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Unraveling cysteinyl leukotrienes and their receptors in inflammation through the brain-gut-lung axis

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ABSTRACT

Cysteinyl leukotrienes (CysLTs), as potent lipid inflammatory mediators, play a pivotal role in systemic multi-organ inflammation and inter-organ communication through interactions with their receptors (CysLTRs). However, However, the function of CysLT3R is unclear and lacks a network of cross-organ metabolite interactions, and the clinical use of leukotriene receptor antagonists (LTRAs) has certain limitations. This review systematically synthesizes existing evidence and proposes future directions by clarifying receptor subtype specificity, optimizing targeted therapies, exploring CysLTs' applications in neuroimmunology, and elucidating the dual roles of CysLTs in chronic inflammation. It is indicated that CysLTs activate eosinophils, mast cells, and airway tuft cells, driving type 2 immune responses and mucus secretion in the lungs, thereby exacerbating respiratory diseases such as asthma. In the nervous system, CysLTs aggravate neurodegenerative disorders like cerebral ischemia and Alzheimer's disease by disrupting the blood-brain barrier, promoting glial activation, and inducing neuronal damage. In the gut, CysLTs regulate anti-helminth immunity via the tuft cell-ILC2 pathway and collaborate with prostaglandin D2 (PGD2) to modulate bile excretion and mucosal protection. Furthermore, CysLTs mediate communication through the gut-lung and gut-brain axes via metabolites such as succinate, contributing to cross-organ inflammatory regulation. In conclusion, this review highlights the complex roles of CysLTs in chronic inflammation, providing a theoretical foundation for precise intervention in multi-organ inflammatory diseases, which provides a theoretical framework for precision interventions in multi-organ inflammatory diseases and inspires interdisciplinary breakthroughs.

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Introduction

Leukotrienes (LTs) are short-lived but highly potent lipid inflammatory mediators. Initially recognized as prominent inflammatory mediators in acute asthma, in recent years, they have been found to play a driving role in the progression of many chronic inflammatory diseases. The gut, often referred to as the "second brain" due to their rich neural network and close connection to the brain, pose a risk of systemic immune imbalance when there is dysbiosis in the intestinal microbiota, alterations in the overall composition of metabolic products, and changes in immune status. Chronic inflammation, as the initial stage of various cardiovascular and respiratory diseases, underscores the noteworthy role of LTs in the process. For example, alterations in gut ecology can affect brain decision-making through the "gut-brain axis" [1–3], The disruption in the balance of gut bacteria and their byproducts can trigger lung inflammation and lead to various secondary illnesses through the "gut-lung axis." [4–6]. As research progresses, there is a growing focus on the overall bodily response to a range of challenges, as opposed to the reaction of individual organs.

Arachidonic acid serves as the precursor to LTs. It undergoes oxidation to form the intermediary compound leukotriene A4 (LTA4) through the mediation of 5-lipoxygenase. Following this, LTA4 can transform into leukotriene C4 (LTC4S) by interacting with reduced glutathione and further action from leukotriene C4 synthase (LTC4S). The enzyme leukotriene A4 hydrolase (LTA4H) is responsible for the production of leukotriene B4 (LTB4). Once transported out of the protocell by specific enzymes, LTC4 converts to leukotriene D4 (LTD4) with the assistance of distinct enzymes. Subsequently, LTD4 is further metabolized

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into leukotriene E4 (LTE4), a stable end product. Within the LTs mentioned earlier, LTA4 and LTB4 are recognized as dihydroxy-acid leukotrienes due to their composition featuring dihydroxyl acids. On the other hand, the presence of cysteinyl groups containing sulfur bonds and amino acid residues characterizes the structure of LTC4, LTD4, and LTE4, which are referred to as cysteinyl leukotrienes (CysLTs) [7].

The receptors for LTs are categorized into two groups: the leukotriene B4 receptor (BLT) and cysteinyl leukotriene receptors (CysLTR). BLT includes two subtypes, BLT1 and BLT2, with BLT1 exhibiting stronger affinity for LTB4 and primarily mediating inflammatory responses. BLT1 can be inhibited by compounds such as LY293111 and BIIL284. Since the intensity of BLT1-mediated inflammation correlates with LTB4 expression levels, inhibitors targeting upstream synthesis of LTB4—for example, Acebilustat, an LTA4H inhibitor – are also considered therapeutically significant [7]. CysLT1R primarily interacts with LTD4. Notable inhibitors for CysLT1R are Montelukast, Zafirlukast, and Pranlukast. CysLT2R, on the other hand, equally binds LTC4 and LTD4 [8] and is targeted by inhibitors like HAMI3379 and BayCysLT2 [9]. LTC4 shows non-preferential binding, engaging both CysLT1R and CysLT2R. CysLT3R, also known as GPR99, displays a preference for LTE4 over LTC4 and LTD4 in both live organisms and laboratory settings, although it also responds to LTC4 and LTD4 in living systems [10,11] (Figure 1).

LTs being a key messaging molecule in inflammatory situations, show potential as a promising target for the treatment of various inflammatory conditions. Within the family of leukotrienes, LTB4 has been a focal point of early research endeavors, with its functions extensively studied and documented across multiple research works [12,13]. Initial studies on CysLTs mainly focused on ailments like asthma and allergic lung disorders. A clinical investigation from Korea, looking into negative reactions to Montelukast and Pranlukast, revealed that gastrointestinal discomforts were the most commonly observed side effects from these anti-leukotriene medications, trailed by instances of mental health issues. Furthermore, the occurrence of adverse effects was noted to differ depending on gender and age categories [14]. It is evident that CysLTs play a crucial role not just in respiratory conditions but also hold immense research potential in various body organs, including the digestive and nervous systems, as well as multi-organ inflammatory intercommunication. While recent years have witnessed a growing interest in its involvement in intestinal and

