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Progress in Research on Nrf2 and TGF-β1 in Chronic Suppurative Otitis Media

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Abstract

Chronic suppurative otitis media (CSOM) is a suppurative inflammatory disease involving the mucosa and periosteum of the middle ear and may extend into the bony structures. It is characterized primarily by intermittent otorrhea, tympanic membrane perforation, and hearing loss. With advances in modern medical research, investigations of CSOM have increasingly extended to the genetic level, revealing that its onset is not solely attributable to infection by pathogenic microorganisms but is also a consequence of dysregulated immune responses. Nuclear factor erythroid 2-related factor 2 (Nrf2) participates in the regulation of oxidative injury mainly by modulating the expression of antioxidant genes. Transforming growth factor-β1 (TGF-β1), by contrast, is a multifunctional cytokine that regulates inflammatory responses, immune function, as well as cellular growth and differentiation. To further clarify the anti-inflammatory role of Nrf2 and its influence on the course of CSOM, and to elucidate the dose-dependent effects of TGF-β1 on disease outcomes and on inflammatory and immunomodulatory processes, this review summarizes the basic profiles of Nrf2 and TGF-β1 and discusses their roles and underlying mechanisms in CSOM, thereby providing theoretical evidence and potential new perspectives for the future prevention and treatment of this disease.

Keywords

Chronic Suppurative Otitis Media (CSOM), Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2), Transforming Growth Factor-β1 (TGF-β1)

1. Introduction

Chronic suppurative otitis media (CSOM) is a chronic purulent inflammatory

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condition involving the mucosa, periosteum, or even the bony structures of the middle ear, and is mainly characterized by persistent otorrhea lasting more than two weeks, tympanic membrane perforation, and hearing loss. In severe cases, inflammation may extend beyond the mucosal epithelium to invade bone tissue, leading to absorptive osteitis and bone destruction, and may further result in deep cervical infections or otogenic intracranial and extracranial complications [1] [2]. CSOM is primarily caused by the following factors: (1) acute otitis media that is not treated promptly or is improperly managed, progressing into a chronic condition; (2) chronic diseases of the nasal cavity or nasopharynx that predispose patients to recurrent middle ear infections; and (3) reduced systemic immunity, strong bacterial virulence, or infections with drug-resistant strains, which may cause acute suppurative otitis media to develop into a chronic state [1]. However, numerous studies have shown that the pathogenesis of CSOM is closely related to the actions of various inflammatory mediators through different signaling pathways, suggesting that reducing the production of inflammatory cytokines may serve as an entry point for treatment. Nuclear factor erythroid 2-related factor 2 (Nrf2) primarily regulates oxidative injury by modulating antioxidant genes, and additionally participates in the progression of LPS-induced otitis media by coordinating inflammatory cells such as macrophages [3]-[5]. Transforming growth factor-β1 (TGF-β1) is a multifunctional cytokine involved in the regulation of inflammatory responses, immune function, cell growth, and differentiation; by modulating systemic immune responses, TGF-β1 influences the development of otitis media. Moreover, as a profibrotic factor, it may play a key role in the adhesion and fibrosis of the middle ear mucosa [6] [7]. This review summarizes studies on the roles of TGF-β1 and Nrf2 in the pathogenesis of CSOM, aiming to provide new insights for the prevention and treatment of this disease.

2. Global Epidemiological Status

Chronic suppurative otitis media (CSOM) is a major global health concern. According to preliminary estimates from the World Health Organization (WHO), approximately 65 million to 330 million people worldwide are currently affected by CSOM, with an estimated global burden of around 300 million individuals. The overall global incidence is approximately 4.8 per 1000 population, and about 31 million new cases occur each year [2]. However, most affected individuals reside in developing countries, particularly in economically disadvantaged regions, where the prevalence can reach 4% - 6% or even higher. These areas often show clustered outbreaks of the disease, primarily due to dense population distribution, poor hygiene conditions, limited medical resources, and low socioeconomic status. Because of variations in environmental factors, dietary patterns, and lifestyle habits among different regions, the prevalence of CSOM also varies globally. In developed countries and high-income populations such as North America and Western Europe, the prevalence of CSOM is typically below 1% (mostly between 0.5% and 1%), and the distribution of cases is more dispersed [8]-[11]. This further supports

the notion that CSOM is essentially a poverty-related disease, with its global distribution map closely overlapping the global poverty map.

