**Neuraminidase degrades the glycocalyx and impairs vascular function in type 2 diabetes**

Endothelial dysfunction is a hallmark of type 2 diabetes (T2D) that is implicated in the progression of cardiovascular disease. However, the mechanisms responsible for the development of endothelial dysfunction in T2D remain unclear. We hypothesized that elevated plasma neuraminidase activity in T2D is implicated in endothelial glycocalyx degradation and the development of endothelial dysfunction. The glycocalyx is a carbohydrate-rich layer lining all cells, including the endothelium, and neuraminidase is an enzyme that removes sialic acid from glycoproteins such as those comprising the glycocalyx. We further hypothesized that inhibition of neuraminidase activity protects the glycocalyx from degradation and improves endothelial function in diabetic mice.

We collected plasma from T2D and non-T2D human subjects (n=8) and found that T2D subjects had greater ($P$<0.05) plasma neuraminidase activity than non-T2D. We also isolated mesenteric arteries from male mice and exposed them intraluminally to vehicle (n=6) or neuraminidase for 1 hour (n=5) and then to increasing rates of shear in order to induce flow-mediated dilation (FMD). Neuraminidase significantly ($P$<0.05) reduced FMD compared to vehicle. To assess the effect of neuraminidase on the glycocalyx, cultured human umbilical vein and aortic endothelial cells were exposed to vehicle, neuraminidase, or neuraminidase plus zanamivir, a neuraminidase inhibitor. We found that neuraminidase caused shedding of glycocalyx structures, while zanamivir prevented it. In diabetic mice (db/db), we found that, compared to control, zanamivir reduced endothelial stiffness in aortic explants, and improved FMD as well as acetylcholine- and insulin-induced vasodilation in isolated mesenteric arteries.

These results indicate that neuraminidase induces the breakdown of the glycocalyx and promotes endothelial dysfunction. They further show that neuraminidase inhibition improves endothelial function in a diabetic mouse model and suggest it and could be used to ameliorate cardiovascular disease in the setting of T2D. Additional confidential experiments interrogated the stimuli responsible for increasing endothelial neuraminidase activity.