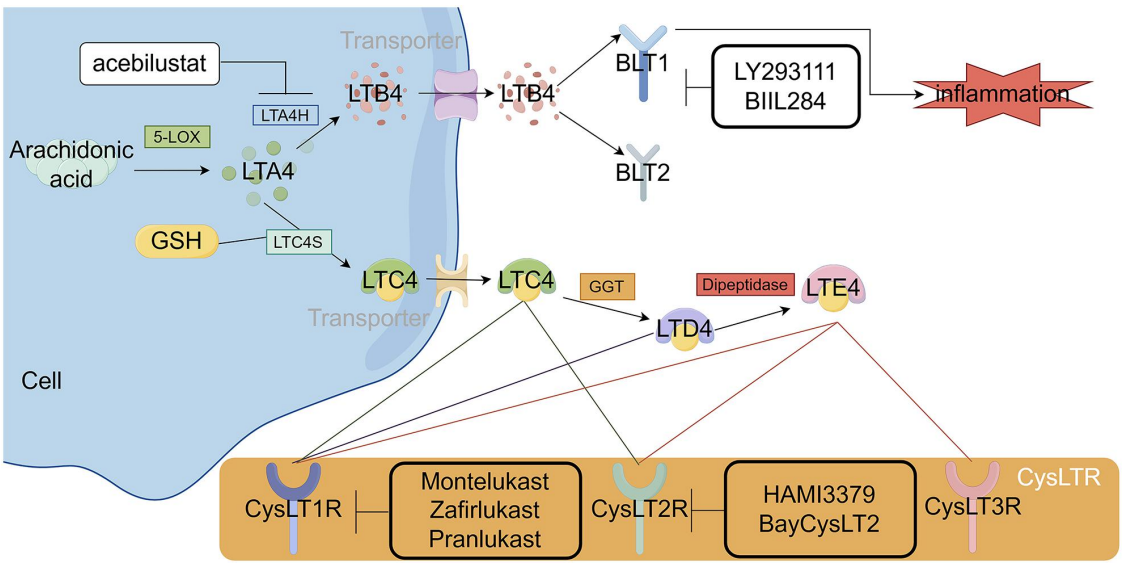

Figure 1. Synthesis, action receptors, and receptor inhibitors of leukotrienes (LTs). Arachidonic acid serves as the primary precursor for LTs synthesis. It is oxidized by 5-lipoxygenase (5-LO) to generate the intermediate LTA4, after which LT production diverges into two metabolic pathways: one branch involves LTA4 conversion by LTC4 synthase (LTC4S) into LTC4 (a cysteinyl leukotriene, CysLTs), which is subsequently metabolized to LTD4 and LTE4. The other branch utilizes LTA4 hydrolase (LTA4H) to produce LTB4 (a dihydroxy acid leukotriene). Synthesis and release: LTB4 and LTC4 are primarily synthesized intracellularly and exported via transport proteins to act on receptors or generate other LTs. Receptors and inhibitors: 1. BLT: BLT1 Binds LTB4 with high affinity, mediating inflammatory responses. Antagonists include LY293111 and BIIL284. BLT2: primarily associated with tissue repair. 2. CysLTR: CysLT1R: preferentially binds LTD4. Antagonists include Montelukast and Zafirlukast. CysLT2R: Binds both LTC4 and LTD4. Antagonists include HAMI3379 and BayCysLT2. CysLT3R (GPR99): selectively responds to LTE4 but can also be activated by LTC4/LTD4. (figure was created by Figdraw).

neuroinflammation, the focus has primarily remained on the inflammation mechanism of individual organs [15,16], there is a lack of clarity on whether CysLTs operate through similar molecular pathways across various organs, produce identical effects, and engage in potential communication between different organs. This review will focus on the multiorgan regulatory role of cysteine leukotrienes (CysLTs) in inflammation across the brain-gut-lung axis, revealing its organ-specific molecular mechanisms (e.g. pro-inflammatory effects in the lung versus protective immune effects in the gut) and its potential for cross-organ communication (e.g. succinic acid-mediated gut-lung interactions). In view of the current research gaps, including the unclear function of CysLT3R, the lack of cross-organ metabolite interaction networks, and the clinical limitations of leukotriene receptor antagonists (LTRAs), we will systematically synthesize the existing evidence and suggest future research directions to clarify the specificity of receptor subtype, optimize targeted therapy, and explore the application of CysLTs in neuroimmunology. By elucidating the dual role of CysLTs in chronic inflammation, this study provides a theoretical framework for precise intervention in multiorgan inflammatory diseases and stimulates interdisciplinary breakthroughs.

CysLTs involved in inflammatory diseases

CysLTs play roles in various pulmonary, cerebral, and intestinal diseases. The mechanisms through which CysLTs exert their effects differ across organs. We have compiled a table to concisely compare their functions in these organs (Table 1).

Role of CysLTs in lung inflammation

CysLTs are mainly synthesized by crucial effector cells, such as eosinophils and mast cells, within the respiratory system, playing a pivotal role in the development of asthma. Furthermore, macrophages have been found to secrete CysLTs involved in the development of asthma. Moreover, recent research has demonstrated that CysLTs are also produced by airway Tuft cells which contribute to the important role played by these cells in the inflammatory response of the airways [17,18]. It was ascertained that CysLT1R and CysLT2R were chiefly dispersed throughout bronchial smooth muscle, eosinophils, macrophages, and mast cells [19]. On the contrary, CysLT3R is specifically found in lung epithelial cells and can react to LTE4, triggering the secretion of mucus proteins [20]. These discoveries offer valuable insights into investigating the impact of leukotriene receptors on asthma and similar conditions, laying a foundation for the potential development of corresponding medicinal treatments (Figure 2).

In cases of acute lung and airway inflammation, eosinophils are typically the initial inflammatory cells to be recruited. The role of CysLT1R is pivotal in facilitating the recruitment of eosinophils in the lungs. A conventional mechanism involves CysLT1R triggering lung inflammation by attracting a significant number of eosinophils, prompting their degranulation, and subsequently inciting mast cells to produce IL-4, IL-5, IL-13 and other type 2 inflammatory agents [18,21,22]. The process above cannot be viewed in complete isolation when considering the concurrent surge of Innate Lymphoid Cells (ILCs) in the pulmonary organs [18,23,24]. CysLT1R operates in synergy with IL-25 to trigger or enhance the functionality

Table 1. Comparison of the effects of CysLTs in the lung/brain/intestine.

