**György Kúnos: The role of the peripheral endocannabinoid system in type-2 diabetes and its complications**

Overactivity of the endocannabinoid/CB1 receptor system plays a prominent role in the pathogenesis of metabolic obesity and its complications, including fatty liver, type-2 diabetes (T2DM) and dyslipidemias. The natural history of T2DM is recapitulated in the Zucker diabetic fatty (ZDF) rat, which progresses from initial compensated insulin resistance to beta-cell failure and overt diabetes. Results to be presented demonstrate that beta-cell failure in ZDF rats is due to CB1R signaling in proinflammatory M1 macrophages infiltrating pancreatic islets, which leads to activation of the Nlrp3 inflammasome and consequent release of cytotoxic interleukin-1B and IL-18 that cause apoptosis of neighboring beta cells. ZDF rats also suffer from severe diabetic nephropathy which, unlike beta-cell failure, is not associated with macrophage infiltration. Instead, it can be attributed to increased CB1R signaling in glomerular podocytes, a cell type responsible for maintaining adequate glomerular structure and function. CB1R signaling in podocytes can be triggered both by the hyperglycemia or the overactive renin/angiotensin system present in ZDF rats, leading to the dysfunction and ultimate loss of podocytes. Chronic treatment of ZDF rats with a novel, non-brain-penetrant CB1R antagonist delayed the development and attenuated the hyperglycemia as well as the associated nephropathy by protecting pancreatic beta cells and glomerular podocytes, respectively. Thus, peripheral CB1R blockade has promise in the treatment of T2DM and its complications.

Relevant reading material: Jourdan et al., *Nature Medicine* 19:1132-40, 2013; Jourdan et al., *PNAS* 111:E5420-8, 2014.