Characterization of Insulin-degrading Enzyme: Using Molecular Visualization Systems to Understand Substrate Recognition in Type 2 Diabetes and Alzheimer’s

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Amyloid-beta (Aß) and insulin, two substrates of insulin-degrading enzyme (IDE), are critically important in the pathogenesis of Alzheimer's disease (AD) and type 2 diabetes (T2D), respectively. IDE is a major Aß-degrading enzyme, linked with slowed AD progression. Conversely, inhibiting IDE results in retention of insulin, thus reducing T2D symptoms. IDE was identified as a cytosolic enzyme despite substrate degradation occurring in the endosome, raising the question of how the enzyme gains substrate access. Recent studies established the role of phosphatidylinositol phosphates (PtdInsPs) which localize IDE to endosomes through the polyanion-binding site. However, the polyanion-binding site partially overlaps the substrate-binding site, raising concerns that disabling IDE’s localization mechanism could disrupt substrate degradation. The purpose of this project is to produce a mutant version of IDE that does not bind to PtdInsPs to localize to endosomal compartments while retaining full enzyme activity. IDE localization could be disrupted to reduce insulin catabolism without affecting cytosolic IDE, thus slowing the progression of T2D. This innovative project utilized molecular visualization systems and online servers to characterize interactions between IDE and substrate peptides using structures deposited in the Protein Data Bank. Structural analysis revealed that a majority of residues mediating substrate binding are not found in the polyanion binding site. Future studies are aimed at better understanding interactions between PtdInsPs headgroups and IDE to define residues to mutate. These studies provide the molecular basis for substrate recognition and offer insight into designing novel IDE-based therapies to control amyloid-beta and blood sugar concentrations.

Awards Won:

The Potamkin Prize for Students: First Award