	Lung	Brain	Intestine
Mechanism of Action	1. Activates eosinophils, mast cells, macrophages, and airway tuft cells, recruiting inflammatory cells and driving type 2 immune responses. 2. Regulates IL-33/IL-25 signaling via CysLT1R/CysLT2R, inducing ILC2 activation and mucus secretion. 3. CysLT3R responds to LTE4, promoting mucin secretion.	1.Disrupts the blood-brain barrier, facilitating pathogen entry. 2. Mediates neuronal damage, glial activation, and vascular endothelial injury via CysLT1R/CysLT2R. 3. Inhibits vascular regeneration in chronic inflammation, exacerbates edema in acute phases.	1. Secretes CysLTs via tuft cells to activate ILC2s, regulating anti-helminth immunity. 2. Cooperates with PGD2 to influence immune and non-immune cells. 3. Stimulates gallbladder smooth muscle contraction for bile excretion.
Related Receptors	CysLT1R, CysLT2R, CysLT3R	CysLT1R, CysLT2R	CysLT1R, CysLT2R
Main Functions	1. Promotes airway inflammation, mucus secretion, and allergic responses. 2. Synergizes with IL-33 to exacerbate pulmonary inflammation. 3. Involved in aspirin-exacerbated respiratory disease (AERD).	1. Aggravates neurodegenerative diseases (e.g. Alzheimer's). 2. Worsens cerebral ischemia-reperfusion injury. 3. CysLTR inhibitors alleviate neuroinflammation and vascular damage.	1. Initiates type 2 immune defense against parasites. 2. Maintains bile excretion and mucus secretion. 3. May exhibit dual roles in intestinal inflammation and tumorigenesis.
Clinical Significance or Disease Associations	Asthma, bronchospasm, allergic pulmonary inflammation, AERD	Cerebral ischemia, Alzheimer's disease, depression, epilepsy	Intestinal infections, inflammatory bowel disease, gallbladder dysfunction

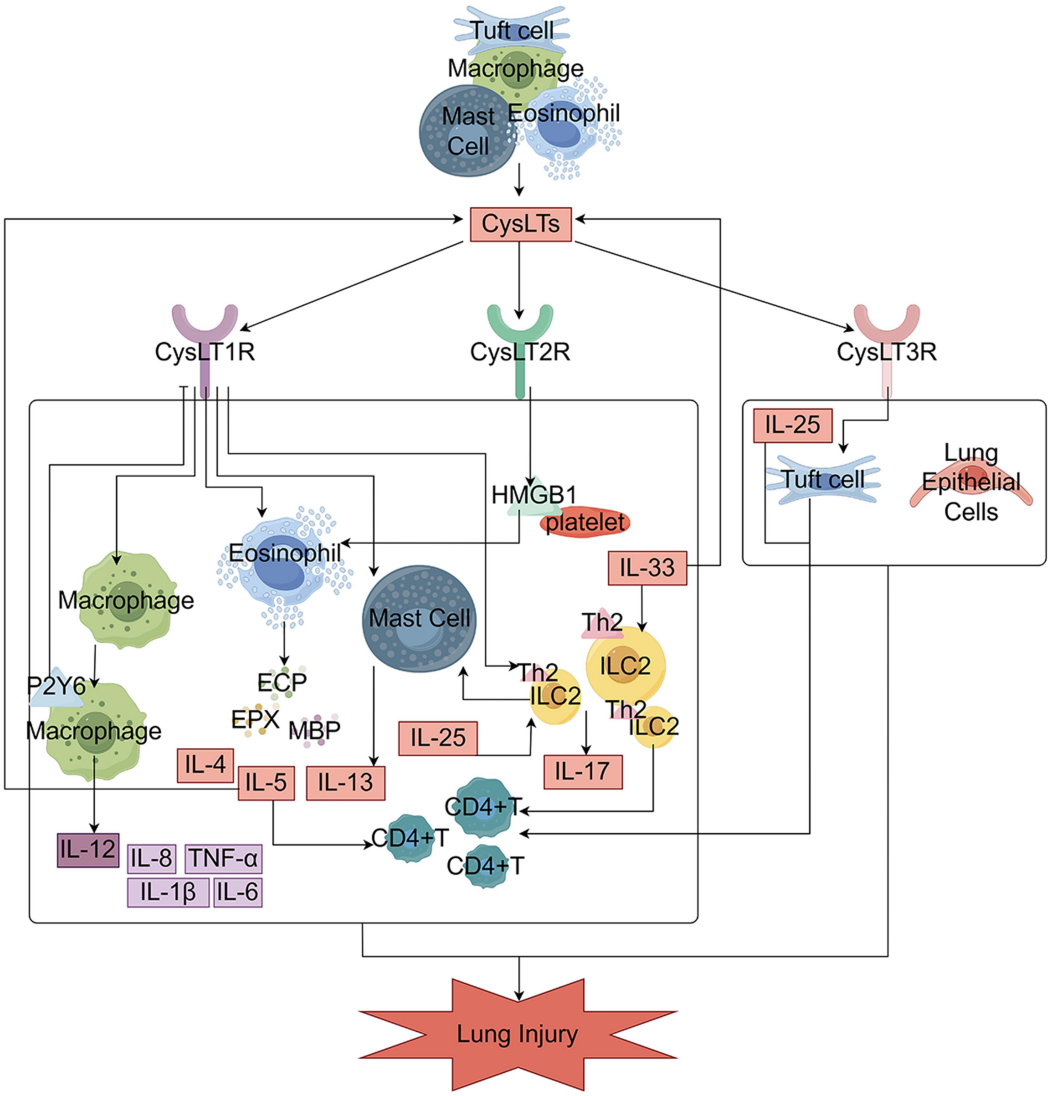

Figure 2. The role of CysLTs in lung injury. By activating different receptors, cysLTs play diverse roles in the lungs. 1. The activation of CysLT1R can trigger degranulation of eosinophils, releasing granule contents including eosinophil cationic protein (ECP), major basic protein (MBP), eosinophil peroxidase (EPX), and eosinophil-derived neurotoxin, among others. These released granule contents can damage tissue cells, activate immune cells such as neutrophils and mast cells, and enhance the Th2 immune response. Eosinophils can also release various cytokines, such as IL-4, IL-5, and IL-13, which can affect the differentiation and proliferation of CD4+ T cells. Furthermore, ILC2s activated by CysLTs can rapidly secrete multiple type 2 cytokines, which are key mediators of type 2 immune responses and can further recruit and activate more immune cells, such as Th2 cells, thereby amplifying the inflammatory response. Alveolar macrophages, upon activation by CysLT1R, release inflammatory factors such as tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8), exacerbating lung inflammation, while the upregulation of the P2Y6 signaling pathway can alleviate inflammation by inhibiting CysLT1R. 2. The activation of CysLT2R primarily manifests in the induction of HMGB1 expression on the surface of platelets, a change that can promote their firm adhesion to eosinophils, facilitate degranulation, and participate in the initiation of inflammation. 3. Research on CysLT3R is still in its infancy, and its activation mainly synergizes with IL-25-dependent signaling pathways to induce the expansion of tuft cells in the airways, leading to the occurrence of type 2 lung inflammation. (figure was created by Figdraw).

