Potential of CXCR1/2 as a target for the treatment of inflammation and cancer (Review)

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Abstract. C-X-C motif chemokine receptor (CXCR)1 and CXCR2 are chemokine receptors that serve critical roles in mediating immune and inflammatory responses. Their activation by chemokines, such as C-X-C motif chemokine ligand (CXCL)8/IL-8, can promote cell migration, proliferation and the release of additional inflammatory mediators, contributing to the progression of inflammatory diseases and cancers. By inhibiting the binding of CXCL8/IL-8 to CXCR1 and CXCR2, SCH527123 aims to disrupt these harmful processes and offers a promising therapeutic strategy. Research on immunotherapy, particularly focusing on targeting specific immune receptors and pathways, is experiencing a surge of interest and progress. Exploration of SCH527123 as a novel CXCR1 and CXCR2 antagonist has highlighted the potential of this approach in treating various diseases, particularly those involving inflammation and cancers. The preclinical success of SCH527123 in animal models of liver, pancreatic and ovarian cancers has underscored its potential as an anti-inflammatory and anti-tumor agent. These findings suggest that targeting CXCR1/2 signaling may represent a viable approach for treating a broad range of malignancies. Furthermore, interest in SCH527123 as a potential treatment for COPD and asthma has suggested its potential applications beyond cancer therapy. Therefore, SCH527123 represents a new drug candidate with potential in the fields of inflammation and cancer. Although challenges remain in translating preclinical findings into clinical benefits, ongoing research and development efforts on using SCH527123 hold promise for improving the survival and quality of life of patients with these devastating diseases.

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Abbreviations: COPD, Chronic obstructive pulmonary disease; RA, rheumatoid arthritis; NKs, natural killer cells; TME, tumor microenvironment; PDAC, pancreatic ductal adenocarcinoma

Key words: C-X-C motif chemokine receptor, IL-8, inflammation, cancers, SCH527123

Content

1. Introduction

Inflammation is a condition that has been a burden for decades. Research on the pathophysiology of inflammation has been gradually deepening over the recent decades (1,2). However, for certain chronic refractory inflammations, such as Crohn's disease, difficult-to-treat rheumatoid arthritis, severe asthma, atopic dermatitis or cutaneous lupus (3-6), no suitable cure has been found. At present, there are various treatments for persistent inflammation, including immunotherapy to restore normal lymphocyte count by using granulocyte-macrophage colony-stimulating factor and granulocyte-colony-stimulating factor pair, anti-inflammatory and antioxidant therapy, anabolic and anti-catabolic therapy and nutritional support therapy (7). For chronic inflammation of the respiratory system, especially chronic obstructive pulmonary disease (COPD), the current use of home oxygen therapy, expectorants, long-acting bronchodilators, such as long-acting muscarinic antagonists or long-acting β_2-agonists, antibiotics, influenza and pneumococcal vaccines, can only relieve the clinical symptoms of patients and prevent the further aggravation of the disease (8). Similarly, the current treatment strategy for asthma, a common chronic non-communicable respiratory disease, is limited to controlling asthma symptoms and reducing the risk of recurrence (9).

By contrast, cancer has become a major public health issue in the 21st century, accounting for 25% of the global mortality cases from non-communicable diseases, according to a 2022 Global Cancer Statistics report (10). With the continuous exploration of cancer treatment, various ILs have been previously shown to serve a critical role in the development of cancer, including IL-2, IL-6, IL-10, IL-12 and IL-35 (11-15). Amongst them, tumors frequently jointly produce IL-8, a chemotactic factor, which serves different roles in promoting tumor processes, such as angiogenesis and survival signal transduction in cancer stem cells (16,17).

Evidence have been accumulating that gradually deepened the knowledge into the various cytokine signaling pathways, which has led to the development of a series of small molecule antagonists and small molecule inhibitors targeting such signaling pathways. For inflammation and cancers, IL-1R1 (MEDI8968), IL-5 (mepolizumab) or IL-5R (benralizumab), IL-8 (ABX-IL8), IL-18 (MEDI2338), IL-33 (MEDI3506) have been developed for the treatment of COPD (18), whereas AZD5069 is in the clinical development stage of cancer such as triple-negative breast cancer (18,19). In addition, AZD8039, danirixin (GSK1325756), ladarixin (DF2156A), reparixin and SB656933 (20), which are more effective compared with traditional treatments for acute respiratory distress syndrome, COVID-19 pneumonia, inflammatory bowel disease (IBD), liver cancer and lung cancer have been garnering interest.

At present, a novel and selective C-X-C motif chemokine receptor (CXCR)1/2 antagonist that can exert therapeutic effects against both inflammation and cancers, SCH527123, which can inhibit the binding (or activation) of chemokines to CXCR1/2 in a high-affinity manner, has been discovered (21,22). It can inhibit signal transduction, neutrophil chemotaxis and myeloperoxidase release (23,24). It may have clinical value for the treatment of diseases such as acquired immune deficiency syndrome, IBD and non-small cell lung cancer directly (or indirectly) mediated by CXCR1/2-expressing cells (25,26).

To the best of our knowledge, the present review is the earliest of SCH527123 in the field of inflammation and cancer treatment. It aims to discuss the history of the development of SCH527123 and its mechanism of action, whilst summarizing the application and achievements of SCH527123 in asthma, COPD, pancreatic cancer and liver cancer and animal models (namely in mice and rabbits) over recent years. In addition, limitations of SCH5271213 development are discussed, where the clinical value of SCH527123 in the treatment of diseases in the future was also explored, to lay a foundation for future research.

