Recent advances in the understanding and management of islet amyloid β-cell toxicity in type 2 diabetes and islet transplantation

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Statement of the Problem: Islet amyloid forms by aggregation of the β-cell hormone human islet amyloid polypeptide (hIAPP). Amyloid formation is a pathologic characteristic of the pancreas in type 2 diabetes (T2D) but also forms in transplanted human islets. Islet amyloid is toxic to β-cells and contributes to progressive β-cell loss in both T2D and islet grafts. The current challenge in developing effective therapies to protect islets from amyloid toxicity is our limited knowledge of the mechanisms of amyloid-induced β-cell death in vivo.

Methodology: We performed detailed mechanistic studies by using human islets from cadaveric donors and by generation of different transgenic mouse models, to investigate the apoptotic pathways that contribute to β-cell death caused by formation of hIAPP aggregates in islets and to develop new strategies to protect islets from amyloid toxicity.

Findings: Based on our studies, we propose a new model that links amyloid formation and islet inflammation in T2D and islet grafts. Our studies show that amyloid formation in human islets promotes interleukin (IL)-1β production which leads to β-cell upregulation of the Fas cell death receptor and activation of the Fas-mediated apoptotic pathway initiated by caspase-8. We further demonstrate that amyloid formation disrupts the balance between IL-1β and natural IL-1 receptor antagonist (IL-1Ra). Moreover, impaired processing of prohIAPP associated with β-cell dysfunction potentiates amyloid formation and aggravates IL-1β production. Finally, we provide evidence to suggest that glucagon-like peptide (GLP)-1 agonists and IL-1R antagonists can effectively protect human islets from amyloid toxicity and introduce new strategies that focus on targeting amyloid apoptotic signaling pathway.

Conclusion & Significance: In summary, amyloid formation is closely linked to islet inflammation and plays a significant role in progressive loss of β-cells in T2D and islet grafts. GLP-1 agonists and IL-1R antagonists may efficiently protect human islets from amyloid toxicity in early stages of T2D and clinical islet transplantation.

Biography

Lucy Marzban is an Associate Professor in the Faculty of Medicine, University of British Columbia, Canada. She is a diabetes investigator with expertise in the areas of islet biology, pathology and pharmacology. Her research program focuses on identifying the mechanisms underlying islet β-cell death in diabetes. In past ten years, her team has intensively investigated the mechanisms by which formation of toxic protein aggregates named islet amyloid causes β-cell death in patients with type 2 diabetes and transplanted human islets in patients with type 1 diabetes. Her studies have led to development of a very interesting model and new strategies to prevent progressive β-cell loss in pathologic conditions associated with islet amyloid formation.

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