REVIEW

Tyrosine phosphatase SHP2 inhibitors in tumor-targeted therapies

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Abstract
Src homology containing protein tyrosine phosphatase 2 (SHP2) represents a noteworthy target for various diseases, serving as a well-known oncogenic phosphatase in cancers. As a result of the low cell permeability and poor bioavailability, the traditional inhibitors targeting the protein tyrosine phosphate catalytic sites are generally suffered from unsatisfactory applied efficacy. Recently, a particularly large number of allosteric inhibitors with striking inhibitory potency on SHP2 have been identified. In particular, few clinical trials conducted have made significant progress on solid tumors by using SHP2 allosteric inhibitors. This review summarizes the development and structure–activity relationship studies of the small-molecule SHP2 inhibitors for tumor therapies, with the purpose of assisting the future

Abbreviations: ALK, anaplastic lymphoma kinase; AML, acute myeloid leukemia; B-ALL, B-cell acute lymphoblastic leukemia; BTLA, B and T lymphocyte attenuator; CADD, computer aided drug design; CSF-1, colony stimulating factor-1; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; EGFR, epidermal growth factor receptor; ERK1/2, extracellular signal-regulated kinase 1/2; FLT3, Fms-like tyrosine kinase-3; GRB2, Grb2-associated binding protein-2; HER2, human epidermal growth factor receptor-2; hERG, human ether-a-go-go-related gene; HGF/SF, hepatocyte growth factor/scatter factor; JAK, Janus kinase; KRAS, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; MAPK, mitogen-activated protein kinase; NLRP3, NLR family, pyrin domain containing protein 3; PDAC, pancreatic ductal adenocarcinoma; PDX, patient-derived xenograft; PD-1/PDL-1, programmed cell death protein-1/programmed death ligand-1; PI3K, phosphatidylinositol 3 kinase; PTK, protein tyrosine kinase; PTP, protein tyrosine phosphatase; RAS, rat sarcoma protein; RTKs, receptor tyrosine kinase inhibitors; SAR, structure–activity relationship; SBDD, structure-based drug design; SCC, squamous cell carcinoma; SCNA, somatic copy number change; SHP2, Src homology containing protein tyrosine phosphatase 2; STAT, signal transducers and activators of transcription; TKIs, tyrosine kinase inhibitors; TIGIT, T-cell immunoglobulin and ITIM domain protein.

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1. Introduction

Protein tyrosine phosphorylation plays a fundamental role in intracellular processes, such as signal transduction, and modifies biotic processes including cell proliferation, differentiation and migration. Reversible phosphorylation is regulated cooperatively by protein tyrosine kinase (PTK) and protein tyrosine phosphatase (PTP). Dysregulation of tyrosine phosphorylation is confirmed to be associated with various diseases, such as cancers, inflammations and diabetes. In addition, hyperactivated mutations of PTK and PTP were observed in multiple malignant tumors. In the last few decades, identifications of dozens of oncogenes led to the gene-targeted therapies becoming the promising strategies for the treatment of cancers, and the development of PTK inhibitors for clinical application has achieved great success. To date, more than 30 tyrosine kinases inhibitors have been identified and approved for clinical treatment. However, in sharp contrast to PTK inhibitors, development of drugs targeting PTP remains challenging.

PTP families member PTPN11 is a unique protooncogene, which encodes Src homology 2-containing protein tyrosine phosphatase 2 (SHP2) that involved in diverse signalling pathways such as RAS-MAPK, PI3K-AKT, JAK-STAT and PD-1/PD-L1. Besides, SHP2 negatively regulates the activation of recombiant NLRP3 (NLR family, pyrin domain containing protein 3) inflammasome via mitochondrial homeostasis. SHP2 has been regarded as an extremely attractive target for human diseases therapies, and the development of SHP2 inhibitors with high bioactivity and selectivity is of great significance for drug discovery. In general, the primary method to block the catalytic activity of SHP2 is the use of traditional inhibitors that target the PTP binding site, such as PHSI, GS-493 and NSC-87877. However, traditional inhibitors are generally suffered from low cell permeability and poor bioavailability. Besides, owing to the high homology (e.g., SHP1 and PTP1B) in catalytic site, it is quite challenging to discover SHP2 inhibitors with high selectively. Encouragingly, the first allosteric inhibitor SHP099 was identified in 2016, which changes the previous strategy of targeting PTP domain and reflects the progress of structure-based allosteric regulator discovery to guide drug development. During the following years, a number of allosteric inhibitors, including TNO155, RMC-4630, JAB-3068 and JAB-3312, are currently under different phases of clinical trials to evaluate the antitumor effects.

SHP2 was traditionally considered as an “undruggable” target in the past, however, the protein allosteric offers a very attractive prospect for the emergence of novel drug targets. Notably, various potent and selective SHP2 inhibitors have been identified through high throughput screening in the past decades. Those inhibitors stabilized the autoinhibited conformation through an allosteric mechanism. More importantly, the combination of allosteric inhibitors and other kinases inhibitors can synergistically reduce the possibility of drug resistance. In this review, we summarized the current knowledge of SHP2 inhibitors and revisited the development of SHP2 inhibitors with improved selectivity, higher oral bioavailability and better physicochemical properties.

2. The structure and function of SHP2 protein

As a non-receptor protein tyrosine phosphatase, SHP2 plays an important role in the downstream of cell signalling transduction which is regulated by growth factors, cytokines and integrin receptors, and is involved in cellular processes including cell survival, proliferation, and migration. SHP2 consists of two SH2 domains in N-terminal (N-SH2 and C-SH2), a PTP domain with catalytic activity, and the C-terminal contains two p-Tyr sites (Y542 and Y580) and a proline-rich motif (Fig. 1A). In its inactive state, SHP2 protein is autoinhibited by the residues in the catalytic surface of the PTP domain and N-SH2 domain, thus suppressing the activity of SHP2 protein and restricting the substrate to access the catalytic site. Under the stimulation of growth factors or cytokines, SHP2 is recruited through its SH2 domain binding to phosphotyrosine sites. The resulting conformational change exposes the catalytic site, thus achieving accurate catalytic activation of SHP2 (Fig. 1B).

Accumulated evidences indicate that SHP2 participates in a number of signalling cascades in cancer cells, including RAS-

**Figure 1** The structure of SHP2 and diagram of SHP2 activation. (A) Crystal structure of the full-length SHP2 (PDB: 2SHP). (B) At closed state, SHP2 is auto-inhibited by N-SH2 domain binding to PTP domain and at an opened state, tyrosine phosphorylation motifs bind to SH2 domains of SHP2, resulting in allosteric regulation and released PTP catalytic activity.
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MAPK, PI3K-AKT and JAK-STAT pathways. Besides, the roles of SHP2 in the PD-1/PDL-1 pathway are also under investigation. The restoration of Th1 immunizing power and T-cell activation are also dependent on the inhibition of SHP2, followed by activating the immune response within the tumor microenvironment. Pharmacological inhibition of SHP2 decreases tumor burden by augmenting CD8+ cytotoxic T-cell mediated antitumor immunity. Moreover, hyperactivated mutations of SHP2 have been identified in Noonan syndrome and various types of cancer including leukemia, non-small cell lung cancer (NSCLC), gastrointestinal cancer and breast cancer. Hence, SHP2 is considered as a potential therapeutic target for cancer treatment, therefore, the development of SHP2 inhibitors has become a hot spot in anticancer drug development.

