Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Targeting protein misfolding to protect pancreatic beta-cells in type 2 diabetes

Safia Costes

The islet in type 2 diabetes is characterized by beta-cell dysfunction and deficit, increased beta-cell apoptosis and amyloid deposits that derived from islet amyloid polypeptide (IAPP). In species such as humans that are vulnerable to developing type 2 diabetes, IAPP has the propensity to form toxic oligomers that contribute to beta-cell dysfunction and apoptosis, defining type 2 diabetes as a protein misfolding disorder. In this report, we review mechanisms known to contribute to protein misfolding and formation of toxic oligomers, and the deleterious consequences of these oligomers on beta-cell function and survival. Finally, we will consider approaches to prevent protein misfolding and formation of toxic oligomers as potential novel therapeutic targets for type 2 diabetes and other protein misfolding diseases.

Address
IGF, CNRS, INSERM, University of Montpellier, Montpellier, France

Corresponding author: Costes, Safia (safia.costes@igf.cnrs.fr)

Current Opinion in Pharmacology 2018, **43**:104–110

This review comes from a themed issue on **Endocrine & metabolic diseases**

Edited by **James Bowe** and **Shanta Persaud**

https://doi.org/10.1016/j.coph.2018.08.016

Introduction: type 2 diabetes as a protein misfolding disease

The islet in type 2 diabetes (T2D) is characterized by beta-cell deficit and dysfunction, increased beta-cell apoptosis and amyloid deposits composed of islet amyloid polypeptide (IAPP), a protein co-expressed and secreted with insulin by pancreatic beta-cells. IAPP and other amyloidogenic proteins have the propensity to misfold and form membrane-permeant toxic oligomers [1]. Protein misfolding diseases are typically manifest in ordinarily long-lived cells such as neurons and pancreatic beta-cells, initially leading to cellular dysfunction and eventually cell loss. Examples of protein misfolding disorders include Alzheimer's disease, Motor neuron disease, Parkinson's disease and T2D. In this review, we will mainly discuss the mechanisms involved in misfolding, aggregation and toxicity of IAPP. IAPP is one of the most aggregate-prone protein of all amyloidogenic proteins, and while its aggregation properties have been extensively investigated *in vitro* by structural biologists, the potential inhibition of IAPP aggregation as a therapeutic target has largely been neglected by the diabetes field. Therefore strategies that inhibit formation and alleviate toxicity of oligomers of misfolded amyloidogenic proteins represent a promising avenue for novel therapeutic targets in T2D.

The two principal client proteins of the ER secretory pathway in pancreatic beta-cells are insulin and IAPP. The burden of protein synthesis, folding and processing of these client proteins is increased with insulin resistance and/or a decreased beta-cell number. The former is a known risk factor for T2D and, given the increased risk of low birth weight with subsequent T2D, it is likely that an innate low beta-cell mass is also a risk factor for T2D [2]. Experimentally, beta-cell dysfunction and death may be induced by increasing the expression of IAPP per beta-cell either by manipulating the gene dosage or insulin sensitivity [3,4]. These experimental models reveal that even in healthy beta-cells, if a critical threshold of expression rate of an aggregate-prone protein is exceeded, toxic oligomers may form and further compromise the capacity of the cell to eliminate misfolded proteins by the degradative pathways introducing a negative cycle. It is therefore logical that formation of toxic protein oligomers in beta-cells can be avoided indirectly by enhancing insulin sensitivity, or directly, by strategies that suppress misfolding and formation of toxic protein oligomers. The deleterious actions of protein misfolding and toxic oligomers might also be selectively suppressed as a third therapeutic approach.

Islet misfolding-prone proteins

Islet amyloid polypeptide

IAPP is a 37–amino acid peptide that is coexpressed and cosecreted with insulin by pancreatic beta-cells. Because of an amyloid-prone sequence (aa 20–29), IAPP has the propensity to form amyloid fibrils in species at risk of spontaneously developing diabetes (e.g. nonhuman primates, cats and humans) [2]. Indeed, more than 90% of individuals with T2D have IAPP deposits in pancreatic islets [5,6]. A missense mutation in the IAPP gene (S20G) that increases IAPP amyloidogenicity [7] is associated with beta-cell dysfunction and early onset T2D [8],

further supporting a role of IAPP misfolding in the development of T2D. In contrast, in rodents, the propensity of IAPP to misfold and aggregate is decreased by three proline substitutions in the amyloidogenic sequence, and rodents do not spontaneously develop T2D [9]. However, transgenic expression of human-IAPP (h-IAPP) in rodents has induced diabetes and recapitulated islet pathology that is comparable to that in humans with T2D [2,9,10]. IAPP forms aggregates of different sizes and properties ranging from small oligomers, larger soluble oligomers, protofibers and large amyloid fibrils [2]. The nature of toxic aggregates and the mechanisms of toxicity are still subject of debate [9,11] but it is now generally accepted that the most toxic form of protein aggregates of amyloidogenic proteins, including IAPP, are small oligomers such as hexamer with a cylindrical barrel structure that has been termed a cylindrin [12].

