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PII: S0005-2736(22)00140-7

DOI: https://doi.org/10.1016/j.bbamem.2022.184002

Reference: BBAMEM 184002

To appear in: *BBA - Biomembranes*

Received date: 28 February 2022

Revised date: 20 June 2022

Accepted date: 6 July 2022

Please cite this article as: G. Guillemain, J.-J. Lacapere and L. Khemtemourian, Targeting hIAPP fibrillation: A new paradigm to prevent β-cell death?, *BBA - Biomembranes* (2022), https://doi.org/10.1016/j.bbamem.2022.184002

Targeting hIAPP fibrillation: a new paradigm to prevent β-cell death?

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Abbreviations. Aβ Amyloid beta protein; AD Alzheimer Disease; AFM Atomic Force Microscopy; cAMP cyclic Adenosine MonoPhosphate; AMY Amylin Receptor; CryoEM Cryogenic Electron Microscopy; EM Electron Microscopy; EPR Electron Paramagnetic Resonance; ERK Extracellular signal-Regulated Kinase, GPCR G Protein-Coupled Receptor; HIF-1α Hypoxia Induced Factor-1α; IAPP Islet Amyloid PolyPeptide; IDP Intrinsically Disordered Protein; IL-1β InterLeukine-1β; LRP1 low density Lipoprotein Receptor-related Protein 1; mTOR mammalian Target Of Rapamycin; NMR Nuclear Magnetic Resonance; O-GlcNAcylation O-linked β-N-Acetylglucosamine addition to serine/threonine; PD Parkinson Disease; PFKFB3 6-PhosphoFructo-2-Kinase/Fructose-2,6-Biphosphatase 3; PrP Protease Resistant Protein; RAGE Receptor for Advanced Glycation End products; RAMP Receptor Activity-Modifying Protein; ROS reactive Oxygen Species; T1DM Type 1 Diabetes Mellitus; T2DM Type 2 Diabetes Mellitus; TSPO Translocator protein.

Abstract

Loss of pancreatic β-cell mass is deleterious for type 2 diabetes patients since it reduces insulin production, critical for glucose homeostasis. The main research axis developed over the last few years was to generate new pancreatic β-cells or to transplant pancreatic islets as occurring for some specific type 1 diabetes patients. We evaluate here a new paradigm consisting in preservation of β-cells by prevention of human islet amyloid polypeptide (hIAPP) oligomers and fibrils formation leading to pancreatic β-cell death. We review the hIAPP physiology and the pathology that contributes to β-cell destruction, deciphering the various cellular steps that could be involved. Recent progress in understanding other amyloidosis such as Aβ, Tau, α-synuclein or prion, involved in neurodegenerative processes linked with inflammation, has opened new research lines of investigations to preserve neuronal cells. We evaluate and estimate their transposition to the pancreatic β-cells preservation. Among them is the control of reactive oxygen species (ROS) production occurring with inflammation and the possible implication of the mitochondrial translocator protein as a diagnostic and therapeutic target. The present review also focuses on other amyloid forming proteins from molecular to physiological and physiopathological points of view that could help to better decipher hIAPP-induced β-cell death mechanisms and to prevent hIAPP fibril formation.

Keywords

Type 2 diabetes; pancreas; β-cells; cross-fibrils; amyloid proteins.

