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Sphingolipids in Ocular Inflammation

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Abstract

Sphingolipids are essential to cell membrane structure and the development and maintenance of neural tissues. The role of bioactive sphingolipids has been established in numerous cellular events, including cell survival, growth, and apoptosis. Ocular inflammatory and autoimmune diseases involve activation and migration of endothelial cells, neovascularization, and infiltration of immune cells into various tissues. Clinically, the impact and role of sphingolipid-mediated signaling is increasingly being appreciated in the pathogenesis and treatment of diseases ranging from multiple sclerosis to neovascularization in age-related macular degeneration and diabetic retinopathy. In this review, we discuss our current knowledge and understanding of sphingolipid metabolism and signaling associated with the pathogenesis of ocular diseases.

Keywords

Sphingolipid; Ceramide; Sphingosine-1-phosphate; Ocular inflammation; Uveitis; Apoptosis

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78.1. Introduction

Significant progress has been made in elucidating the role of sphingolipid signaling in cellular physiology and diseases. A delicate balance is important for cellular homeostasis and signaling, which has been defined as the “sphingolipid rheostat” [1]. Any imbalance in the level of bioactive sphingolipids, such as ceramide (Cer), sphingosine (Sph), and their phosphorylated products, ceramide-1-phosphate (C1P) and sphingosine-1-phosphate (S1P) can alter the signaling for cell survival, inflammatory pathways, and apoptosis [2–5]. The association of sphingolipids in human inflammatory diseases such as asthma, ulcerative colitis and Crohn’s disease has previously been reviewed [6–8]. Here, we review the role of sphingolipids in inflammatory signaling associated with ocular diseases and the implications of sphingolipids as a therapeutic target.

78.2 Uveitis, Multiple Sclerosis and Fingolimod

Evidences are mounting up suggesting roles of sphingolipids in autoimmune eye diseases such as optic neuritis and uveitis. Further, the application of FTY720 (fingolimod) as a drug that can modify the course of experimental uveitis and other inflammatory diseases has provided insights into sphingolipid signaling in such diseases. Multiple sclerosis (MS) is a disease characterized by immune-mediated demyelination and neurodegeneration. FTY720, a synthetic analog of sphingosine (Sph), is an FDA-approved drug used to treat relapsing MS. Once delivered in vivo, native sphingosine kinase 2 (normally phosphorylating Sph to S1P), phosphorylates FTY720, which then mimics S1P and inactivates S1P receptor-mediated signals. Thus a wide range of cell activity is affected, including inhibition of lymphocyte egress from lymph nodes into circulation [9]. As T lymphocytes are linked to the demyelination process, FTY720 can effectively reduce T lymphocyte levels and attenuate disease severity in MS patients. Treatment with FTY720 in animal models also implies a neuroprotective role for the drug by reducing axonal loss and demyelination [10].

Ocular complications in MS include retinitis, optic neuritis, and uveitis. Although it lacks myelination, the retina is a target of inflammation in MS leading to disruption of the blood-retinal barrier [11, 12]. Moreover, the extent of retinal periphlebitis correlates with MS disease severity [13], and retinal ganglion cells begin to degenerate prior to widespread neurodegenerative damage [14]. Up to 1 % of MS patients treated with FTY720 develop macular edema, an uncommon but generally reversible side effect [15, 16]. Macular edema is not typically seen in MS in the absence of uveitis or pars planitis. However, high resolution SD-OCT has led to the finding of a 4.7 % incidence of microcystic macular edema (MME) in patients with MS, none of whom were on FTY720 therapy [17]. This supports the notion of a local blood-retinal barrier breakdown due to subtle inflammatory activity in the retina [17]. Optic neuritis is also a common ocular complication of MS; however, less is known about the role of FTY720 in optic neuritis. Treatment of a rat model for optic neuritis with FTY720 reinforces the findings of reduced inflammation, demyelination, and axonal damage [18]. Yet, FTY720 does not prevent retinal ganglion cell apoptosis despite observations that it inhibits synthesis of ceramide, a pro-apoptotic molecule [19, 20].