3. Roles of SHP2 in cancers

3.1. Function of SHP2 in the majority of the cells in tumor microenvironment

In recent years, more and more research clarified the significant characteristics of SHP2 in the signalling pathway of crucial events during tumorigenesis. Furthermore, SHP2 has important functions in multiple cell types involved in the tumor microenvironment. In T lymphocytes, various immunosuppressive receptors, such as PD-1, B and T lymphocyte attenuator (BTLA), cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), and T-cell immunoglobulin and ITIM domain protein (TIGIT), could recruit SHP2 through their specific phosphotyrosine motifs, thereby regulating the activation of T lymphocytes. For example, SHP2 binds to the phosphotyrosine motif (ITSM) of the immune checkpoint protein PD-1 through its two tandem Src homology domains, activating SHP2-mediated immunosuppression. Therefore, SHP2 inhibitors can interrupt the protein–protein interaction between PD-1 and SHP2. SHP2 are expected to exert superior effect in cancer immunotherapy, which makes SHP2 a potential drug target in cancer immunotherapy. Tumor-associated macrophages have great importance in tumorigenesis, tumor metastasis, angiogenesis and stromal remodelling, indicating that these cells are good targets for anticancer treatment. In macrophages, SHP2 binds to the signalling protein complex of growth factor receptor-bound protein 2/GRB2-associated binding protein-2 (GRB2/ GAB2), which is induced by colony stimulating factor receptor under the stimulation of colony stimulating factor-1 (CSF-1), and promotes macrophage proliferation and M2-type polarization. The CSF-1/CSF-1R signalling pathway plays a significant role in tumor-associated macrophages, and can increase the survival rate of tumor-bearing mice after inhibition. Therefore, the role of SHP2 in macrophages seems to promote tumor progress. In various types of tumor cells, SHP2 is generally considered as a key tyrosine phosphatase in oncogenic signalling pathways. SHP2 is a common node that activates multiple RAS signalling pathways and is vital for the survival, growth and proliferation of tumor cells. SHP2 can act as a signal transmitter from the upstream receptor tyrosine kinase, to activate its downstream signalling. For example, after SHP2 is activated by receptor tyrosine kinases (RTKs), it can recruit the adaptor protein GRB2 and guanine nucleotide exchange factor SOS to activate RAS/MEK signal transduction, regulating tumor growth and survival. Therefore, SHP2 can be a potential drug target for cancer treatment.

3.2. The role of SHP2 in various types of cancer

PTP and PTK together maintain the balance of tyrosine protein phosphorylation, participate in cell signal transduction, and regulate cell growth, differentiation, and metabolism. Deviations in their biological function can cause disturbances in body regulation. Accumulated evidences indicate that, PTPN11, associated with Noonan syndrome, acute myeloid, B-cell acute lymphoblastic, juvenile myelomonocytic leukemia, and myelodysplastic abnormalities, has been thought to cause various types of diseases. Recently, a plethora of studies have shown that SHP2 is closely related to tumorigenesis and tumor progression. With the functions of SHP2 in various types of cancers being revealed, it is by common consent that SHP2 could be a potential target for cancer therapy. The following section summarizes the role of SHP2 in several types of tumors.

3.2.1. Leukemia

Acute myeloid leukemia (AML) is a malignant disease of myeloid hematopoietic stem/progenitor cells, with a low 5-year survival rate. Patients who suffer from AML show mutations in DNA methylation regulators in 10%–30% of their normal karyotypes. Genes involved in regulating DNA methylation such as TET2 and DNMT3A mutate and interact with activation mutations of Fms-like tyrosine kinase-3 (FLT3), which can promote the development of AML. Since patients with mutations do not respond well to established treatments, the prognosis of these patients is poor. Pandey et al. did research on the AML mouse model (a combination of loss-of-function mutations in DNA methylation regulators either Tet2 or Dnmt3a along with expression of Flt3ITD) and found that SHP2 allosteric inhibitor SHP099 was essential for inhibiting cytokine receptor signal transduction. The inhibitory effect of SHP099 could retard tumor growth and induce leukemia cell differentiation without affecting normal hematopoietic cells. Richine et al. found that genetic disruption or pharmacological inhibition of SHP2 reduced STAT5 hyperactivation, excessive cell proliferation, and leukemia-induced mortality. In addition, their research showed that inhibition of Syk kinase and SHP2 phosphatase together reduces STAT5 over-activation and proliferation of acute myeloid leukemia, which is induced by FLT3-ITD. Acquired tyrosine kinase inhibitors resistance is the main problem of chronic myeloid leukemia (CML). Moreover, the effect of TKIs on Ph+ B-cell acute lymphoblastic leukemia (B-ALL) is not obvious. GAB2 is a scaffold adaptor that can bind and activate SHP2, which is critical for BCR-ABL1 to produce leukemia, while GAB2 mutants lacking of SHP2 binding cannot mediate leukemia. Gu et al. used a genetic loss-of-function method to construct a mouse model. Their results showed that SHP2 was essential for causing BCR-ABL1-induced myeloid and lymphoid neoplasia formation through the MEK/ERK pathway.