Introduction

Type 2 diabetes mellitus (T2DM) is a major metabolic disorder characterized by insulin resistance and β-cell dysfunction leading to an insufficient insulin production associated with pancreatic β-cell mass reduction altogether leading to a hyperglycemic state [1]. Type 1 diabetes mellitus (T1DM) is due to autoimmune complete β-cell destruction leading to a total lack of insulin. This world spread pathology has major health, economic and societal consequences [2]. Most treatments target the consequence of the pathologies. Glycaemia measurement and insulin injection permit T1DM patients to have an almost normal life. The situation is slightly different for T2DM patients for which evolution of the pathology has to be followed to manage the impaired insulin sensitivity and the inadequate insulin production. β-cell replacement therapies have been proposed to compensate for the reduced β-cell mass but even though proofs of concept have been provided in rodents [3], their transposition to humans remains to be improved. Recent lines of investigation focus on β-cell regeneration of functional β-cell mass by β-cell neogenesis in T2DM or by islet graft in T1DM. However, islet graft is today restricted to T1DM patients already on graft anti-rejection treatment and does not prevent amyloid deposits [4]. The comprehension of mechanisms of β-cell death in T2DM has been largely improved by studies on pancreatic autopsies that revealed the presence of fibrils composed of amyloid deposits in pancreatic islets of 95% of diabetic patients [5]. The main component of amyloid deposit is the human Islet Amyloid PolyPeptide (hIAPP), also named amylin, which fibrillation mechanisms remain unclear both *in vitro* and *in cellulo* studies. We present in this review a state of the art knowledge about hIAPP fibrillation. We also extend the proposal to what could be learned from other amyloid forming proteins, such as amyloid beta (Aβ), Tau, α-synuclein or prion, all involved in neurodegenerative diseases. We propose that translation of such knowledge may be beneficial for understanding and preventing hIAPP β-cell death.

1. hIAPP physiology and pathology

hIAPP is a 37 amino acid peptide produced as a preprohormone in the endoplasmic reticulum of pancreatic β-cell along with insulin [6] (Figure 1 & Table 1). Before being secreted in the blood, hIAPP is maturated within trans-golgi network and granules (see Figure 1). Among the numerous post-translational modifications existing in cells, some have been clearly described for hIAPP (disulfide bridge and C-terminal amidation) [5]. Some others such as the presence of O- and N-glycosylation are elusive [7] and remain to be studied. hIAPP, as a hormone, regulates gastric emptying and food intake, controls glucagon and insulin secretion and is implicated in glucose homeostasis [5].

hIAPP acts not only on the pancreas but also on several other organs such as the kidney, bones and the heart, where its function promotes renin activity, regulates calcium homeostasis and favors bone resorption and exerts hypotensive effects respectively [8-12].

Mechanism of hIAPP oligomerization. hIAPP belongs to the Intrinsically Disordered Protein (IDP) family, characterized by the lack of secondary structure, making the atomic structure of the monomer difficult to be determined. Several strategies such as the use of detergent at different pH or the complexation with a partner (for example HI18) have been used to stabilize the monomeric form of hIAPP and to enable its structure determination by liquid-state NMR (Table 2). Moreover, the mechanism of hIAPP oligomerization leading to fibrils is complex to decipher. Indeed, hIAPP can form oligomers and supramolecular structure named amyloid fibrils (Figure 2a-c) which toxicity toward

pancreatic β-cells has been implicated in T2DM [5, 13]. It has been shown that heavy metals could be associated to several human pathologies among which is T2DM [14]. However, recent study on a large-scale cohort could not find a direct link between lead and cadmium exposure and T2DM pathology [15]. Meanwhile, biophysical studies have shown that calcium, zinc and copper interact with hIAPP but lead to different effects. Ca^{2+} favors penetration of hIAPP in the membrane, Zn^{2+} is coordinated to His-18 and favors the formation of large aggregates at high concentrations, Cu^{2+} inhibits the formation of fibrils [16-19] but these results are controversial.

Structure of hIAPP fibrils. Isolated fibrils have been studied by several biophysical approaches (Electronic Microscopy (EM), Nuclear Magnetic Resonance (NMR), Electron Paramagnetic Resonance (EPR), Atomic Force Microscopy (AFM)) and atomic models have been obtained by solid-state NMR and cryo-EM (Table 2) [20-23]. Such structure involves consensus beta sheet domains of hIAPP monomer (Figure 2D), however, the amino acids boundaries are different in the published data probably due to the use of various techniques (NMR, cryo-EM, EPR) and different peptide origin, synthetic or expressed or patient-extracted hIAPP. The presence of another protein complexed with hIAPP or the seeds from patient-extracted fibrils gives rise to a variety of polymorphs [20, 21]. The natural mutant S20G, that forms fibrils more rapidly *in vitro* than wild type [24], generates a polymorphism of fibrils with completely different architecture compared to wild type hIAPP [25].

