Protease-activated receptors: mediating pro-inflammatory or anti-inflammatory effects within the airways?

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Protease-activated receptors (PARs) are a novel family of G protein-coupled receptors (PAR_1, PAR_2, PAR_3, PAR_4). Within the respiratory tract, PAR_2 has attracted particular attention because it is expressed by a wide range of resident (*e.g.* epithelial cells) and infiltrating cells (*e.g.* T cells, neutrophils and eosinophils) and its expression is altered following exposure to various inflammatory stimuli including respiratory tract viruses, environmental pollutants, bacterial products and aeroallergens. Studies using animal models of disease indicate that PAR_2 plays an important role in the host response to these inflammatory stimuli, and may be involved in the pathophysiology of respiratory tract disorders such as asthma, COPD and influenza virus infection. However, there is considerable conjecture as to whether promoting or blocking signalling through PAR_2 is the better therapeutic approach in these respiratory tract disorders. Signalling through PAR_2 can be promoted by a limited number of endogenous (*e.g.* mast cell tryptase) and exogenous proteases (*e.g.* Der p 3) that cleave an extracellular region of the receptor to reveal a specific tethered ligand sequence capable of auto-activating the receptor, and *via* non-proteolytic pathways by compounds that mimic the tethered ligand sequence and act as PAR_2 agonists (*e.g.* SLIGRL, GB110). In contrast, signalling through PAR_2 can be blocked by proteases (*e.g.* cathepsin G) that 'disarm' the receptor by cleaving the extracellular region at sites which remove the tethered ligand sequence, and by recently-developed compounds that act as PAR_2 antagonists (*e.g.* GB88). Our recent investigations have centred on the airway biology of PAR_2, with a particular focus on its role in inflammatory diseases driven by exposure to allergens, bacteria and viruses, and address current controversies related to whether PAR_2 mediates primarily pro-inflammatory or anti-inflammatory processes.