2. C-X-C motif chemokine ligand (CXCL)8/IL-8 is involved in inflammation and tumorigenesis

IL-8 is a basic protein containing four cysteine residues and two intramolecular disulfide bonds which stabilize the structure of IL-8, that has strong resistance to deformation processing, such as plasma peptidase, high temperature and acid-base environment (27-31). In addition, IL-8 is a neutrophil chemotactic polypeptide (32). In *in vitro* experiments, IL-8 has shown chemotactic activity to T lymphocytes, basophils and neutrophils Although it can promote the migration of T cells and neutrophils, it requires additional factors to do so (33).

A study performed in 1989 injected IL-8 into the skin of rabbits and observed the accumulation of neutrophils and formation of neutrophil-dependent edema in the rabbit skin (34). Subsequently, 2 years later, clinical trials demonstrated for the first time the presence of bioactive substances such as melanoma growth stimulatory activity, P-thromboglobulin and platelet factor 4 in the synovial fluid of patients with rheumatoid arthritis and the expression of IL-8 mRNA in synovial cells (35). The level of IL-8 detected in patients with metastatic melanoma, among 56 confirmed cases, showed that some had markedly elevated serum IL-8 which correlated with tumour load but was independent of the site of metastasis (36). This clinical observation is supported by mechanistic studies summarized by Waugh and Wilson (37), who described how IL-8, through its receptors CXCR1 and CXCR2, promotes melanoma cell migration and invasion. Additionally, IL-8 contributes to an immunosuppressive tumor microenvironment by recruiting myeloid-derived suppressor cells (MDSCs) and inhibiting lymphocytic infiltration, which together facilitate tumor progression and metastasis (37). Using cell culture, IL-8 has also been found to be involved in airway mucosal tumor progression (38). These aforementioned experimental data all suggest the important role of IL-8 in inflammation and tumor development. The following sections of the present review will discuss the role of IL-8 in inflammation and tumor development.

Inflammation is the typical bodily response to injury, resulting from various causes, such as physical injury, ischemia-reperfusion injury, infection, toxin exposure, malignant tumors and autoimmune reactions, all of which would otherwise lead to tissue damage (39). The capacity of IL-8 to attract and activate neutrophils has rendered it a key inflammatory mediator from the initial stages of this process (33,40). IL-8 can bind to the CXCR2 receptor on the surface of neutrophils, leading to chemotaxis and the activation of neutrophils, causing them to secrete various cytokines, such as TNF-α, IL-1α, IL-1β and IL-8, exacerbating the occurrence of inflammation (Fig. 1) (41). IL-8 is relatively resistant to temperature, protein hydrolysis and acidic environments. These resistances enable IL-8 to maintain its activity under malignant conditions, making it a main molecule at sites of acute inflammation (40). Furthermore, IL-8 is frequently produced early in inflammation and can remain active at the site of inflammation for extended periods, up to several weeks. In acute inflammatory responses, such as bacterial infections or tissue injury, IL-8 activity generally lasts several weeks, whereas in chronic conditions, such as rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), or certain cancers, it may remain elevated for several months. This is in contrast to the majority of the other inflammatory cytokines, such as TNF-α, IL-1β and interleukin-6 (IL-6), which will typically disappear from the site of inflammation within a few hours in the body (42). The prolonged activity of IL-8 may be closely associated with its important role in the occurrence of inflammation.

IL-8 has been shown to be associated with the physiology of various cancers, including melanoma, prostate, colon, pancreatic, breast and lung cancer (43). IL-8 can directly impact tumors by altering the characteristics of tumor cells, inducing the transition of tumor cells to a more mesenchymal phenotype, consequently promoting migration and proliferation (44). This

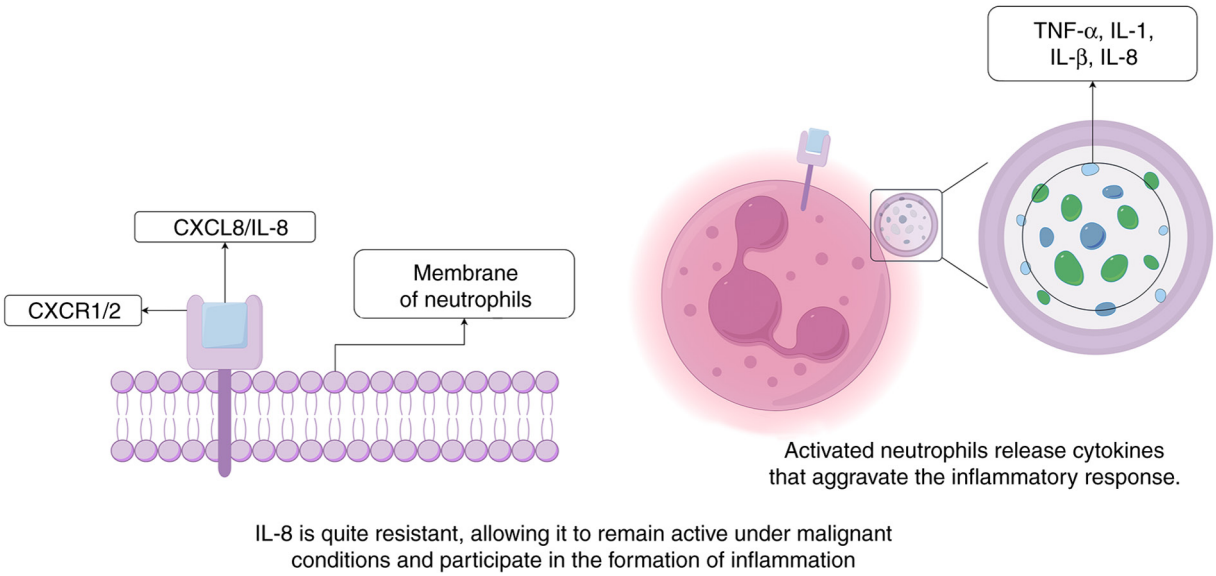

Figure 1. After binding to CXCR2 receptor, IL-8 activates and migrates neutrophils, prompting white blood cells to secrete a variety of cytokines, which promotes the development of inflammation and aggravates inflammatory symptoms. CXCL, C-X-C motif chemokine ligand; CXCR, C-X-C motif chemokine receptor.

