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Inhibition of amylin aggregation and cytotoxicity to β-cells by acids

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Statement of the Problem: Protein aggregation is associated with more than 20 degenerative diseases. Fibrillar aggregates of Aβ, α-synuclein, and amylin are pathological features in Alzheimer's disease, Parkinson's disease, and type II diabetes respectively. Aggregation of amylin causes cytotoxicity to pancreatic β-cells. The purpose of this study is to investigate the effect of different types of acids on the aggregation of amylin and cytotoxicity of aggregates to β-cells.

Methodology & Theoretical Orientation: Amylin-(1-37) was purchased from Sigma-Aldrich. Amylin (15 μM) with or without different types of acids were incubated at 37oC and the amylin fibrils were measured by the thioflavin T (ThT) binding assay at indicated time points. For cytotoxicity test, RIN-m5f, pancreatic β-cells, was incubated in a amylin (15 μM) with or without different types of acids. After 24 h, Thiazolyl blue tetrazolium bromide (MTT) was added to cells and the absorbance of live cells was measured at 570 nm.

Findings: Six acidic small molecules were screened in terms of their ability to inhibit amylin aggregation using ThT assay. Among six acids, two acids, lipoic acid and ascorbic acid, showed highest attenuation in ThT fluorescence intensity of 57.9±17.2% and 57.1±12.8%, compared to amylin (15μM) only. To further assess the cytotoxicity of amylin aggregates with or without two acids, MTT assay was performed using pancreatic RIN-m5f β-cells. Pre-formed fibrillar amylin only caused the cytotoxicity of 67% as compared to freshly prepared monomeric amylin. The addition of two acids to amylin decreased the cytotoxicity to 44% and 49% respectively. Molecular modeling demonstrated that lipoic acid and ascorbic acid interact with amylin via hydrophobic interactions.

Conclusion & Significance: Lipoic acid and ascorbic acid can bind to amylin via hydrophobic interaction, which inhibits or slows down the aggregation of amylin and the toxicity of amylin aggregates to RIN-m5f, pancreatic β-cells.

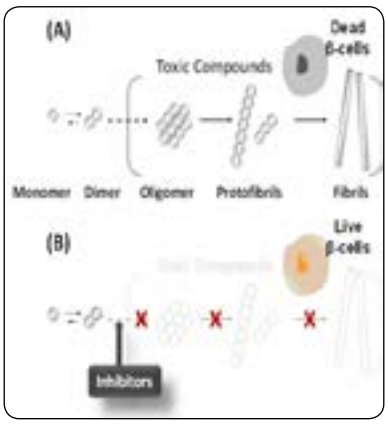

Figure 1: Prevention of amylin aggregation and cytotoxicity. (A) Amylin becomes toxic when it is aggregated, which results in cytotoxicity to β-cells. (B) The addition of inhibitors to amylin can prevent the aggregation of amylin into toxic oligomeric and fibrillar amylin, which protect β-cells from toxic compounds.

Recent Publications

1. Lee S, Al Kaabi L, Mawart A, Khandoker A, Alsafar H, Jelinek H F, *et al.* (2018) Ultrasound-mediated drug delivery by gas bubbles generated from a chemical reaction. J Drug Target 26:172-181.
2. Lee S, Kim Y C and Park J H (2016) Zein-alginate based oral drug delivery systems: Protection and release of therapeutic proteins. Int J Pharm 515:300-306.
3. Lee S (2014) Monocytes: A novel drug delivery system targeting atherosclerosis. J Drug Target 22:138-145.

4. Lee S, Eskin S G, Shah A K, Schildmeyer L A and McIntire L V (2012) Effect of zinc and nitric oxide on monocyte adhesion to endothelial cells under shear stress. Ann Biomed Eng 40:697-706.
5. Lee S, Carson K, Rice Ficht A and Good T (2005) Hsp20, a novel alpha-crystallin, prevents Abeta fibril formation and toxicity. Protein Sci 14:593-601.

Biography

Sungmun Lee is currently working as an Assistant Professor in Khalifa University. He completed his Ph.D. in Texas A&M University, USA. His main research interest is in Development of Novel Drug Delivery System, Cardiovascular Diseases, Diabetes, Alzheimer's disease and Inflammatory Diseases. He has focused on the development of novel drugs and drug delivery systems for treating inflammatory diseases such as diabetes, Alzheimer's disease, and cardiovascular diseases.

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