Based on population distribution characteristics, CSOM is most commonly observed in children, particularly those under five years of age. Because the eustachian tube in children is shorter, more horizontal, and functionally immature, and because their immune system is relatively underdeveloped, they are more susceptible to infections. Inadequately treated or recurrent episodes of acute otitis media triggered by infections may subsequently progress to chronic otitis media. Some studies have also indicated that the highest incidence occurs in individuals aged 51 - 60 years [9]. For most patients, hearing loss is the most significant factor affecting daily life and is the primary reason for seeking medical attention. In adults, hearing impairment may influence occupational performance, daily activities, and even mental health, whereas in children, it can affect language development, cognitive learning, psychological well-being, and academic performance [2] [12] [13].

3. Pathological Changes and Microbiological Studies of Chronic Suppurative Otitis Media

The pathological changes of chronic suppurative otitis media (CSOM) are characterized by a gradual transition from acute inflammation to chronic, irreversible damage. The hallmark of the disease is the coexistence of persistent inflammatory injury and repair in the middle ear mucosa and bony structures, ultimately leading to tissue remodeling and functional impairment. Early morphological changes usually begin in the lamina propria of the middle ear mucosa, manifesting as increased capillary permeability, tissue edema, and extensive recruitment and infiltration of neutrophils. As the disease progresses to the late acute or subacute stages, significant epithelial proliferation occurs, characterized by an increased number of ciliated and epithelial cells, as well as hypersecretion of mucus, which exacerbates inflammatory exudation and pathological changes within the middle ear cavity. In the chronic phase, the predominant infiltrating cells shift from neutrophils to monocytes and macrophages, which promote tissue destruction, collagen deposition, and fibrosis through sustained secretion of various cytokines and proteases. Granulation tissue also forms extensively within the middle ear cavity, invading bony structures such as the ossicles. As the granulation tissue gradually matures and undergoes hyaline degeneration, vascular distribution decreases, ultimately resulting in permanent fibrosis and adhesions, severely impairing middle ear transmission function and cavity patency. In addition, CSOM may be accompanied by complications such as cholesteatoma, cholesterol granuloma, or tympanosclerosis, all of which can further aggravate irreversible structural damage in the middle ear, potentially leading to permanent hearing loss and related intracranial or extracranial complications [14].

However, the pathogenesis of CSOM involves the interplay of multiple factors, which together contribute to the persistence of middle-ear infection and inflammation [15]. CSOM is largely a sequela of acute otitis media that is not treated in

a timely manner or is treated inadequately. The microbial communities associated with CSOM mainly include aerobic bacteria, anaerobic bacteria, and fungi; moreover, the composition of these communities varies with patients' age, geographic region, ethnicity, and the presence or absence of middle-ear cholesteatoma. Bacteria remain the most common pathogens in CSOM [9] [15]. Drug-susceptibility testing based on ear swab specimens has shown that the detection rate of Gram-positive bacilli is higher than that of Gram-negative bacilli [16]. Regarding specific pathogens, Xu *et al.* [11] reported Staphylococcus aureus as the predominant causative organism, followed by *Pseudomonas aeruginosa*. Other studies have indicated that Streptococcus pneumoniae is another common and important pathogen responsible for acute otitis media [8], which may also progress to CSOM; fungal infections are also frequently identified in certain cases. On the basis of detailed microbiological profiling of otitis media pathogens, the rational selection of antimicrobial agents has become a key step in clinical diagnosis and treatment. Microbiological characteristics—such as pathogen distribution, antimicrobial resistance patterns, and biofilm-forming capacity—directly influence the choice of antibiotic regimens and the evaluation of therapeutic efficacy. Shen Zhisen [17] reported that topical antibiotic ear drops, with or without anti-inflammatory components, have long been used for cleansing and treatment in CSOM, and systemic antibiotics may also be administered. Antibiotic selection can be guided by ear swab culture results. Gram-positive bacilli such as S. aureus exhibit substantial resistance to penicillin, whereas quinolones (ciprofloxacin, ofloxacin, and levofloxacin) are among the most commonly used agents for CSOM; nevertheless, some studies have shown meropenem to be the most susceptible antibiotic [18] suggest that meropenem is the most sensitive agent. Rational use of antibiotics in the treatment of CSOM can shorten the disease course, reduce the incidence of complications, and decrease the development of bacterial resistance [19].