in turn also promotes the occurrence of metastasis *in vivo* (45). By recruiting additional infiltrating immunosuppressive cells, IL-8 increases angiogenesis within tumors and alters the immune microenvironment, which further promotes tumor growth and metastasis (46). The formation of tumors requires the support of the surrounding normal matrix, which is referred to as the tumor microenvironment (TME). IL-8 can not only influence the cellular phenotypes of tumors and endothelial cells within the TME, but can also alter the immune composition at the tumor site. IL-8 preferentially recruits pre-tumor immune cells (including myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils and Natural Killer cells), thereby suppressing the anti-tumor immune response of cytotoxic immune cells (16). *IL-8* gene silencing has been shown to suppress the growth of ovarian cancer through an anti-angiogenic mechanism (Fig. 2) (47). The aforementioned factors all indicate that IL-8 serves a promotional role in the process of tumorigenesis.

3. Mechanism of action for SCH527123

Since IL-8 and related chemokines (such as CCL2, CXCL12, CCL5 and CX3CL1) have shown strong association in a variety of inflammatory conditions and cancers, the research discovery of small molecule antagonists of CXCR1/2 as novel targets has been garnering attention. In 1998, the first potent and selective CXCR2 receptor antagonist SB225002 was reported (48). Subsequently, in 2003, PD0220245 was demonstrated to be the most effective IL-8 antagonist at the time, where compared with SB225002, PD0220245 was able to inhibit both CXCR1 and CXCR2 as a dual inhibitor (49). In 2006, Dwyer *et al* (50) discovered that the furan-based derivative of lead (Fig. 3A) was part of the active structure of lead cyclobutene dione, leading to the development of SCH527123 (Fig. 3B). This is a type of selective CXCR1/2 antagonist, also known as navarixin (20). CXCL8/IL-8 has been demonstrated to induce the migration of neutrophils (51), which meant that CXCL8/IL-8 can induce the recruitment of neutrophils to inflammatory sites by interacting with CXCR1/2 expressed on the surfaces of these cells (52). SCH527123 acts as a CXCR1/2 antagonist by blocking the binding of ELR-motif chemokines to CXCR2, thereby inhibiting downstream signaling pathways (AKT, ERK, STAT3 and S6 phosphorylation). This suppresses neutrophil activation and migration toward chemokines, while also reducing tumor cell proliferation and survival, resulting in comprehensive modulation of immune cell function and tumor progression. These chemokines include IL-8, growth homolog (Gro)-α, epithelial cell-derived neutrophil attractant-78 and neutrophil-activating peptide-2 (53). SCH527123 can directly block the binding of CXCL8/IL-8 to CXCR1/2, thereby interrupting the subsequent series of harmful reactions that CXCL8/IL-8 would otherwise trigger in the human body (Fig. 4). Although SCH527123 can bind to CXCR1 and CXCR2, SCH527123 binds to CXCR1 with lower affinity (K_d=3.9±0.3 nM), such that the compound is more CXCR2-selective (K_d=0.049±0.004 nM). Therefore, SCH527123 has a CXCR2-specific antagonistic effect, which also suggests its potential therapeutic effect on inflammation.

4. Role of SCH527123 in relevant diseases

SCH527123 is a novel small molecule antagonist that serves as an effective allosteric inhibitor for both CXCR1 and CXCR2, exhibiting high affinity towards both receptors (albeit with a higher selectivity for CXCR2). It exerts its therapeutic effects by suppressing the chemotactic activity of all chemokines on CXCR1/2, thereby alleviating or treating diseases (25).

Asthma. Asthma is caused by chronic inflammation in the lower respiratory tract. It is a relatively common disease and a 2024 analysis based on the Global Burden of Disease Study found asthma prevalence rates of 9.1% in children, 11.0% in adolescents, and 6.6% in adults worldwide. Variations

