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Role of SHP2 in Colorectal Cancer Development and anti-Tumor Immunity

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Abstract. Colorectal cancer (CRC), with the second fatality rate and the third incidence rate, is among the most prevalent malignant tumors worldwide. Therefore, it is an important task to find targeted drugs for colorectal cancer clinic therapy. Protein tyrosine phosphatase, non-receptor type 11 (PTPN11) encodes SHP2, a non-receptor tyrosine phosphatase, which is widely expressed in a variety of tissues and cells in the human body. In recent years, a number of studies have shown that SHP2 plays an important role in regulating immune cell function and colitis-related colorectal cancer progression. With the emergence of SHP2 allosteric inhibitors, SHP2 has become a promising target for the treatment of colorectal cancer patients. This article mainly discusses the structure, function, the regulatory mechanism of SHP2 in the tumor microenvironment (TME) of CRC, and the current state and prospect of SHP2 allosteric inhibitors in the therapy of CRC. With the advancement of clinical trials for various solid tumors, future research will be able to usher in more effective and safe SHP2-targeted therapies, providing more beneficial treatment options for CRC patients.

Keywords: SHP2; Signal pathway; Anti-tumor immunity; Colorectal cancer.

1. Introduction

Protein tyrosine residue phosphorylation and dephosphorylation have significant regulatory functions in cell signal transmission, which can change cell proliferation, differentiation, migration, apoptosis and other biological processes. Phosphorylation is completed by Protein Tyrosine Kinase (PTK), while phosphorylation is performed by Protein Tyrosine Phosphatase (PTP). Numerous illnesses are linked to dysregulation of reversible phosphorylation, including tumors, inflammation, and diabetes [1]. The protein tyrosine phosphatase (PTP) family includes multiple members, among which SHP2 is a non-receptor PTP encoded by the human PTPN11 gene and widely expressed in multiple tissues. The structure of SHP2 consists of two Src homology 2 (SH2) domains, a catalytic PTP domain, a proline-rich motif, and two tyrosine phosphorylation sites at the C-terminus. Normally, the interaction between the N-SH2 domain and the PTP domain limits the activity of SHP2, preventing the substrate from entering the catalytic site, thereby placing SHP2 in a self-inhibited state. When cells are stimulated by growth factors (GF) or cytokines (CK), the N-SH2 domain selectively binds to phosphorylated tyrosine residues, thereby relieving this self-inhibited state [2].

SHP2 plays a key role in cell signal transduction, and the precise regulation of its activity is essential for maintaining normal cell function. SHP2 ensures that the enzyme remains in an inactive state in the absence of external signal stimulation through a self-inhibitory mechanism between its N-SH2 domain and the PTP domain. However, under the action of growth factors or cytokines, SHP2 releases its self-inhibition by binding to phosphotyrosine residues, thereby activating its catalytic function. This process is essential for a variety of biological processes such as cell proliferation, differentiation and survival. Abnormal SHP2 activity, especially dysregulation caused by gene mutations or abnormal signaling pathways, may be associated with the occurrence of a variety of diseases, including cancer and developmental disorders [2].

The abnormal activation of SHP2 in tumors can be divided into following three forms: ① Gain-of-function (GOF) mutation. ② Overexpression or improper expression of SHP2 adaptor protein. For instance, overexpression of Gab2 in breast cancer leads to excessive activation of SHP2. ③ PTK

with oncogenic activity, such as BCR-ABL, can increase the degree of phosphorylation of substrates that SHP2 binds to thus encourage aberrant SHP2 activation. Among the above three, the most common is the GOF mutation of SHP2. This mainly occurs in the coding SH2 domain of PTPN11 gene, which is encoding SHP2. However, SH2 binds to the catalytic site to make SHP2 activity self-inhibited. Hence, the mutation usually enhances the activity of SHP2 to various extent, as it is called gain-of-function mutation. The most common GOF mutations are E76K and D61G/Y. GOF mutation was first found in hematological malignancy with a mutation rate of 7.52%. With the expansion of research, SHP2 mutation was also found in solid tumors. Studies related to solid tumors reported lung cancer, liver cancer, breast cancer, etc., but the mutation rate of SHP2 in the above solid tumors was very low. The SHP2 mutation rate of lung cancer, liver cancer and breast cancer were 1.79%, 0.47% and 0.15%, respectively. The highest SHP2 mutation rate of solid tumors was 5.75%, which was found in CRC [3]. The discrepancy of SHP2 mutation rate between CRC and hematological malignancies was so small that it is equally clinically significant to study the influence of SHP2 mutation on CRC.