of ILC2 cells, concurrently encouraging the development of CD4+T cells through the attraction of substantial quantities of eosinophils [18]. It is worth mentioning that this particular pathway has been demonstrated to rely on IL-25 and CysLT3R in airway Tuft cells, rather than type 2 inflammatory cytokines [25]. Airway Tuft cells are the primary chemoreceptor cells that come in contact with airborne allergens in the respiratory pathway. Upon exposure to allergenic agents in the airway, cluster cells located in the respiratory tract get activated and trigger a heightened type 2 immune response. From this, it can be inferred that airway cluster cells exert incredible

influence as regulators of type 2 immunity in the pulmonary system.

LTC4, the main ligand of CysLT1R, can lead to the increase of IL-8 expression level in the lungs [26], and the antagonist of CysLT1R can reduce the expression level of IL-6, TNF-α, IL-1β and other inflammatory factors in bronchopulmonary dysplasia [27]. LTC4 can promote ILC2 activation induced by IL-33, and the combination of LTC4 and IL-33 amplifies ILC2-induced lung and peri bronchial inflammation [21], Increased expression of Th2 cytokines and mast cells, amplifies mast cell T2 gene expression and alters the mast cell protease profile by suppressing chymase expression, largely dependent on CysLT1R rather than CysLT2R [22]. IL-33 and IL-5 further promote the production of CysLTs by eosinophils. In addition, the expression of CysLT1R also affects the secretion of ILCs cytokines. LTC4, LTD4, and IL-33 synergistically induce the expression of IL-17 mRNA in ILC2 cells and increase the number of ST2+ILC2 cells expressing IL-17. ST2+ILC2, which produces IL-17, has also been shown to play a pathogenic role in lung inflammation [24]. During lung ILC2 activation, CysLTs can induce nuclear translocation of NFAT and collaborate with IL-33-induced AP-1 and NF-κB to generate the highest level of cytokines [21,28], which is very similar to the situation in the intestine. Macrophages, along with eosinophils, play a role in the CysLT1R pathway. A study on mice sensitized by house dust mites revealed that enhancing the Purinergic receptor 6 (P2Y6) signaling pathway in alveolar macrophages can mitigate leukotriene-driven type 2 allergic pulmonary inflammation by suppressing CysLT1R activity. Conversely, the absence of the P2Y6 receptor worsens eosinophilic lung inflammation and the release of type 2 cytokines (e.g. IL-12) following exposure to allergens [29]. This implies that macrophage signaling could potentially react to misguided type 2 immune reactions.

CysLT2R, serving as an additional receptor for LTC4, functions as a supplementary pathway to CysLT1R in pulmonary allergic conditions. Even without CysLT1R, the dilation of eosinophils and the rise in type 2 inflammatory factors persist [30,31], LTC4 triggers the upregulation of high mobility group protein B1 (HMGB1) on the surface of platelets in a manner that depends on CysLT2R. The signaling of CysLT2R heavily relies on HMGB1 as a bridge to the subsequent aspirin-like 2 respiratory immune response and IL-33-triggered activation of mast cells typically seen in aspirin-exacerbated respiratory disease (AERD). An interesting point to note is that LTD4 disrupts this process by hindering the expression of lung IL-33 induced by LTC4, platelet activation, and the enhancement of adhesion receptors. Consequently, this limits the downstream immune changes typical of type 2 respiratory responses caused by CysLT2R signaling [31].

CysLT3R is a new type of CysLTR that was not discovered until 2013 [32]. It predominantly interacts with CysLTs of the LTE4 type. Owing to its remarkable durability, CysLT3R serves as a crucial marker for urine monitoring and as a biomarker in asthma patients. It plays a key role in measuring the levels of cysteine aspartyl transferase and assessing the eicosanoid acid metabolism [33]. Besides being present in alveolar epithelium, CysLT3R has also been identified in the expression of airway Tuft cells. LTE4 was found to induce the expansion of Tuft cells in mouse airways through the IL-25-dependent signaling pathway, resulting in type 2 lung inflammation. This specific receptor, CysLT3R, plays a role in regulating airway inflammation by influencing the production of Tuft cells and their functionality due to stimulation by the internal lipid LTE4 [25]. Recent studies have indicated that elevated levels of TGF-β1 in patients with Aspirin-Exacerbated Respiratory Disease (AERD) may boost LTE4 production by increasing LTC4S expression, which in turn leads to eosinophilic granulation and hastens airway inflammation [34]. The exploration of CysLT3R is still in its early stages, with several unresolved queries regarding its expression, distribution, and role, all requiring clarification through additional experimental data.

CysLT1R antagonists (LTRAs, such as montelukast and zafirlukast) are commonly used medications for treating asthma, bronchospasm, and related conditions. Compared to classical anti-inflammatory drugs like glucocorticoids, LTRAs offer advantages such as good oral bioavailability and minimal systemic side effects. They alleviate symptoms and improve respiratory function through dual mechanisms: antagonizing the pro-inflammatory effects of leukotrienes and inhibiting bronchoconstriction. Although LTRAs are not yet classified as first-line therapeutic agents for asthma in China, montelukast and zafirlukast remain widely used as adjuvant therapies for chronic pulmonary inflammation due to their lung function improvement benefits. Regarding safety, both drugs demonstrate good short-term tolerability. However, special attention should be paid to their inhibition of the CYP450 enzyme system, which may interfere with the metabolism of other medications (e.g. theophylline) during combination therapy. Zafirlukast exhibits a plasma protein binding rate as high as 99%, requiring vigilance in monitoring blood concentrations when co-administered with drugs like warfarin. Additionally,

zafirlukast has been reported to induce Churg-Strauss vasculitis in adults [35]. How to leverage their therapeutic advantages while addressing existing limitations to optimize their clinical positioning in respiratory disease management remains an area requiring further exploration. In terms of formulation, challenges persist with montelukast, including sensitivity to light, temperature, humidity, and oxidation, inconvenient oral administration for elderly and pediatric populations, and suboptimal oral bioavailability (approximately 70%). Some studies attempt to address these issues through formulation modifications, such as developing liposomal delivery systems [36]. These innovative explorations provide valuable insights for optimizing LTRA utilization.

