Overview of the STAT-3 signaling pathway in cancer and the development of specific inhibitors (Review)

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Abstract. Signal transducer and activator of transcription (STAT) proteins represent novel therapeutic targets for the treatment of cancer. In particular, STAT-3 serves critical roles in several cellular processes, including the cell cycle, cell proliferation, cellular apoptosis and tumorigenesis. Persistent activation of STAT-3 has been reported in a variety of cancer types, and a poor prognosis of cancer may be associated with the phosphorylation level of STAT-3. Furthermore, elevated STAT-3 activity has been demonstrated in a variety of mammalian cancers, both in vitro and in vivo. This indicates that STAT-3 serves an important role in the progression of numerous cancer types. A significant obstacle in developing STAT-3 inhibitors is the demonstration of the antitumor efficacy in in vivo systems and the lack of animal models for human tumors. Therefore, it is crucial to determine whether available STAT-3 inhibitors are suitable for clinical trials. Moreover, further preclinical studies are necessary to focus on the impact of STAT-3 inhibitors on tumor cells. When considering STAT-3 hyper-activation in human cancer, selective targeting to these proteins holds promise for significant advancement in cancer treatment. In the present study, advances in our knowledge of the structure of STAT-3 protein and its regulatory mechanisms are summarized. Moreover, the STAT-3 signaling pathway and its critical role in malignancy are discussed, in addition to the development of STAT-3 inhibitors in various cancer types.

1. Introduction

Signal transducer and activator of transcription (STAT) proteins are a class of transcription factor that are activated by cytokines, growth factors and other peptide ligands. STATs are activated by tyrosine phosphorylation in response to diverse cytokine signals in the cytoplasm. Following activation, the STAT proteins translocate to the nucleus, binding their specific targets and serving as transcription factors (1‑4). STATs influence numerous physiological processes, including cell proliferation, apoptosis, division and differentiation (5). In healthy cells, the activation of STATs is tightly regulated to prevent uncontrolled gene expression; however, prolonged activation of STATs in cancer cells may result in significant adverse effects, such as drug resistance and poor prognosis (5,6). In humans, the STAT family comprises seven proteins, including STAT-1, -2, -3, -4, -5A, -5B and -6, and the genes encoding the STAT family are located on chromosomes 2 (STAT-1 and -4), 12 (STAT-2 and -6) and 17 (STAT-3, -5A and -5B) (7). Among the seven members, STAT-3 and -5 exhibit the strongest association with tumor progression. Persistent activation of STAT-3 or STAT-5 (particularly STAT-3) regulates a variety of functions, including proliferation, cell cycle progression, apoptosis, angiogenesis and immune evasion (8-10). Consequently, STAT-3 mainly contributes to tumor proliferation and survival owing to its role in stromal cells, including immune cells recruitment in the tumor microenvironment to promote tumor growth, and is, therefore, recognized as a promising target for cancer therapy (11-16).

Previous studies have demonstrated that DNA methylation and chromatin modulation may also be regulated by STAT-3 via epigenetic mechanisms (17,18). Moreover, STAT-3 has been recognized as a potent immune checkpoint regulator for
multiple antitumor immune response pathways (12,13). Despite the plethora of evidence implicating STAT-3 in the progression of several types of cancer and indicating it as an ideal target for cancer therapy, there is still no clinical drug available that directly targets STAT-3 (19). Thus, a novel small molecule able to directly target STAT-3 may represent a promising novel STAT-3 inhibitor. Notably, STAT-3 is highly complex in its diverse biological functions, as well as its various activators. Therefore, further investigations into STAT-3 biology and signaling pathways are particularly important.

2. STAT-3 structure

STAT-3 is comprised of ~800 amino acids, and its relative mass is 92 kDa; it has several conserved functional domains, including N-terminal, coiled-domain, DNA-binding domain (DBD), Src-homology-2 (SH-2) domain and transactivation (TA) domain (20-22). DBD has specificity with certain regions of DNA, allowing STAT-3 to bind downstream of the target gene-promoter element to induce the expression of target genes. The SH-2 domain participates in phosphorylation of tyrosine residues, facilitating protein-protein interactions with tyrosine-phosphorylated proteins (23). Furthermore, the SH-2 domain is critical in the formation of the STAT-3 dimer (the region that STAT-3 binds to in order to activate receptors). In between the DBD and SH-2 domain there is a linker protein that mediates the stability of DNA binding and assembly of the transcriptional body (24). The TA domain contains one tyrosine phosphorylation site (Yyr705) and one serine phosphorylation site (Ser727). During STAT-3 activation, tyrosine and serine residues are phosphorylated by upstream kinases and recognized by the SH-2 domain (25), as indicated in Fig. 1.