2. Pathways Regulated by SHP2 in CRC Cells

CRC is mostly sporadic, caused by environmental, dietary and inflammatory factors, accounting for about 75%. In the progression of CRC, inflammation and/or CKs mainly involved in the Ras/ERK, JAK/STAT and PI3K/PKB pathways to influence the proliferation, apoptosis and metastasis of cancer cells. In addition, genetic forms of CRC also include polyposis syndrome and non-polyposis syndrome. HNPCC, or Lynch syndrome, is the most commonly inherited non-polyposis condition. The most prevalent and well-known hereditary polyposis syndrome is called familial adenomatous polyposis (FAP), with an incidence proportion of about 0.5%-1% of it in CRC, in which the Wnt pathway is over-activated [4]. In the process of these signal transduction, SHP2 acts as a downstream crucial member involved in the pathway and directly or indirectly interacts with a variety of signal receptors located on the membranes. In addition, it is also associated with a variety of signal transduction mediators. Through this series of functions, SHP2 regulates various biological processes, thereby affecting the tumorigenesis and progression of CRC [5].

2.1. Ras/ERK Pathway

Ras is a small GTP-binding protein that is activated upon binding to GTP. Activated Ras activates Raf protein, also known as MAPKKK, and then, Raf activates a phosphorylation cascade. Finally, MAPK enters the nucleus to regulate transcription factor activity. In normal circumstances, cells are stimulated by external stimuli to produce signal molecules such as EGFR. K-Ras is temporarily activated and activates downstream signaling proteins, followed by rapid inactivation, and its activation/inactivation effect can be controlled. However, the mutant K-Ras protein can still keep active in the absence of the stimulation of signal molecules. Ras can bind to GTP, but cannot hydrolyze it to GDP, and its functional state is uncontrollable, causing cancer cells to continue to proliferate [6].

SHP2 plays an important role in the complete activation of the Ras/ERK pathway. In response to extracellular stimuli, SHP2 recruits phosphotyrosine binding substrates such as GRB2 to membrane receptor tyrosine kinases (RTKs). GAB1/2 (GRB2-related binding protein 1/2) is an important SHP2 binding molecule. GAB has two SHP2 binding sites that, during GAB1/2 activation, are auto-phosphorylated in the first step, resulting in a double-phosphorylated tyrosine activation motif that attaches to the SHP2's SH2 domain, and then SHP2 is activated [7]. Since SHP2 binds to GRB2 via GAB1/2 or GRB2 attaches to GF receptors which are already phosphorylated, SOS proteins are aggregated at the cell membrane and in turn act as guanine nucleotide exchange factors (GEF) to activate downstream signaling. SHP2 can also indirectly bind to molecules in the Ras/ERK pathway, such as Src family kinases (SFK), then trigger a series of stimulating signals through rapid dephosphorylation of the conservative tyrosine residues in SFK [8]. Besides, SHP2 can also regulate the Ras/ERK pathway through other multifaceted mechanisms [9].

Prahallad et al. performed a genetic screen based on RNA interference in BRAF-mutated colon cancer cells to search for a certain phosphatase whose knockdown induced sensitivity of CRC cells to BRAF inhibitors [10]. And it was found that SHP2 inhibition sensitized CRC patients to BRAF inhibitors, due to the blockade of signal transduction between the RTK and the Ras-MEK-ERK pathway by SHP2 inhibition. Rivard et al. [11] demonstrated that in CRC cells, and in intestinal epithelial cells (IECs) which are transformed by oncogenic KRAS, the invasion, proliferation, and other processes can be restricted by SHP2-silencing.

In conclusion, existing studies have shown that SHP2 has a complex regulatory role in the Ras pathway, and gene knockout or inhibition of SHP2 may inhibit Ras/ERK signaling, thereby limiting the progression of CRC which depends on RTK activation or mutant Ras proteins [12].