The role of CysLTs in neuroinflammation

CysLTs are also closely related to neurodegenerative diseases of the central nervous system [37–39] and cerebral ischemia [40–42]. These conditions, including cerebral ischemia, epilepsy, Alzheimer's disease, and depression, display acute or chronic inflammation in the central nervous system. Interestingly, the pathogenesis and progression of these diseases are akin to those affecting the lungs. Notably, CysLTs could potentially facilitate the breach of the blood-brain barrier. Some research indicates that this compound may serve as a novel facilitator in enabling external pathogens to enter the brain, triggering brain inflammation [43,44]. Additionally, N-methyl-D-aspartate receptor (NMDAR) mediated activation of 5-lipoxygenase (5-LOX) also influences the synthesis of downstream cysteinyl leukotrienes (CysLTs), thereby participating in their associated brain injury mechanisms [45]. In the healthy brain, CysLTs expression is weak, and in aging and some pathological conditions, CysLTs expression is increased [38,42]. The level of CysLTR1 expression tends to be lower compared to that of CysLTR2. CysLTR1 is commonly found in the cortex, hippocampus, and nigrostriatum, while also being present in cerebrovascular endothelial cells [46], astrocytes, microglia, and a range of neuron types [47–49]. On the other hand, CysLTR2 has been identified in various brain regions like the cortex, hippocampus, substantia nigra, and periventricular. It is detected in multiple cell types including vascular smooth muscle cells, endothelial cells, astrocytes, microglia, neurons, and branching cells [50–54]. However, little is known about the distribution and role of CysLTR3.

There are three distinct stages in the progression of cerebral ischemia pathology. The impact of CysLTs varies across the acute, subacute, and chronic phases. During these phases, the presence of CysLTs aligns with the escalation of acute neuronal damage. By administering receptor inhibitors, the severity of acute brain injury can be mitigated, potentially averting vascular endothelial injury in the subacute phase of cerebral ischemia [47,51,55]. The breach of the blood-brain barrier initiates the formation of vasogenic cerebral edema, serving as a primary pathological indicator. CysLTs further worsen vasogenic cerebral edema at this juncture by orchestrating the rupture of the blood-brain barrier. The use of CysLTRs inhibitors, including Montelukast, Pranlukast, and HAMI3379, can slow down this pathological process, and CysLTR1/CysLTR2 double antagonists provide more obvious protection for cerebral vessels than single CysLTRs antagonists [50,55]. While endothelial damage and dysfunction can worsen subacute brain injury, research indicates that endothelial growth, movement, and formation of new blood vessels in the surrounding area following ischemia may contribute to the healing of brain tissue and the improvement of long-term functions after ischemic episodes, and ERK1/2 phosphorylation may be involved [56]. A higher presence of small blood vessels in the region surrounding an infarct is linked to better survival rates among individuals suffering from ischemic strokes [57]. Cerebral blood vessel regrowth was observed within the cortex 8 days following a traumatic incident in humans, with heightened expression of CysLTR1 in all small blood vessel lining cells [46]. In a rat study involving blockage of a midbrain artery, there was an increase in CysLTR1 expression in small blood vessel lining cells at the border area two weeks post-reperfusion [47]. These findings indicate a potential key role of CysLTR1 in the formation of scar tissue and new blood vessel growth after prolonged cerebral blood flow restriction. Studies have indicated that the N-methyl-D-aspartic acid receptor (NMDAR) is involved in regulating the expression of cysteinyl leukotrienes (CysLTs) during the acute phase of brain ischemic injury [58]. In the subacute phase, CysLTs may contribute to damage by altering blood-brain barrier (BBB) function [59]. However, the deeper molecular mechanisms underlying these processes currently lack experimental validation.

The presence of CysLTs in neurodegenerative diseases is generally believed to promote the damage of neurons and normal glial cells, thus exacerbating neuroinflammation [37,60]. This phenomenon is particularly significant in cases of chronic neuroinflammation. Recent research has identified the potential of targeting CysLTs as a therapeutic approach for treating Alzheimer's disease [16]. In Alzheimer's disease, cysteinyl leukotrienes (CysLTs) and their receptor CysLTR1

exacerbate damage by promoting M1 polarization of microglial cells and the generation of Aβ senile plaques in neuronal cells, with the former process being linked to nuclear translocation of CysLTR1[83]. Additionally, LTD4 has been shown to aggravate pathology by increasing amyloid precursor protein (APP) expression [61]. Upstream, ALOX5 not only participates in disease progression by regulating CysLTs synthesis but also activates the cyclic AMP response element-binding protein (CREB) to modulate Aβ formation, thereby contributing to pathological effects [62]. Utilizing CysLTs receptor inhibitors has shown promise in mitigating or partly hindering neuroinflammatory conditions such as Huntington's disease [37], cognitive decline [38], depression [63], gray matter abnormalities [64], etc. Nonetheless, a more in-depth investigation and independent validation are necessary to elucidate its specific mechanism.

Currently, research on leukotriene receptor antagonists (LTRAs) in neuroinflammatory-related diseases primarily focuses on montelukast. Montelukast can influence disease progression by modulating neuronal excitability and the release of related neurotransmitters through its effects on calcium channels. Experimental results indicate that montelukast has benefits such as improving cognitive function and reducing the frequency of epileptic seizures. However, most of these studies are limited to animal models, with a lack of clinical research findings. Studies on other LTRAs, such as zafirlukast and pranlukast, are even less conclusive [65]. Overall, the potential and therapeutic value demonstrated by LTRAs in this field still warrant further exploration.