However, it has been demonstrated that STAT-3 contains three different isomers: The full-length α form, and two shorter isoforms, β and γ, which are the result of mRNA splicing and proteolysis, respectively. STAT-3α primarily participates in cell proliferation and transformation, while STAT-3β regulates cell differentiation mediated by granulocyte colony-stimulating factor (G-CSF) and lacks a serine phosphorylation site (26). Activated STAT-3γ has been identified in differentiated neutrophils and does not contain a transactivation domain (27,28). A previous study also suggested that these isoforms may exert a dominant-negative effect on their full-length counterparts (29).

3. STAT-3 signal transduction cascade

Transient STAT3 activation is a key determinant of tissue integrity restoration, wound healing and immune response resolution, given its critical biological functions (30). STAT-3 is heavily regulated to ensure transient activation under standard conditions. To mediate this process, three classes of proteins located upstream of STAT-3 influence negative regulation of its activation, including tyrosine phosphatases, protein inhibitors of activated STATs (PIAS) and suppressors of cytokine signaling (SOCS) (31). Tyrosine phosphatases downregulate Janus kinase (JAK)/STAT signaling via dephosphorylation of STAT and its upstream kinases (32). It has been reported that the protein tyrosine phosphatase receptor T specifically dephosphorylates the Tyr705 residue in the TA domain of STAT-3 (32). The PIAS family comprises four members: PIAS-1, -3, -x and -y (33). Of these, PIAS-3 is associated with STAT-3 inhibition via blocking its binding to DNA, recruiting co-repressors or serving as SUMOylation E3 ligases (34-36). The SOCS family of proteins, also known as cytokine-induced SH-2-containing proteins, inhibit STAT-3 binding and decrease JAK activity via competitive binding to phosphorylated tyrosine residues on activated cytokine receptors or JAK (19). As the receptor lacks its own enzymatic activity, STAT-3 is primarily activated via the JAK-dependent pathway (37).

The JAK/STAT-3 pathway is typically considered the most crucial signaling pathway in the activation of STAT-3 (18). Notably, interleukin (IL)-6 is the most well-characterized upstream cytokine, which binds specifically to membrane-bound receptors in the JAK/STAT-3 pathway (38-40). IL-6 binds IL-6 receptor-α on the cell surface, inducing conformational changes and resulting in the formation of a homodimer and heterodimer. This initiates the activation of JAK, followed by recruitment and activation of cytosolic STAT-3 (18). Consequently, activated STAT-3 translocates to the nucleus and binds to its target gene (Fig. 2).

Certain other IL family members can induce STAT-3 translocation to the nucleus, including IL-11 and -31, leukemia inhibitory factor, ciliary neurotrophic factor and oncostatin M. Moreover, it has been reported that IL-6-class cytokines serve crucial roles in the progression of numerous tumor types, including breast, lung and prostate cancer, and also multiple hematopoietic malignancies (41-50). Although other IL-6-class cytokines contribute to tumor development, IL-6 is considered the most significant regulator of the JAK/STAT-3 pathway in tumors. Furthermore, certain reports have demonstrated that IL-6 is regulated by specific oncopgenes, such as breakpoint cluster region-ABL protooncogene and RAS (51,52). Recent studies have reported that IL-6 promotes cell migration via the induction of epithelial-mesenchymal transition (EMT), and IL-6-mediated EMT in breast cancer may be a consequence of STAT-3 activation (53-55). These findings indicate that STAT-3 may represent a target that can inhibit tumor development mediated by the aforementioned oncopgenes (53).