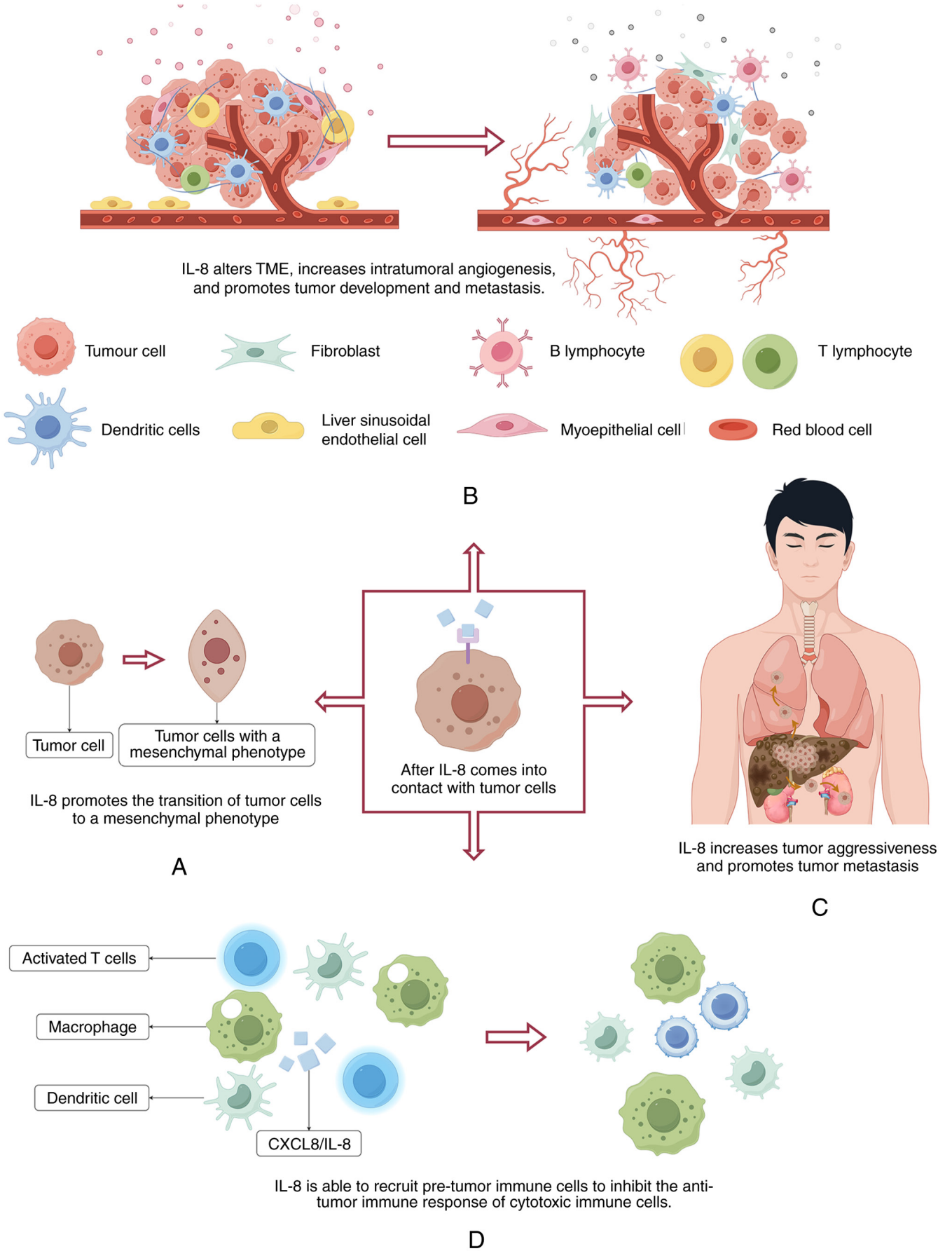

Figure 2. IL-8 is involved in cancer development through four pathways. (A) It promotes the transformation of tumor cells into a more epidermal mesenchymal phenotype. (B) It increases angiogenesis in the tumor and changes the immune microenvironment by recruiting more invasive immunosuppressive cells. (C) It increases the possibility of tumor cell migration and invasion *in vitro* and metastasis *in vivo*. (D) It recruits pre-tumor immune cells to inhibit the anti-tumor immune response of cytotoxic immune cells. TME, tumor microenvironment; CXCR, C-X-C motif chemokine receptor.

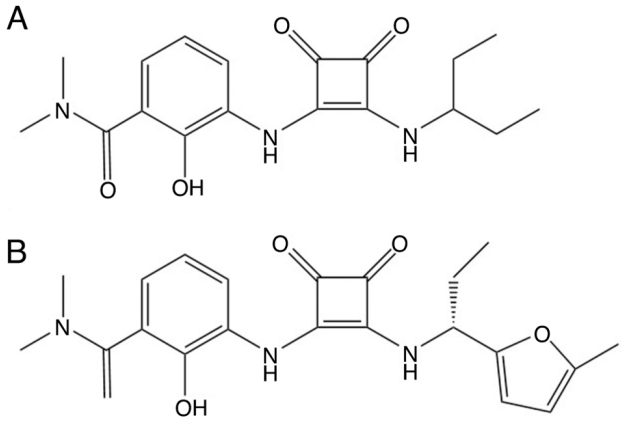

Figure 3. Chemical structures. (A) Lead cyclobutenedione and (B) SCH527123.

across regions highlight asthma as a common and significant public health concern (54). The main symptoms of asthma are breathing difficulties, shortness of breath, cough and chest tightness (54). During severe asthma, neutrophils and eosinophils can be found in the lung epithelium and mucus. The expression of ELR+ chemokine and its receptor was found to be increased (ELR+ chemokines, including IL-8 and CXCL1-3) (55), where CXCR1/2 was observed to be expressed on airway smooth muscle cells and mediated cell contraction and migration to enhance airway responsiveness and remodeling, causing bronchoconstriction. IL-8/CXCR2-dependent neutrophil recruitment is critical for the development of asthma, where blocking this signaling pathway may provide a novel approach for its treatment (56).

In 1996, a clinical trial on patients with asthma with a mean age of 39 years found that their bronchoalveolar lavage fluid contained higher levels of IL-8 compared with those from healthy individuals, suggesting that non-specific inflammation may be occurring in the airway (57). Neutrophils are recruited to the lungs in response to various chemokines, such as IL-8, GRO-α, MIP-2 and MIP-1 α, which then accumulate in the airways of patients with asthma (58). The biological effects of IL-8 are mediated through chemokine receptors CXCR1 and CXCR2 (59). In 2012, a number of clinical studies have reported that blocking CXCR1/2 was safe and well-tolerated, which could reduce the numbers of sputum neutrophils in patients with severe asthma (58). In 2016, 19 non-smoking patients with mild allergic asthma were included in a clinical study. This previous study demonstrated that CXCLs, including IL-8 and their receptors CXCR1 and CXCR2, are upregulated in the airways during asthma exacerbations (60). Therefore, inhibiting neutrophil chemotaxis by blocking CXCR1 and CXCR2 may provide an alternative therapeutic strategy for patients with asthma complicated with neutrophilic inflammation. By targeting cells that accumulate in airway tissues through chemotaxis mediated by CXCR1 and CXCR2, the 2016 study conducted by Todd *et al* (61) showed that SCH527123 has emerged as a novel therapeutic agent that may exert a specific therapeutic effect on inflammation.