3.2.2. Non-small cell lung cancer

So far, lung cancer is one of the most threatening malignant tumors to human health. Non-small cell lung cancer (NSCLC) accounts for about 80% of all lung cancers, and most patients are in the middle and advanced stages when they are diagnosed. At present, small-molecule inhibitors targeting PTKs have achieved good development, with high specificity, good selectivity and convincing safety. Clinically, TKIs are widely used in epidermal growth factor receptor (EGFR) mutant NSCLC. However, patients with v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations respond poorly to TKIs, which is usually an
important factor in the poor prognosis of patients with NSCLC. Therefore, searching for targeted drug therapy for these patients is the goal for cancer research. Two companion papers clarified the key role of SHP2 in oncogenic KRAS-driven tumors \textit{in vivo}\textsuperscript{40,41}. The loss of \textit{PTPN11} will profoundly inhibit the occurrence of lung cancer driven by \textit{KRAS}\textsuperscript{41,42}. In addition, the inactivation of SHP2 triggered lung cancer cells with KRAS mutation to be sensitive to MEK inhibition. In the patient-derived xenograft (PDX) model of KRAS mutant NSCLC, SHP2 inhibition induced senescence of tumor cells and impaired tumor growth. The authors proposed that dual MEK and SHP2 inhibition is a feasible treatment strategy for treating lung cancer harboring KRAS mutant\textsuperscript{45}. Recent researches also showed that SHP2 is a key factor in the compensatory activation of ALK inhibition on RAS and ERK signalling. The combined application of SHP2 inhibitor SHP099 and ALK inhibitor ceritinib could enhance the efficacy of ceritinib and overcome its drug resistance \textit{in vivo} and \textit{in vitro}. Inhibition of SHP2 can eliminate RAS and ERK1/2 activation in ALK-resistant mutant cancers, suggesting that a dual inhibition strategy which simultaneously inhibits ALK and SHP2 may provide a new cancer therapy\textsuperscript{42}. Jiang et al.\textsuperscript{43} demonstrated from the perspective of the stemness of tumor cells that combination of SHP2 inhibitors and tyrosine kinase inhibitors could be applied to treat NSCLC with KRAS mutation. Their results found that TKIs treatment can promote the stemness of KRAS mutant NSCLC cells. It is worth noting that they found the activation of SHP2 in KRAS mutant NSCLC cells after TKIs treatment. Suppression of SHP2 weakened the enhanced stemness of tumor cells after TKIs treatment. Their results suggest that the combination of SHP2 inhibitors and TKIs can act as a new therapeutic strategy for KRAS mutant NSCLC.

3.2.3. Gastroesophageal cancer
KRAS is recognized as the most common mutant oncogene in human cancer. Researches on cancers driven by RAS generally focus on RAS coding mutations. Wong et al.\textsuperscript{44} explored the second method of KRAS activation in cancer: in the absence of coding mutations, the KRAS gene is locally amplified at a high level. They characterized the somatic copy number change (SCNA) of gastric, esophageal and colorectal adenocarcinoma and found that KRAS was at the most significant peak of amplification. The increased expression level of KRAS in gastric cancer cells and the low survival rate in gastric cancer patients are related to the expansion of wild-type KRAS. \textit{In vitro} and \textit{in vivo}, the combined application of SHP2 inhibitor SHP099 and MEK inhibitor exerts excellent antitumor activity in KRAS-amplified gastric adenocarcinoma.

3.2.4. Breast cancer
Breast cancer is a malignant tumor that occurs in the epithelial tissue of the breast glands. The majority of breast cancer patients are women, and this specific cancer is a common threat to women’s physical and mental health. Triple-negative breast cancer is the highest risk of death among all breast cancer subtypes. Currently, there is no effective treatment for triple-negative breast cancer. The main reasons of poor clinical prognosis are shortage of targeted therapies and diversity of molecular diseases. In an early study, it was reported that SHP2-related signalling pathways are activated in breast cancer cells, indicating that SHP2 is involved in breast tumorigenesis\textsuperscript{45}. Accorto et al.\textsuperscript{46} clarified that SHP2 promotes the progression of breast cancer and maintains tumor-initiating cells by increasing the activity of the key transcription factors (c-Myc and ZEB1) and a positive feedback signalling loop. Notably, they found that SHP2 is activated in most breast tumors associated with poor prognosis, which highlights the significance of SHP2 in malignant breast tissue. Matalkah et al.\textsuperscript{47} reported that inhibition of SHP2 in BTBC cells could suppress occurrence and metastasis of tumors, and promote the transformation and invasion of BTBC cells through upregulating the signal transduction of multiple RTKs. SHP2 is the main regulator of various RTKs signalling pathways, and participates in both their upstream and downstream signalings, promoting basal-like and triple-negative breast cancer. Recently, Zhao et al.\textsuperscript{48} reported that the SHP2 protein is essential for ERBB2-induced tumorigenesis. Conditional knockout of the \textit{Ptpn11} gene encoding the SHP2 protein in the mammary glands of ERBB2 breast cancer model mice can eliminate the occurrence of breast tumors. Furthermore, inhibition of SHP2 in breast cancer cells induced a normal-like cellular phenotype and suppressed tumorigenesis and metastasis by interrupting human epidermal growth factor receptor-2 (HER2) overexpression.

3.2.5. Pancreatic ductal adenocarcinoma
Pancreatic cancer is a malignant tumor of the digestive tract, which is difficult to diagnose and treat. Most of the ductal adenocarcinomas originate from ducal epithelium. Researchers used genome database analysis and protein expression profiles in tissue samples of pancreatic ductal adenocarcinoma (PDAC) patients and cell lines to reveal the epithelial presence of SHP2. The deletion of \textit{PTPN11} gene encoding SHP2 protein will inhibit the occurrence of pancreas driven by \textit{KRAS}\textsuperscript{41,42}. Besides, researchers have found that the loss of SHP2 would slow the tumor progression and tumor cells would be sensitive to MEK inhibition\textsuperscript{44}. Zheng et al.\textsuperscript{49} evaluated the expression of SHP2 protein in 79 specimens of PDAC using immunohistochemistry. Their results indicated that the ratio of high expression of SHP2 in PDAC tissues (55.7%) was remarkably higher than that in adjacent non-cancerous tissues (10.1%). Furthermore, patients with high SHP2 expression have shorter overall survival time compared with patients with low SHP2 expression. This research proved that the high expression of SHP2 might be related to the development of PDAC, indicating that SHP2 may be a potential prognostic marker and therapeutic target.

RTKs (such as EGFR, c-MET, ERBB2, and FLT3) were considered sensitive to SHP2 depletion, suggesting that almost all RTKs could recruit SHP2 to activate RAS signalling pathway. The activation of RAS is very important for cancer cell survival, indicating the importance of SHP2. Researchers from Novartis\textsuperscript{50,51} have demonstrated the allosteric inhibitor SHP099 of SHP2 could inhibit the proliferation of cancer cells by suppressing RAS-ERK signal transduction, and show antitumor effect in mouse xenograft model. The results provide evidence that inhibition of SHP2 is a new strategy to target RTK-driven cancers and drug resistance, as well as immune-checkpoint modulation. Of note, allosteric inhibition of SHP2 is a promising strategy for cancer immunotherapy. Previously, we reported the inhibitory effect on SHP2 triggered antitumor immunity and had a synergistic effect in combination with PD-1 blockade\textsuperscript{52}. Moreover, we reviewed the current comprehension of the regulation of SHP2 and the significant functions of SHP2 in T lymphocytes, macrophages and cancer cells\textsuperscript{53}.

