Wednesday, March 23, 2022
4:00 P.M.

Ackert Hall, Room 120

Biochemistry & Molecular Biophysics **Seminar**

Control of Insulin Sensitivity by the Tribbles Pseudokinase: Lessons from Drosophila

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In vertebrates and Drosophila, The Tribbles (Trib) family of pseudokinases bind Akt kinase to increase insulin insensitivity in peripheral tissues. Tribbles pseudokinases share an overall structure in common with catalytically active kinases, with an activation loop in the cleft domain that undergoes a conformational change upon substrate binding, switching from an "out" configuration to an "in" conformation that activates the protein. In the mouse model, Trib levels increase following over-feeding, starvation and exercise; in humans, increased Trb3 levels and activity has been associated with diabetes and cardiovascular disease. Drosophila metabolic models of insulin resistance have focused on the role of Trbl in the larval fat bodies, insulin-sensitive storage tissues analogous to the liver and adipose tissues of mammals, where Trbl binds Akt kinase to block Akt-mediated insulin responses. We will present recent data showing that in response to fasting, Trbl trafficks to the fat body cell membrane to block Akt activation and the role of the activation loop of the Trbl pseudokinase domain in regulating membrane association. In light of the regulated trafficking of the insulin receptor to the fat body cell membrane in response to cellular stress cues, our data suggest that changes in the subcellular distribution of key components of the insulin signaling pathway in response to environmental influences effectively modulates insulin sensitivity in the fat body.