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Abstract Title: Platelet and myeloid cell phenotypes in a rat model of Fabry Disease

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Lysosomal storage diseases (LSDs) are a class of approximately 70 genetic disorders and are among the most common genetic disorders in newborns. Frequently caused by mutations in lysosomal enzymes, LSDs are typically progressive, impact multiple organ systems and significantly decrease quality of life and lifespan. Of LSDs, Fabry disease is most common and is caused by mutations in the X-linked gene GLA which encodes for the acid hydrolase α-galactosidase A (α-GalA). Patients with Fabry disease typically experience pain crises early in life and develop GI disorders and kidney dysfunction during adolescence. As adults, Fabry patients experience progression of renal insufficiency and often suffer serious cardiovascular or cerebrovascular events responsible, in part, for the significant decrease in lifespan observed for Fabry patients. Currently, the mechanism underlying the increased risk of stroke and myocardial infarction in patients with Fabry disease is incompletely understood.

As many lysosomal enzymes are responsible for the degradation of selective substrates in lysosomes, LSDs are often characterized by the accumulation of these enzyme substrates, leading to their designation as storage diseases. In Fabry disease, patients accumulate glycosphingolipids, specifically the α-GalA substrates globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3). Recently, we have developed a rat model of Fabry disease that closely recapitulates human disease phenotypes including the pain, renal and cardiac symptoms observed in patients. Utilizing our rat model of Fabry disease, we are investigating how the accumulation of the α-GalA substrates Gb3 and lyso-Gb3 contribute to the underlying mechanism of cardiovascular disease that occurs in patients. Here, using our rat model of Fabry disease, we observed an increase in platelets, neutrophils and monocytes (1.4-, 2.5-, and 2.6-fold, respectively). Additionally, platelets from α-GalA deficient animals had an increased responsiveness to the agonist ADP that significantly increased platelet aggregation (17.5%). Studies are ongoing to further examine platelet and myeloid cell abundance, activity, and localization utilizing the rat model of Fabry disease. Using our model, we will define how the accumulation of the α-GalA substrates Gb3 and lyso-Gb3 contribute to cardiovascular pathology, improving our understanding and treatment strategies for the cardiovascular disease present in patients with Fabry disease.

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