G-protein-coupled receptors (GPCRs) are not traditional receptors in the JAK/STAT-3 pathway; however, several findings suggested that GPCRs may be a STAT-3 activator contributing to tumor progression (56). Sphingosine-1-phosphate receptor-1 (SIPR-1) is a type of GPCR that is upregulated in malignant, immune and endothelial cells. Previously, SIPR-1 was revealed to be associated with tumor cell survival and resistance to chemotherapy in a variety of cancer cells (57-62). Moreover, sphingosine-1-phosphate receptor 1 (SIPR-1) activates STAT-3 via JAK-2, resulting in the cyclical upregulation of SIPR-1 expression (63). In general, toll-like receptors (TLRs) participate in innate immune system responses, connecting specific immunity to non-specific immunity. Nevertheless, recent studies have demonstrated the crucial role of TLRs in the activation of STAT-3 and tumor progression. It has been reported that TLR-4 induces STAT-3 activation via upregulation of IL-6 and microRNA (miR)-21, resulting in the neoplastic progression of colon cancer in vivo (64). Furthermore, TLR-2, -7 and -9 were all identified to correlate with STAT-3 activation and tumor progression (65-67). These findings indicate that GPCRs and TLRs activate the JAK/STAT-3 signaling
pathway and support the potential of targeting GPCRs and TLRs to inhibit STAT-3-induced tumor growth. Although numerous STAT-3-associated regulatory mechanisms mediating cancer progression have been revealed, the targeting of STAT3 in oncotherapy remains a challenge. This is due to the shallow surface pockets of STAT3 molecules, which make it difficult to form effective binding.

Additionally, inactivation can also occur via two pathways: i) The RAS/MAPK pathway; and ii) the non-receptor tyrosine kinase pathway. Mitogen-activated protein kinase (MAPK) is a serine/threonine-protein kinase and a downstream signaling molecule of the RAS pathway, which influences cell proliferation and differentiation, the inflammatory response and cell pathology. Various reports have demonstrated that RAS mediates STAT-3-induced autophagy and tumorigenesis via regulation of MAPK signaling (68-70), and that the influence of STAT-3 on gene transcription is significantly decreased following inhibition of MAPK (71,72). This is due to phosphorylation of tyrosine residues during signal transduction of STAT-3 and phosphorylation of serine residues.

Independent of the JAK/STAT-3 and RAS/MAPK pathways, STAT-3 influences numerous other cytokine signal transduction pathways by interacting with molecules such as cardiotrophin-1, angiotensin II and epidermal growth factor receptor. Moreover, certain non-receptor tyrosine kinases also activate STAT-3, such as Src (37). Oncogenic Src can activate STAT-3, while BCR-ABL fusion protein can co-activate STATs -1, -3 and -5 (73). A recent study revealed aberrant activation of
STAT-3 in normal and neoplastic colorectal epithelial cells and tumor tissues with upregulated Src (74). Src homology region 2 domain-containing phosphatase 1 (SHP-1) is a non-receptor protein tyrosine phosphatase and serves as a tumor suppressor gene in numerous cancer types. Liu et al (75) demonstrated that SHP-1 expression levels are downregulated in the majority of tumor types and correlate with high expression levels of p-STAT3 expression. Thus, the SHP-1/p-STAT3 signaling axis may represent a potential therapeutic target and a clinical prognostic indicator in patients with cancer.

4. Target genes regulated by STAT-3

Activation of STAT-3 is transiently and rapidly sustained for a few minutes in the normal physiological state. However, persistent activation of STAT-3 can induce abnormal expression of various genes associated with cell proliferation, differentiation and apoptosis (76). Due to its significant carcinogenic properties, STAT-3 has been recognized as an oncogene. Numerous genes downstream of STAT-3 have been identified, including Mcl-1, cyclin D1, MYC proto-oncogene bHLH transcription factor (c-Myc) and vascular endothelial growth factor (77). Bcl-xL and Mcl-1 are both members of the Bcl-2 anti-apoptotic family. Bcl-xL and Bcl-2 bind Bax via BH-1 and BH-2, forming homologous and heterologous dimmers that influence cellular apoptosis (78). In addition, Mcl-1 inhibits the release of cytochrome c, which may induce the intrinsic apoptosis pathway. A recent study have demonstrated that the Bcl-xL promoter initiates transcription during the activation of STAT-3, resulting in a malignant transformation (79). Typically, cancer cells originate from healthy cells due to the combinatorial effects of various factors at different phases of cell division and growth, resulting in abnormal cell proliferation and differentiation. Notably, the cell cycle is a key aspect of this malignant transformation. STAT-3 binds Src proto-oncogene non-receptor tyrosine kinase via its SH-2 domain, activating c-myc and inducing the upregulation of cyclin D1. However, cyclin D1 and c-myc participate in the regulation of cell cycle progression, and their upregulation results in dysfunction of the cell cycle and uncontrolled cell proliferation (80). Angiogenesis is essential for cancer cell proliferation and metastasis, as it provides tumor cells with the nutrients and oxygen required for survival. Increasing evidence has indicated that persistently activated STAT-3 stimulates tumor angiogenesis (81). It has been reported that STAT-3 not only regulates the expression of VEGF in a variety of human cancer types, but that it also influences other critical angiogenic factors, including angiopoietin, matrix metalloproteinase-9, chemokine (C-X-C motif) ligand 16 and insulin-like growth factor binding protein (81-84).

