Public Abstract
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Title:The Role of the P2X7 Nucleotide Receptor in Salivary Gland Inflammation

Salivary gland inflammation is a hallmark of Sjögren's syndrome (SS), a common autoimmune disease characterized by lymphocytic infiltration and the consequent impairment of the salivary gland and loss of saliva secretion, predominantly in women. The current therapeutic management of SS is relatively ineffective and does not address the underlying inflammatory processes contributing to the pathology of SS. In this study, two novel therapeutic approaches were evaluated to limit salivary gland inflammation and improve secretory function, i.e., antagonism of the P2X7 nucleotide receptor (P2X7R) which prevents salivary gland inflammation or activation of the P2Y2 nucleotide receptor (P2Y2R) which stimulates the regeneration of damaged salivary glands. The P2X7R is an ATP-gated non-selective cation channel that regulates inflammatory responses in cells and tissues, including salivary gland epithelium. The P2X7R contributes to the pathology of a variety of inflammatory diseases, including rheumatoid arthritis and inflammatory bowel disease. In immune cells, P2X7R activation induces the production of pro-inflammatory cytokines, including IL-1? and IL-18, by inducing the oligomerization of the multiprotein complex NLRP3-type inflammasome. This study (Chapter II) sheds light on the role of the P2X7R in salivary gland inflammation and hyposalivation. Our results show that in primary mouse submandibular gland (SMG) epithelial cells, P2X7R activation induces the assembly of the NLRP3 inflammasome and the maturation and release of IL-1?, responses that are absent in SMG cells isolated from mice devoid of P2X7Rs (P2X7R-/-). P2X7R-mediated IL-1? release in SMG epithelial cells is dependent on downhill transmembrane Na+ and/or K+ fluxes, the activation of heat shock protein 90 (HSP90), a protein required for the activation and stabilization of the NLRP3 inflammasome, and the generation of mitochondrial ROS. In vivo administration of the P2X7R antagonist A438079 in the CD28-/-, IFN?-/-, NOD.H-2h4 mouse model of salivary gland exocrinopathy ameliorated salivary gland inflammation and enhanced carbachol-induced saliva secretion. These findings demonstrate that P2X7R antagonism in vivo represents a promising therapeutic strategy to limit salivary gland inflammation and improve secretory function. The P2Y2R, a G protein-coupled receptor equipotently activated by ATP and UTP, is upregulated in a variety of tissues, including salivary gland epithelium, in response to injury or stress and is proposed to play a role in tissue regeneration. The results indicated that P2Y2R activation with UTP enhances the migration, aggregation and self-organization of dispersed salivary epithelial cells forming spheres that display characteristics similar to differentiated acini in salivary glands.
One of the consequences of the chronic inflammatory disease SS is the fibrosis of the salivary gland. The role of transforming growth factor-b (TGF-?) is well established in the fibrosis and regeneration of various organs, including the liver, lung and kidney. In this study, results with a submandibular gland (SMG) duct ligation-induced mouse model of fibrosis indicated that 7 days of SMG duct ligation resulted in upregulation of TGF-? signaling components which correlated with the upregulation of the fibrosis markers collagen 1 and fibronectin, responses that were inhibited by administration of the TGF-? receptor 1 inhibitors. These results suggest that TGF-? signaling contributes to duct ligation-induced changes in salivary epithelium that correlate with glandular fibrosis.