Regulation of protein reversible phosphorylation is the most widespread and common regulation method in cell signalling.
pathways. This process is precisely regulated by RTKs and protein phosphatases. RTKs perform phosphorylation and protein phosphatases perform dephosphorylation to positively drive RAS-MAPK signalling pathway. SHP2 is a common node that activates multiple RAS signalling pathways. Activation of RAS is significant for the survival and proliferation of cancer cells. Therefore, a suitable SHP2 inhibitor has the potential to become a broad-spectrum anticancer drug. In addition, due to overlap of PTK and SHP2 signalling pathways, the SHP2 inhibitors can be used in conjunction with kinase inhibitors to simultaneously inhibit interconnected signalling pathways. This combination therapy, which could avoid drug resistance and reverse the acquired drug resistance of PTK inhibitors, is more effective than monotherapy. In a word, combining small-molecular TKIs with tyrosine phosphatase inhibitors may provide a new strategy for the clinical treatment of drug-resistant tumors.

4. Small molecular SHP2 inhibitors

4.1. Traditional PTP site inhibitors

4.1.1. Phenylhydrazonopyrazolone sulfonate derivatives

In the light of the roles of SHP2 in promoting multifarious malignant behaviors of tumor cells, the development of small-molecular inhibitors has attracted extensive attention. Traditional inhibitors bind to the catalytic PTP pocket, preventing the substrates of tyrosine phosphorylation from entering the catalytic sites, thus inhibiting the phosphatase activity of SHP2.

Hellmuth et al. reported the phenylhydrazonopyrazolone sulfonate (PHPS) compounds with SHP2 inhibitory activity from high throughput docking. The group discovered PHPS1 (1) as a potential phosphotyrosine inhibitor, and the sulfonic acid group in PHPS1 shows drug-like properties (based on five principles of drugs) as well as membrane permeability \((\log P = 2.7)\). PHPS1 displayed strong inhibition on SHP2 (the \(K_i\) value was 0.73 \(\mu\)mol/L), which is 8- and 15-fold more potent compared with its inhibition on homologous PTP families members PTP1B and SHP1, respectively, indicating that PHPS1 is a selective inhibitor. SAR studies on 1 by replacing the sulfonic acid moiety with sulfonamide or carboxylate and changing the pyrazolone scaffold with nonaromatic groups led to almost loss of SHP2 inhibitory activity. Finally, refinement strategies furnished cell permeable compound PHPS1. PHPS1 could also affect proliferation of cancer cell HT-29 (inhibition ratio \(74\%\)) with the concentration of 30 \(\mu\)mol/L (Fig. 2A). Mechanism studies indicated that PHPS1 interacts with PTP domain of SHP2 and affects the SHP2 downstream signalling pathway. Based on the above information, we summarized and outlined the main forces between PHPS1 and PTP domain amino residues in Fig. 2B. As is shown, the sulfonate moiety forms six hydrogen bonds with the PTP domain amino residues (Cys-459 to Arg-465), the pyrazolone scaffold and the aromatic ring of His-426 and Tyr-279 can be observed.

To optimize the pyrazolone ring structure of PHPS1 and its substituents that point outside of the phosphotyrosine binding pocket, Grosskopf et al. studied the three substituents (R1–R3) within PHPS1, in which R2 binds to the catalytic pocket. The group initially identified compound 2a (GS-447, carrying 3,4-methylenedioxyphenyl at R3 with SHP2 IC50 value of 0.37 \(\mu\)mol/L) and compound 2b (GS-458, carrying 3,4-ethylendioxyphenyl at R3 with SHP2 IC50 value of 0.15 \(\mu\)mol/L) as the potent SHP2 inhibitors (Fig. 3A). Further SAR studies found the most active SHP2 inhibitor GS-493 (2, Fig. 3B), which carrying 4-nitrophenyl at the R3 position, could inhibit SHP2 with an IC50 value of 0.071 \(\mu\)mol/L and was 29-, 45-fold more selective compared SHP2 with SHP1 and PTP1B, respectively. Computer docking showed that the benzene ring of R2 in GS-493 is embedded between Lys-366 and Thr-357 to make hydrophobic interaction. The nitrobenzene group in R3 forms a cation–π stacking interaction with Arg-362, and the nitrobenzene group in R3 forms a hydrogen bond with Thr-507, thus inhibiting the catalytic activity of SHP2 (Fig. 3C). Additionally, GS-493 not only blocks scattering of the human HPAF II pancreatic cancer cells which are induced by hepatocyte growth factor/scatter factor (HGF/SF), but also blocks the growth of LXFA526L (NSCLC cancer cell line) in xenograft model.

4.1.2. Quinoline hydrazine derivatives

Chen et al. identified quinoline hydrazine derivative NSC-87877 (3) that potently inhibited SHP2 with an IC50 of 0.318 \(\mu\)mol/L, but it showed poor selectivity toward SHP2 over SHP1 (SHP1 IC50 = 0.335 \(\mu\)mol/L) \textit{in vitro} and approximately 5-fold selectivity toward SHP2 over PTP1B (PTP1B IC50 = 1.691 \(\mu\)mol/L, Fig. 4). Interestingly, NSC-87877 inhibits the activation of PTP domain and RAS/RAF/ERK1/2 signalling pathway in tumor cells, suggesting that it holds high selectivity compared with other kinases and could inhibit SHP2-PTP domain without off-target effect. Analysis of the molecular model of SHP2 with NSC-87877 suggests that the sulfonic acid in naphthalene ring forms two hydrogen bonds with the amino residues Lys-280 and Asn-281 on the side-chain of SHP2-PTP domain, and compound SHP2 with an IC50 of 0.071 \(\mu\)mol/L.

4.1.3. Oxindole derivatives

From a hit screened through the national cancer institute (NCI) diversity set, Lawrence et al. discovered oxindole derivative NSC-117199 (4) with the SHP2 IC50 value of 47 \(\mu\)mol/L. Initial SAR studies determined that the replacement of R1 at the 5-position of the oxindole scaffold with polar group such as carboxylic acid, sulfonamides, and carboxylamides together with the replacement of R2 at the ortho-, meta- or para-position of the
phenylhydrazone moiety with nitro or carboxylic acid are beneficial for SHP2-PTP inhibitory activity (compounds 4a to 4r displayed SHP IC50 values of 1e10 µmol/L and with more than 5-fold selectivity over SHP1). Further optimization efforts led to identifying bis-carboxylic acid derivative 5 which displays the IC50 value of 0.8 µmol/L, with 20-fold SHP2 selectivity over SHP1 (Fig. 5A). A comparison of the docking study between 4 and 5 is shown in Fig. 5B, in which the main forces between compounds and PTP domain amnio residues are outlined (PDB: 2SHP)15. The substituent on the 5-position of the oxindole ring is superimposed and displays favorable interactions with both Lys-366 and Arg-362 residues, which are likely to contribute the most affinity of the SHP2 towards the ligands. The orientation of the hydrazine aromatic ring in inhibitor 5 forms additional hydrogen bond interactions with Cys-459, Gly-464 and Ile-463 in the catalytic site.

