INVESTIGATING SPATIO-TEMPORAL DYNAMICS OF GLUT4 DISPERSAL IN CARDIOMYOCYTES

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Individuals with Type 2 diabetes mellitus (T2DM) are at significantly increased risk of cardiovascular disease and the development of diabetic cardiomyopathy [1]. One of the major hallmarks of T2DM is a significant decrease in myocardial glucose uptake. Glucose transport in fat, skeletal and cardiac muscle is mediated by the glucose transporter GLUT4 that is mobilized to the cell surface from intracellular stores in response to insulin. Recently, total internal reflection microscopy was used to reveal that insulin not only regulates GLUT4 translocation to the plasma membrane (PM) but also its distribution within the PM [2].

The emergence of super resolution microscopy techniques has allowed cell biologists to examine characteristics of molecules such as GLUT4 organization in the PM at the single-molecule level beyond the diffraction limit of conventional light microscopy [3]. Stochastic reconstruction microscopy (STORM) investigated GLUT4 dispersal in basal and insulin-stimulated adipocytes and suggested that dispersal of GLUT4 within the plasma membrane was a key action of insulin. In my project, I have applied STORM with state of the art nanobody technology to investigate spatio-temporal dynamics of GLUT4 dispersal and significantly reduce fluorescent label linkage error using cardiomyocytes as a model system. Super resolution images showed that GLUT4 clusters are present in the basal state and retained at the plasma membrane fusion site; by contrast insulin stimulated a different kind of exocytosis that dispersed GLUT4 to the PM consistent with the findings of previous studies [2, 4]. GLUT4 trafficking is more complex in muscle tissues and therefore our ongoing work is focused on elucidating GLUT4 dispersal in cardiomyocytes. In particular key research questions include does exercise regulate GLUT4 dispersal, how specific is the dispersal process and it is impaired in conditions of insulin resistance.

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