5. Advances in antitumor therapeutics targeting STAT-3

STAT-3 is essential in various cellular processes, including the cell cycle, cell proliferation, cellular apoptosis, tumorigenesis and the regulation of the tumor niche. In healthy cells, STAT-3 activation is regulated to prevent uncontrolled gene regulation; however, abnormal activation of STAT-3 can result in the occurrence of numerous disease types (18). Increasing evidence has indicated that high-frequency abnormal activation of STAT-3 is associated with a variety of cancer types, including brain, lung, pancreatic, renal, colorectal, endometrial, cervical, ovarian, breast and prostate cancer, melanoma, glioma, head and neck squamous cell carcinoma, lymphoma and leukemia (85-87). Grivennikov et al (43) constructed a colitis-associated cancer model using mice with intestinal epithelial cell STAT-3-specific deletion and demonstrated that STAT-3-specific deletion significantly inhibits the occurrence of tumors and their progression (44). In addition, STAT-3 inhibits p53 synthesis and reduces its protective effect on genomic stability. Following the stimulation of inflammatory mediators, the probability of DNA damage and gene mutation in parenchymal cells increases significantly, and STAT-3 is also able to reduce the tolerance of ovarian cancer cells to stress and damage (67). Another study revealed that STAT-3 activates miR-608, which inhibits the proliferation, migration.
and invasiveness of lung cancer cells (88). Moreover, STAT3 also serves a critical role in the regulation of tumor niche. Sun et al. (89) reported that Annexin10 promotes extrahepatic cholangiocarcinoma metastasis by stimulating EMT via the STAT-3 pathway. Taken together, the aforementioned evidence indicates that persistent activation of STAT-3 contributes to cell proliferation, differentiation, migration and survival, and consequently, researchers have attempted to inhibit the STAT-3 signaling pathway as a method of cancer treatment (11-16).

In previous research, attempts were made to inhibit the effect of receptor tyrosine kinase (RTK), but mechanistic studies indicated that the inhibition of specific RTKs initiated the activation of STAT-3. Although certain small molecules targeting RTKs were used clinically, the therapeutic efficacy was limited by the development of drug resistance (90). Drug resistance represents a significant challenge for effective anti-tumor therapy, as it often ultimately results in treatment failure. Thus, activation of STAT-3 may contribute to the development of drug resistance; therefore, inhibition of the STAT-3 pathway can restore the efficacy of chemotherapeutics agents (91).

Notably, only one compound (BBI-608) targeting STAT-3 has been approved by the Federal Drug Administration for clinical use. However, a few small molecules have been demonstrated to antagonize the STAT-3 signaling pathway as a method of cancer treatment (11-16).

In order to target STAT-3 tyrosine phosphorylation, researchers have attempted to identify a small inhibitor molecule that directly binds the SH-2 domain of STAT-3, and prevents tyrosine phosphorylation, protein dimerization and transcriptional activity (92,93). Recently, structure-based drug design and computational docking techniques have been widely used for the identification of small molecules. For example, STA-21 (deoxytetrangomycin) is an analog of tetrangomycin (a non-peptide small molecule STAT-3 inhibitor) that was discovered using structure-based drug design and has successfully completed phase I/II clinical trials (94,95). Furthermore, a variety of STA-21 analogs with improved potency, including LLL-12, S-3I-201, BP-1-102 and S-3I-1757, have been demonstrated to inhibit malignant transformation, tumor cell proliferation, migration and invasion. LLL-12 is a structurally optimized analog of STA-21 and inhibits the activation of STAT-3 in a similar manner to STA-21 (96-99). Additionally, LLL-12 exerts no inhibitory effects on STAT-1 and other RTKs, indicating its specificity to STAT-3, and is more sensitive to a variety of cancer cell lines (100,101).