The function of CysLTs in enteritis

In the past few years, the exploration of CysLTs and their connection to gastrointestinal inflammatory conditions has emerged as a promising new area of study. The occurrence of gastrointestinal inflammation involves multiple chemokines, including CXCL8, CXCL1/CXCL2, CXCL12, CCL2, CCL5, CX3CL1, and CXCL10. These chemokines primarily exert their effects by amplifying inflammatory signals and recruiting immune cells [66]. Although direct experimental evidence regarding the relationship between CysLTs and chemokines in gastrointestinal inflammation is currently lacking, studies in other diseases have demonstrated that CysLTs (such as LTD4) can bind to CysLT1R and CysLT2R, activating downstream signaling pathways (e.g. NF-κB and MAPK) to regulate chemokine gene expression [67,68]. Current thinking suggests that CysLTs are primarily a result of metabolic changes in Tuft cells during pathological conditions, playing a crucial role in regulating intestinal function. Cysteinyl leukotriene receptors (primarily CysLTR1 and CysLTR2) are widely expressed in the intestine, such as in intestinal epithelial cells, enteric neurons, and vascular endothelial cells. Their involvement in intestinal inflammatory damage is linked to mechanisms that affect intestinal barrier function and intestinal motility [69–71]. As research advances, the biological functions, molecular mechanisms, and clinical implications of CysLTs in intestinal inflammation will become clearer, offering innovative strategies for managing and understanding the development of enteritis and the interactions between the gut and other body systems.

Intestinal Tuft cells are activated by parasite colonization during anti-helminth immunity, and the resulting CysLTs have an effect similar to ILC2 activation in the lung and can activate ILC2S in the small intestine. The anti-worm immune process was specifically regulated by the Tuft-ILC2 circuit [72–74] if the production of CysLTs is specifically blocked by the ablation of Tuft cells, it will result in a weakening of type 2 immunity and a delay in the clearance of worms [15]. These four studies each independently recognized succinate as a potent activator of the Tuft-ILC2 loop. Succinate, a common metabolite of gut bacteria, typically triggers Tuft cells through the succinate receptor 1 (SUCNR1), IL-25, and POU2F3 in a dependent manner. The remodeling of the small intestinal mucosa and epithelium linked to type 2 immunity in the small intestine is facilitated by the promotion of Tuft cell proliferation, small intestinal ILC-2 proliferation, and IL-13 expression. The tuft cell, identified as a cell type with the ability to sense microbial metabolites in the small intestine, can trigger a type 2 immune reaction in response to alterations in particular metabolites. Consequently, this mechanism serves to combat microbial communities that have the potential to disrupt the immune balance within the intestines. Apart from succinate, Tuft cells situated in the gallbladder play a crucial role as chemoreceptors in interacting with their external environment. In addition to responding to succinate, these Tuft cells can detect propionate as well as other microbial metabolites, leading to a unique release of acetylcholine and CysLTs from gallbladder cluster cells through the activation of the FFAR2-TRPM5 signaling pathway. Whereas CysLTs stimulate smooth muscle contraction and facilitate bile release from the gallbladder, acetylcholine triggers the secretion of mucin to safeguard the biliary tract, thus initiating a dual innate defense mechanism [75].

It is worth noting that Tuft cells universally demonstrate the expression of ALOX5 and its activating

molecules FLAP, COX-1, COX-2, and LTC4S, alongside prostaglandin D synthase [74,76–78]. This enzymatic expression signifies the ability of these cells to generate both CysLTs and prostaglandin D2 (PGD2), resulting in a diverse array of effects on both immune and non-immune cells [79,80]. Apart from mast cells, which are primary PGD2 producers, dendritic cells, alveolar macrophages, Th2 cells, and osteoblasts also possess the biosynthetic capacity for PGD2 [79]. PGD2 can be further metabolized into bioactive metabolites with anti-inflammatory effects, including the ligand 15-Deoxy- (12,14) -PGJ2 (15d-PGJ2) of peroxisome proliferator-activated receptor-γ (PPARγ) [81]. The PGD-2 receptor DP2 or CRTH2 (a G-protein-coupled receptor found in Th2 cells, eosinophils, and basophils) is present in Th2 cells and ILC2S [82–84]. Thus, PGD2, together with LTs, which provide an NFAT-dependent activation signal for ILC-2s [28], forms an alternative "circuit" whereby Tuft cells can enhance IL-25 signaling through IL-17RB (IL-25 receptor) when IL-25 is absent. CRTH2 may be more broadly distributed across tissues and cell types than IL-17RB, allowing Tuft cells to influence a wider range of tissue-resident cells, including Th2 cells.

Despite the growing interest in the involvement of Tuft cells and CysLTs in enteritis diseases, there remains uncertainty regarding the potential connection between the proliferation of Tuft cells and alterations in their expression profile and the metabolic activity of eicosanes compounds. Previous research has indicated that a decline in colonic clusters and goblet cells occurs in cases where the phagocytic function of bone marrow cells is compromised, indicating that elevated levels of PGE2 are associated with a reduction in cluster cell frequency [85]. Nevertheless, the report fails to delve deeper into how PGE2 influences the regulation or function of the Tuft cell lineage. Moreover, current research typically discusses the involvement of CysLTs in a broad context, leaving the specific contribution of the three receptor subtypes to the development of enteritis unclear. The anatomical positioning of Tuft cells within the intestinal tract dictates their potential to bridge sensory nerves, endocrine cells, and the intestinal lumen [86], Despite the current research indicating that Tuft cells play a critical role in regulating immune and neural responses during intestinal infection and inflammation, these cells also possess carcinogenic properties [87]. This conflicting functionality warrants further investigation.

Current research on the role of leukotriene receptor antagonists (LTRAs) in gastrointestinal inflammation remains limited. Some evidence suggests that montelukast may alleviate gastrointestinal inflammation, particularly improving symptoms in eosinophilic gastrointestinal inflammatory disorders [88,89]. However, the precise mechanisms underlying this therapeutic effect remain unclear, and LTRAs are not considered first-line therapies in such contexts. They are primarily reserved as alternative options for patients' intolerance to systemic glucocorticoid therapy or dietary modifications. Additionally, a separate study focused on LTB4 receptor antagonists demonstrated that SC-41930, an LTB4 receptor antagonist, significantly reduces granulocyte infiltration in the intestine caused by ischemia-reperfusion injury, thereby exerting protective effects [90]. These findings may provide insights for further exploration of LTRAs in the diagnosis and treatment of gastrointestinal diseases.

CysLTs facilitate communication through the brain-gut-lung axis

Organ-to-organ communication is one of the emerging research hotspots. Due to their special physiological roles, CysLTs are considered to have potential exploration value in lung/brain/intestinal inflammatory diseases. A figure was used to briefly illustrate the role of CysLTs in brain-gut-lung axis communication (Figure 3).

