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MEETING ABSTRACT Open Access

The pulmonary microvascular endothelial barrier function is controlled by the PGE_2-EP_4 signaling axis

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Background

Endothelial cells, like gate-keepers of the vascular bed, can actively protect against the inflammatory process. Prostaglandin E_2 (PGE_2) could be one of the mediators that can promote the barrier function of endothelial cells. PGE_2 exerts its cellular effects by binding to four different E-prostanoid receptors (EP_{1-4}) that belong to the family of G protein-coupled receptors. This project aimed at characterizing the barrier-protective properties of PGE_2 and especially EP_4 receptor on human pulmonary microvascular endothelial cells (HMVEC-L).

Methods

The endothelial barrier properties were analyzed by measurements of transendothelial electrical resistance (TEER) by Endohm and by ECIS (Electric Cell substrate Impedance Sensing) devices. Morphological studies were performed with immunofluorescence microscopy. Different protein expressions were detected by flow cytometry. Leukocyte diapedesis was studied by performing transendothelial migration assays of neutrophils and eosinophils.

Results

We found that the EP_4 receptor is expressed on HMVEC-L. PGE_2 and the selective EP_4 receptor agonist (ONO-AE1-329) prevented the barrier-disrupting effect of thrombin on the endothelial monolayer, as it was visualized by VE-cadherin staining. Selective blocking of EP_4 receptors (EP_4 antagonist ONO-AE3-208) inhibited the protective effect of PGE_2 on endothelial monolayers. PGE_2 and the EP_4 agonist enhanced the regeneration of electrically wounded endothelial monolayers. The specificity of EP_4 receptor involvement was proven by using the EP_4 receptor antagonist and selective agonists for EP_2 and EP_3 receptors. PGE_2 and the EP_4 receptor agonist attenuated the TNF-α-induced up-regulation of E-selectin. Surprisingly, this effect was not affected by an adenylyl cyclase inhibitor, but inhibition of PKC activity reversed the effect of the EP_4 receptor agonist and PGE_2 at reducing the E-selectin expression. In the cell interaction assays, thrombin or TNF-α increased the permeability of endothelial monolayers which also enhanced the transmigration of neutrophils and eosinophils, respectively. These effects were prevented by the selective activation of EP_4 receptors.

Conclusions

Our data support the hypothesis that endothelial cells, as gate-keepers of the vessel wall can actively participate in the inflammatory process. We have shown that PGE_2, via activating EP_4 receptors, enhances the barrier function of the endothelium by protecting the endothelial adherent junctional network and preventing leukocyte diapedesis. Therefore, EP_4 agonists might be promising new therapeutic tools in treating inflammatory diseases.

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