Another drug discovery campaign centered on oxindole derivatives uncovered SPI-112 (6, IC50 value of SHP2 was 1.0 µmol/L with 18-fold selectivity over SHP1) derived from NSC-117199 (Fig. 5A)57,61. However, 6 contains negatively charged carboxyl group, which results in poor cell permeability. Derivatization at carboxyl group by methyl ester led to the identification of the optimal prodrug SPI-112Me (7, Fig. 6) which could inhibit the activation of SHP2-PTP in intact cells, but in vitro inhibition assay demonstrated that SPI-112Me could not inhibit SHP2-PTP activity (IC50 > 100 µmol/L). Meanwhile, SPI-112Me could inhibit SHP2-PTP activity and the activation of ERK1/2 in MDA-MB-468 cells, which is stimulated by epidermal growth factor.

4.1.4. Salicylic acid derivatives
In another drug discovery campaign to disclose novel SHP2 inhibitors, Zhang et al.62 developed a series of substituted salicylic acid derivatives including compound 8a (SHP2 IC50 = 212 µmol/L) by screening hits from the library and using click reaction. SAR studies of 8a showed that naphthyl and polyanromatic salicylic acid derivatives (compounds 8b to 8g displayed IC50 = 5e10 µmol/L) exhibited improved affinity towards PTPs in comparison with the corresponding single ring compounds (Fig. 7A)63. Finally, II-B08 (8) was witnessed to be the most potent compound for SHP2 (IC50 = 5.5 µmol/L) and exhibited 2.9- and 2.6-fold selectivity for SHP2 over SHP1 and PTP1B, respectively56. Similarly, II-B08 can block the activation of ERK1/2 which is stimulated by growth factor65. The X-ray analysis of the SHP2/8 complex showed that the salicylic acid group dominates the catalytic region of SHP2, while the benzene ring at the far end is bound to the β5eβ6 loop around the active site (Fig. 7B). These studies of salicylic acid derivatives furnish a solid platform for the drug discovery of more potent SHP2-based tumor therapies.

4.1.5. Diterpenoid quinone derivatives
In 2013, Liu et al.66 identified cryptotanshinone (9) with the inhibitory ability of SHP2 displaying the IC50 value of 22.50 µmol/L by screening from natural products database. Compound 9 exhibits 1.7-, 1.5-fold selectivity toward SHP2 over SHP1 and PTP1B (IC50 = 39.5, 33.5 µmol/L), respectively (Fig. 8A). As the major active ingredients extracted from the traditional medicinal herbal plant Salvia miltiorrhiza Bunge (Danshen), cryptotanshinone has been used in Asian countries to treat plenty of diseases such as Alzheimer’s disease, cardiovascular and cerebrovascular diseases, hepatitis and abnormal renal function.67e71 In their study, cryptotanshinone could block cell signalling transduction and cell proliferation which is mediated by SHP2 in Ba/F3 cells. Furthermore, this compound could inhibit the activation of SHP2E76K mutation in mouse myeloid progenitors and patient leukemic cells. Computer docking showed that two carbonyl oxygen atoms in diterpenoid quinone scaffold form an H-bond with Lys-364 and Lys-366. The cycloalkane
contains two methyl groups inserting into a hydrophobic pocket. And benzene ring of cryptotanshinone forms the aromatic π–π stacking with Tyr-279 is almost parallel to the benzene ring (Fig. 8B).

In addition, several other SHP2 inhibitors have been reported and were summarized in the following section (Fig. 9). Wu et al.\textsuperscript{72,73} reported pyrogallic acid derivatives \textsuperscript{10} exhibited poor inhibition selectivity between SHP2 (IC\textsubscript{50} = 2.1 μmol/L) and SHP1 (IC\textsubscript{50} = 2.3 μmol/L). Yu et al.\textsuperscript{74} reported a series of triazine \textsuperscript{[5,6-b]indol} SHP2 inhibitors (Fig. 9). The representative compound \textsuperscript{11} effectively inhibits SHP2 with an IC\textsubscript{50} of 14 μmol/L and blocks SHP2-mediated signal transductions and cellular function without off-target effects. Scott et al.\textsuperscript{75} developed estramustine phosphate (\textsuperscript{12}, Fig. 9) as a SHP2 inhibitor (SHP2 IC\textsubscript{50} = 17.1 μmol/L), followed by performing the SAR studies at triterpenoid derivative to identify the enoxolone (\textsuperscript{13}, IC\textsubscript{50} = 9.6 μmol/L, Fig. 9) and celastrol (\textsuperscript{14}, IC\textsubscript{50} = 3.3 μmol/L, Fig. 9), all exhibiting SHP2-PTP inhibitory activities.

The development of SHP2 inhibitors gradually led to the development of highly selective SHP2 inhibitors, including PHPS1 and NSC-87877. NSC-87877, cryptotanshinone and II-B08 were envisioned to be used in the treatment of leukemia, prostate cancer, mast cell leukemia, etc. However, traditional PTP inhibitors targeting the catalytic sites of phosphatases could compete with tyrosine phosphate substrates, leading to the lack of selectivity in the highly homologous PTP family (e.g., SHP1 and PTP1B). It is worth noting that those inhibitors with highly charged functional groups lead to poor cell membrane permeability and low oral bioavailability, which also makes PTP an “undruggable” target protein for quite some time.

4.2. Novel allosteric inhibitors

Up to date, a number of potent and selective inhibitors of SHP2 were identified based on high throughput screening. Those inhibitors concurrently bind to the interface of the N-SH2, C-SH2 or PTP domains, and inhibit SHP2 activity through an allosteric mechanism. The allosteric inhibition strategy opens up new window for targeting SHP2 and leads to the discoveries of more than ten different structural allosteric inhibitors that have been reported so far.

4.2.1. SHP099 and its analogs

Fortanet et al.\textsuperscript{50,51} developed an allosteric SHP2 inhibitor SHP386 (\textsuperscript{15}, Fig. 10A) based on aminopyrimidine scaffold from the library of the Novartis compound archive. Compound \textsuperscript{15} inhibits the full-length SHP2 with the IC\textsubscript{50} value of 12 μmol/L and

![Figure 5](image_url) Structures, optimization paths and X-ray cocrystal diagram of NSC-117199 derivatives. (A) The structure of oxindole derivatives NSC-117199 (\textsuperscript{4}) and \textsuperscript{5}. (B) Overlay of \textsuperscript{4} (blue) and \textsuperscript{5} (purple) docked in the SHP2-PTP active site, blue arrows represent H-bonds.

