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"The heart of the matter: Cardiac specific discrepancies between human and mouse models of Friedreich Ataxia"

Friedreich Ataxia (FRDA) is a relentlessly progressive neurodegenerative disease that manifests with multiple symptoms, which may include progressive gait and limb ataxia, loss of vibratory and position sense, progressive motor weakness, diabetes mellitus, and scoliosis. This condition also affects the heart, and hypertrophic cardiomyopathy is the cause of death in approximately 60% of patients. FRDA is a DNA repeat disorder, caused by the somatic expansion of GAA•TTC repeats within the first intron of the frataxin (FXN) gene. This leads to decreased FXN mRNA expression. The length of the repeat tract correlates with the severity of FRDA symptoms and inversely with age of onset. Repeat expansion in FRDA occurs in a tissue specific manner and presents in multiple organ systems, with the greatest expansion bias and longest repeat tracts observed in the heart and pancreas.

The underlying causes of DNA repeat expansion were not well understood until relatively recently, when DNA mismatch repair (MMR) complexes MutSβ and MutLγ were shown to play a critical role. The MutS recognition complex identifies and binds mismatched bases and insertion or deletion loops while the MutL endonuclease makes a cut to excise the lesion. Our lab has shown that MutSβ and MutLγ are required for DNA repeat expansion, and function as part of a central mechanism shared by all DNA repeat expansion disorders.

Our current work focuses on applying this mechanistic knowledge in both human cell and mouse models to test potential therapeutic targets, as there is currently no treatment for FRDA or any other DNA repeat disorder. However, our lab has found that in contrast to extensive somatic expansion in heart tissue of FRDA patients, there is no repeat expansion in the heart of FRDA mouse models. Other tissues studied (cortex, cerebellum, liver, kidney, and gastrocnemius) all exhibit expansion. We predict that this lack of expansion in the mouse heart reflects a difference in some component of MMR between human and mouse hearts. Here, I used Western blotting to detect the presence of proteins critical to the MMR pathway either as part of MutS recognition complexes (MSH2, MSH3, MSH6), or MutL endonucleases (MLH1, PMS1, PMS2), in mouse cortex, cerebellum, and heart tissues, as well as in human and mouse cell lines. This work is ongoing and will inform our understanding of the capabilities and limitations of the mouse model in addressing the cardiac symptoms and developing therapies for Friedreich Ataxia.