Reduced Endocochlear Potential in vivo Prevents Hair Cell Degeneration in Tmprss3-deficient Mice

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Background: Transmembrane serine protease 3 (TMPRSS3) is a transmembrane serine protease with proteolytic activity essential for normal auditory function in mice and humans. While Tmprss3 mutations are the most common gene variant adain cochlear implant recipients, details behind its cellular mechanism remain elusive. Tmprss3-mutant mice exhibit normal hair cell (HC) development until postnatal day 12 (P12), followed by rapid HC degeneration within 48 hours, resulting in deafness. The HC degeneration temporally correlates with the rapid rise in endocochlear potential (EP) that is required for hearing. This phenotype mirrors other mouse models with defects in genes expressing tight junctions (TJs). Thus, we hypothesize that TMPRSS3 regulates tight junctions and cell death is mediated through high EP.

Methods: Our laboratory has previously demonstrated that performing cochlear explants at P7 followed by in vitro cultures for an additional 7 days leads to complete preservation of HCs in Tmprss3-mutant mice. It is unknown if the observed HC survival is due directly from removing EP or from other extracellular factors. Here we investigated the role of EP in Tmprss3-deficient mice using in vivo experiments. We crossed the Tmprss3-mutant mice with Pou3f4-mutant mice, which fail to generate EP. Cochlear whole mounts were dissected, fixed, and stained for four groups of mice: wild-type, Tmprss3-mutant, Pou3f4-mutant, and double-mutant mice. Inner and outer hair cells were quantified within a span of 125 μm and compared between groups.

Results: We found significant preservation of HCs ($p<0.001$) in double mutant mice with reduced EP compared to Tmprss3-mutant mice. Thus, HC degeneration in Tmprss3-deficient mice is due to endocochlear potential driven K+ toxicity. Tmprss3-deficient mice likely have faulty apical TJs that result in leakage of K+ ions from the endolymph to the basolateral side of HCs, leading to HC degeneration.

Concluson: Future research should work to elucidate TMPRSS3's proteolytic target and its mechanism of TJ-related regulation.

General Excellence Award
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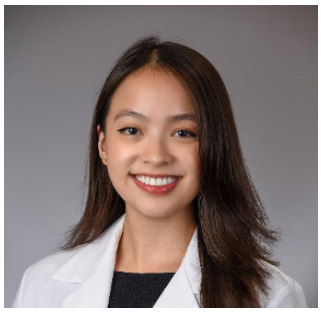
Year: Class of 2026
Specialty Interest: Anesthesiology with a potential fellowship in Neuroanesthesia or Obstetric Anesthesia.



Biggest takeaway: My research experience this past summer taught me how to analytically create tangible results from microsurgical procedures and meticulous benchwork technique. The process of thoroughly isolating the cochlea and Organ of Corti from mice served as direct hands-on-experience and insight to the precision and patience that the surgical field necessitates. I distinctly remember feeling proud to see the hair cells that I stained being visualized underneath the microscope. Most gratifying of it all was to know that I, with the help of my lab mates, contributed a small part in the current understanding of the cellular dysfunction behind Tmprss3-related deafness.