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Pancreatic Amylin Turnover, Misfolding and Toxicity: Molecular Mechanisms

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Introduction

All polypeptides have the intrinsic trait of amyloidogenesis, in which soluble proteins aggregate into insoluble, structurally stable, unbranched fibres. These exhibit dye binding selectivity, organised -sheet rich structure, and resistance to proteinase K digestion. Amyloids can be roughly divided into beneficial and harmful types. Curli, Chaplin, URE2p, and PmeL17 are examples of functional amyloids that are an essential component of the regular physiology of the cell. Curli, a component of E. coli, participates in the development of biofilms and facilitates infection. Chaplin, which is present in Streptomyces, aids in preventing the effects of water surface tension [1]. The S. Cerevisiae gene URE2p participates in the catabolism of nitrogen. Pmel17, a human protein, is involved in the production of melanin. On the other hand, a variety of harmful amyloids have been identified through clinical and molecular researches that lead to protein misfolding in amyloid-driven illnesses. These include huntingtin, which has been linked to Huntington's disease, -synuclein, which has been linked to Parkinson's disease, prion protein, which has been linked to Creutzfeld-disease, Jacob's superoxide dismutase, which has been linked to Amyotrophic Lateral Sclerosis, amyloid-(A) peptide, which has been linked to Alzheimer's disease, transthyretin, which has been linked Apolipoproteins connected to systemic amyloidosis and atherosclerosis, serum amyloid A linked to inflammation-linked amyloidosis, and human pancreatic islet amyloid polypeptide (hIAPP), also known as amylin, which is a main ingredient and the cause of islet amyloidosis, are other significant instances. In addition, pancreatic beta-cells also synthesise and secrete hIAPP, a tiny 37 aa-long peptide hormone. To control blood glucose levels and other critical cellular processes, insulin and hIAPP work in concert [2].

Description

The inability of pancreatic -cells to release enough insulin, a reduction in the sensitivity of peripheral tissues to insulin, and the amyloid deposition from hIAPP are the three elements that determine the development of T2DM. Understanding the cytotoxic mechanism of human amylin oligomers and aggregates generated intracellularly, extracellularly, or both has advanced significantly over the past 20 years. The idea that islet amyloidosis and -cell apoptosis are two important factors in islet dysfunction is supported by studies done on primates [3]. However, little is known about the cellular mechanisms controlling amylin turnover and hIAPP-evoked apoptosis in human islets. As a result, there are no effective treatments available to stop the aggregation and toxicity of hIAPP in humans. hIAPP poisoning is a significant medical problem. In varying amounts, toxic amylin oligomers and aggregates are present in more than 90% of type-2 diabetes patients, where they contribute to the loss of -cell mass. The molecular mechanisms that regulate hIAPP biosynthesis, recycling, and interactions in healthy and stressed pancreatic -cells have received less research compared to the extensive body of studies on the mechanisms of hIAPP aggregation and toxicity in the pancreas. The avoidance of hIAPP intracellular accumulation, aggregation, and detoxification in -cells may depend on the dynamics and processes of hIAPP intracellular synthesis, secretion, and destruction (together referred to here as turnover) [3-5]. It may be possible to treat T2DM in innovative ways if we have a better understanding of the hIAPP turnover mechanisms and how they relate to islet amyloidosis.

Conclusion

Novel mechanistic insights into the structure, function, and toxicity of amyloid proteins, such hIAPP, have been revealed through molecular and cellular investigations conducted over the past two decades. Studies have shown that metals, membrane-associated lipids, and cholesterol are key biological components that potently control the aggregation and cytotoxicity of hIAPP. This, in turn, may alter other cellular and system functions, such as glucose homeostasis. In addition to revealing the crucial roles played by metal-amyloid and lipid-amyloid complexes in the aetiology of amyloid diseases, new emerging evidence suggests that hIAPP and other amyloid proteins act synergistically, interact, and cross-seed at various sites throughout the human body, most notably the pancreas and the brain. The design of novel small-molecule drugs that will efficiently and selectively stimulate the cellular processes and pathways involved in hIAPP clearance and detoxification in pancreatic and other tissues has a new frontier thanks to recent technological advancements in computational biology, structural biology, and synthetic chemistry. The use of amyloid inhibitors created to specifically target and destroy cytotoxic amyloid aggregates can be combined with this gain-of-function strategy or used alone.

Conflicts of Interest

The authors declare no conflict of interest.

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