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Type 2 Diabetes as a Protein Aggregation Disease: Islet Amyloid Polypeptide, Cellular Stress Pathways, and Therapeutic Targets

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Abstract. Protein aggregation has emerged as a critical pathogenic mechanism underlying β-cell dysfunction in type 2 diabetes mellitus (T2D). Among aggregation-prone proteins, islet amyloid polypeptide plays a central role, forming toxic oligomers and amyloid fibrils that disrupt cellular homeostasis. Increasing evidence indicates that protein aggregation triggers multiple interconnected stress pathways in pancreatic β-cells. Notably, endoplasmic reticulum stress is activated through the unfolded protein response, while mitochondrial dysfunction contributes to impaired energy metabolism and enhanced oxidative stress. In parallel, the accumulation of protein aggregates overwhelms cellular proteostasis systems, including the ubiquitin–proteasome system and the autophagy–lysosome pathway, leading to defective clearance of misfolded proteins. Furthermore, aggregated proteins can stimulate innate immune responses, particularly through activation of the NOD-like receptor family pyrin domain containing 3 inflammasome, thereby promoting chronic inflammation and β-cell injury. These pathological processes collectively drive progressive β-cell loss and deterioration of insulin secretion. Importantly, recognition of protein aggregation as a key contributor to T2D pathogenesis has opened new avenues for therapeutic intervention. Strategies targeting aggregation inhibition, enhancement of protein clearance pathways, and alleviation of cellular stress responses hold promise for preserving β-cell function. This review summarizes current advances in understanding the molecular mechanisms linking protein aggregation to β-cell dysfunction and highlights emerging therapeutic opportunities aimed at restoring proteostasis in T2D.

Keywords: Islet Amyloid Polypeptide, Protein Aggregation, β-cell Dysfunction, Endoplasmic Reticulum Stress, Proteostasis.

1. Introduction

Type 2 diabetes mellitus (T2D) ranks among the most widespread metabolic disorders globally and represents a major public health challenge as its rising incidence and related complications continue to escalate. The disease is traditionally characterized by peripheral insulin resistance combined with progressive pancreatic β-cell dysfunction [1]. Although many current therapies focus on improving

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insulin sensitivity or stimulating insulin secretion, these treatments often prove insufficient in halting the progressive loss of β-cell mass that ultimately leads to disease progression.

Pancreatic β-cells are highly specialized secretory cells responsible for producing large quantities of insulin and other peptide hormones. Because of this intense biosynthetic activity, β-cells rely heavily on efficient protein folding and quality control mechanisms within the endoplasmic reticulum (ER). Under conditions of chronic metabolic stress, such as persistent hyperglycemia and insulin resistance, the protein folding capacity of the ER becomes increasingly challenged. When protein quality control mechanisms fail, misfolded proteins accumulate and form aggregates that disrupt cellular homeostasis.

One of the most striking pathological features of T2D is the accumulation of amyloid deposits within pancreatic islets. These deposits are primarily composed of islet amyloid polypeptide (IAPP), a hormone co-secreted with insulin by β-cells [2]. Historically, amyloid accumulation was considered a secondary consequence of β-cell dysfunction. However, increasing evidence indicates that intermediate oligomeric aggregates formed during IAPP misfolding are highly cytotoxic and may actively contribute to β-cell failure [3].

Protein aggregation is a well-established pathogenic mechanism in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, where misfolded proteins form toxic aggregates that damage cellular structures [4]. Similar processes appear to occur in diabetes. Studies have shown that aggregated IAPP species can disrupt cell membranes, induce calcium dysregulation, activate ER stress responses, and impair mitochondrial function, ultimately leading to β-cell apoptosis.

Despite growing recognition of protein aggregation in diabetes, several key knowledge gaps remain. First, the molecular mechanisms linking metabolic stress to protein misfolding in β-cells are not yet fully understood. Second, while IAPP aggregation has been widely studied, other aggregation-prone proteins and proteostasis pathways may also contribute to disease progression but remain less clearly defined. Finally, the therapeutic potential of targeting protein aggregation pathways in T2D has not been fully explored.

