Research Progress of SHP2 Modulator in Anti-Tumor Biological Mechanism

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Abstract: Src homology phosphotyrosyl phosphatase 2 (SHP2) is a protein tyrosine phosphatase encoded by PTPN11 that catalyzes the dephosphorylation of proteins at the tyrosine site. SHP2 can not only regulate the growth and proliferation of tumor cells but also mediate the immune escape of tumor cells by affecting the tumor microenvironment, which plays a dual biological function in tumor regulation and is a promising tumor therapeutic target. This paper comprehensively reviewed the research progress on the biological functions of SHP2 regulators, introduced the structure and basic mechanism of SHP2 in detail, and deeply discussed the biological functions in the pathological process of tumors. Meanwhile, the research and development status of SHP2 regulators, including small molecule inhibitors and biologics, were analyzed. The research challenges and application prospects of SHP2 modulators in the field of tumor immunotherapy were discussed.

1 Introduction

SHP2 serves a critical function in cell signal transduction and preserves its normal function, which is crucial to the physiological balance of organisms. The study of SHP2 regulators provides a new way to understand and intervene in related biological processes. The in-depth study of the biological function of SHP2 regulators will help to reveal its complex mechanism of action in health and disease states and bring new breakthroughs in the diagnosis and treatment of diseases.

2 Structure and basic mechanism of SHP2

2.1 Structure

SHP2 (Src homology phosphotyrosyl phosphatase 2, SHP2) is a widespread cytoplasmic nonreceptor protein tyrosine phosphatas (PTPs) encoded by the proto-oncogene PTPN11 [1][2]. SHP2 consists of four major components, including two Src homology 2 (SH2) domains (N-SH2 and C-SH2), a highly conserved PTP catalytic domain, and a C-terminal tail containing phosphorylation sites (Figure 1) [3][4]. Two SH2 domains identify and attach to phosphotyrosine, which is the first step in SHP2 functioning. The intermediate catalytic domain contains amino acid residues that exert phosphatase activity and have tyrosine dephosphorylation of substrate proteins. C-tail can regulate the interaction between proteins and has a role in subcellular localization [5].

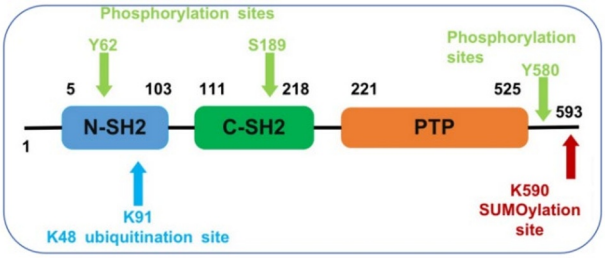

Figure 1. SHP2 structure

2.2 Action mechanism

In signal transduction, SHP2 mainly interacts with membrane receptors of receptor tyrosine kinases (RTKs). When RTKs are activated by ligands, SHP2 is concentrated near the membrane and phosphorylated, thereby activating its phosphatase activity. Activated SHP2 can dephosphorylate downstream signaling molecules, such as guannylate activating protein (RAS-GAP) dephosphorylation can enhance Ras activity, thereby activating mitogen-activated protein kinase (RAS-MAPK) signal transduction cascade.

At the same time, SHP2 can also interact with other signaling pathways, such as phosphatidylinositol 3 kinase (PI3K-AKT), to form a complex signal regulation network [3]. In addition, SHP2 also serves a critical function in tumor immune regulation, thus achieving the dual efficacy of the combination of targeted therapy and immunotherapy.

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2.2.1 Dual biological functions of SHP2 regulators in signal transduction

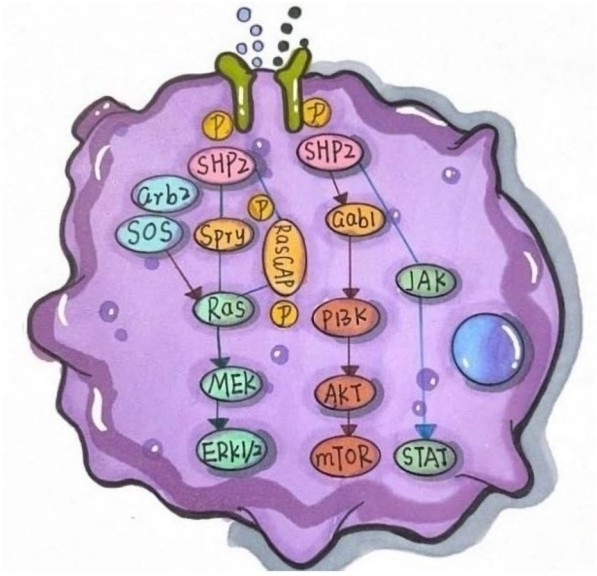

Figure 2. The dual functions of SHP2 in tumor cells.