Amyloid forming protein family. hIAPP also belongs to the amyloid forming proteins family observed in different organs, such as the brain in which fibril formation leads to severe degenerative pathologies such as Alzheimer, Parkinson and Creutzfeldt-Jakob diseases. The biological and physicochemical characteristics for this amyloid proteins family are summarized in Tables 1 & 2. Among these data, it has to be noted that some of these proteins are expressed in different tissues and can circulate through the blood from one organ to another (Figure 3). The most studied proteins Aβ, Tau, α-synuclein, prion involved in Alzheimer, Parkinson and Creutzfeldt-Jakob diseases, have very different primary amino acid sequences and lengths (Table 1), but all involve, in solution, secondary structure transition from random coil to beta sheet leading to similar quaternary structure looking like bundles as seen by EM. However, the recent cryo-EM data (gained in vitro from synthetic proteins) reveals that even if the beta sheet is present in all the monomers, the quaternary packing of the monomers involves different stacking shapes such as “L”, “S” and “LS” for Tau, hIAPP and Aβ, respectively (Figure 4). It has to be mentioned that the interface between two monomers making the fibrils involves hydrophobic residues like glycine, alanine or valine, except for PrP where interacting residues are charged. In addition, polymorphisms of structures have been described starting either from synthetic peptide of natural mutants or from patient-extracted fibrils used as fibril growth seeds. For example, six Tau isoforms [26], three isoforms α-synuclein [27], four isoforms of hIAPP [20] and Aβ [28] have been described.

Cross-fibers. At the cellular level, degenerative pathologies are induced by one or more amyloid forming proteins. In some cases, the fibril formation requires co-factors such as heparin or RNA for Tau [29], or is accelerated by extrinsic factors such as ApoE for Aβ [29] or lipids for hIAPP [30]. Indeed, in the diabetic context, the hyperlipidemic content has been described to correlate with an increase in fibrils [31]. In some other cases, these pathologies involve cross-fibrils formed by at least two amyloid proteins [32] raising the question of the circulation of the amyloid forming proteins or of their local production. This makes the description of the mechanisms of fibril formation and of their toxicity more complex. For example, hIAPP synthesized in the pancreas has been observed in brain deposits of Alzheimer or Parkinsonian patients, involving Aβ and α-synuclein, respectively [33]. The absence of hIAPP transcript in the brain and the presence of hIAPP fibrils observed post-mortem

in the brain blood vessels favors the hIAPP circulation hypothesis [34]. Conversely, Aβ and α-synuclein have been observed in the pancreatic fibril deposits of T2DM patients [35] in agreement with a possible local production of α-synuclein, but intrinsic cell production of Aβ has not been yet characterized [36, 37]. The formation of these cross-fibrils in the pancreas is not clear yet. In some cases, the presence of a second amyloid forming peptide accelerates the fibril formation both *in vitro* and *in vivo* (hIAPP and Aβ [38]), but in some other cases it slows down the fibril formation *in vitro* (hIAPP and α-synuclein [38]). More generally, the circulation of hIAPP and other amyloid forming proteins between brain and pancreas (Figure 3) raises the question of the links between diabetes and senility in agreement with epidemiologic data showing that patients with neurodegenerative diseases have a higher risk to develop T2DM and vice-versa [39-42]. From a structural point of view, the formation of cross-fibrils might involve the hydrophobic residues that are already a part of each specific fibril, but this has to be characterized.

2. When physiology becomes pathology

Along the maturation process, hIAPP segregated in the secretory granules is protected against fibrillation both by the intra-granular acidic pH [43] and by the presence of insulin [44] . The process of such insulin-dependent protection mechanism has been studied recently by molecular dynamics and interaction between Y16 in insulin and R19 in IAPP, and could be a key factor in stabilizing the complex [45]. However, if the granular balance (Figure 5, step 1) is disrupted, hIAPP will be released in the cytoplasm of β-cells and might be able to aggregate and form fibrils.

After synthesis and maturation, hIAPP is secreted in the blood stream (Figure 5, steps 2 and 3) but also acts locally on the neighbouring pancreatic β-cells (Figure 5, step 4) [10]. When circulating, hIAPP may reach other organs but also encounter proteins such as C4bp, a protein of the complement system, inducing non-toxic hIAPP fibrillation in blood, thus preventing hIAPP oligomers' toxic effects on cells [46, 47]. Conversely, hIAPP interacting with cell plasma membrane or entering cells may generate fibrils leading to cell death. Even if the complete process of fibril

formation *in cellulo* and cell toxicity are not known, several key features have been already described.