This review synthesizes current evidence supporting the concept that T2D can be viewed as a protein aggregate–associated disease characterized by disrupted proteostasis in pancreatic β-cells. In particular, this article focuses on IAPP, the principal aggregation-prone peptide in pancreatic islets and the major component of amyloid deposits observed in patients with T2D. By integrating findings from experimental studies and clinical observations, this review examines how IAPP misfolding and aggregation initiate a cascade of cellular stress responses, including ER stress, mitochondrial dysfunction, and inflammatory signaling pathways that ultimately contribute to β-cell failure. Furthermore, the article discusses emerging therapeutic strategies aimed at targeting IAPP aggregation and restoring proteostasis in pancreatic β-cells. By highlighting the mechanistic links between IAPP aggregation, cellular stress pathways, and β-cell dysfunction, this review provides a framework for understanding T2D within the broader context of protein aggregation diseases and emphasizes the therapeutic potential of proteostasis-based interventions in metabolic disorders.

2. The common molecular mechanisms of protein aggregation diseases

Protein aggregation arises when proteins fail to properly adopt or maintain their native conformations, leading to the formation of misfolded intermediates that assemble into soluble oligomers and insoluble fibrillar aggregates [3]. Under physiological conditions, cells preserve protein homeostasis through an integrated network of quality control mechanisms, including molecular chaperones, the ubiquitin-proteasome system, and autophagy–lysosome pathways (ALP).

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However, under pathological conditions these proteostasis mechanisms can become overwhelmed or impaired, allowing misfolded proteins to accumulate and aggregate.

Pancreatic β-cells are particularly susceptible to protein aggregation because they function as highly specialized secretory cells that continuously synthesize and secrete large amounts of insulin and other peptide hormones to maintain glucose homeostasis. This high biosynthetic demand places a substantial burden on the ER protein folding machinery. Under conditions of chronic metabolic stress, increased insulin production intensifies this burden and increases the risk of protein misfolding [5,6]. One of the most compelling lines of evidence linking protein aggregation to T2D comes from studies of IAPP. Histopathological analyses of pancreatic tissue from patients with T2D consistently reveal amyloid deposits within pancreatic islets [1,2]. IAPP is a 37–amino acid peptide hormone co-secreted with insulin that possesses a strong intrinsic propensity to form β-sheet–rich amyloid fibrils. Notably, accumulating evidence indicates that soluble oligomeric intermediates generated during the aggregation process represent the primary cytotoxic species responsible for β-cell dysfunction and death [7,8].

Experimental studies have demonstrated that oligomeric intermediates of IAPP can directly disrupt plasma membrane integrity by forming pore-like structures that permeabilize lipid bilayers and permit uncontrolled Ca^{2+} influx into pancreatic β-cells [7,9,10]. Elevated intracellular calcium levels activate multiple stress signaling pathways and impair mitochondrial function, thereby exacerbating β-cell dysfunction. Consistent with these cellular findings, transgenic mouse models expressing human IAPP develop progressive β-cell degeneration, islet amyloid deposition, and diabetes-like phenotypes. These in vivo studies provide strong experimental evidence supporting a causal role for IAPP aggregation in the pathogenesis of T2D [11,12].

Beyond IAPP, protein aggregation in diabetes reflects a broader disruption of cellular proteostasis within pancreatic β-cells. In particular, misfolded proinsulin has been detected in β-cells under conditions of metabolic overload, where defects in protein folding within the ER activate stress signaling pathways and further exacerbate β-cell dysfunction [13,14]. These findings suggest that T2D may involve a more global disturbance of protein homeostasis rather than a pathology driven solely by a single aggregation-prone peptide.

3. Cellular stress pathways triggered by protein aggregates in T2D

Protein aggregation can act as an upstream trigger that activates multiple interconnected stress pathways in pancreatic β-cells. Because β-cells possess a highly developed secretory apparatus and continuously synthesize large amounts of insulin and other peptide hormones, disturbances in protein folding rapidly translate into cellular stress responses. Among these mechanisms, ER stress represents one of the most critical links between metabolic overload and β-cell dysfunction.

