A healthy person produces ~1-1.5 litres of saliva/day. Saliva performs many protective and physiological functions by providing the oral cavity with water and electrolytes along with essential proteins, including lubricants, antibacterial, antifungal, antiviral and remineralization agents, digestive enzymes and growth factors. Thus, hyposalivation (reduced saliva production) due to salivary gland dysfunction, primarily resulting from Sjögren’s Syndrome (an autoimmune disease) or unintended damage during irradiation therapy for head and neck cancers, leads to deterioration of oral health and greatly affects the quality-of-life of patients. Current therapies for hyposalivation are symptomatic whereas regenerative therapy can provide a radical cure for the problem. Strategies for salivary gland regeneration include stem cell therapy as well as bioengineering of artificial glands and transplanting them back into the patients. Previous reports suggested the capability of dispersed salivary epithelial cells to self-organize forming spheres with structural features, differentiation markers and/or functional responses that resemble the acini in the native glands. In this study, we demonstrate that the activation of the P2Y$_2$ nucleotide receptor (P2Y$_2$R) with the extracellular nucleotide UTP enhances the self-organization of dispersed salivary epithelial cells forming acinar-like spheres. Our results also delineate some mechanisms by which the P2Y$_2$R mediates this response, which revealed for the first time the involvement the $\alpha_5\beta_1$ integrin and the Rho GTPase Cdc42 in the P2Y$_2$R-mediated signaling network. Our data, along with previous reports, hold promise for the cell-based reconstitution of salivary glands and provide insights into novel approaches for the bioengineering of salivary glands that should lead to better regenerative/replacement strategies for damaged salivary glands.