2.2. Wnt/β-catenin Pathway

Mutations in the adenomatous polyposis coli (APC) gene have been detected in more than 80% of CRC patients. APC is involved in the composition of destruction complex in the Wnt pathway, which is responsible for the degradation of β-catenin. About 95% of APC mutations result in the formation of premature stop codons in downstream, which makes the APC protein truncated. Consequently, β-catenin is difficult to degrade, and the Wnt pathway is over-activated. After entering the nucleus, β-catenin binds to TCF and LEF to regulate gene expression [13].

There are few studies on the association between SHP2 and Wnt in CRC, but some research still demonstrates their connection. Zhang et al. [14] demonstrated that E76K, a GOF mutation of SHP2, promoted the tumor progression of CRC and up-regulated Wnt/β-catenin signaling, enhancing epithelial-mesenchymal transition (EMT) in CRC. In addition, Wu et al. [15] found that, in CRC cells, which SRY transcription factor 7 (SOX7) was overexpressed, using PHPS1 to inhibit SHP2 expression, the expression of Wnt and β-catenin would be increased. As it has been reported that SOX7 can inhibit Wnt signal, researchers demonstrated that the regulation of SOX7 to Wnt signal was mediated by SHP2. But the results also showed that when SHP2 was overexpressed, inhibition of it would increase the activation of Wnt/β-catenin/ROS pathway, thus inhibiting the proliferation and migration of CRC cells. Based on these studies, it is possible that lack of or over-activation of SHP2 can both increase the Wnt/β-catenin signal, thus promoting the progression of CRC.

2.3. IL-6/JAK/STAT3 Pathway

When T cells and fibroblasts get activated, they produce IL-6. As a pro-inflammatory CK, IL-6 plays a crucial role in the transformation of colorectal inflammation to cancer. Studies have shown that bloody IL-6 levels, both in inflammatory bowel disease (IBD) and CRC patients, are significantly increased [16]. The binding of IL-6 to its receptor, IL-6R, causes dimerization of the receptors, which consequently triggers JAK phosphorylation and activation. Activated JAK catalyzes the phosphorylation of tyrosine residues in the intracellular segment of the receptor. STAT3 binds to the phosphotyrosine residues of the receptors through its SH2 domain, and then is phosphorylated by JAK to form a dimer, which enters the nucleus to regulate CRC cell proliferation, survival and angiogenesis. IL-6 plays an important role in promoting tumor growth in colitis-associated colon cancer. STAT3, as a downstream molecule, is essential in its signal transduction [17].

Studies have shown that SHP2 acts as a tumor suppressor and negatively regulates STAT3 activity through dephosphorylation in CRC progression [18]. Huang et al. [19] found that SHP2 knockdown promoted the proliferation of SW480 cells induced by IL-6, while SHP2 could inhibit the proliferative and migrative processes of CRC cells, and this was because of that SHP2 played a tumor suppressor function by regulating STAT3 phosphorylation.

Cai et al. [20] used Western Blot to detect the expression of SHP2 in colon cancer cells SW480, SW620, CACO2, HCT116, HT29 and normal colonic epithelial cells FHC and CCD841 in vivo, and they found that: SHP2 expression was significantly reduced in colon cancer cells compared with normal colon epithelial cells. Rivard et al. [11], in their research, demonstrated that IEC cells

specifically expressing the SHP2E76K GOF mutant were not enough to induce occurrence of tumor in mice, but could significantly promote tumor development with expression of ApcMin/+. In contrast, colitis-associated CRC was linked to the chronic activation of Wnt/β-catenin, NF-κB, and STAT3 signaling in the colonic mucosae of mice with SHP2 conditional deletion in IEC as they aged. In summary, the current findings suggest that SHP2 regulates multiple pathways in cancer cells during the progression of CRC. SHP2 usually promotes tumor progression through Ras/ERK pathway. As for Wnt/β-catenin and IL-6/STAT3 pathways, whether it can promote or restrict tumorigenesis depends on tumor inflammatory microenvironment [9, 11].

3. Pathways Regulated by SHP2 in Immune Cells

Many studies have illustrated the regulatory mechanism of SHP2 on immune cells in the TME, including T lymphocytes and macrophages. Through involved in a variety of pathways, SHP2 plays a regulatory role in the proliferative and activation processes of immune cells, thereby affecting the progression of CRC.

