Department of Molecular and Cellular Biology

Graduate Seminar MCB*7500

Friday, March 16, 2018 in SSC 1511 @ 12:45 p.m.

presented by:

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(Advisor: N. Jones)

"Reduced Nephrin Phosphorylation in the Development of Diabetes and Diabetic Nephropathy"

The multi-functional membrane protein, nephrin, is a potential factor in diabetes pathogenesis. Nephrin signaling is partly controlled by three tyrosines in nephrin's cytoplasmic region (Y1176, Y1193, and Y1217). These residues can be phosphorylated to stimulate cell processes like actin remodeling, nephrin endocytosis, and cell survival. Nephrin expression is localized to specialized cell types, including podocytes and pancreatic β cells. In the kidney, decreased phosphorylation of Y1176/1193/1217 is observed in various pathologies like diabetic nephropathy (DN). Whether decreased phosphorylation contributes to, or is a consequence from DN, remains unclear. In the pancreas, nephrin's role in β cells is largely unexplored. Nephrin likely aids in glucose-stimulated insulin secretion, and further research is required to determine the influence of reduced nephrin phosphorylation in β cells. Taken together, it is hypothesized that the absence of nephrin phosphorylation at Y1176/1193/1217 affects 1) DN pathogenesis, and 2) insulin secretion. This project will study Y3F nephrin knockin mice, which have phenylalanine substituted at Y1176/1193/1217 to prevent their phosphorylation. Diabetes will be induced in wild-type and Y3F mice by streptozotocin-injection. Kidneys will be collected to detect differences in podocyte structure and/or physiology (e.g. nephrin endocytosis) by qPCR, western blotting, periodic acid-Schiff staining, immunofluorescence, and electron microscopy. As a separate objective, pancreatic phenotypes of Y3F mice will be examined. For this, Y3F mice will undergo glucose tolerance tests, and primary β cells will be isolated for RNASeq and physiological/structural analyses. Overall, this study aims to provide novel insight into nephrin signaling to help elucidate the complexities of diabetes pathophysiology.