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SPP1/Osteopontin in Oncology: A Multifaceted Player in Tumor Progression

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Abstract: Secreted Phosphoprotein 1 (SPP1), also known as Osteopontin (OPN), is a multifunctional glycoprotein widely involved in biological processes such as cell adhesion, migration, signal transduction, and immune regulation. Studies have shown that SPP1 is highly expressed in various tumors and is closely associated with tumor invasion, metastasis, and poor prognosis. Additionally, SPP1 can help tumor cells evade immune surveillance by regulating the function of immune cells in the tumor microenvironment. This article reviews the research progress of SPP1 in tumors from three aspects: first, the molecular biological characteristics of SPP1; second, the clinical value of SPP1 as a prognostic marker in various tumors, analyzing the correlation between its expression levels and patient prognosis; and finally, the mechanisms of SPP1 in the tumor microenvironment. Through this review, we aim to provide a theoretical foundation for a deeper understanding of the role of SPP1 in tumor development and to offer new insights and directions for developing SPP1-based tumor diagnostic markers and targeted therapeutic strategies.

Keywords: Secreted phosphoprotein 1; Tumor microenvironment; Prognostic marker; Osteopontin

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1. Structure and function of SPP1

The SPP1 gene is located on human chromosome 4q13 and consists of 7 exons and 6 introns [1,2]. The encoded protein is a secreted glycoprotein with a molecular weight of approximately 44 kDa. The SPP1 protein contains multiple functional domains, including the Arg-Gly-Asp (RGD) sequence, calcium-binding domain, and integrin-binding domain [3]. The RGD sequence is a key region for SPP1 binding to integrin receptors, while the calcium-binding domain is involved in the mineralization of the extracellular matrix [4]. SPP1 binds to cell surface receptors (such as integrin αvβ1, αvβ3, αvβ5, α8β1, α5β1) [2], activating downstream PI3K/AKT, MAPK, and NF-κB signaling pathways, thereby

regulating cell proliferation, migration, invasion, and survival [5–8]. Post-translational modifications (PTMs) of SPP1, including phosphorylation, glycosylation, sulfation, and proteolytic processing, are pivotal mechanisms underlying its functional diversity and regulatory complexity. These modifications profoundly influence its biological activity and interactions with distinct receptors, enabling precise regulation of cellular adhesion, immune responses, and disease progression[9]. Additionally, SPP1 is involved in immune regulation by modulating the functions of macrophages, CD8+ T cells, and dendritic cells [10–13], influencing the immune status of the tumor microenvironment and the efficacy of immunotherapy.

2. SPP1 as a prognostic marker in various tumors

The CancerSeek test uses liquid biopsy to screen for up to eight solid tumors, with SPP1 being one of the eight protein markers [14]. Pan-cancer analysis indicates that SPP1 is highly expressed in various tumors, including breast cancer, liver cancer, lung cancer, gastric cancer, and colorectal cancer [15]. Its expression levels are correlated with tumor stage, invasiveness, and metastatic potential.

In lung adenocarcinoma, SPP1 regulates the downstream molecule COL11A1, promoting invasion and migration, and may be a marker for metastasis and prognosis [16]. In melanoma patient samples, SPP1 is highly expressed and enhances cell proliferation, migration, and invasion, making it a potential driver of melanoma. Overexpression of SPP1 predicts poor prognosis in melanoma [17]. In liver cancer, a bioinformatics analysis found that SPP1 can activate oncogenic signaling pathways and promote epithelial-to-mesenchymal transition (EMT), thereby enhancing resistance to receptor tyrosine kinase inhibitors (TKIs) such as sorafenib and lenvatinib. Pre-treatment plasma SPP1 levels are a potential biomarker for predicting treatment response, with higher pre-treatment plasma SPP1 levels being an independent predictor of poorer progression-free survival (PFS) and overall survival (OS) in advanced HCC patients treated with TKIs [18].

SPP1 affects tumor prognosis through various mechanisms. It activates integrin-mediated signaling pathways, enhancing tumor cell migration and invasion [19,20]. SPP1 can also induce angiogenesis by upregulating the expression of angiogenic factors such as VEGF, promoting tumor vascularization and providing nutritional support for tumor growth and metastasis [21]. Additionally, SPP1 helps tumor cells evade immune surveillance by inhibiting anti-tumor immune responses, such as suppressing T cell activity and promoting M2 macrophage polarization [5,22].