Protein folding and post-translational modification of secretory proteins occur primarily within the ER. When misfolded or unfolded proteins accumulate within the ER lumen, cells activate the unfolded protein response (UPR), an adaptive signaling network orchestrated through three primary sensors that monitor ER stress: protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1α (IRE1α), and activating transcription factor 6 (ATF6) [15]. In the early stages, the UPR initially operates to reestablish ER equilibrium through suppressing overall protein synthesis, upregulating molecular chaperones, and promoting the degradation of misfolded proteins. However, persistent or excessive activation of the UPR can shift this adaptive response toward maladaptive signaling that ultimately promotes apoptotic pathways [15].

Experimental evidence strongly supports the involvement of ER stress in aggregation-induced β-cell injury. Studies using transgenic mouse models expressing human IAPP have demonstrated

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progressive β-cell dysfunction accompanied by elevated expression of ER stress indicators such as binding immunoglobulin protein and C/EBP homologous protein [6,11]. Consistent with these in vivo findings, in vitro experiments show that exposure of pancreatic β-cell lines to oligomeric IAPP activates PERK and IRE1 signaling pathways, leading to increased apoptotic signaling and impaired insulin secretion [6,8]. Together, these observations indicate that protein aggregates can directly disrupt ER homeostasis and initiate β-cell death pathways. As illustrated in Figure 1, these interconnected stress pathways highlight how metabolic stress-driven IAPP aggregation serves as a central pathological trigger that integrates ER stress, mitochondrial dysfunction, impaired proteostasis, and inflammatory signaling within pancreatic β-cells.

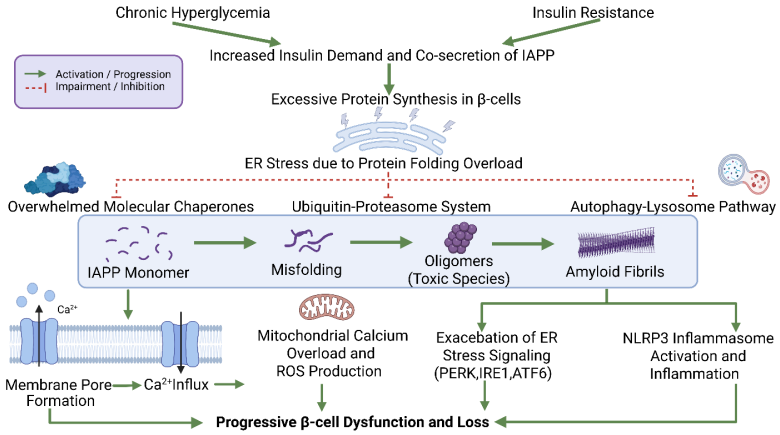


Figure 1. Metabolic stress-driven IAPP aggregation and β-cell dysfunction. Chronic hyperglycemia and insulin resistance increase insulin demand and IAPP co-secretion, leading to ER overload and impaired proteostasis. Misfolded IAPP forms toxic oligomers that disrupt membranes, induce Ca^{2+} influx, trigger ER stress (PERK, IRE1, ATF6), cause mitochondrial dysfunction and ROS production, and activate NLRP3 inflammasome signaling, ultimately resulting in progressive β-cell dysfunction and loss. Created with BioRender.com.

In addition to ER stress, mitochondrial dysfunction plays a central role in mediating the cytotoxic effects of protein aggregates. Oligomeric IAPP can insert into cellular membranes and form pore-like structures that permit uncontrolled calcium influx into β-cells [7]. Elevated intracellular calcium levels subsequently cause mitochondrial calcium overload, impair oxidative phosphorylation, and reduce ATP production. Moreover, mitochondrial dysfunction promotes excessive generation of reactive oxygen species (ROS), which further destabilizes protein folding and promotes additional protein aggregation [4,16]. This self-reinforcing cycle accelerates β-cell damage under conditions of metabolic stress.