3.1. T lymphocytes

SHP2 plays a role in T cell signaling downstream of immunological checkpoint PD-1, which is important for cancer treatment. After the dimerization of PD-1, the immunoreceptor tyrosine switch motif (ITSM) at its C-terminus binds to the SH2 domain of SHP2 to encourage tumor cells' immune escape and activate immunosuppression mediated by SHP2 [21]. Hui et al. [22] found that PD-1 induced CD28 dephosphorylation rather than TCR, mainly through SHP2, indicating a major cause of which SHP2 inhibits T cell tumor-killing function. In addition, SHP2 can also inhibit CD28-mediated PI3K signaling and downstream Akt phosphorylation, and consequently inhibit the activation of various transcription factors, such as NF-κB, mTOR, and AP-1, thereby preventing T cell activation [23]. After recruitment to the cytoplasmic tail of PD-1, SHP2 can also promote dephosphorylation of ZAP70, which is also called zeta-chain-associated protein kinase 70, in the TCR signaling complex. Thus, the downstream PI3K/Akt and Ras/MEK signals are inhibited, resulting in the slowing down of T cell proliferation [24].

In addition to PD-1, SHP2 can also be recruited through cytotoxic T lymphocyte-associated protein 4 (CTLA-4), B/T lymphocyte attenuator (BTLA), and T cell immunoglobulin and ITIM domain (TIGIT), and regulate the activation state of T cells through their different motifs in the cytoplasm. When SHP2 binds to CTLA-4, it causes CD28 dephosphorylation, thereby inhibiting the transmission of downstream signals [25]. BTLA and TIGIT interact with SHP2 through the immunoreceptor tyrosine inhibitory motif (ITIM) in the cytoplasmic tail [26], but their downstream signaling mechanisms still need further study. The study of Liu et al. showed that CD4+ T cells lacking sufficient SHP2 expression are more susceptible to stimulation and tend to differentiate into Th1 cells, which secrete IFN-γ and activate CD8+ T cells, thereby preventing colitis-related CRC to a certain extent. Based on these mechanisms, SHP2 is thought to mediate the process of T cell immunosuppression in CRC [27]. These findings suggest that regulation of SHP2 may play an important protective role in CRC immune surveillance. Therefore, future studies may focus on the regulatory mechanism of SHP2 and its interaction with immunosuppressive receptors.

3.2. Microphages

There are two different types of macrophages: M1 macrophages, which highly express proinflammatory CKs such as tumor necrosis factor and MHC-II and play an anti-tumor role. M2 macrophages highly express anti-inflammatory CKs including arginase 1 (ARG1) and CD206, which play a role in promoting tumor. Existing studies suggest that tumor-associated macrophage (TAM) is similar to M2 macrophages in phenotype and plays a crucial regulatory role in tumor progression, such as angiogenesis and tumor metastasis [28].

At present, many studies have elucidated the pathways regulated by SHP2 in macrophages. Based on the connection of CSF-1 to its receptor, SHP2 binds to CSF-1R, and then the Ras/ERK signal is activated. CSF-1/CSF-1R axis is engaged in sustaining tumor cell living and proliferative processes [29]. Signal regulatory protein α (SIRPα) is expressed on the plasma membrane of all myeloid cells (including macrophages) and nerve cells. SIRPα is a transmembrane glycoprotein that regulates cell migration and phagocytic activity, as well as immune homeostasis and neural network formation. It is also the endogenous ligand of CD47. Tumor cells have CD47 located on their external side, which participates in the immune escape of cancer cells. After binding to SIRPα, CD47 activates SIRPα by phosphorylation, thereby recruiting and activating SHP2, which in turn mediates myosin dephosphorylation and actin depolymerization, leading to the weakening of macrophage contraction and phagocytosis to cells carrying CD47 [30].