4. Role of Nrf2 in Chronic Suppurative Otitis Media

Chronic suppurative otitis media (CSOM) is considered a multifactorial disease, with bacterial infection being one of the primary causes. The middle ear mucosa serves as the first line of defense against bacterial invasion, primarily functioning as a protective barrier. As infection progresses, it further activates mucosal immune responses, promoting leukocyte infiltration, epithelial cell proliferation, and middle ear effusion [20]. CSOM often develops as a transition from acute otitis media, although the underlying mechanisms remain unclear. Nuclear erythroid 2-related factor 2 (Nrf2) is an amino acid-based transcription factor that also plays a role in oxidative stress. By interacting with antioxidant elements, Nrf2 exerts certain anti-inflammatory effects [3] [21]. In the context of otitis media, Nrf2 participates in pathological regulation through multiple mechanisms, thereby providing protective effects. These include direct modulation of inflammation and oxidative stress, as well as influencing the overall progression of the disease.

4.1. Involvement in Inflammatory Responses

During the onset of otitis media, the middle ear mucosa activates inflammatory pathways such as NF-κB, leading to the release of large amounts of proinflammatory cytokines including TNF-α, IL-6, and IL-1β, which cause mucosal congestion, edema, and increased secretions. Upon activation, Nrf2 can interact directly with key molecules in the NF-κB pathway or activate the Nrf2/HO-1 signaling pathway. Studies have shown that [3] within the Nrf2/HO-1 pathway, upregulation of HO-1 expression significantly inhibits NF-κB activity, reducing the production and release of inflammatory cytokines. This alleviates mucosal swelling, inflammatory cell infiltration, and fibrous tissue proliferation, thereby thinning the mucosa and relieving symptoms such as redness and pain, preventing further exacerbation of inflammation that could lead to suppuration or tympanic membrane perforation. Additionally, Nrf2 exerts indirect anti-inflammatory effects by regulating the TLR4 signaling pathway. Research has indicated [22] that in chronic suppurative otitis media (CSOM), Nrf2 expression is negatively correlated with TLR4 levels; high Nrf2 expression downregulates TLR4, whereas silencing Nrf2 upregulates TLR4, thereby inhibiting the secretion of proinflammatory factors and reducing the chronic inflammatory burden. This mechanism is particularly critical in the transition from acute otitis media to CSOM, preventing prolonged inflammation.

However, when inflammation persists, sustained activation of Nrf2 may exert pathological, pro-disease effects. Studies have suggested [23] that Nrf2 activation can be exploited by bacteria (e.g., *Pseudomonas aeruginosa*). Specifically, bacteria may use host-derived antioxidant molecules (such as glutathione) as nutrients and leverage the activated Nrf2 signaling pathway in host cells to promote biofilm maturation and virulence, thereby enhancing biofilm-forming capacity and resistance to host immune clearance. This, in turn, facilitates chronic bacterial colonization and persistent infection, ultimately exacerbating the chronic progression of the disease.

4.2. Attenuation of Oxidative Stress Damage and Enhancement of Middle Ear Mucosal Defense

In the pathological progression of CSOM, excessive accumulation of reactive oxygen species (ROS) is a key factor exacerbating tissue damage. Upon pathogen invasion of the middle ear, recruited neutrophils and macrophages produce large amounts of ROS through pathways such as NADPH oxidase during phagocytosis. Simultaneously, epithelial cells stimulated by inflammatory factors experience mitochondrial dysfunction, further increasing ROS generation. When ROS levels exceed the endogenous clearance capacity, cellular lipids, proteins, and DNA are damaged, delaying mucosal repair.

