Online Proceedings

POSTER SESSION 4

MGH 241, Easel 144

4:00 PM to 6:00 PM

Protection and Temporal Investigation of Aminoglycoside-Induced Hair Cell Death Using the Zebrafish Lateral Line

Toby Chen, Senior, Speech and Hearing Sci (Com Disorders)
Mentor: Edwin Rubel, Otolaryngology, Head and Neck Surgery
Mentor: David Raible, Biological Structure
Mentor: Patricia Wu

The loss of mechanosensory hair cells in the inner ear gives rise to many hearing and balance-related disorders. The most common causes of acquired hair cell loss are normal aging, ototoxic medications and frequent exposure to unusually loud environments, noise exposure. Two main drug classes, aminoglycoside antibiotics and cisplatin-based chemotherapeutic drugs, are known to be ototoxic, with usage resulting in varying levels of temporary or permanent hearing loss through hair cell death. Our goals are to understand and eventually prevent hearing loss due to treatments with these drugs. Because of the inaccessibility and complexity of the mammalian inner ear, hair cells in the zebrafish lateral line have emerged as an outstanding system for studying hair cell death. The external location of the hair cells allows for direct access and visualization of the hair cells, in order to study the cellular pathways underlying hair cell death, and for large drug library screens to identify compounds that protect against ototoxic effects. As a result of a drug screen and subsequent compound analog analysis, a compound named ORC-13661 has been found to be robustly protective against several aminoglycosides in a dose-dependent manner. We have found that there are distinct mechanisms that underlie antibiotic-induced toxicity, distinguished by different temporal events. Some aminoglycosides, including neomycin, kill hair cells rapidly, within one hour of exposure. Other aminoglycosides, including gentamicin, have a much slower time course, taking up to 24 hours to kill hair cells after an initial one-hour exposure. We find that ORC-13661 provides maximal protection to both classes of aminoglycosides if it is present at the same time as the toxic compound. Additionally, the delayed aminoglycoside exposure paradigm gives us an opportunity to use compounds with known effects on cell death pathways to shed light on new mechanisms underlying hair cell death.