

## A10

### **Endothelial prostaglandin I<sub>2</sub> restrains eosinophil trafficking**

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#### **Background**

Enhanced eosinophil extravasation into the tissue is a characteristic feature of bronchial asthma and other allergic diseases. The barrier-forming vascular endothelial cells release prostaglandin I<sub>2</sub> (PGI<sub>2</sub>, prostacyclin) as the major prostanoid, and it has been previously observed that PGI<sub>2</sub> receptor (IP)-deficient mice show enhanced eosinophilic inflammation in response to allergens. Our aim was to define the role of PGI<sub>2</sub> in endothelial function and in eosinophil trafficking across endothelial monolayers.

#### **Methods**

Eosinophils were freshly isolated from human blood. Eosinophil chemotaxis through cell-free filters and adhesion to fibronectin were studied. Cell interaction assays, like adhesion and transmigration of eosinophils, were performed on confluent monolayers of human lung microvascular endothelial cells. The endothelial barrier properties were analyzed by measurements of transendothelial electrical resistance (TEER). Morphological studies were performed with immunofluorescence microscopy.

#### **Results**

Exogenous PGI<sub>2</sub> markedly attenuated the chemotaxis of isolated eosinophils through cell-free filters. This effect was prevented by the IP receptor antagonist CAY10441 and the adenylyl cyclase inhibitor SQ29548. Expression of IP receptors on eosinophils was shown by indirect flow cytometry and Western blot. PGI<sub>2</sub> reduced eosinophil adhesion to fibronectin, inhibited the activation and up-regulation of CD11b/CD18 adhesion molecule, and blocked podosome formation in response to eotaxin. PGI<sub>2</sub> production of endothelial cells was abolished by diclofenac, a non-selective COX inhibitor, which resulted in enhanced eosinophil adhesion to endothelial monolayers. Similarly, the IP receptor antagonist CAY10441 enhanced the adhesion of eosinophils to endothelial cells. Transendothelial migration of eosinophils was likewise augmented by diclofenac. The diclofenac treatment itself decreased the electrical resistance of endothelial monolayers and disrupted the intercellular junctions as visualized by VE-cadherin and F-actin staining.

#### **Conclusions**

Based on these observations, endothelium-derived PGI<sub>2</sub> might be an important protective factor in keeping inappropriate eosinophil infiltration under control and might modulate allergic responses by inhibiting eosinophil responsiveness to chemoattractants in terms of adhesion and migration, and by strengthening the barrier function of the endothelium against infiltrating leukocytes. Therefore, IP agonists might be a useful therapeutic option for otherwise inadequately controlled inflammation in eosinophilic diseases, by blunting their extravasation into tissue.