![Figure 6](image_url) The structures of SPI-112 and SPI-112Me.
with 8-fold selectivity over the SHP2-PTP domain (IC\text{50} > 100 \, \mu \text{mol/L})\textsuperscript{76,77}. Interestingly, 15 binds to a tunnel-like region which is formed between the C-SH2, N-SH2, and PTP domain rather than the PTP catalytic domain. SAR studies at the phenyl regions showed that the chlorines in the phenyl ring is critical for SHP2 activity, and removal or reposition of the chlorines can led to almost loss SHP2 inhibition (15a, 15b, and 15c, SHP2 IC\text{50} = 99, 54 and > 100 \, \mu \text{mol/L}, respectively). SAR studies on the amine part suggested that substituted the piperazine ring with a 4-aminopiperidine motif increased the inhibition of SHP2 activity by 10-fold (15d, SHP2 IC\text{50} = 1.3 \, \mu \text{mol/L}), but increased substitution on the nitrogen led to reduced inhibition potency (15f, SHP2 IC\text{50} = 6.5 \, \mu \text{mol/L}). Introducing a methyl at the 4-position of piperidine further improved SHP2 activity (16, SHP2 IC\text{50} = 0.26 \, \mu \text{mol/L}). The SAR studies on central pyrimidine ring showed that the 1,2,4-triazine helps to maintain the SHP2 inhibition (16a, SHP2 IC\text{50} = 0.30 \, \mu \text{mol/L}). SHP099 (17, Fig. 10B), the first potent, selective and orally bioavailable allosteric SHP2 inhibitor (SHP2 IC\text{50} = 0.071 \, \mu \text{mol/L}) was obtained by the introduction of a pyrazine ring\textsuperscript{78}. SHP099 could inhibit RAS/ERK signalling pathway which drives proliferation in human cancer cells and exhibits strong antitumor activity in KYSE-520 xenograft models without obvious toxicity and side effects.

Figure 7  Structures, optimization paths and X-ray cocrystal diagram of II-B08 derivatives. (A) Structural optimization from compounds 8a to 8g. (B) The structure of II-B08 and crystal structure of SHP2/8 complex (PDB: 3B7O).

Figure 8  Structure and X-ray cocrystal diagram of cryptotanshinone. (A) The structure of cryptotanshinone. (B) Crystal structure of SHP2–9 complex.
Bagdanoff et al. reported a series of pyrazolopyrimidinone derivatives as SHP2 inhibitors (Fig. 12). By comparing the binding model of previously reported SHP2 allosteric inhibitors with the SHP2 co-crystal structure, compound 21 was identified as an allosteric inhibitor (SHP2 IC₅₀ = 0.067 μmol/L). However, compound 21 also can be metabolized by aldehyde oxidase and inhibit hERG (human ether-a-go-go-related gene) potassium heart channels (hERG IC₅₀ = 0.20 μmol/L). To increase the metabolic stability, compound 21a with improvement in SHP2 potent inhibition and hERG selectivity (SHP2 IC₅₀ = 0.034 μmol/L, hERG IC₅₀ = 0.98 μmol/L) was designed by extending the basic amine. Cyclization to the spiro[4.5]-amine to obtain compound 21b exhibited more than 10-fold anti-proliferation ability in the KYSE cells (anti-proliferation IC₅₀ = 0.465 μmol/L). Replacement of the amine with tetrahydropyran to obtain compound 21c (SHP2 IC₅₀ = 0.05 μmol/L) yielded significantly less potent than 21b. Substitution on the tetrahydropyran ring showed that the methylated spiropenic ether is critical for potency and selectivity (compound 22, SHP2 IC₅₀ = 0.028 μmol/L, hERG IC₅₀ = 0.29 μmol/L). The SAR studies at dichlorophenyl subunit showed that substituting it with dichloropyridine (compound 22a) moderately reduced hERG inhibition (IC₅₀ = 1.2 μmol/L). All the pyridine substitution compounds have similar anti-SHP2 activity (22a to 22g, IC₅₀ values are 0.008–0.055 μmol/L). Further optimization identified that compound 23 (SHP394, Fig. 12B) with 2-cyclopropyl amide and 3-chloro aminopyrimidinone at pyrazolopyrimidinone ring could improve SHP2 biochemical and cellular potency (SHP2 IC₅₀ = 0.036 μmol/L and anti-proliferation IC₅₀ = 0.36 μmol/L) in trend with low hERG inhibition (IC₅₀ = 17 μmol/L). Unfortunately, compound 23 has poor oral bioavailability (~2%), thus preventing further antitumor efficiency evaluation in xenograft model.

The cocrystal complex of 23 with SHP2 was obtained and is shown in Fig. 12C. The major polar interactions include the interactions between the pyrazolopyrimidinone ring and Arg-111, Glu-250. Similarity, 2-amino, 3-chloropyridine heterocycle is also formed a cation–π stacking interaction with Arg-111 (Fig. 10C).

**4.2.4. SHP394 and its analogs**

Sarver et al. identified a novel compound 24 (SHP IC₅₀ = 0.012 μmol/L, hERG IC₅₀ = 6.0 μmol/L, Fig. 13A) with monocyclic pyrimidinone scaffold on the basis of SHP389. Based on the pyrimidinone core structure, initial SAR studies at R₂ determined that substitution at aminopyrimidinones ring by a spiro [4.5]-furanyl-amine moiety remarkably influenced SHP2 activity (compound 24a, SHP2 IC₅₀ = 0.005 μmol/L). To improve the hERG selectivity, a wide variety of optimization were performed at the R₁ position, compounds 24b, 24c and 25 depicted some of these modifications, and the ortho-trifluoromethyl pyridine analog 25 appeared optimal. Compound 25 (SHP394, Fig. 13B) efficaciously inhibited SHP2 with the IC₅₀ of 0.023 μmol/L and showed the anti-proliferative IC₅₀ of 0.297 μmol/L in pharyngeal carcinoma cell line Detroit-562 in vitro and high selectivity over hERG (IC₅₀ > 30 μmol/L), synchronously. To further explore the most qualified candidate based on the central pyrimidinone ring, SAR studies on het showed that the removal of the 6-position NH₂ leads to loss of inhibition of phosphatase (compound 25a, SHP2 IC₅₀ = 0.026 μmol/L, p-ERK IC₅₀ = 0.096 μmol/L), and removal of 3-Me further decreased the inhibition of cells (compound 25b, SHP2 IC₅₀ = 0.031 μmol/L, p-ERK IC₅₀ = 1.06 μmol/L). Replacement of the nitrogen with carbon at the 1-position of the N-methylpyrimidinone to obtain compound 25c and 6-amino pyridine compound 25d, which substantially impaired the inhibition of SHP2 activity (IC₅₀ values were 0.177 and 0.429 μmol/L, respectively). Further medicinal chemistry efforts led to the discovery of compound 26 with poor permeability and absorption (Fig. 13B). To modify the pharmacokinetic properties, introduction of a β-fluorine at the cyclopentane ring led to compound 27 with promising potency (SHP2...
However, the synthetic challenges of the stereocenters reduced the attractiveness of this analog.

