Investigating the molecular mechanisms that govern stemness versus differentiation in salivary mucoepidermoid carcinoma

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Mucoepidermoid carcinoma (MEC) is the most common salivary gland malignancy (up to 80% of all cases) and is primarily driven by a fusion oncogene. This oncogenic gene fusion arises from a chromosomal translocation event creating an in-frame fusion of CRTC1 and MAML2 genes (C1/M2). The majority of salivary MEC patients present with slow-growing, highly differentiated tumors (low-grade) and exhibit promising prognosis (90% 5yr-survival). However, some patients present with aggressive, poorly differentiated tumors (high-grade) that frequently recur and metastasize leading to dismal outcomes (25% 5yr-survival). We and others have shown that C1/M2 exerts its oncogenic abilities by acting as a constitutive co-activator for the 'master' transcription factor CREB, and a novel and previously unappreciated ability of C1/M2 to interact with another 'master' transcription factor and proto-oncogene MYC. Our recent work suggests that these interactions govern opposing functions of the CRTC1-MAML2 oncogene that regulate salivary MEC differentiation and stemness, respectively. However, their functional contribution towards MEC tumor biology, specifically in the low to high grade tumor transition, still remains entirely unknown. In this study, we found that expression of a dominant negative CREB molecule (ACREB) which effectively blunts C1/M2-CREB interactions, causes a dramatic change in cell morphology and behavior. Specifically, blunting CREB function in MEC cells leads to epithelial-mesenchymal transition (EMT), whereby cells exhibit increased single cell mobility, collective migration, and invasion which are all hallmarks of aggressive, poorly differentiated tumors (high grade) tumors. Thus, we have uncovered a novel and previously unreported role of CREB towards regulating salivary MEC tumor progression.