3. Role of SPP1 in the tumor microenvironment

The tumor microenvironment is composed of the structural framework of tumor tissue, including stromal cells such as connective tissue cells, vascular components, and immune cells. These components play a crucial role in tumor metastasis and progression. Cancer-associated fibroblasts (CAFs) are important components of the tumor microenvironment and can secrete various cytokines and growth factors to promote tumor progression [23]. SPP1 promotes tumor growth and survival by regulating tumor cell reprogramming. In prostate cancer, androgen inhibition activates TGF-β signaling, reprogramming inflammatory CAFs into SPP1+ myofibroblasts, which further leads to resistance to androgen deprivation therapy (ADT) through the SPP1-ERK paracrine mechanism [24]. Blocking SPP1 derived from CAFs can resensitize prostate cancer cells to ADT. SPP1 binds to integrin receptors on CAFs, activating their proliferation and activation, thereby promoting tumor cell invasion and metastasis [25]. Additionally, SPP1 can induce CAFs to secrete more extracellular matrix (ECM) components, altering the physical properties of the tumor microenvironment [26].

Another immune cell closely related to SPP1 is tumor-associated macrophages (TAMs). Emerging evidence

underscores the pivotal role of TAMs in driving oncogenic processes, spanning tumor initiation, proliferation, immunosuppression, angiogenesis, and metastatic dissemination [27]. SPP1 maintains the M2 phenotype of macrophages, which have immunosuppressive functions that inhibit CD8+ T cell activity and promote tumor immune evasion [28]. TAMs secrete cytokines and growth factors that act on both malignant and endothelial cells, while simultaneously releasing proteolytic enzymes to facilitate ECM degradation, such as SPP1 stimulates IL-12 and inhibits IL-10 production at sites of inflammation in macrophages, with a strong proinflammatory effect [29]. Past research found that macrophages with high SPP1 expression show poor response to anti-PD-L1 therapy, with limited clinical benefits. This may be due to the significant concentration of SPP1+ macrophages in tumor tissue and their synergistic interaction with fibroblasts, promoting connective tissue proliferation in the tumor microenvironment and hindering the efficacy of immunotherapy [30].

SPP1 also plays a key role in cellular metabolic reprogramming. To meet the demands of rapid proliferation, tumor cells often undergo metabolic reprogramming to adapt to nutrient-deprived microenvironments. This reprogramming includes changes in glucose metabolism, glutamine metabolism, and lipid metabolism [31]. In the process of tumor metabolic reprogramming, SPP1 may support tumor cell growth and survival by influencing key metabolic pathways. For example, SPP1 may promote glycolysis in tumor cells by regulating key enzymes in the glucose metabolism pathway, such as pyruvate kinase M2, thereby supporting tumor cell survival under hypoxic and nutrient-poor conditions [32]. Additionally, SPP1 may promote the use of glutamine as an alternative energy source in the absence of glucose, maintaining cell proliferation and growth [33]. In summary, SPP1 promotes tumor growth and survival by regulating tumor cell metabolic reprogramming. This metabolic reprogramming not only helps tumor cells survive in unfavorable microenvironments but may also provide new targets and strategies for tumor treatment.

4. Conclusion and future perspectives

SPP1 as a multifunctional glycoprotein, has been widely demonstrated to play a crucial role in tumorigenesis and progression. Studies have shown that SPP1 participates in tumor progression through multiple molecular mechanisms. Firstly, it activates key signaling pathways such as PI3K/AKT and MAPK, promoting tumor cell proliferation and survival. Secondly, SPP1 enhances tumor cell migration and invasion by interacting with molecules such as integrin receptors and CD44. Furthermore, SPP1 modulates the tumor microenvironment by promoting angiogenesis, matrix remodeling, and immune suppression, thereby creating favorable conditions for tumor progression. Clinical research data further confirm that high expression of SPP1 is significantly associated with poor prognosis in various malignancies, including breast cancer, liver cancer, and lung cancer, suggesting its potential as an important prognostic biomarker and therapeutic target.

However, there are still many unknowns regarding the specific mechanisms of SPP1 in tumors. Firstly, the regulatory mechanisms of SPP1 expression in different types of tumors have not been fully elucidated. Secondly, the interaction network between SPP1 and other components of the tumor microenvironment, such as immune cells and fibroblasts, requires further exploration. Additionally, the mechanisms by which SPP1 mediates tumor immune evasion remain to be thoroughly investigated. Addressing these scientific questions will contribute to a more comprehensive understanding of the role of SPP1 in tumor progression. Given the significant role of SPP1 in tumors, the development of targeted therapeutic strategies against SPP1 holds broad clinical application prospects.

In conclusion, as a novel therapeutic target in oncology, in-depth research on SPP1 will not only help elucidate the molecular mechanisms of tumorigenesis and progression but also provide new strategies for precise diagnosis and treatment of tumors. With a deeper understanding of the mechanisms of SPP1 and the development of targeted drugs, it is believed that SPP1 will play an important role in future cancer diagnosis and treatment, offering new hope for

improving the prognosis of cancer patients.

Disclosure statement

The author declares no conflict of interest.

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