In addition to the above mentioned SHP2 inhibitors, Novartis identified the pyrazine ring and $\gamma$-hydroxy spiro[4.5]-amine compounds 28 and 29 with the SHP2 IC$_{50}$ inhibition values of 0.003 and 0.004 $\mu$mol/L, respectively (Fig. 14). The dual inhibitory activities of compounds 28 and 29 against ALK and SHP2 were further evaluated. Those compounds are able to inhibit ALK-rearranged NSCLC cell growth in vitro and inhibit tumor growth in MGH049 and MGH045-2A xenograft models in vivo.

4.2.5. Other potent SHP2 inhibitors

In addition to the compounds described above, few other phosphatase SHP2$^{WT}$ allosteric inhibitors with good selectivity and cell permeability were also reported. However, some carcinogenic SHP2 mutant proteins (such as SHP2E76A, SHP2E69K, SHP2D61Y and SHP2C459S, etc.) are insensitive to SHP2$^{WT}$ inhibitors. In line with developing SHP2 inhibitors with mutants activity, Xie et al. identified a thiazol scaffold compound 30 (Fig. 15A) as a SHP2$^{E76A}$ inhibitor with an IC$_{50}$ of 19.1 $\mu$mol/L, and confirmed that 30 had no effect on SHP2-PTP. Structure optimization by keeping the amine part intact and changing the phenyl ring with biphenyl (30a and 30b) or naphthyl (31) led to the increased IC$_{50} = 0.018$ $\mu$mol/L, hERG IC$_{50} > 30$ $\mu$mol/L, (Fig. 13B).

Figure 10 Structures, optimization paths and X-ray cocrystal diagram of SHP099 and its analogs. (A) Structural optimization from compounds 15 to 17. (B) The structure of SHP099. (C) X-ray structure of SHP099 and SHP2.

Figure 11 Structures, IC$_{50}$ values and X-ray cocrystal diagram of SHP244 and its analogs. (A) The structure of SHP244. (B) The structure of SHP844. (C) The structure of SHP504. (D) X-ray structure of SHP244 and SHP2 (PDB: 6BMR).
SHP2E76A inhibition efficiency with the IC50 of 3.27, 5.32 and 2.55 μmol/L, respectively. To elucidate the binding pattern of compound 30a to SHP2 protein and guide further optimization, the crystal structure of 30a/SHP2E76A complex was analysed. Compound 30a adopts an autoinhibited conformation as previously reported for SHP099 but with distinct interactions (30a forms a hydrogen bond with Arg-111, and methyl substituted tetramethylpiperidine ring forms several van der Waals interactions with Thr-108, Glu-110, His-114, Glu-249, and Thr-253). The diphenyl moiety is sandwiched owing to the formation of cation–π interaction between the side-chains of Arg-111 and Lys-492 (Fig. 15C). To stabilize the interactions between compounds with amino acids residues and further improve the inhibition potency, SAR studies were carried out by keeping the aminothiazole core structure and successively exploring the impact of the piperidine regions and aryl. The SAR studies at amines showed that removal of the methyl group in piperidine increased activity (compared compound 31a with 31b, SHP2E76A IC50 values were 2.55 and 0.73 μmol/L, respectively). Increasing the nitrogen substitution impaired inhibition (compound 31c, SHP2E76A IC50 Z 2.81 μmol/L), suggesting that the terminal NH group may provide critical hydrogen bond interactions with surrounding residues. Replacing piperidine ring with pyrrolidine ring or extending the carbon chain in a N-linker is beneficial for SHP2 activity (compounds 31d and 31e, SHP2E76A IC50 values were 1.65 and 1.49 μmol/L, respectively). Other substitutions on piperidine led to reduce SHP2 inhibition (compounds 31f and 31g). Finally, linking thiazole with piperidine led to compound 32 with SHP2E76A IC50 value of 1.48 μmol/L, which is slightly more active compared to 31, suggesting that the piperidine ring is critical for interacting with surrounding residues via hydrogen bonds. Further optimization at aryl region on compound 31 showed that replacement of substitutions on naphthalene, for instance halogen, methoxy group, cyanogroup, and carboxylic ester were tolerable to maintain the inhibition on SHP2, suggesting that the electron donating or withdrawing groups were accepted to occupy hydrophobic pocket (compounds 32a to 32e, SHP2E76A IC50 were 1.08–2.68 μmol/L, respectively). Replacement of the substitutions with carboxyl group or hydroxymethyl group reduced the activity (compounds 32f and 32g with IC50 values were >100 μmol/L, respectively). Substitution of 1,3-diphenyl group was better than 1,4-diphenyl group for SHP2 activity (compounds 32h to 32i, SHP2E76A IC50 values were 3.63, 1.76, 3.38, 14.2 and 20.3 μmol/L, respectively). Other aryl groups resulted in dramatic reduced inhibition of SHP2 (compounds 32m to 32o with IC50 >45 μmol/L). Finally, compound 33 (Fig. 15B) was identified as the most potent SHP2E76A inhibitor with the IC50 of 0.71 μmol/L and displayed 48-fold selectivity toward SHP2 over SHP1 (IC50 = 34.62 μmol/L). Besides, 33 could effectively suppress the activation of signalling pathways such as ERK1/2 and AKT pathways in cancer cells. Meanwhile, 33 exhibits dose-dependent antitumor activity in a MV-4-11 xenograft model without a mean of body weight lost. This study may pave way for developing novel mutant SHP2 inhibitors.

Recently, Wu et al. reported a novel SHP2 inhibitor LY6 (34, Fig. 16A) by using computer aided drug design (CADD) screening. LY6 exhibits the inhibition of SHP2 with the IC50 of 9.8 μmol/L, which is 7-fold more selective toward SHP2 over
SHP1 (IC₅₀ = 72.7 µmol/L). Besides, it also inhibits the full-length SHP₂E⁷⁶K mutant with an IC₅₀ of 7.67 µmol/L. It was worth noting that LY6 is much more sensitive in inhibiting leukemia cells which carrying SHP₂E⁷⁶K mutation than control cells with SHP₂WT. The X-ray crystal structure of LY6/SHP₂ complex showed that LY6 inserts very well into the binding site and forms three strong hydrogen bonds with Arg-111, Lys-129 and Arg-229 (Fig. 16B). In addition, molecular dynamics simulation demonstrated that LY6 suppresses the movement of the SHP₂, suggesting that it can stabilize the pose of autoinhibitory conformation of SHP₂. The small-molecule SHP₂ inhibitor LY6 has been considered as a lead compound for further studies and development of novel anti-SHP₂ therapeutic drugs.