Uveitis is the most common presentation of ocular inflammatory disease. Experimental autoimmune uveoretinitis (EAU) is a well-characterized animal model. FTY720 has been found to suppress both the incidence and intensity of inflammation in a dose-dependent manner in EAU [21]. When administered prior to the onset of EAU, FTY720 prevents inflammatory cells from infiltrating the retina [22, 23]. The same has been reported in clinical cases of uveitis [24]. While the nuances of how sphingolipids affect inflammatory cellular activity remain under investigation, the modulation of Cer and S1P biosynthesis by FTY720 strengthens the role of sphingolipids in the pathogenesis of inflammatory neural and ocular diseases [25–27].

78.3 The Sphingolipid Inflammatory Link to Retinopathies

Advanced age-related macular degeneration (AMD) and proliferative diabetic retinopathy characteristically develop choroidal and retinal neovascularization (CNV and RNV respectively), and currently account for the greatest number of cases of untreatable blindness. Multiple animal models exist to support inflammatory mediators (including complement, cytokines, and chemokines) as part of the pathogenesis of CNV and RNV [28]. For example, intravitreal injection of alpha-galacto-sylceramide (αGal-Cer), a ligand for natural killer T cells, can promote CNV, thus supporting an inflammatory link to the induction of CNV [29]. In ischemia-induced retinopathy models, while control mice develop vitreous neovascularization, S1P receptor 2 (S1P2) knockout mice do not. Furthermore, these mice demonstrate reductions in endothelial gaps and inflammatory cells in the retina, indicating a role for S1P2-mediated signaling in pathologic ocular angiogenesis [30]. Sonepcizumab, a humanized monoclonal antibody that selectively binds to S1P, is currently under evaluation in phase III clinical trials for treatment of advanced AMD. Intraocular injection of sonepcizumab in CNV mouse models results in a significant reduction in the area of CNV and degree of leakage from the residual CNV [31]. Similar results have also been achieved in laser-induced CNV models of mice [32].

Although proliferative diabetic retinopathy (characterized by RNV) does not manifest in rodent models, decreased Cer levels and a concomitant increase in glucosylceramide content have been observed in the retinas of streptozotocin-induced diabetic rats [33]. Finally, in human retinal endothelial cells (HRECs), activation of sphingomyelinase (SMase), the enzyme that produces Cer from sphingomyelin, has been shown to mediate cytokine-induced inflammation [34]. Treatment with the SMase inhibitor, docosahexaenoic acid, significantly reduces cytokine signaling in HREC cells [34–36]. Thus, although inflammatory pathways have long been established in models for CNV and RNV, signaling via sphingolipids is an evolving theory for how these pathways interact and ultimately lead to disease.

78.4 Anterior Segment Diseases

As sphingolipid signaling becomes more significant in posterior segment inflammation, the mechanisms of Cer modulation of inflammation in the anterior segment of the eye are less clear. Liposomal delivery of short-chain Cer is reportedly effective in inhibiting inflammation induced by either lipopolysaccharides or *S. aureus* in mouse corneas [37]. Cer

can also suppress corneal haze caused by exposure to ultraviolet B (UVB) radiation during photorefractive keratectomy (PRK) [38]. FTY720 is effective in increasing survival rates of corneal transplantation in mouse models, providing potential utility in corneal allografts [39]. Furthermore, oral administration of FTY720 in rats after corneal transplantation reduces the infiltration of lymphocytes and significantly prolongs allograft survival [40]. Finally, in primary Sjogren's syndrome (an autoimmune disease involving inflammation and destruction of lacrimal and salivary gland cells), increase of S1P receptor 1 expression in the infiltrating inflammatory cells has been noted, indication S1P signaling is involved in the autoimmune response [41].

78.5. Conclusions

Lysosomal storage diseases due to genetic dysfunction in sphingolipid metabolism have long been associated with various forms of ocular pathogenesis and blindness. Most recently, cellular activities associated with ocular inflammatory and autoimmune diseases have been linked with sphingolipid signaling. Investigation into sphingolipid signaling has also determined these molecules to be important mediators in the pathogenesis of blinding diseases. Nevertheless, there are still many details of how these bioactive molecules interact with each other and with other signaling pathways are yet to be elucidated. Deciphering the regulatory role of sphingolipids in these diseases ultimately presents an opportunity to pursue them as future therapeutic targets.

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