IAPP Oligomers as a Target for Type 2 Diabetes Novel Immunotherapy (Ramot)

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Technology

Stabilized human IAPP (hIAPP) oligomers were used for the development of active immunization of type 2 diabetes. This promising novel approach for the treatment of type 2 diabetes is doable due to the establishment of a new protocol for the formation of stable islet amyloid polypeptide (IAPP) amyloidal soluble oligomers in vitro, leading to isolation of specific anti-oligomers antibodies.

The need

The transition of soluble peptides and proteins into highly-ordered amyloid structures is associated with major human disorders including Alzheimer's disease (AD), Parkinson's disease (PD), Prion disorders and Type II Diabetes (T2D). While amyloid fibrils were previously considered as the main pathological elements that facilitate tissue degeneration observed in amyloid-related disorders, there is an increased body of evidence which suggest a key role for early soluble oligomeric assemblies in the process of cytotoxicity and cell death. Gazit group was extensively involved in the paradigm shift in several systems.

Islet amyloid polypeptide, IAPP, Amylin, is a 37 amino acid peptide which is co-stored with insulin in beta-cell secretory granules. The release of IAPP from the beta-cell occurs in response to nutrient stimuli. Islet amyloid is a pathological hallmark of the pancreatic islet present in a substantial proportion of individuals from all ethnic groups with type 2 diabetes.

An amyloidogenic form of IAPP is required for the cytotoxic effect to occur, with human IAPP, but not the non amyloidogenic rat IAPP, resulting in increased cell death when incubated with isolated islets or islet cells.

These results point to the possibility of developing a novel drug to treat pancreatic degeneration in Type II Diabetes, based on this first demonstration of role of the characterized and isolated oligomers in IAPP toxicity and identification of the minimal recognition module.

Potential Application

Utilizing the protocol of hIAPP oligomers will enable screening for potential inhibitors of hIAPP assembly.

hIAPP oligomers can serve to:

1. Develop active immunization against type 2 diabetes.

2. Isolate specific hIAPP oligomers antibodies and use them for passive immunization

Stage of development

A protocol for the isolation of stable IAPP cytotoxic oligomers was described for the first time. These oligomers induce apoptosis in cultured pancreatic cells, permeate model lipid vesicles and interact with the cell membrane following complete internalization. Characterization of IAPP oligomers include toxicity, structure, stability and environmental influence.

Antibodies that specifically recognize these assemblies were exclusively identified in diabetes patients and were able to neutralize the apoptotic cytotoxic effect of these oligomers. Our findings shows that human IAPP oligomers are not only stable and highly toxic to cultured cells, they are also

found in Type II diabetes patients and probably play a major role in the disease progression.

Nowadays we are exploring the possibility of using stable hIAPP oligomers as active immunization agents for the treatment of type 2 diabetes. Preliminary results in type 2 diabetes mice model show significant improvement (reduction in blood glucose concentration) in the treated group compared to the placebo group. The newly identified structural epitope provides new mechanistic insights also for future therapy.

Patent

PCT patent application (PCT/IL2011/000436)

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