solid malignancies. As a result, the SPP1/CD44 axis may stand as one of the most significant mechanisms of intercellular communication between cancer cells and TAM. Through targeting SPP1, mAbs may help to overcome tumor drug resistance. The development of mAbs against SPP1 is a promising therapeutic strategy that may effectively inhibit tumor cell motility and infiltration by blocking the interaction of SPP1 with its receptor and is potentially valuable in overcoming tumor drug resistance.

In summary, there are three main directions for potential future therapeutic options targeting SPP1, which are from the use of gene editing technology to directly knockdown or silence the expression of the SPP1 gene; the development of small molecule drugs sufficient to inhibit the downstream pathway of SPP1, which can be used in conjunction with other therapeutic means to improve therapeutic efficacy; and the development of mAbs to SPP1, which, by blocking the interaction of SPP1 with its receptors, may effectively inhibit tumor cell migration and invasion, and have potential value in overcoming drug resistance. By blocking the interaction between SPP1 and its receptor, the development of mAbs against SPP1 may effectively Block the locomotion and penetration of tumor cells and may be of potential value in overcoming drug resistance in tumors.

5. Conclusion

This paper investigated the role of SPP1 in immune escape in LC and its potential as a therapeutic target. SPP1 promotes LC progression by affecting immune cell function and the TME, and its high expression correlates with poor prognosis. The results support SPP1 as an immunotherapeutic target and provide new directions for future therapeutic strategies. However, the TME is highly complex, involving interactions among various cells and pathways. The article might not fully address all relevant factors. While potential therapeutic options targeting SPP1 are suggested, these treatments may not have been completely validated in clinical trials, and their safety and efficacy still require further investigation.

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