Proinsulin

Proinsulin, the precursor of insulin, is also prone to misfold in beta-cells. Proinsulin misfolding occurs in the ER in consequence of disordered post-translational processing with mispaired disulfide bonds, including both intramolecular and intermolecular disulfide mispairing [13•]. The link between proinsulin misfolding and diabetes progression is supported by genetic studies of patients with mutant INS gene-induced Diabetes of Youth (MIDY), where all MIDY alleles encode a misfolded proinsulin [14].

Misfolded proteins known from neurodegenerative disorders

Other amyloid-prone proteins have been found to misfold and aggregate in beta-cells in T2D. Aggregated amyloid beta and hyperphosphorylated Tau, biological markers in Alzheimer's disease, were detected in the pancreatic islets of humans with T2D [15]. In addition, the levels alpha-synuclein, an amyloidogenic protein that accumulates in brain in Parkinson's disease, were increased in islets of T2D patients [16]. These findings highlight the closely shared molecular pathology between neurodegenerative disorders and T2D.

Mechanisms involved in protein misfolding in islets in type 2 diabetes

Exceeding the threshold of misfoded-prone proteins in beta-cells is an important determinant of aggregation and toxicity. The threshold can be outreached by several processes such as increased production rate, defective chaperone activity in the ER, naturally acquired or transmitted mutations and defective clearance of misfolded/aggregated proteins.

Increased IAPP production

IAPP is assembled in the ER as an 89-amino acid pre-proIAPP, and then enzymatically processed to its mature 37-amino acid form within the secretory pathway. Processed IAPP is stored with insulin in the secretory vesicles. The ER and the secretory vesicles provide a protective microenvironment (pH, zinc) and chaperones to favor appropriate folding and maturation of IAPP (*for review see Ref.* [2]), but disturbance of this microenvironment is likely to favor IAPP aggregation. In the context of high insulin demand such as insulin resistance, not only insulin but also IAPP production is increased [3,17,18]. Insulin resistance plays thus a key role in IAPP misfolding and aggregation since it leads to an increased IAPP production that, when reaching a certain threshold, will favor its aggregation. This negative circle involved in IAPP production may be further accentuated by the increased transcriptional expression of IAPP mediated by Thioredoxin-interacting protein (TXNIP), a pro-apoptotic factor induced by high glucose in beta-cells [19].

Altered degradation of IAPP

In long-lived secretory cells, such as beta-cells, that bear a high burden of protein synthesis and folding, the removal of misfolded proteins is also particularly important. The autophagy/lysosomal pathway plays a key role in clearance of misfolded proteins, damaged organelles and oligomerization-prone proteins. Autophagy is crucial for beta-cell homeostasis under high-fat diet conditions [20,21]. But most importantly, autophagy is a major pathway for IAPP degradation [22], and lack of beta-cell autophagy leads to an accumulation of IAPP toxic oligomers in transgenic mouse beta-cells [22–24]. Evidence of altered autophagy and accumulation of intracellular IAPP toxic oligomers in beta-cells of humans with T2D [1,25], further suggest that defective autophagy/lysosomal system contributes to IAPP aggregation in T2D.

In addition to autophagy, IAPP may also be degraded by enzymes such as neprilysin [26,27], matrix metalloproteinase-9 [28] and insulin-degrading enzyme [29]. Whereas their exact contribution in IAPP degradation remains to be clarified, deficiency of these enzymes could contribute to increase levels of IAPP and other amyloidogenic-prone proteins in islets.

Increased levels and altered degradation of misfolded proinsulin

Increased proinsulin synthesis upon metabolic demand is certainly one mechanism involved in increased abundance of misfolded proinsulin in islets. Altered proinsulin clearance can also play a major role in proinsulin misfolding. Several studies point to the ER-associated degradation (also known as ubiquitin-proteasome system) and autophagy as mechanisms for misfolded proinsulin removal (*for review see Ref.* [13•]).

Mechanisms of misfolded protein-induced toxicity in beta-cells

Membrane permeability, ER stress and calpain-2 activation

Increasing evidence suggest that the cytotoxic form of amyloidogenic proteins are small non-fibrillar oligomers