Cells activate the antioxidant defense system via the Nrf2 signaling pathway. Studies have shown [24] that the Keap1 protein contains multiple cysteine residues that can serve as sensors during redox reactions and, under physiological con-

ditions, continuously mediate the ubiquitination and degradation of Nrf2. When reactive oxygen species (ROS) oxidize or covalently modify these residues on Keap1, Keap1 undergoes a conformational change that disrupts its binding to Nrf2, allowing Nrf2 to escape degradation, translocate into the nucleus, and initiate transcription of antioxidant genes. Superoxide dismutase converts superoxide anions into hydrogen peroxide, whereas glutathione peroxidase uses glutathione to reduce hydrogen peroxide to water. Together, these enzymes synergistically eliminate excess ROS and protect the structural integrity of cells. Moreover, the Nrf2 pathway exerts multifaceted protective effects: it enhances mucosal barrier function by upregulating tight junction protein expression, thereby inhibiting pathogen adhesion; it regulates mucin synthesis and promotes antimicrobial peptide production, assisting in the clearance of pathogens and inflammatory secretions. Collectively, these mechanisms mitigate oxidative stress damage, control infection progression, facilitate resolution of inflammation, and play a critical role in maintaining middle ear mucosal homeostasis [3] [4].

4.3. Regulation of Macrophage Polarization to Prevent the Transition from Acute to Chronic Otitis Media

Macrophages, as key inflammatory cells, are generally classified into pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes. They participate in both innate and adaptive immune responses during infection, and their activation state or phenotype depends on signals received from the tissue microenvironment [4] [25] M1 macrophages are typically associated with the initiation and maintenance of inflammation and are activated by pro-inflammatory cytokines and microbial products such as lipopolysaccharide (LPS). Through their pro-inflammatory and chemotactic effects, M1 macrophages help eliminate infections. In contrast, M2 macrophages are mainly associated with the resolution of inflammation or chronic infection. They are activated by anti-inflammatory cytokines, growth factors, and apoptotic cells, and their anti-inflammatory and pro-repair activities contribute to appropriate tissue healing and remodeling [25] [26].

In acute otitis media (AOM), macrophages are typically activated toward the M1 phenotype, which promotes the recruitment of other immune cells to the site of infection by producing pro-inflammatory chemokines and cytokines, thereby facilitating pathogen clearance. In contrast, during chronic otitis media, macrophages may shift toward the M2 phenotype. In the short term, M2 macrophages secrete anti-inflammatory growth factors and cytokines to promote tissue repair; however, if the infection is not eliminated over a prolonged period, M2 macrophages may contribute to persistent inflammation and tissue damage [27]. Evidence suggests that macrophages do not exist as a single fixed phenotype during inflammation; instead, they can transition along a spectrum of phenotypic states [25] [28]. During the repair phase of AOM, an effective switch from the M1 to the M2 phenotype is a critical step for resolving inflammation and initiating tissue regeneration. As a central regulator of oxidative stress, Nrf2 plays a pivotal regulatory role in this process. Nrf2 is activated in response to elevated reactive oxygen

species (ROS) levels and subsequently induces the expression of downstream antioxidant genes (e.g., HO-1), thereby promoting the clearance of excessive ROS. Meanwhile, Nrf2 restrains the hyperactivation of pro-inflammatory signaling pathways (such as NF-κB), driving macrophage polarization from the pro-inflammatory M1 phenotype toward the reparative M2 phenotype. Conversely, reduced Nrf2 expression in macrophages impairs M2 polarization, resulting in sustained predominance of pro-inflammatory M1 macrophages, increased neutrophil recruitment, persistently elevated pro-inflammatory mediators (including IL-1β and IL-6), and heightened oxidative stress, ultimately leading to unresolved AOM or progression to chronic otitis media (COM). Therefore, therapeutic strategies aimed at enhancing Nrf2 signaling may represent a promising direction for modulating macrophage function and improving the clinical outcome of otitis media.

5. Role of TGF-β1 in Chronic Suppurative Otitis Media

Transforming growth factor-β1 (TGF-β1), as a multifunctional cytokine, regulates inflammatory responses, immune function, cell growth, and differentiation. In otitis media, TGF-β1 primarily promotes the occurrence, progression, and severity of the disease by modulating systemic immune responses [6], encompassing inflammation initiation, tissue repair, and disease outcome. Moreover, because the effects of TGF-β1 depend on precise signaling pathway regulation, this characteristic offers new avenues for targeted pharmacological interventions in otitis media.