Stimulated by extracellular signals such as cytokines or growth factors, SHP2 can bind to growth factor receptor-bound protein 2, son of sevenless, Grb2 associated binder-1, Ras GTPase-activating protein (RasGAP), and Sprouty Protein interactions are involved in the regulation of RAS-RAF-MEK-ERK, PI3K-AKT-mTOR (mammalian target of rapamycin) and JAK-STAT pathway, mediating biological effects, for example, cell development, diffusion, differentiation and migration [6][7]. Studies have shown that SHP2 can be used as both a carcinogenic factor and a tumor suppressor to regulate the diffusion, differentiation, invasion, and metastasis of cancer cells, and significantly impacts tumor incidence, progression, and prognosis (Figure 2) [3].

In general, PTPN11 variants correlate strongly with blood cancer incidence and developmental disorders, including 35% of juvenile myelogenous leukemia, 50% of Noannan's syndrome, 80% of LEOPARD syndrome, 10% of myelodysplastic syndrome, 7% of precursor B-cell acute lymphoblastic leukemia, and 5% of acute myeloid leukaemia [8][9].

In addition, by interacting with the kirsten rat sarcoma virus (KRAS) and epidermal growth factor receptor (EGFR), the synergistic effect of mutations of other upstream signaling factors, SHP2 overexpression or mutation is also involved in the occurrence and growth of solid tumors, for example, malignancies of the breast, lung, liver, stomach, larynx, and oral cavity [3]. In different biological contexts, SHP2's "double-edged sword" function based on substrate specificity significantly increases its functional complexity in different diseases [3].

SHP2 exhibits elevated expression across diverse cancer cell types and is involved in malignant biological behaviors, for example, infinite proliferation, metastasis, invasion, metabolic abnormalities, and immune escape of tumor cells. SHP2 plays a carcinogenic role in most tumors, For example, in breast cancer, SHP2 mainly regulates the stability of cyclin D1 through the PI3K-AKT-Glycogen synthase kinase-3β (GSK3β) signaling pathway to promote the proliferation of breast cancer cells [10]. In some tumors, SHP2 can also play a certain anticancer role, for example, SHP2 plays an anticancer role in lung adenocarcinoma cell A549. SHP2 suppression boosts lung adenocarcinoma cell growth, induces cisplatin resistance in A549 cells, and impairs apoptosis [11]. In addition, the dual role of SHP2 in tumorigenesis and development is also reflected in different stages of the same tumorigenesis and development, and the difference in its role depends on the heterogeneity of cells and the different signaling pathways of SHP2. Research has demonstrated that the inhibition of SHP2 exerts a suppressive effect during the early stages of hepatocellular carcinoma and a promotive effect during the advanced stages of the disease [12]. In liver cancer, whether SHP2 plays a role in promoting or suppressing cancer has been controversial, and the specific pathological reasons remain to be further explored.

SHP2 also affects tumor stem cell division and specialization by DNA interaction at oncogenes. For example, in tumor cells, SHP2 can promote cell cycle processes by interacting with cyclin D [3]. Current studies have shown that [11] SHP2 functions related to cell cycle mainly include the following aspects: (1) Regulation of cell cycle: Differential expression of SHP2 in cell cycle has been found in all benign and malignant tumors, and the expression levels of SHP2 in malignant tumors were generally observed to be significantly higher compared to those in benign tumors; (2) Involved in DNA damage repair; (3) Involved in cell differentiation; (4) Maintaining chromosome stability; (5) Regulate gene transcription; (6) Participate in gene expression regulation.

In tumors, SHP2 is involved in the genesis and development of tumors by regulating tumor angiogenesis and inhibiting apoptosis. Therefore, inhibition of SHP2 can be used as a new target for tumor treatment, and also provide a new idea for tumor treatment. Therefore, an in-depth study of the mode of action of SHP2 in tumor occurrence and development is helpful in expressing its biological function, so as to establish a conceptual underpinning for the prevention, diagnosis, and treatment of malignant tumors.

