Cell Polarity in Salivary Progenitors as a Target for Glandular Regeneration

The symptom of xerostomia (severe dry mouth) is a common side effect of radiotherapy for head and neck cancers due to radiation-induced damage to the salivary epithelium. Xerostomia often predisposes to a multitude of other complications, such as esophageal dilation, difficulty swallowing, and increased oral infections. Regrettably, there is currently no treatment for xerostomia or salivary gland dysfunction. Restorative therapies utilizing salivary gland stem cells are an attractive alternative, but the mechanisms underlying the response of these cells to radiation or their role in gland repair remain vastly unknown. In mice, systemic administration of IGF-1 following radiation allows for full recovery of salivary gland function. While radiation promotes an abnormally sustained compensatory proliferation response, post-therapeutic IGF-1 modulates the proliferative activity of salivary progenitors. Several studies in drosophila and mammalian epithelial cells have shown that proliferation and function of stem/progenitor cells is regulated by signaling from the surrounding cellular niche as well as intracellular polarity cues. In particular, the Par3-aPKC polarity complex, which defines the apical membrane, has been associated with stem cell division and differentiation. Here we demonstrate that radiation decreases phosphorylation of aPKC in salivary progenitors in vivo and in salivary gland-derived cells in vitro. Further, radiation prevented the formation of acinus-like structures and caused a reduction of E-cadherin and B-catenin at the lateral membranes in salivary gland cells in vitro, suggesting a disruption during the establishment of cell-cell contacts, possibly due to alterations in cell polarity. The importance of this work lies in the potential therapeutic applications of targeting cell polarity to restore function of the irradiated salivary glands.