5.1. Regulation of Middle Ear Inflammatory Responses

In bacterial infection-induced otitis media, the expression of TGF-β1 is closely associated with the inflammatory process. In the early stages of infection, middle ear epithelial cells and macrophages are activated and release TGF-β1, which, on one hand, inhibits NF-κB pathway activity, reducing excessive release of pro-inflammatory cytokines such as IL-1β and TNF-α, thereby preventing exacerbation of mucosal congestion and edema; on the other hand, it limits the excessive recruitment of neutrophils and T cells into the middle ear cavity, reducing secondary inflammatory damage to the mucosa and providing conditions for subsequent repair.

Studies have shown [29] that in a chronic otitis media model using Tgif knockout mice, the TGF-β1 signaling pathway is suppressed, while levels of inflammatory mediators such as IL-1β and TNF-α in middle-ear effusion are elevated. This finding suggests that the negative regulation of pro-inflammatory cytokines by TGF-β1 is crucial for maintaining the stability of the middle-ear microenvironment. In a rat experiment conducted by Wang Lizhu *et al.* [6], serum TGF-β1 levels in the pneumococcus-induced otitis media model group were significantly higher than those in the normal control group, implying that TGF-β1 may exacerbate inflammatory infiltration of the middle-ear mucosa by acting in concert with the release of pro-inflammatory factors. Mechanistically, TGF-β1 can aggra-

vate inflammatory injury by modulating immune responses and promoting epithelial-mesenchymal transition (EMT) in middle-ear mucosal epithelial cells. As a key signal transducer, STAT3 participates in abnormal tissue proliferation and differentiation and can also activate the NF-κB pathway to enhance the release of inflammatory mediators, thereby further worsening the disease. TGF-β1 may function as an upstream initiating factor that activates STAT3 via phosphorylation, subsequently promoting NF-κB nuclear translocation and inducing the transcription of pro-inflammatory cytokines. This process may constitute a "TGF-β1-STAT3/NF-κB-inflammatory cytokine" signaling cascade, ultimately amplifying the inflammatory response.

However, the anti-inflammatory effect of TGF-β1 is dose-dependent [30]. In the early stages of disease, insufficient TGF-β1 expression can lead to prolonged otitis media and increase the risk of suppurative otitis media, while low concentrations of TGF-β1 help stabilize the immune system and exert anti-inflammatory effects. As the disease progresses and TGF-β1 continues to be activated, its concentration in the body gradually rises, potentially suppressing immune clearance and indirectly promoting further bacterial colonization, thereby facilitating the progression from acute to chronic disease.

5.2. Involvement in Bidirectional Tissue Repair and Disease Outcome

TGF-β1, as a "core regulatory factor" in middle ear mucosal repair, exhibits a bidirectional nature of precise versus excessive repair [31] [32] which is crucial for disease outcome and structural remodeling in otitis media. During the recovery phase of inflammation, activated TGF-β1 exerts chemotactic effects, recruiting various anti-inflammatory cells to the injury site and promoting tissue repair. Additionally, by activating the Smad2/3 signaling pathway, TGF-β1 performs two key functions to further facilitate repair [32]: first, it promotes migration and proliferation of middle ear epithelial cells, accelerating coverage of epithelial defects and restoring the physical barrier function of the mucosa; second, it induces differentiation of submucosal fibroblasts into myofibroblasts, driving the production of extracellular matrix components such as type I and III collagen and fibronectin, thereby filling tissue defects and enhancing structural stability of the mucosa. TGF-β1 also promotes angiogenesis, providing nutrients and oxygen to support tissue repair. Clinical studies [6] [29] [33] have shown that TGF-β1 levels in middle ear effusions of acute otitis media patients are positively correlated with the rate of mucosal repair; adequate expression can shorten the disease course and reduce the risk of tympanic membrane perforation.

However, as the disease progresses and TGF-β1 expression continues to increase, the repair process becomes dysregulated, and TGF-β1 may shift toward a "detrimental role" [34]. This primarily involves three aspects: persistent activation of myofibroblasts, excessive extracellular matrix deposition, and inhibition of cell regeneration with promotion of apoptosis. Studies [33] [35] in models of induced tympanic sclerosis have shown that sustained elevation of TGF-β1 overactivates

fibroblasts, leading to abnormal extracellular matrix accumulation, mucosal thickening, and disorganized collagen fibers, thereby promoting the development of tympanic sclerosis. This bidirectional effect is also reflected in tissue morphology; for example [29], in chronic otitis media models using Tgif knockout mice, mucosal thickness was significantly increased, directly associated with dysregulated repair due to suppression of TGF-β1 signaling.

