**Abstract**

Pathogenic mitochondrial DNA (mtDNA) variants are responsible for diverse pathologies and can result in childhood lethality. To date, no effective therapies have been identified.1 These mtDNA variants are typically heteroplasmic, where both the wild-type and pathogenic variant coexist within the same cell, which makes shifting heteroplasmy a potential therapeutic strategy as heteroplasmy load directly correlates with disease penetrance and severity.2 The T>C variant at m.10191 is associated with Leigh syndrome, a pediatric disorder present in around 1:40,000 individuals. We previously found that this change resulted in an increased potential to form a local guanine quadruplex (G4).3 G4s are non-canonical DNA secondary structures formed by short poly-guanine tracks which can stall polymerase activity.4 Therefore, the G4 structure can be utilized to decrease transcription and replication of the pathogenic C variant, hence increasing the proportion of the wild-type T variant inside the cell and shifting heteroplasmy.

First part of my PhD aimed to identify small molecule compounds with high specificity towards m.10191C which are able to shift heteroplasmy therapeutically. Through a collaboration, I screened over 20,000 small molecule compounds for those with G4 binding propensities based upon interaction with the m.10191C;5 I performed downstream assays to characterize the effect of candidate compounds on patient fibroblasts. The second part of my project aimed to understand the molecular mechanism behind heteroplasmy shift. As our lab has previously identified G4 binding agents (G4BA) capable of shifting heteroplasmy, I wanted to better understand its mechanism to help future drug discovery efforts and to uncover potential synergistic treatment options. Better understanding of small molecule based heteroplasmy shifting may prove worthwhile for not just metabolic disorders, as mitochondrial function has been implicated in mental health disorders as well, notably autism spectrum disorder (ASD).6,7 Some recent research have demonstrated a potential link between mtDNA heteroplasmy and manifestation of ASD,8 the third chapter of my thesis aims to further explore this in the MSSNG patient cohort.

Taken together, my thesis provides a strategy towards mitochondrial heteroplasmy shifting, uncovers the role of fission and autophagy in mitochondrial heteroplasmy, as well as explore the role of heteroplasmy in ASD patients.

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