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Establishing the FGFR1 Downstream Signaling Pathways Responsible for Regulating the Differentiation of Cochlear Hair Cells

Yutao Su
Washington University in St. Louis

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Mentor: David Ornitz

Hearing loss affects a large portion of the population and results from the loss or damage of the cells that sense sound. These cells, called hair cells, lack regenerative capabilities in mammals. However, by elucidating the mechanisms that regulate hair cell differentiation during developmental stages we may inspire pro-regenerative therapies applicable in adult auditory systems to restore hearing. Previous studies have shown that a vital component of hair cell differentiation is Fibroblast Growth Factor (FGF) signaling and that it acts through FGF Receptor 1 (FGFR1) in the undifferentiated sensory epithelium. However, the signaling pathway downstream of FGFR1 that is required for hair cell differentiation is not known. There are four candidate pathways that FGFR1 is known to activate: MAPK, PLCγ, AKT, and STAT. We use cochlear explant cultures given specific pathway inhibitors that block each pathway individually to determine which pathway(s) affect hair cell differentiation: U-73122 inhibits PLCγ, LY-294002 inhibits AKT, and U-0126 and SB-203580 inhibit the p38 and MEK1/2 branches of the MAPK pathways, respectively. Our preliminary results show that treating explants with the inhibitors U-0126 and SB-203580 resulted in a decreased number of hair cells. Other inhibitors tested yielded hair cell counts similar to their vehicle controls. These results suggest that the ERK and p38 MAPK pathways could play a crucial role in the development of hair cells. As this is an ongoing project, additional trials and studies are needed to further validate these results.