COPD. COPD is an insidious but progressive chronic inflammatory disease of the respiratory system, characterized by an obstructive ventilation pattern, manifested as incompletely reversible airflow limitation. In severe cases, it can lead to chronic respiratory failure (53,62). Due to the inhalation of harmful particles and gases (such as chemicals in cigarette smoke) or aberrant innate immune responses, epithelial cells and resident macrophages can become activated. These cells in turn release cytokines and chemokines, thereby recruiting neutrophils to the lungs. The number of activated macrophages and neutrophils in the lungs then increases, where the proteases they secrete causes alveolar damage, leading to the spread of inflammation during COPD (53,63).

CXCR1/2 serves an important role in the chemotaxis of neutrophils. By studying eight patients with COPD and eight smokers without COPD, IL-8 was demonstrated to serve a major role in neutrophil chemotaxis induced by alveolar macrophage-derived conditioned medium, where blockade of CXCR1 and CXCR2 was observed to inhibit this chemotaxis. Furthermore, the dual CXCR1/2 antagonist SCH527123 exerted a superior inhibitory effect on neutrophils compared with that mediated by the single CXCR2 antagonist SB656933, whilst also demonstrating a greater role in blocking the chemotaxis of IL-8 (63). Another study conducted a single-point, randomized, double-blind, multi-dose, placebo-controlled, three-way cross-over study on healthy non-smoking volunteers with normal airway reactivity, which found that SCH527123 could inhibit the migration of neutrophils to CXCLs, thereby reducing the number of neutrophils in the sputum of healthy non-smoking volunteers exposed to ozone (53). Various stimuli, such as cigarette smoke, air pollution and ozone, can activate lung macrophages, leading to the secretion of several cell factors, such as IL-8, TNF-α, IL-1β, IL-6, CCL2 and GM-CSF, which causes an inflammatory response and the aggregation of neutrophils at the site of inflation. Subsequently, the various enzymes released by neutrophils and the mucus produced by hypertrophic goblet cells can also contribute to the progression of COPD (64-67). Therefore, controlling the number of neutrophils using medications appears to be key to treating COPD. Therefore, it can be hypothesized that SCH527123 can be a treatment option for COPD, where its ability to reduce the number of neutrophils may serve a role in the disease treatment process.

5. CXCL8/IL-8 and SCH527123 in cancers

Accumulating evidence has indicated that TME serves a key role in promoting cancer progression and regulating the response to standard treatments (68,69). Various components can coexist and interact within the TME, including tumor-associated macrophages, CD4+ and CD8+ T cells, dendritic cells, natural killer cells, tumor-associated endothelial cells, the abnormal tumor vasculature, cancer-associated fibroblasts and myeloid-derived suppressor cells (70). The presence of inflammatory cells and immune regulatory mediators in the TME polarizes the host immune response towards specific phenotypes that affect the progression of tumors (71). Various studies have previously found that CXCLs are expressed at increased levels through both autocrine and paracrine pathways in different types of tumors, suggesting their involvement in tumor growth and metastasis (72,73). CXCR2 chemokine ligands, including CXCL1-8, have all been known to be

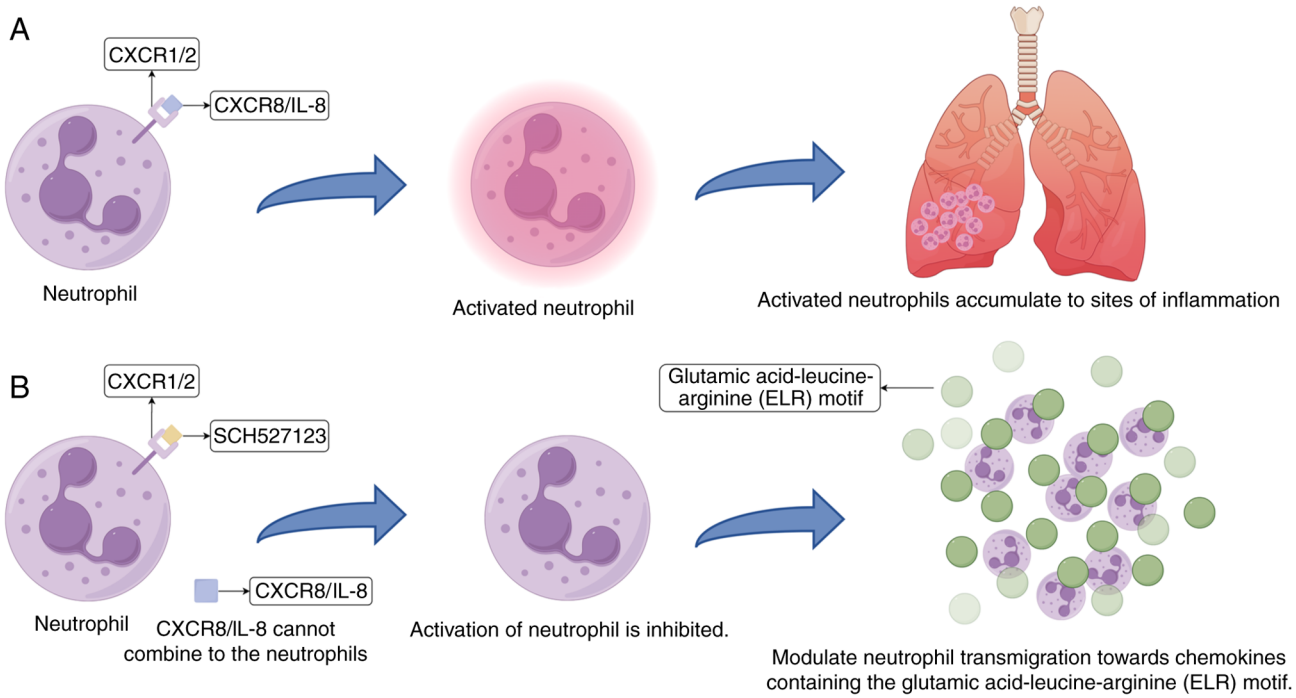

Figure 4. (A) CXCL8/IL-8 binds to CXCR1/2 on neutrophils, resulting in their activation and subsequent accumulation at sites of inflammation. (B) SCH527123 blocks the binding of CXCL8/IL-8 to CXCR1/2, thereby inhibiting neutrophil activation. This inhibition further modulates neutrophil transmigration towards chemokines containing the ELR motif, preventing excessive inflammatory responses. CXCL, C-X-C motif chemokine ligand; CXCR, C-X-C motif chemokine receptor.