(i) Interaction of hIAPP as well as other amyloid forming protein with lipids (Figure 5, step 5), cholesterol and GlycosAminoGlycans (GAG) have been suggested to induce membrane damages such as pore formation (Figure 5, step 6) and cell toxicity through fibril formation [48-52].

(ii) Direct cell internalization or endocytotic mechanism of hIAPP (Figure 5, step 7) have been characterized leading to intracellular fibril formation [53].

(iii) hIAPP binds to three different plasma membrane receptors, named AMY 1-3 [53, 54] formed by the calcitonin receptor (belonging to the GPCR family) and different receptor activity-modifying protein (RAMP 1,2,3). At low concentration, to exert its physiological effect, hIAPP binding leads to an activation of the signaling pathway involving adenylate cyclase, cAMP production and ERK signaling (Figure 5, step 8) [55] then, inhibiting insulin secretion [10]. At high concentration**,** hIAPP binding also leads to a non-endocytotic internalization (Figure 5, step 8) [53]. It has to be mentioned that Aβ also binds to AMY receptor in the brain but does not induce any activation [55] thus acting like an inhibitor. In line with this, the IAPP antagonist (AC253) has been suggested to treat Alzheimer disease in mouse model by reducing the microglial activation [56]. These data raise the question of the link between the binding of the ligand to AMY receptors and their activation.

(iv) hIAPP oligomers bind to another plasma membrane receptor named RAGE (Receptor for Advanced Glycation Endproducts) that mediates cellular stress, inflammation, metabolic dysfunction and apoptosis (Figure 5, step 9) [57]. RAGE is composed of a single transmembrane domain, a small intracellular C-terminus and a large immunoglobulin like extracellular domain. When cleaved the extracellular domain, called soluble RAGE (sRAGE), can interact with small oligomers preventing hIAPP fibrillation and cell toxicity (Figure 5, step 10) [57]. Does hIAPP bind to RAGE or sRAGE in its glycated or non-glycated form since these proteins bind both glycated and non-glycated substrates? It has been shown that hIAPP can be glycated as observed for other amyloid proteins, this modification leading to an increased rate of fibrillation [58-61]. It is well characterized that the monomer of hIAPP is not a toxic molecule, but the size of the toxic species is not clear (small oligomer, large oligomer or protofibril). As mentioned earlier, amyloid forming proteins such as Aβ can bind to the hIAPP described receptors [54] thus it may be questioned if hIAPP could also bind to other receptors of amyloid forming protein, such as LRP1 described for Tau [62]. Such binding could be governed by post-translational modifications of hIAPP such as glycosylation or phosphorylation that have been described for tau, leading to inhibition or activation of tau fibrillation, respectively [58]. However, no such data is available for hIAPP, in particular O-GlcNAcylation that has been described to inhibit α-synuclein, Aβ and tau fibril formation and cell toxicity [63, 64]. Conversely, the PTMs such as disulfide bonds and C-ter amidation have a minor effect on hIAPP fibrillation *in vitro* [65], whereas they have an effect *ex vivo* on the insulin-stimulated rates of glycogen synthesis when present concomitantly [66].

(v) When in cell, hIAPP can interact with cell organelles such as mitochondria inducing different type of dysfunctions but molecular mechanisms are still unclear (Figure 5, step 11). Do amyloid peptides interact with lipids or proteins of these organelles? The question remains still to be answered. Mitochondrial membrane depolarization induces ROS production that in turns increases fibril formation and can lead to mitophagy involving mTor pathway [67]. A clear association between amyloid fibril formation and mitochondria dysfunction has been identified for T2D and Alzheimer's disease [68, 69]. However, it has to be mentioned that the interaction of hIAPP does not only lead to cytotoxicity since the mitochondrial peptidase pitrilysin degrades hIAPP and might be involved in its regulation *in vivo* [70] .