At present, SHP2 has been identified as a target for various cancers such as lung, breast, prostate, pancreatic, and cervical malignancies [13]. The expression of SHP2 is obviously up-regulated in many tumors, so the malignant degree of tumors can be judged by detecting the expression level of SHP2. In leukemia, the activation and mutation of SHP2 can lead to its continuous activation and enhance the diffusion and survival capacity of leukemia cells [14]. The detection of different types of cervical cancer tissues indicated that the expression of SHP2 was observably upregulated in cervical cancer tissues, and its expression was negatively correlated with regard to patient survival probability, indicating that SHP2 could be used as a predictive factor for prognosis in cervical cancer patients [3][11]. In prostate cancer cells, SHP2 interacts with several target genes it regulates. In addition, the survival time of cancer patients with elevated SHP2 levels was significantly shorter than that of patients with reduced

SHP2 levels. Studies have shown that SHP2 serves a critical function in the occurrence and development of prostate cancer, and SHP2 is negatively correlated with the overall survival of prostate cancer patients. In solid tumors, such as lung cancer and gastric cancer, SHP2 expression can promote the malignant transformation of tumor cells [13]. Through the activation of carcinogenic signaling channels such as MAPK and PI3K-AKT, tumor cells acquire stronger proliferation, anti-apoptosis and invasion capabilities [3][11]. In conclusion, SHP2 serves a critical function in the development of diverse types of tumors and has the underlying to be used as a biological therapeutic goal for tumors.

2.2.2 Role of SHP2 in immuno-oncology

SHP2 is an enzyme that hydrolyzes proteins in the extracellular matrix into small molecules and keeps them active, thereby inhibiting their role in tissue damage and repair. SHP2 serves a critical function in the immune system, it can activate or inhibit the differentiation of immune cells, thus affecting the normal conduct of the immune response. SHP2 is considered a therapeutic target in certain diseases such as autoimmune diseases and immunoneoplasms. At the same time, SHP2 plays an important role in primary autoimmune diseases, which are associated with immune system abnormalities caused by SHP2 deficiency. The immune response caused by SHP2 deficiency can damage normal tissue and affect human health.

In tumor immunotherapy, SHP2 activity is also associated with immune escape. Tumor cells can use SHP2 to inhibit the antitumor activity of immune cells. For example, by regulating immune checkpoint signaling channels such as programmed death receptor (PD-1), SHP2 can be able to tumor cells to evade the attack of the human immune system and reduce the effect of immunotherapy [6].

In addition, SHP2 regulates signal transduction in immune cells. In T cells, SHP2 takes part in the T cell receptor (TCR) signaling pathway. Proper regulation of SHP2 can enhance the activation and proliferation of T cells, so that T cells can better recognize and kill tumor cells. For example, by inhibiting SHP2, it is possible to prevent the over-activation of signaling channels associated with T cell depletion and maintain the continued anti-tumor function of T cells. For macrophages, SHP2 regulators can affect the polarization of macrophages. Macrophages have two polarized states: M1 (pro-inflammatory, anti-tumor) and M2 (anti-inflammatory, pro-tumor). SHP2 regulation can promote the polarization of macrophages towards M1 type, enhance their ability to phagocytic tumor cells and release pro-inflammatory cytokines, and thus inhibit tumor growth [11].

3 Research status of SHP2 modulators

According to the binding mode, SHP2 inhibitors currently used in the field of tumor immunity can be divided into orthostatic inhibitors and allosteric inhibitors. Among them, PHPS1 is the orthostatic inhibitor, and RMC-4550, BBP398 and HBI-2376 are allosteric inhibitors [15][16][17][18].

3.1 PHPS1

Phenylhydrazonopyrazolone sulfonate 1 (PHPS1) is a kind of specific SHP2 is compose inhibitor can be combined with SHP2 inhibits PTP activity center inhibit phosphorylation of tyrosine phosphatase, blocking SHP2 downstream RAS-MAPK signaling pathways, play a role of anti-tumor. In addition, PHPS1 can also regulate the immune microenvironment and play a role in tumor immune regulation [15]. SHP2 is a key regulator of eosinophil differentiation and promotes the formation of eosinophils, which can infiltrate airway and lung tissue, thereby causing allergic asthma. PHPS1 can inhibit SHP2, block the differentiation of eosinophils, and reduce allergic airway inflammation.

3.2 RMC-4550

RMC-4550 was developed by Revolution Medicine. A high-potential and highly selective allosteric inhibition of SHP2 synthesized by the company using SHP099 as a lead compound [19]. Similar to SHP099, RMC-4550 also acts as a tumor suppressor by stabilizing the autoinhibitory conformation of SHP2 and blocking RAS-ERK signaling. RMC-4550 can also modulate the immune microenvironment to infiltrate $CD8^+$T cells, inhibit CSF-1 receptor signaling, and further selectively deplete M2-type macrophages, via $CD8^+$T cells or IFN-γ mechanisms increase the number of M1-type macrophages and activate tumor immune responses in vivo. Worth noting, the study showed that RMC-4550 had a significant effect on the expression of V-raf murine sarcoma viral oncegene homolog B class 3 mutations, oncogenic RAS mutations, and neurofibromatosis type 1 (NF1) loss-of-function mutations all play effective anti-tumor effects in human cancer models.