secreted and expressed in various types of cancers, including solid tumors, such as melanoma, breast, lung, bladder, pancreatic, liver, prostate and colorectal cancer, in addition to hematological malignancies (43). This section primarily focused on liver, pancreatic, ovarian and colon cancer, as the CXCL/CXCR2 signaling pathway is highly active in these tumors and closely linked to inflammatory tumor microenvironment, tumor growth and metastasis. Moreover, these types of cancer are clinically common with poor prognosis, making them ideal targets for evaluating the potential efficacy of the CXCR2 antagonist SCH527123 (Table I).

Liver cancer. Liver cancer is one of the most common fatal cancers worldwide. HCC ranks as the 6th most common cancer and the 3rd leading cause of cancer-related death worldwide (74). Even after curative surgical resection, hepatocellular carcinoma patients have a 5-year overall survival rate of 30-50% and a median survival of 60 months. This reflects high recurrence risk and poor long-term prognosis post-resection, highlighting the malignancy's aggressiveness and therapeutic challenges (75). There are various risk factors for liver cancer, including hepatitis virus infection, fatty liver disease, alcohol-related cirrhosis, smoking, obesity, diabetes, iron overload and various dietary exposures (aflatoxins, high-fat diet, red and processed meats and alcohol consumption) (76). A definitive diagnosis is typically made when patients are already in the advanced stages of the disease, where due to the high frequency of recurrence and distant metastasis after surgical excision, prognosis is poor (76,77). Previous studies have discovered that the expression of IL-8 is upregulated and involved in the progression of various human cancers, including liver cancer (78,79). In *in vitro* cultured human liver cells, IL-8 has been shown to serve a role in promoting cell migration and/or invasion (77). Therefore, inhibiting the function of IL-8 may suppress liver cancer malignancy.

Although there is no direct *in vivo* evidence that CXCR1 and CXCR2 are expressed in liver cancer, according to an analysis of immunohistochemical results in China (78) by Bi *et al* (77), IL-8, CXCR1 and CXCR2 levels were elevated in peripheral blood mononuclear cells of liver cancer patients and immunohistochemistry showed higher CXCR1 and CXCR2 expression in tumor tissues compared with adjacent non-cancerous tissues. CXCR1/CXCR2 expression correlated with clinical stage and metastasis. *In vitro*, IL-8 promoted liver cancer cell migration and invasion, which was attenuated by CXCR1/CXCR2 blockade. These findings indicate that high IL-8 secretion induces CXCR1 and CXCR2 overexpression on both tumor and inflammatory cells, contributing to liver cancer progression. This can further confirm that the high level of IL-8 secretion by liver cancer cells induces the overexpression of CXCR1 and CXCR2 on both liver cancer and inflammatory cells, which in turn participate in the occurrence, invasion and metastasis of liver cancer (77). The study by Bi *et al* (77) provides experimental evidence that IL-8 promotes liver cancer cell migration via CXCR1 and CXCR2. Immunohistochemical and RT-qPCR analyses showed that IL-8, CXCR1, and CXCR2 were significantly upregulated in liver cancer tissues compared with normal liver tissues, with IL-8 mRNA expression positively correlated with CXCR1 ($r=0.618$, $P<0.01$) and CXCR2 ($r=0.569$, $P<0.01$). *In vitro*, treatment of Huh-7 and HepG2 cells with 50 ng/ml IL-8 for 24 h increased wound closure from 35-78 and 32-72%, respectively in wound healing assays, and significantly enhanced Transwell migration and invasion ($P<0.01$). Pre-treatment

Table I. Summary of the role of SCH527123 in various cancers.

First author/s, year	Disease	Experimental result	(Refs.)
Goral *et al*, 2015	Liver cancer	CXCR1, CXCR2 and IL-8 proteins were highly expressed in the cytoplasm of hepatocellular carcinoma cells, where IL-8 induced the expression of CXCR1/2.	(82)
Fu *et al*, 2018	Pancreatic cancer	SCH527123 can inhibit the proliferation of PDAC cells by reducing the activity of cancer cells, inhibiting cancer cell proliferation and blocking signaling pathways, including the IL-8/CXCR1/2 signaling pathway.	(26)
Ning *et al*, 2012		SCH527123 was found to inhibit tumor growth in a mouse subcutaneous xenograft model.	(87)
Fu *et al*, 2018		The combination of SCH527123 and bazedoxifene showed a potent inhibitory effect on PDAC cells.	(88)
Zhang *et al*, 2022	Ovarian cancer	Bazedoxifene hydrochloride and SCH527123 were used to inhibit the proliferation of ovarian cancer cells in mice by blocking the IL-6 and IL-8 pathways.	(93)
Singh *et al*, 2011		*IL-8* gene silencing can inhibit the invasion of tumor cells.	(98)
Singh *et al*, 2011		Silencing *CXCR1/2* regulated endothelial cell growth, migration, survival and new vessel formation, in addition to ERK1/2 phosphorylation by using shRNA.	(98)
Varney *et al*, 2011	Colon cancer	Oral administration of SCH527123 inhibited CXCR1/2 signaling, malignant cell survival and new vessel formation to inhibit liver metastasis by human colon cancer in a mouse model.	(80)
Ning *et al*, 2012		IL-8/CXCR2 pathway is the key to the development of colon cancer. SCH527123 has anti-tumor effect through NF-κB/AKT/MAPK signaling pathway.	(87)

CXCL, C-X-C motif chemokine ligand; CXCR, C-X-C motif chemokine receptor; PDAC, pancreatic ductal adenocarcinoma.

with 5 μM CXCR1 or CXCR2 antagonists for 30 min reduced IL-8-induced migration by ~60% ($P<0.01$), indicating that the effect is mediated through these receptors. These results demonstrate that IL-8 facilitates liver cancer cell migration and invasion in a CXCR1/2-dependent manner. SCH527123 can inhibit the binding of IL-8 with CXCR1 and CXCR2, thereby suppressing the chemotactic migration and angiogenic response of malignant human colon cancer cells (80), slowing down or preventing the progression of liver cancer, which has development potential for treating liver cancer or extending the survival cycle of patients with advanced liver cancer.

