Uncover *Irf6*-dependent regulatory pathway involved in Salivary Gland Development and Maturation

Matthew Pham[1], Derrick Thomas[1], and Walid Fakhouri[1,2], [1]Center for Craniofacial Research, Department of Diagnostic and Biomedical Sciences, University of Texas Health Science Center at Houston (UTHealth Houston), School of Dentistry, [2]Department of Pediatric, McGovern Medical School, UTHealth Houston, Houston, Texas, USA.

Objectives: Hyposalivation, reduced salivary flow, is a prevalent oral health problem that is often seen to result from aging, medications, and radiation treatment. Saliva plays such a critical role in oral pharyngeal health by aiding in swallowing, pH buffering, washing of the oral cavity, and taste. Patients with hyposalivation often have various oral health complications such as dental erosion, caries, and halitosis. One factor contributing to hyposalivation is the substantial disruption of secretory acinar cells in salivary glands (SG). This study aims to establish evidence of a mechanistic pathway involving Interferon Regulatory Factor 6 (*Irf6*) in the development and differentiation of acinar cells in SG. IRF6 is a transcription factor that plays a key role in regulating the expression of interferons and genes involved in ectoderm differentiation. As such, we hypothesized that *Irf6* is critical for the development of SG.

Experimental Methods: Histological sections of irf6 null and wild-type mouse embryos at various ages were subjected to Hematoxylin and Eosin staining to observe any phenotypic differences between the SG. Additionally, Salivary gland explants from E13 *Irf6* null and wild-type mice embryos were subjected to various growth factors to rescue the *Irf6* null phenotype and RNA-Seq analysis was performed.

Results: Histological sections showed that the loss of *Irf6* causes disrupted branching morphogenesis, myoepithelial detachment from ductal cells, and nuclear disorganization in various SG cells. Among all the growth factors, TGFβ3 treated SG explants saw a partial rescue of the mutant phenotype with increased terminal bud numbers and more defined branching. RNA-Seq identified 168 differentially expressed genes, with Col9a2, Hoxb6, Egr1, and Ltbp4 were notable due to their roles in the TGFβ3 pathway.

Conclusion: In conclusion, our data gives a foundation for a novel model of a regulatory pathway for the mechanistic role of irf6 and TGFβ3 in SG development and maturation.

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