(vi) hIAPP fibrils activate HIF1α/PFKFB3 signalling in cells that in turn increases non mitochondrial glycolysis maintaining the cells alive and preventing their elimination [71], that could favor the fibrils' expansion to other cells. It has been suggested that the inhibition of this pathway could be a strategy to increase the removal of cells containing misfolded proteins. However, it has to be taken into account that β-cell renewal is slow in non-pathological conditions in adults and implies β-cell neogenesis and not cell proliferation [72] .

(vii) Cross-talk between macrophages and pancreatic β-cells (Figure 5, step 12) has been described to participate in T2D progression [73] . hIAPP oligomers trigger the Nlrp3 inflammasome and generate mature interleukin (IL)-1β [74] leading to local and chronical inflammation which in turns could expand hIAPP fibril formation. Indeed, it has been observed that in humanized mouse pancreatic isolated islets IL-1β increases of hIAPP secretion and oligomerization [75]. However, the molecular mechanisms involved are not known to decipher a specific therapeutic approach.

3. Perspectives

Among the numerous strategies to prevent and/or cure T2DM, a new paradigm consisting in preservation of β-cells by preventing hIAPP's toxic effects has to be considered and developed.

First, the early diagnostics of functional and non-functional β-cells without pancreatic biopsies has to be developed. Imaging approaches have a spatial resolution that is too low to reach such a goal without a breakthrough in technologies advances. Moreover, specific tracers to distinguish *in vivo* the functional and non-functional β-cells have to be designed to allow a follow-up of the pathology. This implies a definition of what is the good component-marker of a functional cell that secretes insulin in response to glucose is needed. In addition, amyloid oligomers and fibrils are only observed post-mortem, the development of a specific tracer of hIAPP oligomerization *in vivo*, would permit to correlate β-cells destruction and fibril formation. It has to be mentioned that the accessibility of tracers to β-cells will be facilitated by the high vascularization of the pancreatic islets [76].

Second, from the therapeutic point of view, the development of new tools will come from the study of the action mechanism of hIAPP at different levels from *in vivo* to *in vitro* using cell lines (Figure 6). The first step to control might be the inhibition of granule opening in cells, if this process could occur (Figure 6, step1), however such event has never been described yet! Following strategies target the inhibition of fibril formation (Figure 6, step 2) to prevent the transition from monomer to small oligomers and larges fibrils. A natural compound, epigallocatechin gallate (EGCG) [77] is efficient *in vitro* and *in vivo*, but seems to be pleiotropic and non-specific to hIAPP. Several clinical trials of EGCG are currently being performed, in particular to assess its pharmacokinetics and hepatic safety. Small organic molecules, such the anle145c, have been designed and observed to inhibit hIAPP fibril formation by trapping small oligomers, but is also able to break mature fibrils [78]. Clinical trials should be performed to convert anle145c in a good therapeutic drug. Nanoparticles have been shown to prevent hIAPP fibrillation by trapping small intermediates or monomeric amyloidogenic peptides [79]. Similar results on hIAPP fibril inhibition by nanoparticles were obtained in NIT-1 cells and shown to prevent cell toxicity [80]. More generally, several nanomaterials have been studied to prevent amyloidosis [81], but there is still a long way to convert it in nanomedecine [82]. Several peptide mimics of hIAPP have been also developed. Pramlintide, a peptide of the same length as hIAPP with three proline substitutions [83], is currently used as subcutaneous co-injection with insulin for the treatment of patients with dysregulated glycaemia T2DM in the USA [84]. It seems that it induces to some patient severe hypoglycemia, making it not a first intention treatment. It has been shown that single mutations of hIAPP generate peptide mimics with reduced fibril formation and cell toxicity [85, 86]. Modified hIAPP, with N-methylation of residues G and I, has also been designed, leading to the inhibition of fibril formation both *in vitro* and *in vivo* [87]. Moreover, this molecule has been described to prevent inflammation cascade triggered by hIAPP oligomers [88]. Small hIAPP peptides with constrained β-hairpin structure have been designed to inhibit hIAPP aggregation [89]. A non-natural class of peptide such as foldamer has also been showed to inhibit hIAPP fibril formation [90]. However, none of these peptides or peptidomimetics are currently in clinical trial. A new strategy to design inhibitors should take into account the recent high resolution atomic structure of the fibrils of wild type and polymorphs from the main amyloid forming proteins and try to target for instance the protofilament interface.