S-31-201 is another specific inhibitor of STAT-3 that inhibits STAT-3 phosphorylation and dimerization. However, molecular modeling indicated that S31-201 selectively binds to the SH-2 domain (102). Consequently, a library of S31-201 analogs has been developed and, of these, S31-201 and -1-066 exhibit potent inhibition of STAT-3 dimerization, both in vitro and in vivo (103,104). Furthermore, via structure modification, BP-1-102 (an analog of SF-1-066) demonstrated improved specificity and oral bioavailability. BP-1-102 binds three locations of the STAT-3-Sh-2 domain and inhibits STAT-3 activation at concentrations of 4.1-6.8 µM (105,106). In addition, certain analogs of BP-1-102 have been synthesized and evaluated to improve potency, such as Sh-5-07 and -4-54 (107). These features indicate that BP-1-102 and its analogs may represent promising anticancer agents.

LY-5 is another small molecule that inhibits STAT-3 by selectively binding the major pTyr-705 region, as well as a sub-pocket of the STAT-3-Sh-2 domain. LY-5 was designed by computer models using docking simulation and evaluated for inhibitory effects on STAT-3 activation and functions in human medulloblastoma cells (108,109). Further studies demonstrated that LY-5 not only suppressed various cancer cells with an IC50 range of 0.5-1.4 µM, but that it also inhibited tumor growth in an in vivo mouse model. Furthermore, previous reports have

| Inhibitor name | Mechanism | Disease type (clinical trial phase) | ClinicalTrials.gov identifier (Refs.) |
|----------------|-----------|------------------------------------|-------------------------------------|
| STA-21         | SH-2 domain inhibition | Psoriasis (phase I/II) | NCT01047943 (84,85) |
| Pyrimethamine  | STAT-3 inhibitor       | Chronic lymphocytic leukemia, small lymphocytic leukemia (phase I/II) | NCT01066663 (108) |
| OPB-51602      | SH-2 domain inhibition | Nasopharyngeal carcinoma (phase I) | NCT02058017 (103,104) |
|                | Advanced cancer (phase I) | Multiple myelomas, non-Hodgkin lymphoma, acute myeloid leukemia, chronic myeloid leukemia (phase I) | NCT01423903 NCT01344876 |
| OPB-31121      | SH-2 domain inhibition | Leukemia (phase I) | NCT01184807 (99,100,106,107) |
|                | Advanced cancer, solid tumor (phase I) | Non-Hodgkin’s lymphoma, multiple myeloma (phase I) | NCT00955812 NCT00511082 |
|                | Hepatocellular carcinoma (phase I/II) | Solid tumor (phase I) | NCT01406574 NCT00657176 |

STAT-3, signal transducer and activator of transcription-3; SH-2, Src-homology-2.
demonstrated that a combination of a MEK inhibitor and LY-5 may represent a potential therapeutic strategy for overcoming resistance to MEK inhibitors in multiple human cancer cell lines (108,109). Notably, further evidence has demonstrated that the SH-2 domain is an effective target for small molecule STAT-3 inhibitors. For example, it has been demonstrated that OPB-31121 and -51602 represent two potent STAT-3 inhibitors (110,111). OPB-31121 and -51602 also bind to the SH-2 domain; however, molecular docking and dynamic simulations indicate that their binding site do not overlap with any other STAT-3 inhibitors (110,111).

Typically, the STAT-3 SH-2 domain is considered a prime target for various STAT-3 inhibitors, due to the lack of selectivity for other domains. However, previous studies have reported that InS3-54 (designed by an improved in silico approach) effectively inhibits the STAT-3 DBD. ‘In silico’ refers to the use of computers to solve biological problems. In the present study, optimization and design of the lead compound were performed by simulating and calculating the interaction between receptor and ligand. This approach is known to notably improve the discovery of novel drugs (112). Notably, an optimized compound (InS3-54A18) has been identified with improved specificity and pharmacological properties, which not only inhibits STAT-3 activation via targeting the DBD of STAT-3, but also significantly inhibits the downstream target gene of STAT-3 (113-115). The aforementioned findings indicate that InS3-54A18 may be a starting point for the further development of anticancer therapeutics targeting the DBD of STAT-3.

