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The role of PGE_2 EP_4 receptors in the regulation of endothelial barrier function

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Background

Prostaglandin E_2 plays a crucial role in inflammation, including pain, fever and tumorigenesis. Inflammatory cells, fibroblasts and epithelium are the main source of PGE_2 throughout an immune response. There are four known receptors for PGE_2, E type prostanoid receptors 1–4 ($EP_{1,2,3,4}$). According to recent reports, the EP_4 receptor seems to be a potential target of therapeutic treatment for attenuating inflammation as well as increased endothelial permeability.

Methods

Primary human microvascular endothelial cells of the lung (HMVEC-L) were cultured and transfected using siRNA approach. The mRNA level of the EP_4 receptor was determined using RT-PCR. EP_4 receptor protein expression was evaluated via Western blotting and flow cytometry. Changes in electrical impedance were measured using an ECIS application. Morphological alterations were observed via immunofluorescent staining of β-catenin and F-actin. Cell cycle and apoptosis analysis were performed using flow cytometry.

Results

The pulmonary microvascular endothelial cells express the PGE_2 receptor EP_4, which was shown by flow cytometry and Western blotting. In endothelial cells, EP_4 receptor protein expression was down-regulated to less than 40% by using the siRNA transfection approach. Also, the mRNA level of the EP_4 receptor was significantly down-regulated below 15% using siRNA transfection. In the endothelial impedance measurements, the EP_4 agonist and PGE_2-induced barrier enhancement was significantly suppressed in EP_4 receptor-silenced cells. Morphological studies revealed that the thrombin-induced disruption of endothelial monolayers could be reversed by stimulation of EP_4 receptors. Cell-cell contacts were enhanced and stress fibre formation was prevented by pre-treatment with PGE_2 and an EP_4-selective agonist. PGE_2 and the EP_4 agonist did not induce any changes in the endothelial cell cycle; however, EP_4 receptor activation appeared to be protective against staurosporine-induced apoptosis. Apoptotic cells were determined in the sub-G_1 phase of the cell cycle.

Conclusions

These data suggest EP_4 receptor agonists as potential therapeutic intervention for diseases with increased vascular permeability such as acute lung injury.

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