Another important consequence of protein aggregates is disruption of cellular proteostasis mechanisms responsible for degrading misfolded proteins [14,17]. Under physiological conditions, the ubiquitin–proteasome system, a targeted proteolytic route wherein substrate proteins undergo ubiquitin conjugation prior to 26S proteasome-mediated degradation, and the ALP, a lysosome-dependent degradation system that mediates the clearance of long-lived proteins, protein aggregates, and damaged organelles via autophagosome formation, cooperate to maintain protein quality control [18-20]. However, chronic metabolic stress can overwhelm these systems. Experimental studies have shown that impaired autophagy in pancreatic β-cells leads to increased accumulation of protein aggregates and exacerbates β-cell dysfunction [21-23]. Reduced clearance of aggregated proteins therefore further amplifies cellular stress and promotes progressive β-cell loss. In addition to

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organelle dysfunction, protein aggregates can also activate inflammatory signaling pathways within pancreatic islets. Aggregated proteins are capable of stimulating innate immune responses, including activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome [23,24]. Activation of this pathway promotes the production of pro-inflammatory cytokines such as interleukin-1β, which further impairs β-cell function and triggers inflammatory cell death pathways including pyroptosis [25]. Chronic inflammation within pancreatic islets therefore represents an additional mechanism linking protein aggregates to progressive β-cell loss.

Taken together, these interconnected stress pathways highlight how protein aggregates act as the central pathological triggers that integrate ER stress, mitochondrial dysfunction, impaired proteostasis, and inflammatory signaling within pancreatic β-cells. The convergence of these processes ultimately drives progressive β-cell dysfunction and cell death in T2D.

4. Beyond IAPP: multiple aggregation-prone proteins in T2D

Although IAPP represents the most extensively studied aggregation-prone protein in T2D, accumulating evidence suggests that β-cell proteotoxic stress involves multiple proteins rather than a single aggregating peptide. This broader view of diabetes pathogenesis reflects the concept that chronic metabolic stress disrupts global protein homeostasis within pancreatic β-cells.

One important contributor to this process is proinsulin misfolding. Insulin biosynthesis begins with the production of proinsulin, which must undergo precise folding and disulfide bond formation within the ER before being processed into mature insulin. Under conditions of excessive insulin demand, such as chronic hyperglycemia, the folding capacity of the ER can become overwhelmed. Consequently, misfolded proinsulin accumulates within the ER and activates the UPR [13,14]. Studies of genetic forms of diabetes caused by mutations in the insulin gene further demonstrate that misfolded proinsulin can directly induce ER stress and β-cell dysfunction [13,26].

In addition to proinsulin, other amyloid-associated proteins may also influence metabolic disease. Transthyretin (TTR), a plasma transport protein known to form amyloid aggregates in systemic amyloidosis, has been implicated in metabolic regulation and may contribute to aggregation dynamics under certain conditions [27,28]. Emerging evidence suggests that TTR can interact with metabolic pathways and may influence β-cell function and insulin secretion, although its precise role in pancreatic β-cells remains incompletely understood. These findings raise the possibility that multiple aggregation-prone proteins may interact to influence β-cell health and proteostasis.

Importantly, several studies have proposed that T2D may represent a broader disorder of protein misfolding that shares mechanistic features with classical amyloid diseases. Mukherjee et al. suggested that T2D shares key pathogenic characteristics with neurodegenerative disorders, including the accumulation of misfolded proteins, formation of toxic oligomeric intermediates, and activation of stress pathways that ultimately lead to cell death [29]. Experimental and mechanistic studies further support these parallels, indicating that aggregation-prone peptides such as IAPP can engage cellular pathways similar to those implicated in neurodegenerative proteinopathies [30]. These observations strengthen the concept that diabetes may be considered within the broader framework of protein aggregation diseases. Understanding the contribution of multiple aggregation-prone proteins may therefore provide a more comprehensive view of β-cell dysfunction and help explain the progressive nature of T2D.