Currently, only a few small-molecule inhibitors targeting STAT-3 are undergoing the early phases of clinical trials (Table I), and there is no inhibitor of STAT-3 approved by the FDA except BBI-608, which is a STAT-3 and cancer cell stemness inhibitor. STA-21, OPB-31121 and OPB-51602 have already completed phase I/II clinical trials in leukemia. OPB-31121 and -51602 are currently in phase I/II clinical trials for advanced solid tumors. STA-21 is not undergoing a clinical trial at present. Phase I/II studies of OPB-31121 and -51602 revealed that these compounds exert potent antitumor activities with an acceptable safety profile (116-119). Pyrimethamine is another STAT-3 inhibitor used in the treatment of chronic lymphocytic and small lymphocytic leukemia, and is currently in phase I/II clinical trials (120).

Notably, JAKs serve a crucial role in JAK/STAT-3 signaling pathway; thus, inhibiting the activity of JAKs may be a novel approach to inhibit STAT-3 activation. AG490, a JAK inhibitor, reduces the proliferation of cancer cells by inhibiting JAK-2 activity and blocking the activation of STAT-3. In addition, AG-490 has been tested in models and in clinical trials (121-123).

A range of plant-derived compounds exhibit antitumor activity against a variety of cancer types. Notably, during the previous decade, a number of STAT-3 inhibitors derived from natural sources have been employed and shown to exhibit significant efficacy in regulating STAT-3 activation. Recent studies have demonstrated that certain natural therapeutic agents serve an inhibitory role in the genesis, progression and metastasis of various cancer types (37). Betulinic acid, a pentacyclic triterpene, extracted from Zizyphus mauritiana, displayed potency in inhibiting STAT-3 activation, Src kinase, and JAK-1 and -2 (124,125). Furthermore, it has been reported that betulinic acid induces apoptosis in thyroid, breast, lung and colon carcinomas, indicating its potential as a chemotherapeutic agent (124). Furthermore, caffeic acid is a phenolic compound discovered in plants, and certain studies have reported that caffeic acid exerts potent antioxidant and anti-inflammatory properties (126-128). However, a previous study demonstrated that caffeic acid exhibits antitumor properties via the inhibition of STAT-3, preventing STAT-3 recruitment and inhibiting the formation of a transcriptional unit between STAT-3, HIF-1α and p-300 on the VEGF promoter (129). Moreover, celastrol, obtained from Tripterygium wilfordii, is a Chinese medicinal plant. Certain reports have indicated that celastrol can inhibit proliferation, induce apoptosis and suppress invasion/migration and angiogenesis via modulation of the DNA-binding activity of STAT-3 in a wide variety of in vitro and in vivo tumor models (130-133). In addition, a variety of agents derived from natural plants have also been demonstrated to exert antitumor effects, such as curcumin, diosgenin and honokiol derived from curcuma longa, and fenugreek and mangnolia officinalis, respectively. Furthermore, a number of reports confirmed their antitumor effects were mediated via modulation of constitutive STAT-3 activation in glioma cells, HCC cells and HepG2 cells (134-136).

6. Conclusions

At present, specific inhibitors of STAT-3 predominantly target the disruption of the protein-protein interactions or DNA-binding activity, such as inhibitors that prevent the recruitment of STAT-3 to the IL-6/IL-6Rα/gp-130 complex, upstream kinase inhibitors and, primarily, JAK inhibitors. Over the past decade, small-molecule drugs that directly target STAT-3 have been identified; nevertheless, there are no STAT-3-specific drugs available clinically. It has been demonstrated that STAT-3 activation promotes oncogenesis via phosphorylation or acetylation. STAT-3 inhibition has been revealed to reverse acquired resistance, synergistically inhibit tumor growth, induce apoptosis and stimulate an immune response. Therefore, this signifies a requirement to reassess ongoing strategies in order to develop clinically useful drugs. Future research should focus on the development of therapeutic molecules with STAT-3-inhibitory modalities, as this has the potential to improve the treatment of a plethora of cancer types.

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Authors' contribution
The paper was conceived and designed by ZL. YCG wrote the paper, and ISM revised the paper. All authors read and approved the final manuscript.

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Not applicable.

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Competing interests
The authors declare that they have no competing interests.

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