In addition, Barkal et al. [31] found that CD24 expressed by tumor cells can interact with the inhibitory receptor Siglec-10 (sialic acid-binding Ig-like lectin 10) on macrophages to transfer inhibitory signals and inhibit destructive inflammatory responses. This inhibition requires SHP2 to be recruited to the ITIM of Siglec-10. Xiao et al. [32] showed that the expression of SHP2 in colonic macrophages and monocytes was increased in IBD patients compared with healthy controls, and that knockdown of SHP2 in macrophages protected mice against colitis and colon cancer associated with colitis. The reason for this is that SHP2 suppresses the IL-10/STAT3 pathway and anti-inflammatory responses which relied on IL-10/STAT3 signal in macrophages. Gao et al. [33] also revealed a new pathway regulated by SHP2 in macrophages, that is, SHP2 inhibits the STING/TBK1/IRF3 pathway and then down-regulates type I interferon signaling to promote immune escape in the TME of CRC. To sum up, in the progression of CRC, SHP2 is demonstrated to being involved in the immunosuppression of T cells and macrophages, while it also promotes tumor immune escape.

4. Targeting SHP2 in CRC Immunotherapy

SHP2 inhibitors can be divided into two categories, namely, enzymatic inhibitors (traditional PTP site inhibitors) and allosteric inhibitors. The former could bind to the PTP domain of SHP2 and prevent the phosphotyrosine substrate from entering the catalytic site to inhibit the SHP2 activity, while later simultaneously bind several domains including N-SH2, C-SH2, and PTP to restrict SHP2 activity through the allosteric mechanism.

SHP2 allosteric inhibitors are currently showing promise in CRC anti-tumor immunotherapy, according to numerous research. For instance, SHP099 significantly inhibited the growth of tumors in animal tumor xenograft models as well as in vitro cell tests. In order to create a mouse CRC xenograft model, Zhao et al. [34] employed the MC38 cell line. They also concurrently administered SHP099 and PD-1 inhibitors. The findings demonstrated that PD-1 blockage and SHP2 inhibition worked in concert to enhance anti-tumor immune responses, activate T cells, and stop tumor development. As a SHP2 allosteric inhibitor, SHP099 can counteract PD-L1's T cell-inhibiting effects. This feature of anti-tumor immunity "normalization" is what the researchers term it. SHP2 inhibition has the additional ability to increase T cell activation, or "enhancement" of T cells. Additionally, SHP2 inhibitor SHP099 and WWP1 blocker together can synergistically suppress tumor cell growth, enhance cell apoptosis, and induce G1 cell cycle arrest in SW480, RKO, and Caco2 cells. The combination of SHP2 and WWP1 inhibitors dramatically reduced tumor growth in in vivo trials utilizing a nude mouse subcutaneous tumor model, while also boosting the death of CRC cells and decreasing their proliferation [35]. This dual mechanism of action suggests that SHP2 allosteric inhibitors could be used as monotherapy or in combination with other immune checkpoint inhibitors to achieve more effective anti-tumor treatment.

However, the current problems for SHP2 inhibitors are: ① The SHP2 enzyme inhibitors which have been covered by researches have not yet used the clinical stage, and the most important reason is that the conservative catalytic sites of SHP2 protein generally tend to bind negatively charged compounds, and the negative functional groups carried by SHP2 inhibitors tend to have low cell membrane

permeability, limiting the effectiveness and oral bioavailability of these inhibitors in vivo [3]. ② The reported allosteric inhibitors, such as SHP099, have been used in T cells and macrophages to promote anti-tumor immunity, but for the common SHP2 mutant in clinical cases, the inhibitory effect of SHP2 inhibitors will be greatly weakened because of the significant structural difference between SHP2 mutant and SHP2 wild type [36]. Moreover, the efficacy of other allosteric inhibitors against tumor immunity is limited. ③ Studies in hepatocellular carcinoma, multiple myeloma and chondrosarcoma showed that the use of SHP2 inhibitors in these tumors activated the important pro-tumor factor STAT3.

5. Conclusion

Until now, studies have suggested that SHP2 is a hopeful immunotherapy target. Not only targeting SHP2, but also combination treatment have enormous promise in CRC immunotherapy. In order to promote the immunotherapy of SHP2 in CRC, it is undoubtfully necessary to understand the various binding targets of SHP2 in different inflammatory environments and to reduce the side effects of SHP2 or improve the efficacy of SHP2 through combination drugs. At the same time, it is also needed to search for new allosteric inhibitors of SHP2 to cope with the problems caused by the resistance to SHP2 inhibitors because of the mutations of SHP2 or other genes. With the progress of clinical trials in a variety of solid tumors, we hope that in the immediate future, we will usher in more effective and safe SHP2 targeted therapies, providing more treatment that is helpful for CRC patients.