The entrance of hIAPP into cells and hIAPP fibril formation seem to be governed by lipid membrane composition such as cholesterol (Figure 6, step 3) [91]. In line with this, therapeutic approaches relying on modifying the cholesterol homeostasis are currently considered for Parkinson diseases [92]. Characterization of the molecular mechanism of the interaction of hIAPP with AMY or

RAGE receptors (Figure 6, steps 4 and 5) and atomic models of the complexes would permit to develop specific inhibitors and to prevent the activation of toxic cellular pathways and/or hIAPP internalization. The design of a peptide that mimic sRAGE is a good target to gain a therapeutic candidate that recruits hIAPP and stabilize it in a non-toxic form.

Upon its internalization, hIAPP can be sequestrated into liquid phases (Figure 6, step 6) [93], its liberation from these phases by ROS for example may act on various cell signalling pathways but also induce fibril formation either in the cytoplasm or in interaction with intra-cellular membranes such as mitochondria. Development of specific inhibitors that maintain non-structured hIAPP within liquid phases is a strategy that has to be taken into account. A class of "indirect" inhibitors of fibril formation could be developed through their potency to reduce ROS production. The translocator protein, or TSPO (Figure 6, step 7), localized in the outer mitochondrial membrane, has been described as a therapeutic target in Alzheimer disease [94]. It could also represent a good candidate in T2DM and β-cell protection. Indeed, it has been observed that in human pancreatic islets, TSPO is overexpressed upon IL-1β-induced inflammation with ROS production [95]. TSPO ligands have been demonstrated to reduce ROS production in colonic cells [96] and have been described as protecting agents for neuropathology [97, 98].

Third, studies at the integrated level using animal models remain crucial to better understand the role of hIAPP not only in diabetes but also in neurodegenerative diseases. (i) the selective destruction of pancreatic β-cells in animal models by streptozotocin injection could be used to determine if another tissue (for example enteroendocrine cells) could be able to compensate the lack of pancreatic IAPP and help to reduce hyperglycaemia. (ii) overexpression of hIAPP in rat and mouse have generated different working models showing various phenotypes raising from glucose intolerance to T2DM [99]. Crossing these animals with mouse over-expressing other amyloids would help to understand the respective contribution of the various amyloids in the glucose regulation, since all amyloid forming proteins are able to interact with each other (cross-fibrils) and importantly are all involved in glucose metabolism [100-102].

Finally, the study of the *in situ* hIAPP fibrillation mechanisms and toxicity to prevent β-cell death after transplantation is also a question to be solved. Studies on human islets are limited by their difficulty to be obtained and maintained alive for long-term experiments. The development of organoids models versus islets could help and will permit to decipher the mechanisms of hIAPP action in the pancreas in a more physiological environment than in isolated cells [103]. Furthermore, the specific development of pancreatic islets organoids, *Langerhanoids*, that closely mimic human pancreatic islets physiology [104], would facilitate the further transplantation since these cells can be more simply amplified, generating more diabetic patients grafted. It also generates a new model to study hIAPP's physiological role and counteract hIAPP physiopathological effects. Recent progress toward the transplantation has been made by mixing islet cells, human amniotic epithelial cells and human umbilical vein endothelial cells that improve the vascularization giving a more favorable transplantation [105].

Deciphering all these lines of research will definitely help to propose new therapeutic tools and treat all forms of diabetes.

Acknowledgements: Concepts reported herein were supported by the INSERM and FRM (grant FRM, EQU201903007868) to GG and CNRS to JJL and LK. We thank S. Noinville and B. Blondeau for helpful discussion along the writing of the manuscript.

Author Contribution: GG, J-JL and LK equally contributed to design and to write the reviewed manuscript.