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5. Shared stress pathways between type 1 and type 2 diabetes

Although type 1 diabetes (T1D) and T2D arise from distinct etiological mechanisms, accumulating evidence indicates that both diseases share common intracellular stress pathways within pancreatic β-cells. These overlapping mechanisms highlight the intrinsic vulnerability of β-cells to disturbances in protein homeostasis and cellular stress responses.

In T1D, autoimmune destruction of β-cells is driven by immune-mediated inflammation. Cytokines released by infiltrating immune cells, including interferon-γ and tumor necrosis factor-α, induce ER stress and oxidative stress in β-cells [31,32]. These stress responses impair insulin biosynthesis and promote β-cell apoptosis even before complete immune-mediated destruction occurs.

Similarly, metabolic stress in T2D activates many of the same intracellular stress pathways. Chronic hyperglycemia and lipotoxicity induce ER stress, oxidative stress, and mitochondrial dysfunction, ultimately compromising β-cell survival [33]. Although the initiating triggers differ between the two diseases, both converge on common stress responses that impair β-cell function.

Recognition of these shared mechanisms suggests that therapeutic strategies targeting cellular stress responses may have benefits across multiple forms of diabetes. In particular, interventions aimed at restoring ER homeostasis or enhancing protein folding capacity may help protect β-cells from both metabolic and inflammatory insults.

6. Therapeutic targeting of protein aggregation and proteostasis

Recognition of protein aggregation as a pathogenic mechanism in T2D has opened new avenues for therapeutic intervention beyond conventional glucose-lowering strategies. Targeting aggregation and proteostasis pathways may provide disease-modifying approaches capable of preserving pancreatic β-cell function.

One promising strategy involves directly inhibiting IAPP aggregation. Several studies have identified peptide inhibitors and small molecules capable of preventing oligomer formation or stabilizing non-toxic conformations of IAPP [34,35]. These molecules reduce membrane disruption and improve β-cell survival in experimental models. Such aggregation inhibitors therefore represent a promising class of therapeutics aimed at addressing the upstream cause of β-cell toxicity.

Another therapeutic strategy focuses on restoring ER homeostasis. Pharmacological chaperones and ER stress modulators have been shown to reduce misfolded protein accumulation and improve β-cell survival in experimental models [36]. By enhancing the capacity of the ER protein folding machinery, these compounds may help alleviate proteotoxic stress associated with chronic metabolic overload.

Enhancing protein clearance pathways represents an additional therapeutic approach. Activation of autophagy can promote degradation of aggregated proteins and restore cellular proteostasis in β-cells. Experimental studies demonstrate that pharmacological activation of autophagy improves β-cell survival under conditions of metabolic stress [23,37].

Targeting downstream consequences of protein aggregation may also provide therapeutic benefits. Antioxidants that reduce mitochondrial ROS production may help interrupt the cycle linking oxidative stress and protein misfolding. Similarly, anti-inflammatory therapies targeting inflammasome signaling may reduce protein aggregate-associated β-cell injury [24]. Together, these emerging therapeutic strategies highlight the potential of targeting protein aggregation and proteostasis pathways as disease-modifying approaches for T2D.

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7. Conclusion and future perspectives

The aggregation of proteins represents a significant pathogenic contributor to β-cell impairment in T2D. Accumulating evidence indicates that IAPP and other protein aggregates trigger ER stress, mitochondrial dysfunction, inflammatory signaling, and progressive β-cell loss.

Rather than representing a single pathological event, protein aggregates appear to initiate a cascade of interconnected cellular stress responses that ultimately compromise β-cell survival. Understanding these mechanisms may therefore provide critical insights into the progressive nature of T2D.

Subsequent investigations ought to prioritize the discovery of early-stage biomarkers indicative of protein aggregation in diabetes, clarifying the roles of multiple aggregation-prone proteins, and developing therapeutic strategies capable of restoring cellular proteostasis. A deeper understanding of protein aggregate-driven β-cell dysfunction may ultimately enable the development of targeted therapies aimed at preserving β-cell function and altering the long-term course of T2D.

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