The significance of CysLTs in the gut-lung axis

There is widespread agreement that maintaining a balance within the intestinal microbial communities is crucial for overall body well-being. For instance, alterations in metabolites resulting from shifts in the composition of intestinal microbiota, like short-chain fatty acids, tryptophan metabolites generated in the intestines, and bile acids, play a significant part in the gut-lung axis [4–6]. Although the lungs and intestines are structurally and functionally distant organs, they both originate from the endoderm, preserving certain anatomical resemblances that form the foundational theory for the gut-lung axis [91]. Some chemosensory epithelial cells (EpCs) in the respiratory tract are believed to share core transcriptional features with intestinal EpCs. The former are involved in P2Y2 receptor-mediated upregulation of CysLTs expression in allergic airway diseases, suggesting a potential gut-lung axis [92].

CysLTs are recognized for their significant impact on intestinal anti-helminth immunity. Moreover, they are intricately tied to the regulation of the gut-lung axis through their interaction with Tuft cells. In the small intestine, CysLTs trigger ILC2 activation, playing a crucial role in the modulation of anti-helminthic

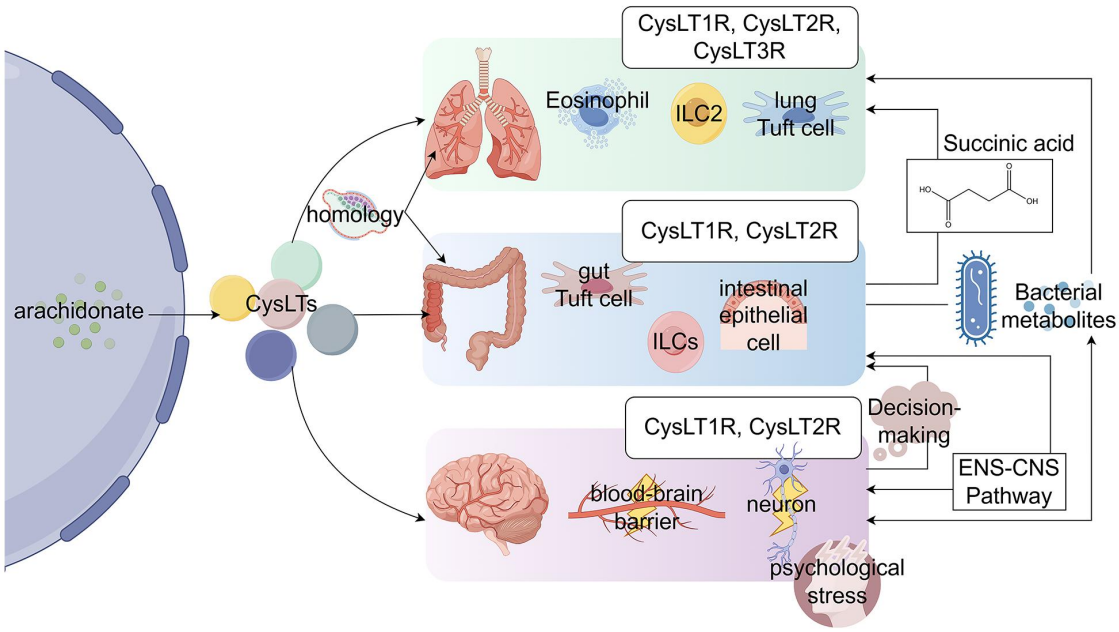

Figure 3. The role of CysLTs and their receptors in brain-gut-lung axis communication. Gut microbiota metabolites (e.g. short-chain fatty acids, bile acids) regulate systemic immunity via the gut-lung axis, with an anatomical basis rooted in the endodermal homology of the lungs and intestines. CysLTs exhibit dual roles in the gut-lung axis: in the gut, they enhance anti-helminth immunity by activating the tuft cell-ILC2 pathway, while in the respiratory tract, they mediate leukotriene-dependent type 2 allergic inflammation. Succinate, a key metabolite, synergizes with CysLTs in the gut to initiate immune defense but exacerbates gut-originated lung injury via the SUCNR1 pathway, suggesting CysLTs' potential hub role in cross-organ inflammation. Bidirectional gut-brain communication involves immune cell migration, neural transmission, and microbiota metabolite regulation, where psychological stress and gut inflammation mutually disrupt neuroimmune homeostasis. Studies indicate that CysLTs may participate in gut-brain interactions by modulating brain decision-making circuits (e.g. inducing allergen-avoidance behaviors), and their receptor expression in neural nociceptive pathways implies conservation of related mechanisms in humans. (figure was created with by Figdraw).

immune responses via the Tuft-ILC2 pathway. In the biliary tract, CysLTs are responsible for stimulating smooth muscle contractions and aiding in the emptying of bile from the gallbladder. On the other hand, acetylcholine promotes the secretion of mucin to safeguard the biliary tract, thus initiating a dual innate defense mechanism. Additionally, CysLTs expression is significantly elevated in the airways of *Nippostrongylus brasiliensis* (Nb)-infected mice, a phenomenon similar to that observed in house dust mite (HDM) infection, which may be associated with macrophage activity and inflammatory responses [93]. Despite triggering a similar immune cell differentiation pathway in the gut, Tuft cells in the respiratory system ultimately result in highly polarized leukotriene-dependent type 2 allergic lung inflammation, which contrasts significantly with the protective role they play in the gut. An additional piece of evidence is that succinate acts as a potent Tuft-ILC2 circuit agonist in the gut, co-initiating anti-helminthic immunity with CysLTs. A study on acute intestinal ischemia-reperfusion revealed that intestinal succinate induces the polarization of alveolar macrophages through the SUCNR1-dependent pathway, exacerbating acute lung injury caused by intestinal ischemia-reperfusion [4]. While the involvement of CysLTs remains uncertain, the discrepancies regarding succinate serving as the precise precursor of CysLTs in cases of bowel and pneumonia could potentially bolster the significance of CysLTs, necessitating further molecular biological confirmation. Indeed, succinate has been shown to regulate type 2 immunity in chronic sinusitis by producing CysLTs through a SUCNR1-dependent pathway, thereby triggering chronic sinusitis [94].