References

[1] TONKS, N. K. Protein tyrosine phosphatases: from genes, to function, to disease. Nature Reviews Molecular Cell Biology, 2006, 7(11): 833-846.

[2] HOF, P., PLUSKEY, S., DHE-PAGANON, S., et al. Crystal structure of the tyrosine phosphatase SHP-2. Cell, 1998, 92(4): 441-450.

[3] LIU, Q., QU, J., ZHAO, M., et al. Targeting SHP2 as a promising strategy for cancer immunotherapy. Pharmacological Research, 2020, 152: 104595.

[4] O'KEEFE, S. J. Diet, microorganisms and their metabolites, and colon cancer. Nature Reviews Gastroenterology & Hepatology, 2016, 13(12): 691-706.

[5] SONG, Y., ZHAO, M., ZHANG, H., et al. Double-edged roles of protein tyrosine phosphatase SHP2 in cancer and its inhibitors in clinical trials. Pharmacology & Therapeutics, 2022, 230: 107966.

[6] PUNEKAR, S. R., VELCHETI, V., NEEL, B. G., et al. The current state of the art and future trends in RAS-targeted cancer therapies. Nature Reviews Clinical Oncology, 2022, 19(10): 637-655.

[7] FEDELE, C., RAN, H., DISKIN, B., et al. SHP2 Inhibition Prevents Adaptive Resistance to MEK Inhibitors in Multiple Cancer Models. Cancer Discovery, 2018, 8(10): 1237-1249.

[8] TEFFT, D., LEE, M., SMITH, S., et al. mSprouty2 inhibits FGF10-activated MAP kinase by differentially binding to upstream target proteins. American Journal of Physiology-Lung Cellular and Molecular Physiology, 2002, 283(4): L700-706.

[9] CHEN, X., KELLER, S. J., HAFNER, P., et al. Tyrosine phosphatase PTPN11/SHP2 in solid tumors: bull's eye for targeted therapy?. Frontiers in Immunology, 2024, 15: 1340726.

[10] PRAHALLAD, A., HEYNEN, G. J., GERMANO, G., et al. PTPN11 Is a Central Node in Intrinsic and Acquired Resistance to Targeted Cancer Drugs. Cell Reports, 2015, 12(12): 1978-1985.

[11] GAGNé-SANSFAçON, J., COULOMBE, G., LANGLOIS, M. J., et al. SHP-2 phosphatase contributes to KRAS-driven intestinal oncogenesis but prevents colitis-associated cancer development. Oncotarget, 2016, 7(40): 65676-65695.

[12] CHEN, Y. N., LAMARCHE, M. J., CHAN, H. M., et al. Allosteric inhibition of SHP2 phosphatase inhibits cancers driven by receptor tyrosine kinases. Nature, 2016, 535(7610): 148-152.

[13] LIU, J., XIAO, Q., XIAO, J., et al. Wnt/β-catenin signalling: function, biological mechanisms, and therapeutic opportunities. Signal Transduction and Targeted Therapy, 2022, 7(1): 3.

[14] ZHANG, Q., LI, Y., ZHAO, R., et al. The gain-of-function mutation E76K in SHP2 promotes CAC tumorigenesis and induces EMT via the Wnt/β-catenin signaling pathway. Molecular Carcinogenesis, 2018, 57(5): 619-628.

[15] XUELIANG, W., LIKUN, W., HONGQING, M., et al. SOX7 inhibits the proliferation, invasion, and migration of colorectal cancer cells by targeting the SHP-2/Wnt/β-catenin/ROS pathway. Journal of Anhui Medical University, 2024, 59(07): 1237-1243.

[16] ZENG, J., TANG, Z. H., LIU, S., et al. Clinicopathological significance of overexpression of interleukin-6 in colorectal cancer. World Journal of Gastroenterology, 2017, 23(10): 1780-1786.

[17] YITONG, L., YANG, S. Research progress on the regulatory mechanisms and chemical interventions in colitis-cancer transformation. Acta Pharmaceutica Sinica, 2022, 57(05): 1273-1281.

[18] XU, D., QU, C. K. Protein tyrosine phosphatases in the JAK/STAT pathway. Frontiers in Bioscience, 2008, 13: 4925-4932.

