ISER 2024

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ISER 2024
PROGRAM ABSTRACTS

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cells induced by lipopolysaccharide (LPS).

Objectives
This work aims to study the effects of PLD2 inhibition in ocular inflammation using an endotoxin-induced uveitis (EIU) animal model.

Methods
Female Sprague Dawley rats (~250 g, 6–8 weeks old) were used and EIU was induced by the injection of 0.1 mL of 1 mg/kg LPS of Salmonella typhimurium solution into one footpad. After 2 or 4 h of LPS injection, (1, 4 or 8 mg/kg) of PLD2i (VU0285655-1) were injected intraperitoneally (IP) in 200 µl solution. 6 % DMSO was used as a PLD2i vehicle. PBS was injected instead of LPS in the negative control group of animals and dexamethasone was used as an anti-inflammatory positive control. Ethics approval for this study was obtained from the Animal Experimentation Ethics Committee of the CUHK. To evaluate clinical manifestations of EIU and the effects of PLD2i, rats were quantified using a score from 0 to 4 based in the presence of hyperemia, edema and synachesia, at baseline and 24 h after LPS injection. EIU were considered positive when clinical score >1 in at least one eye. To characterize the influxes of proteins into the aqueous humor (AH) in the different experimental conditions, protein concentrations were measured by the BCA Protein assay.

Results
After 24 h LPS injection, we observed ocular inflammation indicated by the presence of hyperemia and edema in the iris. The quantitative evaluation of clinical scoring showed a significant reduction by 30 % ($p < 0.0001$) in animals treated with 8 mg/kg PLD2i at after 2 h of LPS injection. The protein concentration in AH from LPS-treated rats was increased by 116 % ($p < 0.001$) compared to the negative control animals. Additionally, the elevated AH protein levels were significantly reduced by 33 % ($p < 0.01$) and by 49 % ($p < 0.0001$) in rats treated with 4 mg/kg or 8 mg/kg PLD2i, respectively. No statistically significance was observed between the 2 PLD2i treated groups and the negative control group.

Conclusion
Our study reports for first time the promising role of PLD2 inhibition as a potential early treatment for inflammatory ocular diseases.

Abstract ID: 472

Sphingosine-1-phosphate: Potential mediator in retinal proliferative disorders?

Section: Retinal Degeneration

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Introduction
Fibrosis is a common feature of retina proliferative diseases, as diabetic retinopathy and proliferative vitreoretinopathy, which lead to vision loss. Dysregulation of cell attachment, migration and de-differentiation of Müller glial cells (MGC) and retinal pigment epithelium (RPE) cells, which provide structural and metabolic support in the retina contribute to the fibrotic process. Modulation of this process might hold the key to prevent the development of proliferative retinopaties. Sphingolipids such as sphingosine-1- phosphate (S1P), which regulates critical cellular functions, like proliferation, inflammation, migration, survival and differentiation, advance fibrosis in different tissues, but their role in the retina is still unclear.

Objectives
To study the role of S1P in the regulation of processes leading to fibrosis in the retina.

Methods
Primary MGC cultures and RPE cell line cultures (ARPE-19 and D407) were exposed to 5 uM S1P for 24 h. We incubated cell cultures with sphingosine kinase inhibitors SphKI2 and PF-543, to study the role of endogenous S1P, with W146, JTE-013 and BML241, specific S1P1, S1P2 and S1P3 antagonists, respectively, to analyze the involvement of S1P receptors . The ERK/MAPK

and PI3K signaling pathways were analyzed with specific inhibitors U0126 and Ly294002, respectively. Cell migration was determined by the scratch wound assay, RPE cell morphology and localization of adherent proteins were analyzed by immunocytochemistry, pro-inflammatory cytokines were evaluated by PCR.

Results
We demonstrated that MGC synthesize S1P, which signals through S1P3 and the PI3K and ERK/MAPK pathways to induce glial migration. S1P also stimulated RPE cell migration and this effect required endogenous synthesis of S1P. S1P increased the transcription of pro-inflammatory cytokines IL-6 and IL-8, and of epithelial to mesenchymal transition (EMT) marker α-smooth muscle actin (α-SMA) in RPE cells. Blocking S1P syntesis led to RPE cell retraction, and to the disassembly of focal adhesions and cell-cell contacts. Exogenous S1P prevented these changes, signalling through S1P1 and S1P2.

Conclusion
Our results showed that S1P promoted MGC and RPE cell migration, and RPE release of pro-inflammatory cytokines, which might contribute to retinal fibrosis. However, they also imply that endogenous S1P regulates RPE proper attachment to neighboring cells and to the extracellular matrix, thus preserving monolayer integrity. This suggests a dual role for S1P in the retina, either protective or deletereous. Uncovering the molecular cues that modulate these S1P effects might provide new tools for treating retina proliferative disorders.

Abstract ID: 511

Growth hormone releasing hormone signaling in retinal inflammation

Section: Retina Cell Biology

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Introduction
We have studied the growth hormone releasing hormone receptor (GHRH-R) signaling pathway in various ocular diseases including retinoblastoma, uveitis and diabetic retinopathy. Our previous published paper demonstrated GHRH-R was highly expressed in infiltrating polymorphonuclear cells and retinal endothelial cells in the fibrovascular membranes of proliferative diabetic retinopathy patients. We also found that inhibiting GHRH-R genetically or pharmacologically could suppress autoimmune uveitis via reducing naïve T cell differentiation into T helper 17 cells. However, the effects of GHRH-R inhibition on retinal resident immune cells is not very well known.

Objectives
This study aims to investigate the impacts of GHRH-R inhibition on microglial cells.

Methods
The identity of microglial cells was confirmed by Iba1 immunofluorescence staining. Cells were challenged with high glucose (20mM) or negative control mannitol (20mM). Cells were also co-treated with GHRH-R agonist (10μM) or solvent control for 48 hours. Cells were then collected for immunofluorescence staining and western blot analyses.

Results
In western blot analysis, higher molecular weight polymers of NFkB could be observed in cells treated with high glucose. In addition, high glucose treatment led to more nuclear localization of NFkB, indication of the elevation of inflammation. Co-treatment of GHRH-R agonist could suppress the elevated nuclear localization of NFkB in high glucose treated cells.

Conclusion
Our results indicated GHRH-R agonist could suppress inflammation in retinal resident immune cells challenged by high glucose. Understanding the roles of GHRH-R in retinal inflammation could help us develop novel treatments in multiple retinal diseases.