While direct studies on the role of CysLTs in the gut-lung axis remain limited, this area holds significant importance. It not only represents a theoretical breakthrough in deciphering cross-organ immune regulation but may also pave the way for innovative therapies targeting allergic diseases, infectious lung injury, and gut-originated systemic inflammation. The implications span from fundamental mechanistic exploration to clinical translation, while simultaneously promoting advancements in multidisciplinary research paradigms. Future efforts should focus on elucidating organ-specific signaling pathways, mapping metabolite-

CysLTs interaction networks, and developing precision intervention strategies.

Understanding the role of CysLTs in the gut-brain axix

Numerous studies have confirmed associations between gut and brain disorders. For instance, maternal gut inflammation-derived cytokines such as IL-17 can cross the placental barrier and correlate with autism-like behaviors in offspring [95]. A diet high in sugar and saturated fats disrupts hypothalamic activity by triggering microglia-mediated inflammatory factor release, increasing anxiety risk [96,97]. Migratory gut immune cells to the central nervous system are implicated in neurodegenerative diseases including cerebral ischemia and Parkinson's disease, with specific agents like intestinal α-synuclein fibrils traveling via the vagus nerve from enteric neurons to the brain, inducing neuroinflammatory responses [98].

Gut-brain communication during intestinal inflammation involves multiple mechanisms. Certain immune cells, such as cytotoxic CD8+ T cells, exert dual roles in both gut and brain tissues. Neurons and glial cells of the enteric nervous system (ENS) contribute to gut injury and subsequent dysregulation of gut-brain signaling. Inflammatory stimuli activate enteric neurons to transmit signals via the vagus nerve to central circuits governing sickness behaviors and immune regulation, while efferent neurons reciprocally modulate gut inflammation through immune cell interactions. Furthermore, gut-derived inflammatory factors not only compromise intestinal barrier integrity but also disrupt blood-brain barrier function upon systemic dissemination, ultimately perturbing cerebral homeostasis [98].

Beyond these pathways, gut microbiota serves as a pivotal mediator within the gut-brain axis. In the gut-brain axis communication, intestinal flora, as an extremely important component of the intestinal environment, can affect the progression of intestinal inflammation by changing the structure of intestinal flora and the composition of metabolites, and regulating the expression of intestinal barrier protein to control the content of intestinal flora, metabolites, neurotransmitters, cytokines and other components in peripheral blood, or affect the differentiation of immune cells and the expression of related proteins, thereby regulating neuroinflammation [99–101]; Either through the regulation of the enteric nervous system, through the enteric nervous system-central nervous system affects the decision-making of the brain [1,2,102], or causes diseases of the central nervous system [103]. It is important to emphasize that the gut-brain connection works in both directions. The latest evidence shows that psychological stress can induce transcriptional immaturity of inflammatory intestinal glial cells and intestinal neurons, leading to motor disorders, and predisposing the intestine to monocyte-mediated inflammation [104], Sympathetic output enriches intestinal symbiotic *Lactobacillus murinus* and increases the production of indole-3-acetate, resulting in metastatic loss of intestinal secretory cells, thus disrupting intestinal balance [105].

The direct effect of CysLTs on gut-brain communication is still lacking experimental verification. The main role of CysLTs in the current study of gut-brain axis communication processes is realized by influencing brain decision-making. In a study of food allergies in BALB/c mice, CysLTR2 was shown to induce antigen-specific allergen avoidance behavior through the hypertrophic epithelial cell circuit by promoting the production of GDF-15 by epithelial cells and stimulating the nucleus of the fasciculus to produce an aversive brain response before allergic inflammation has developed in the gut [1,2], the distinct avoidance behavior exhibited by this species might be linked closely to the selection of habitats by various species. Concurrently, another study revealed that CysLTR2 transcripts were notably active in dorsal root ganglion neurons linked to itchiness in mice, and were found in a considerable amount of human root ganglion neurons [3], suggesting that this allergen avoidance behavior may occur in human body responses. Considering the role of CysLTs and their receptors in intestinal and cerebral inflammation, as well as the important role of inflammatory factors and immune cells in gut-brain communication, we believe that this exploration has research value, and confirming the role of CysLTs in the association of intestinal and cerebral diseases may provide reference significance for the diagnosis and treatment of related diseases and the development of new drugs.

Conclusions and prospects

As research progresses, the study of CysLTs in inflammation pathogenesis has evolved beyond being solely a pro-inflammatory mediator in acute asthma. Its scope now encompasses the development of inflammation in various organs and diseases throughout the body, ranging from the brain, intestines, and gallbladder to the lungs. Generally speaking, the expression level of CysLTs under pathological conditions (such as respiratory tract and intestinal infections, acute phase of cerebral ischemia, etc.) is often higher than that of physiological conditions, and can trigger a series of inflammatory reactions downstream through a variety of pathways, accelerating the course of the disease. However, this effect is not absolute,

and the protective effect of CysLTs in intestinal helminth infection and its potential role in post-traumatic microangiogenesis suggest that the effect is two-sided. Particularly noteworthy is the role of CysLTs in chronic and long-term inflammation. This expansion of focus has led to the discovery of organ-specific actions of CysLTs. CysLTs and their associated succinate play a crucial role in quickly developing intestinal resistance against helminth infections, but they appear to trigger an exaggerated type 2 immune response in the respiratory system. Further research is needed to understand the mechanisms behind this phenomenon and its implications for biological organisms. The significance of CysLTs in the gut-brain axis has garnered increased attention in recent research. It is just one of several mechanisms facilitating communication between the gut and the brain. The question remains whether the inflammation triggered in the brain is linked to the excessive activity of CysLTs in the gut. But this opens up the prospect of CysLTs being involved in gut-lung axis communication through succinate. It also raises the intriguing possibility of CysLTs potentially traveling through alternative pathways in various organs. However, these theories lack evidence, and more molecular biological evidence is needed.

Disclosure statement

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Authors' contributions

Conceptualization: Xiao-Ru Liu, Ming Li, Qian-Qian Hao; Writing – original draft, figures and tables preparation: Xiao-Ru Liu, Ming Li, Qian-Qian Hao; Data analysis, Investigation, software: Xiao-Ru Liu, Qian-Qian Hao, Cai Liao, Rui Yu, Ya-Jie Yu; Writing – review and editing: Ming Li, De-Lei Kong, Yun Wang; Funding acquisition: De-Lei Kong, Yun Wang. All the authors have read and approved the manuscript.

Availability of data

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