Pancreatic cancer (PC). PC is a deadly cancer among the most insidious cancers at early stages; typically asymptomatic and hard to detect early, leading to late diagnosis and poor outcomes, with 90% cases being of the ductal adenocarcinoma (PDAC) subtype (81). Because the pancreas is located in the retroperitoneum (82) and its deep position, its malignancies cannot be readily found during the early stages clinically, where a variety of inherent factors (such as age, sex, environment, blood type and family history) and lifestyle factors (such as smoking, drinking, eating habits and obesity) have all been reported to be risk factors for PC (83). All of these factors further exacerbate the already high mortality rate of PC. The traditional treatment method of PC includes surgery, chemotherapy, radiotherapy and palliative treatment (84). Over the previous decade, research on the immunotherapy of this cancer has been gradually expanding (82).

Although the etiology of PC remains unclear, accumulating evidence has shown that IL-8 and its receptors CXCR1 and CXCR2 are involved in various tumor initiation and developmental stages (85,86). Inhibition of the CXCR1/2 signaling pathway has been reported to reduce the activation of downstream effectors AKT, ERK, STAT3 and S6, inhibiting the proliferation of PDAC cells (27). SCH527123 has also been shown to inhibit tumor growth in a xenograft model (87). Fu and Lin (88) previously found a potent inhibitory effect of SCH527123 in combination with bazedoxifene on PDAC cells (88). Taken together, these results suggest that SCH527123 may serve be a novel targeted therapy drug that can be used for the treatment of PC clinically.

Ovarian cancer. Ovarian cancer has one of the poorest survival rates of all cancers of the female reproductive system (89), which also ranks as the seventh most common female cancer in the world, 10th in China (90). Between 1990 and 2019, the incidence of ovarian cancer in China increased by an average of 2.03% annually and the mortality rate by 1.58% annually.

This three-decade data change shows the growing disease burden of ovarian cancer in China, with rising new cases and deaths continuously threatening women's health (90). A number of factors, such as older age, genetic factors, family history, history of other cancers, smoking and high fat diet, are risk factors of ovarian cancer (91). Despite the recognition of ovarian cancer, treatment and survival trends have not changed significantly, because the means of early diagnosis are not accurate, where >50% patients are diagnosed already at advanced stages. In addition, ~75% patients will relapse due to intrinsic and acquired chemotherapy resistance, contributing to cancer recurrence. These are the two main reasons for the low 5-year overall survival rate (92). Therefore, the development of targeted therapy with a precise site of action and few side effects is crucial for the treatment of ovarian cancer.

Previous mouse experiments have used bazedoxifene hydrochloride and SCH527123 combined to block IL-6 and IL-8 pathways to inhibit ovarian cancer cell proliferation (93,94). It has also been previously found that targeted therapy with IL-8 siRNA-1,2-dioleoyl-sn-glycero-3-phosphocholine combined with chemotherapy effectively reduced tumor growth in both chemotherapy-sensitive and chemotherapy-resistant ovarian cancer models, by observing human ovarian cancer section specimens and female athymic mouse orthotopic cancer models (48,95,96). To the best of our knowledge, no study has reported targeting IL-8 as a treatment strategy for ovarian cancer, but it has been previously found that silencing the *IL-8* gene can inhibit ovarian tumor cell invasion (97). Furthermore, it has been demonstrated that silencing *CXCR1* or *CXCR2* can modulate endothelial cell proliferation, migration, survival and new vessel formation, in addition to ERK1/2 phosphorylation (98). Silencing *CXCR1* or *CXCR2* has been shown to modulate endothelial cell proliferation, migration, survival, and angiogenesis through pathways including ERK1/2 phosphorylation. CXCL1 and CXCL2, as ligands of CXCR2, further regulate endothelial cell proliferation by activating ERK1/2 and PI3K/AKT signaling, promoting cell cycle progression and survival (99). In ovarian cancer, the IL-8/CXCR1/2 axis plays a critical role in tumor progression by promoting tumor-associated angiogenesis, which supplies nutrients and oxygen to support tumor growth. Activation of this pathway also enhances tumor cell migration and invasion, facilitating metastasis, particularly within the peritoneal cavity. Furthermore, CXCR1/2 signaling contributes to chemoresistance and shapes an immunosuppressive tumor microenvironment by recruiting myeloid-derived suppressor cells. Therefore, targeting CXCR1/2 not only inhibits neovascularization but also suppresses ovarian cancer cell survival and invasiveness, highlighting its potential as a therapeutic strategy (95,100,101). Therefore, it can be speculated that blocking the binding of IL-8 to CXCR1/2 using SCH527123 can inhibit the proliferation of ovarian cancer cells, which has prospects for the control of invasion and metastasis of ovarian cancer cells clinically.

Colon cancer. Colorectal cancer is a leading cause of mortality from gastrointestinal malignancies and the third most commonly diagnosed cancer, of which >50% patients succumb due to its associated complications (102). Modifiable risk factors with clear environmental components include the lack of activity, sedentary behavior, obesity, smoking, alcohol consumption, excessive intake of red meat and processed meat. In addition, hereditary colorectal cancer syndrome, inflammatory bowel disease and history of colorectal adenoma are also reported risk factors for colon cancer (103).

