Elucidating the Mechanisms of Drug-Induced Hearing Loss: Characterization of Interferon Gamma Signaling as a Regulator of Hair Cell Regeneration and Inflammation in Zebrafish

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As a common side-effect of aminoglycoside antibiotics and cancer-related medications, drug-induced hearing loss (ototoxicity) can severely deplete inner ear hair cells and cause long-term sensorineural hearing damage as a result, especially considering that there are currently no USFDA-approved drugs specifically designed for this condition. Although signaling pathways like FGF, Jak-Stat, and Notch have been well-characterized in the context of ototoxicity, Interferon Gamma signaling remains largely unexplored, having only been examined through the lens of inner ear antigens and inflammation-mediated cochlear injury. To elucidate the regulatory role of IFN-Gamma, Differential Gene Correlation Analysis revealed that heat shock proteins, activators of microglia, and a host of pro-inflammatory cytokines were differentially co-expressed with Interferon Gamma to a statistically significant degree, suggesting that IFN-Gamma is likely involved in mediating response to stress and environmental stimuli immediately after ototoxin exposure. Additionally, Weighted Gene Co-Expression Network Analysis indicated that Interferon Gamma and its broader co-expression network were significantly correlated to the earlier timepoints post-treatment. Downstream gene ontology analyses demonstrated cell-dependent mechanisms of Interferon Gamma - while its co-expression network for the support cells was strongly correlated with p38-MAPK signaling, ubiquitin-protease activity was heavily enriched for the mantle cells. By providing some of the first insights into the functional groups associated with the regulatory response of Interferon Gamma to ototoxic drug, this study has significant long-term implications for the development of more clinically efficacious otoprotective pharmaceuticals.