[19] HUANG, Y., WANG, J., CAO, F., et al. SHP2 associates with nuclear localization of STAT3: significance in progression and prognosis of colorectal cancer. Scientific Reports, 2017, 7(1): 17597.

[20] CAI, P., GUO, W., YUAN, H., et al. Expression and clinical significance of tyrosine phosphatase SHP-2 in colon cancer. Biomedicine & Pharmacotherapy, 2014, 68(3): 285-290.

[21] YOKOSUKA, T., TAKAMATSU, M., KOBAYASHI-IMANISHI, W., et al. Programmed cell death 1 forms negative costimulatory microclusters that directly inhibit T cell receptor signaling by recruiting phosphatase SHP2. Journal of Experimental Medicine, 2012, 209(6): 1201-1217.

[22] HUI, E., CHEUNG, J., ZHU, J., et al. T cell costimulatory receptor CD28 is a primary target for PD-1-mediated inhibition. Science, 2017, 355(6332): 1428-1433.

[23] HOFF, H., BRUNNER-WEINZIERL, M. C. The tyrosine phosphatase SHP-2 regulates differentiation and apoptosis of individual primary T lymphocytes. European Journal of Immunology, 2007, 37(4): 1072-1086.

[24] SHEPPARD, K. A., FITZ, L. J., LEE, J. M., et al. PD-1 inhibits T-cell receptor-induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Letters, 2004, 574(1-3): 37-41.

[25] RUDD, C. E., TAYLOR, A., SCHNEIDER, H. CD28 and CTLA-4 coreceptor expression and signal transduction. Immunological Reviews, 2009, 229(1): 12-26.

[26] CELIS-GUTIERREZ, J., BLATTMANN, P., ZHAI, Y., et al. Quantitative Interactomics in Primary T Cells Provides a Rationale for Concomitant PD-1 and BTLA Coinhibitor Blockade in Cancer Immunotherapy. Cell Reports, 2019, 27(11): 3315-3330.e7.

[27] LIU, W., GUO, W., SHEN, L., et al. T lymphocyte SHP2-deficiency triggers anti-tumor immunity to inhibit colitis-associated cancer in mice. Oncotarget, 2017, 8(5): 7586-7597.

[28] CASSETTA, L., POLLARD, J. W. Targeting macrophages: therapeutic approaches in cancer. Nature Reviews Drug Discovery, 2018, 17(12): 887-904.

[29] ACHKOVA, D., MAHER, J. Role of the colony-stimulating factor (CSF)/CSF-1 receptor axis in cancer. Biochemical Society Transactions, 2016, 44(2): 333-341.

[30] ORONSKY, B., CARTER, C., REID, T., et al. Just eat it: A review of CD47 and SIRP-α antagonism. Seminars in Oncology, 2020, 47(2-3): 117-124.

[31] BARKAL, A. A., BREWER, R. E., MARKOVIC, M., et al. CD24 signalling through macrophage Siglec-10 is a target for cancer immunotherapy. Nature, 2019, 572(7769): 392-396.

[32] XIAO, P., ZHANG, H., ZHANG, Y., et al. Phosphatase Shp2 exacerbates intestinal inflammation by disrupting macrophage responsiveness to interleukin-10. Journal of Experimental Medicine, 2019, 216(2): 337-349.

[33] GAO, J., WU, W., QU, P., et al. SHP2 inhibition triggers anti-tumor immunity and synergizes with PD-1 blockade. Acta Pharmaceutica Sinica B, 2021, 11(5): 1235-1248.

[34] ZHAO M, GUO W, WU Y, et al. SHP2 inhibition triggers anti-tumor immunity and synergizes with PD-1 blockade. Acta Pharmaceutica Sinica B, 2019, 9(2): 304-315.

[35] FAN Hao. Study on the synergistic lethality of combined blockade of WWP1 and SHP2 in colorectal cancer and its mechanism. Naval Medical University, 2024. DOI: 10.26998/d.cnki.gjuyu.2024.000052.

[36] LAROCHELLE J R, FODOR M, VEMULAPALLI V, et al. Structural reorganization of SHP2 by oncogenic mutations and implications for oncoprotein resistance to allosteric inhibition. Nature Communications, 2018, 9(1): 4508.