Nichols et al.⁹⁰ reported RMC-4550 (35, Fig. 17A) as a small-molecular SHP₂ allosteric inhibitor (IC₅₀ value was 0.583 nmol/L) which stabilizes the pose of autoinhibitory conformation of SHP₂ and exhibits the potent efficiency compared with previous generation SHP099 (IC₅₀ value was 71 nmol/L). It has been proved that RMC-4550 treatment could block RAS-ERK signalling and tumor growth via inhibiting the activity of RAS protein. However, RMC-4550 failed to bind to the hyperactive mutant SHP₂E⁷⁶K and SHP₂T²⁵₃M/Q²⁵⁷L pockets, thus significantly reduced its efficiency. Compound 36 is a quinoline scaffold SHP₂ allosteric inhibitor with interesting binding features (SHP₂WT-PTP IC₅₀ was 36 µmol/L, Fig. 17B)⁹¹. As a covalent inhibitor, it can be placed in the central of SHP₂ pocket via an allosteric mechanism and binds to the protein by a nonconserved cysteine residue (Cys-333). These findings provide a novel paradigm and help to guide the discovery of targeting SHP₂’s active site.

Since the first SHP₂ allosteric inhibitor reported by Novartis in 2016, a large number of research teams worldwide started to invest in this field and subsequently more than three small-molecular inhibitors entered the clinical research trials. In July 2019, Mirati Therapeutics⁹² announced a partnership agreement with Novartis to evaluate KRASG₁₂C inhibitor MRTX849 in combination with SHP₂ inhibitor TNO155 (37) in clinical trials for treating solid tumors carrying mutation in KRASG₁₂C. In pre-clinical studies, MRTX849 showed significant effect in some tumors with KRASG₁₂C mutant combined with SHP₂ inhibitors, exhibiting significantly increased antitumor activity compared with that of drug administration alone. Currently, TNO155 is applied to treat solid tumors on phase I clinical trials (ClinicalTrials.gov, NCT03114319 and NCT04000529)⁹³,⁹⁴. This clinical project is aiming at patients with advanced EGFR mutant NSCLC, KRASG₁₂C mutant NSCLC, esophageal squamous cell carcinoma (SCC), head/neck SCC, and melanoma. Similarly, another allosteric SHP₂ inhibitor RMC-4630 (38) discovered by Revolution
Medicines\textsuperscript{95,96}, is being tested in phase I clinical trials (ClinicalTrials.gov, NCT03634982 and NCT03989115). The clinical studies of RMC-4630 are for solid tumors and it is worth noting that RMC-4630 combined with pembrolizumab (a humanized antibody, PD-1 inhibitor) in the treatment of patients with advanced malignant tumors. In China, two candidate drugs JAB-3068 (39) and JAB-3312 (40) developed by Jacobio, are currently under clinical trials. In June 2019, JAB-3068 received phase IIa clinical research approval from the food and drug administration (FDA), which had previously granted an orphan drug for esophageal cancer (ClinicalTrials.gov, NCT03518554 and NCT03565003)\textsuperscript{97,98}. The clinical studies of JAB-3068 are for NSCLC, head and neck cancer, esophageal cancer and other metastatic solid tumors. JAB-3312 was also licensed for clinical trials in the United States (ClinicalTrials.gov, NCT04045496)\textsuperscript{99}. However, the structures of those drugs have not been disclosed.

5. Perspectives

The use of protein tyrosine kinase (PTK)-targeted precision medicine has always been the goal of people’s diligence for a long time. PTKs have emerged as ideal drug targets in tumor research due to the high degree of drug active site and their indispensable roles in cell signalling pathways. However, difficulties in developing protein tyrosine phosphatase (PTP)-directed inhibitors resulted in the viewpoint that PTPs are “undruggable”, emphasizing the need for PTPs that target new means.

Encouragingly, the tyrosine phosphatase SHP2 is involved in regulating several cancer-related processes. Over the past decades, the researchers focused on the development of SHP2-PTP domain inhibitors with polarity groups, such as carboxylic acids and sulfonic acids. However, these compounds with negative charge are difficult to enter the blood circulation by oral administration due to the poor cell membrane permeability, thus limiting the clinical research. Recent progress in allosteric mechanism “molecular glue” targeted SHP2 inhibitors discovery aroused the particular interests to this long-pursued target. Since the first allosteric inhibitor SHP099 reported in 2016, a number of effective anti-SHP2WT drugs have been identified. Most of these allosteric inhibitors are structurally characterized by three sections: (1) a central nitrogen heterocyclic core where various interactions with waters exist; (2) the halogen substituted phenyl resides in a hydrophobic cleft forms a weak cationic–π stacking interaction with surrounding residues; (3) the amino groups that harbouring H-bonding with backbone carbonyl of surrounding residues and van der Waals interactions with receptor, thus modifications of which using a structure-based drug design (SBDD) strategy are highly potent and selective to inhibit the excitation of SHP2. The most clinically advanced SHP2 inhibitors include TNO155, RMC-4630, JAB-3068 and JAB-3312. JAB-3312 has achieved orphan designation from regulatory authorities. In particular, using SHP2 inhibitors in combination with other targets inhibitors for treating drug-resistance cancer is a promising strategy.

However, SHP2 allosteric inhibitors still face the challenges that SHP2 is involved in the regulation of various physiological processes in normal conditions, thus potential side-effects induced by SHP2 inhibition should be paid much attention. In addition, SHP2 phosphatase has a wide range of substrates, potential toxicity may occur in the treatment of cancers, therefore, local drug administration may be one of the ways to reduce side-effects.
Another thing worth noting is that although the scientists have made a major breakthrough on the research of SHP2, it has shown a tumor-suppressor role in liver cancer. In the latest study, Luo et al.\(^1\) found that Shp2 gene and Pten gene synergistically inhibit liver tumor formation in mice. Therefore, to treat solid tumors such as liver cancer, SHP2 inhibitors should be used with caution since they could also activate STAT3, an important cancer-promoting factor. Thus, the phosphorylation level of STAT3 should be paid close attention to when trying to treat related solid tumors with SHP2 inhibitors.

Like TKIs, the drug-resistance of SHP2 inhibitors may be occurred owing to amino acid mutations at the binding site or the efflux of transporter (e.g., P glycoprotein). In addition to the clinical efficacy of the SHP2 inhibitors, SHP2 mutations, such as SHP2\(^{E76A}\), SHP2\(^{E69K}\), SHP2\(^{D61Y}\) and SHP2\(^{C459S}\) will ultimately occur in patients and may prevent the application of these inhibitors, which suggests that more SHP2 inhibitors for the treatment of SHP2 multi-mutations need to be identified in future. Overall, to develop SHP2 inhibitors in combination with KRAS, MEK inhibitors or identify multi-target inhibitors will be worthy to investigate. With the research progress that achieved in SHP2, it is believed that targeting tyrosine phosphatase SHP2 will become a therapeutic target in fighting with cancers.

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Author contributions

Xiao-Feng Xiong and Yang Sun conceived the project and provided the writing ideas. Zhendong Song and Meijing Wang summarized the literature and composed the manuscript. Yang Ge, Xue-Ping Chen and Ziyang Xu proofread the formats and references. Xiao-Feng Xiong and Yang Sun revised the manuscript. All authors gave approved to submit the final manuscript.

Conflict of interest

The authors have no conflicts of interest to declare.

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