SCH527123 was previously reported to inhibit colon cancer cell survival and new blood vessel formation by inhibiting CXCR2 and possibly CXCR1 signaling. This in turn inhibited liver metastasis by human colon cancer cells in a mouse model (77). It has also been demonstrated that the IL-8/CXCR2 pathway can serve a key role in mediating the development of colorectal cancer. Specifically, it was found that SCH527123 can inhibit cancer cell proliferation, motility and angiogenesis through NF-κB/AKT/MAPK signaling pathway (87). Oxaliplatin is used as an adjuvant therapy for colon cancer (104). When it is combined with SCH527123, the NF-κB/AKT/MAPK signal transduction pathway was found to be further inhibited (87). Based on the results of the aforementioned previous studies, CXCR2 may be a novel therapeutic target for colon cancer, where SCH527123 as an antagonist of CXCR2 pathway may provide an idea for the subsequent drug treatment of colon cancer.

6. Discussion

In the context of increasing refractory inflammation and rising tumors incidence, in the present review, the relationship between IL-8, CXCR1/CXCR2 and inflammation and cancers were discussed, with focus on the CXCR1 and CXCR2 antagonist SCH527123 to illustrate its possible application for the treatment of inflammatory diseases and tumors.

Starting in 2007, cytological experiments were implemented on a cellular level to report that SCH527123 represents a novel and specific CXCR2 antagonist, with clinical potential in a variety of inflammatory diseases (21,25,53,62). In subsequent animal experiments, inhibition of CXCR1- and CXCR2-mediated chemotaxis by SCH527123 has been observed in rodents and cynomolgus monkey models, where it was speculated that SCH527123 may prove beneficial in the treatment of inflammatory lung diseases, by monitoring bronchoalveolar lavage mucin content in cynomolgus monkeys (21). To further confirm the clinical safety of SCH527123 in the human body, two clinical trials were conducted in 2007 and 2012, which also yielded certain clinical curative effects (53,58). In a 2007 trial, oral SCH527123 significantly reduced ozone-induced airway neutrophilia in healthy subjects, demonstrating good tolerability and inhibition of neutrophil recruitment (53). In a 2012 multicenter study in patients with severe refractory asthma, it reduced exacerbation rates, improved lung function, and decreased airway neutrophil levels, indicating potential clinical value in chronic inflammatory diseases (58). In 2011, gene silencing experiments found that by silencing the *CXCR1/2* gene in human microvascular endothelial cells (HMEC-1) significantly inhibited IL-8-dependent proliferation, survival, migration and angiogenesis, and attenuated ERK phosphorylation and cytoskeletal reorganization; these findings suggest that targeting CXCR1/2 may offer a novel anti-angiogenic strategy for cancer treatment (98). In 2018, a cytological experiment inhibiting the IL-6/IL-8 pathway achieved inhibitory effects

on triple-negative breast cancer and PDAC. In particular, it also showed that SCH527123 was more effective in inhibiting the progression of triple-negative breast cancer and PDAC when combined with bazedoxifene or rempacine (88). In addition, when combined with bazedoxifene hydrochloride, SCH527123 was found to block the IL-6 and IL-8 pathways and inhibited ovarian cancer cell proliferation in a mouse model (93).

As information on SCH527123 accumulates further, clinical trials are becoming a possibility to assess the role of SCH527123 for disease treatment. In 2016, a randomized, double-blind, placebo-controlled, multicenter crossover trial involving 19 non-smoking subjects with mild atopic asthma was performed (60). For patients with mild asthma, SCH5271213 was found to effectively reduce the number of blood neutrophils migrating to the airway, thereby relieving symptoms without causing adverse effects on bone marrow cells (60). In 2017, another clinical trial used SCH527123 in 58 patients with acute exacerbations of chronic liver failure (ACLF), which found that blocking CXCR1/2 could significantly suppress hepatocyte cell death, which may alleviate ACLF (23). It has also been observed that the CXCR1/2 antagonist SCH527123 can inhibit melanoma, lung, breast, pancreatic and liver tumor cell proliferation and metastasis (22-24,105-107), in addition to inhibiting chemotaxis of neutrophils to control the development of COPD and asthma (Table I) (58,62).

However, there are also limitations to the clinical application of SCH527123 at present. SCH527123 research is relatively mature only at the preclinical stages. Clinical trials have only begun over the past decade, where the focus has been mainly on tumors and chronic refractory diseases in the respiratory system. The role of SCH527123 in inflammation in other organs has not been tested. In addition, its safety for the treatment of chronic refractory inflammation and tumors remains to be proven, such that the biosafety of SCH527123 will become a major testing avenue for future clinical studies. It has been previously reported that SCH527123 is generally well-tolerated, where neutropenia is the most common adverse event, with an incidence rate of 9% (58). Although SCH527123 has conferred inhibitory effects on the metastasis of colon cancer and melanoma cells, neutrophils also serve a dual role in tumor immune surveillance (108). Therefore, its long-term use may weaken anti-tumor immunity.

7. Conclusion

Although research on SCH527123 has only been limited to pre-clinical trials, the existing experimental data suggest that SCH527123 is more reliable compared with other small molecule antagonists. Oral administration of SCH527123 is generally safe and well tolerated, with few adverse reactions. SCH527123 has shown advantages in combating inflammation and inhibiting tumor growth, especially with particular potential for the treatment of refractory inflammation and cancers. However, current experimental evidence is not sufficient to support the large-scale clinical use of SCH527123, though it provides a ideas for clinical treatment of inflammation and cancers. In the future, with the continuous development of novel therapeutic strategies, SCH527123 is expected to bring hope to patients.

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Authors' contributions

JMZ and JWH made major contribution to manuscript writing and figures. YX contributed to the conception of the manuscript and performed literature searches. MZL participated in writing and revising the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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