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Meeting abstract

Endothelial prostaglandin I_2 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_2 (PGI_2, prostacyclin) as the major prostanoid, and it has been previously observed that PGI_2 receptor (IP)-deficient mice show enhanced eosinophilic inflammation in response to allergens. Our aim was to define the role of PGI_2 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_2 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_2 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_2 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.

Conclusion

Based on these observations, endothelium-derived PGI_2 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.