Therefore, as a key factor in tissue repair, TGF-β1 drives beneficial repair in the early stage, but as its expression continues to rise, otitis media gradually progresses from acute to chronic, and tissue repair shifts toward pathological fibrosis, ultimately resulting in tympanic sclerosis.

5.3. Dual Value of Signaling Pathways and Therapeutic Targets

The functional effects of TGF-β1 depend on precise regulation of its signaling pathways, and dysregulation of these pathways is considered a critical pathological event in the development of otitis media, providing potential targets for clinical intervention [6] [34] [35]. At the signaling level, TGF-β1 primarily modulates gene transcription through activation of the Smad pathway, such as phosphorylation of Smad2/3. Proteins including Tgif, Fbxo11, and Evi1 participate in regulating this pathway through different mechanisms. Studies have shown [29] that the Tgif gene can recruit histone deacetylases (HDACs) to suppress Smad2 activity or inhibit Smad2 phosphorylation by interacting with cPML protein. Fbxo11 regulates the overall activity of the pathway by modulating phosphorylated Smad2 levels. Research using Tgif knockout animal models further confirmed that when TGF-β1/Smad signaling is suppressed, expression levels of pSmad2 and p21 are significantly reduced, directly inducing middle ear inflammation; conversely, restoring the balance of this pathway helps improve the corresponding pathological manifestations.

Based on these mechanisms, modulation of the TGF-β1 signaling network has become an important direction in drug development. Experimental studies have demonstrated [33] that angiotensin-converting enzyme inhibitor captopril combined with angiotensin receptor antagonist losartan can effectively suppress excessive TGF-β1 expression. In guinea pig models, this combination significantly reduced the incidence of tympanic sclerosis induced by Streptococcus pneumoniae infection, mitigated mucosal thickening and calcium deposition in the middle ear, and improved auditory brainstem response thresholds. The mechanism primarily involves regulation of the renin-angiotensin system, indirectly inhibiting abnormal TGF-β1 signaling, thereby blocking the pathological cascade from middle ear inflammation to tissue fibrosis and calcification. These findings experimentally support the feasibility and scientific value of targeting TGF-β1 for clinical intervention [36] [37].

6. Summary and Prospects

As chronic suppurative otitis media (CSOM) continues to impact human health

globally, its associated symptoms—such as hearing loss, otorrhea, and tinnitus—not only severely disrupt patients' daily work and life but also impose long-term burdens on public health systems. This reality has driven ongoing investigations into its pathogenic mechanisms. The progression of CSOM is regulated by multiple inflammatory factors and signaling pathways; however, the complexity of these mechanisms provides a diversified theoretical basis for innovative therapeutic strategies.

Clinical management of CSOM is shifting from conventional conservative pharmacotherapy and surgical intervention toward more precise treatment strategies. Immunomodulatory therapy and gene therapy have emerged as frontier directions for investigation. As suggested by the studies reviewed above, with the progression of otitis media, Nrf2 may gradually shift from exerting protective effects to playing a pathological, disease-promoting role, whereas TGF-β1 may also transition from facilitating tissue repair in the early stage to becoming a key target that continuously activates pro-inflammatory signaling pathways. It is therefore reasonable to hypothesize a potential positive association between these two factors. In the course of CSOM, whether blocking the expression of either factor could slow disease progression and alleviate certain clinical manifestations represents an innovative direction for future clinical research. Moreover, CSOM-related factors (e.g., Nrf2 and TGF-β1) might serve as potential targets for earlier detection of CSOM onset, and intervention at the level of their expression may influence disease development. Nevertheless, translating these hypotheses into widely applicable clinical practice remains challenging. First, CSOM involves numerous candidate factors, and identifying specific, high-value targets is difficult. Second, cost-effective methods for detecting the expression of such factors are required. Finally, strategies must be feasible for implementation and dissemination in routine clinical settings, particularly in resource-limited regions. Therefore, despite ongoing progress, substantial efforts are still needed to elucidate CSOM pathogenesis and to develop effective, scalable therapeutic approaches.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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