3.3 BBP398

BBP398 was developed by BridgeBio Pharma. It is a highly selective, highly potential, and orally available small molecule allosteric inhibitor of SHP2 [17]. BBP398 not only acts as a single drug, but also can be used in combination with other MAPK signaling pathway inhibitors to exert a synergistic inhibitory effect on tumor growth. At present, the application of BBP398 combined with PD-1 antibody in the field of tumor immunity has been reported, but whether BBP398 alone has anti-tumor immune function remains to be studied [20].

3.4 HBI-2376

HBI-2376, an orally bioavailable, selective allosteric inhibitor of SHP2, is being studied in clinical trials in patients with KRAS or EGFR mutated solid tumors such as non-small-cell lung cancer and colon cancer. In addition to regulating the growth and proliferation of

tumor cells,HBI-2376 can also inhibit tumor growth by regulating the activity of immune infiltrating cells in the tumor immune microenvironment, such as inhibiting the infiltration of M2 macrophages. Compared with RMC-4550, HBI-2376 had a better anti-tumor effect either as a single agent or in combination with PD-1. In light of this, HBI-2376 has been approved by the US Food and Drug Administration for clinical studies in patients with non-small cell lung cancer or colorectal cancer [18]

4 Summary

SHP2 not only serves a critical function in promoting cancer, but also serves a critical function in suppressing cancer during the genesis and development of tumor cells. SHP2 is a potential target for cancer therapy, and the growth of its modulators is already as a hot pints in current tumor-targeting drug research [3]. In recent years, with the deepening of tumor immunotherapy, the application of SHP2 modulators in the field of tumor immunity has opened a new chapter. SHP2 modulates several immune checkpoint pathways. and mediates the occurrence of immune escape, so the development of SHP2 modulators is particularly important for enhancing tumor immune response. SHP2 modulators can not only regulate the tumor microenvironment through monotherapy but also improve the immune microenvironment in combination with immune checkpoint blockers or kinase-targeting drugs, thereby synergistic anti-tumor influence [21]. So far, the application of normal inhibitors, allosteric inhibitors and activators targeting SHP2 in the field of tumor immunity has been reported, among which allosteric inhibitors targeting the unique allosteric regulatory mechanism of SHP2 play a significant advantage in tumor immune regulation [17]. It is worth mentioning that clinical trials on the single use of SHP2 allosteric inhibitors and their combination with immune checkpoint blockers have attracted much attention [22]. However, there are still many problems to be solved in the study of SHP2 modulators in tumor immune regulation.

As a result of the highly conserved active site of SHP2 phosphatase and the polar charged environment, the normal inhibitors targeting the phosphatase catalytic domain have the shortcomings of low selectivity, limited membrane passage and low oral absorption, which limits the clinical application of SHP2 normal inhibitors. Due to the inherent non-specific and possible off-target effects of allosteric inhibitors, it is urgent to develop more effective and specific inhibitors. In addition, mutations may destroy the integrity of SHP2 domain and lead to inhibitor resistance, so the combination of SHP2 allosteric inhibitors with upstream and downstream inhibitors and bypass signaling molecules may be a new approach. It is worth mentioning that SHP2 activators are a double-edged sword, which can be used to treat diseases related to SHP2 inactivation. However, overactivation of SHP2 may also have a potential carcinogenic risk, so SHP2 activation status should be precisely regulated. In addition to PD-1/PD-L1, the combination mechanism of SHP2 inhibitors with other immune checkpoint blockers such as VISTA, CTLA-4, CSF-1R, LAG-3, TIM-3, TIGHT, SIRP-α, BTLA, LILRB and SIGLC-7 remains to be further studied [22]. The combination of SHP2 inhibitors and activators is rarely reported. In addition, the molecular mechanism of the combination of SHP2 inhibitors and Kinase-targeting drugs to regulate tumor immunity still needs to be further studied to lay a foundation for the clinical application of the combination of the two [21]. In summary, targeting SHP2 is a promising method of tumor immunotherapy, which can not only inhibit tumor growth by targeting signaling pathways such as RAS and PI3K, but also enhance anti-tumor immune function, thus achieving the dual efficacy of the combination of targeted therapy and immunotherapy [11]. In addition, combining SHP2 modulators with immune checkpoint inhibitors shows promise as a tumor immunotherapy approach, potentially offering effective cancer treatment for a variety of patients with different types of cancer [15].

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