Effect of Prostaglandin D2 on VEGF Release by Nasal Polyp Fibroblasts

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Background

Vascular endothelial growth factor (VEGF) is known to be associated with the pathogenesis of chronic rhinosinusitis with nasal polyps (CRSwNP). VEGF is produced by a variety of cells including fibroblasts. It was recently reported that prostaglandin (PG) E2 induces VEGF release by nasal polyp fibroblasts. However, little is known regarding possible regulation of VEGF by other PGs. We have reported that molecules that regulate PGD2 metabolism play roles in the pathogenesis of CRS including in local eosinophilia and type 2 cytokine production. In the present study, we sought to determine whether PGD2 regulates VEGF release by nasal polyp fibroblasts.

Methods

Nasal polyp fibroblasts were established from nasal polyps. These fibroblasts were stimulated with serial dilutions of PGD2 or PGD2 receptor (DP/CRTH2)-selective agonists in the presence or absence of receptor-selective antagonists. The concentration of VEGF in the culture supernatants was determined using ELISA.

Results

5mM of PGD2 significantly induced VEGF release by nasal polyp fibroblasts. VEGF release was also obtained by stimulation with a DP receptor-selective, but not with a CRTH2 receptor-selective agonist. In addition, PGD2-induced VEGF release was significantly inhibited by pre-treatment with DP receptor-selective antagonists. In contrast, pre-treatment with a CRTH2 receptor-selective antagonist significantly enhanced PGD2-induced VEGF release.

Discussion

Stimulation with BW245C, the DP receptor-selective agonist, but not with DK-PGD2, the CRTH2 receptor-selective agonist, mimicked the effect of PGD2 on VEGF release by NPDF. In addition, treatment with MK0524 and ONO-4053, the DP receptor-selective antagonists, but not with OC000459, the CRTH2 receptor-selective antagonists, significantly abrogated the effect of PGD2. These findings suggest that PGD2 induced VEGF release via coupling to DP but not CRTH2 receptor in nasal polyp fibroblasts.

The predominant expression of the DP receptor is consistent with our previous report showing that the DP receptor is expressed by a variety of cells including constitutive cells and infiltrating inflammatory cells, whereas the CRTH2 receptor is mainly expressed by infiltrated inflammatory cells in nasal polyp. This selective release through the DP receptor may be due to the predominant expression of the DP receptor over that of the CRTH2 receptor in nasal polyp fibroblasts as shown using real-time PCR.

Interestingly, treatment with OC00045, the CRTH2 receptor-selective antagonists, significantly augmented
PGD2-induced VEGF release by nasal polyp fibroblasts. In the present study, although not significant, treatment with 10μM of DK-PGD2, the CRTH2 receptor-selective agonist, tended to inhibit VEGF release by nasal polyp fibroblasts. These results suggest that blockage of CRTH2 receptor signaling augments DP receptor signaling, which then enhances VEGF release in nasal polyp fibroblasts. The lack of dose-dependent effect by PGD2 but not DP receptor-selective agonist on VEGF release may be due to the stimulation of CRTH2 receptor by high concentration of PGD2.

Conclusions

DP was dominantly expressed in nasal polyp fibroblasts as compared with CRTH2. PGD2 stimulates VEGF production via DP but not CRTH2 receptor in nasal polyp fibroblasts. The DP receptor-selective antagonists inhibited PGD2-induced release of VEGF in a dose-dependent manner. Thus, DP receptor may be a target for controlling CRS with nasal polyps.