Duality of Interest: No potential conflicts of interest relevant to this article were reported

References

1. Butler, A.E., et al., *Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes.* Diabetes, 2003. **52**(1): p. 102-10.
2. Organization, W.H., *Global Report on Diabetes.* 2016.
3. Courty, E., et al., *Adaptive beta-Cell Neogenesis in the Adult Mouse in Response to Glucocorticoid-Induced Insulin Resistance.* Diabetes, 2019. **68**(1): p. 95-108.
4. Lablanche, S., et al., *Five-Year Metabolic, Functional, and Safety Results of Patients With Type 1 Diabetes Transplanted With Allogenic Islets Within the Swiss-French GRAGIL Network.* Diabetes Care, 2015. **38**(9): p. 1714-22.
5. Westermark, P., A. Andersson, and G.T. Westermark, *Islet amyloid polypeptide, islet amyloid, and diabetes mellitus.* Physiol Rev, 2011. **91**(3): p. 795-826.
6. Smeekens, S.P., S.J. Chan, and D.F. Steiner, *The biosynthesis and processing of neuroendocrine peptides: identification of proprotein convertases involved in intravesicular processing.* Prog Brain Res, 1992. **92**: p. 235-46.
7. Zraika, S., et al., *Toxic oligomers and islet beta cell death: guilty by association or convicted by circumstantial evidence?* Diabetologia, 2010. **53**(6): p. 1046-56.
8. Young, A., *Amylin and the integrated control of nutrient influx.* Adv Pharmacol, 2005. **52**: p. 67-77.
9. Young, A., *Inhibition of food intake.* Adv Pharmacol, 2005. **52**: p. 79-98.
10. Young, A., *Inhibition of insulin secretion.* Adv Pharmacol, 2005. **52**: p. 173-92.
11. Young, A., *Renal effects.* Adv Pharmacol, 2005. **52**: p. 251-68.
12. Young, A., *Effects on bone.* Adv Pharmacol, 2005. **52**: p. 269-80.
13. Milardi, D., et al., *Proteostasis of Islet Amyloid Polypeptide: A Molecular Perspective of Risk Factors and Protective Strategies for Type II Diabetes.* Chem Rev, 2021. **121**(3): p. 1845-1893.
14. Galvez-Fernandez, M., et al., *Gene-environment interaction analysis of redox-related metals and genetic variants with plasma metabolic patterns in a general population from Spain: The Hortega Study.* Redox Biol, 2022. **52**: p. 102314.
15. Jun Ho Ji , M.H.J., Jung-Hun Kang, Soon Il Lee, Suee Lee, Sung-Hyun Kim, Sung Yong Oh *Relationship between heavy metal exposure and type 2 diabetes: a large-scale retrospective cohort study using occupational health examinations.* BMJ Open, 2021. **11**(3): p. e039541.
16. Brender, J.R., et al., *Role of zinc in human islet amyloid polypeptide aggregation.* J Am Chem Soc, 2010. **132**(26): p. 8973-83.
17. Khemtemourian, L., et al., *Investigation of the effects of two major secretory granules components, insulin and zinc, on human-IAPP amyloid aggregation and membrane damage.* Chem Phys Lipids, 2021. **237**: p. 105083.
18. Li, H., et al., *Rapid assessment of human amylin aggregation and its inhibition by copper(II) ions by laser ablation electrospray ionization mass spectrometry with ion mobility separation.* Anal Chem, 2015. **87**(19): p. 9829-9837.
19. Sciacca, M.F., et al., *Calcium-activated membrane interaction of the islet amyloid polypeptide: implications in the pathogenesis of type II diabetes mellitus.* Arch Biochem Biophys, 2008. **477**(2): p. 291-8.
20. Cao, Q., et al., *Cryo-EM structures of hIAPP fibrils seeded by patient-extracted fibrils reveal new polymorphs and conserved fibril cores.* Nat Struct Mol Biol, 2021. **28**(9): p. 724-730.
21. Cao, Q., et al., *Cryo-EM structure and inhibitor design of human IAPP (amylin) fibrils.* Nat Struct Mol Biol, 2020. **27**(7): p. 653-659.

22. Luca, S., et al., *Peptide conformation and supramolecular organization in amylin fibrils: constraints from solid-state NMR.* Biochemistry, 2007. **46**(47): p. 13505-22.
23. Roder, C., et al., *Cryo-EM structure of islet amyloid polypeptide fibrils reveals similarities with amyloid-beta fibrils.* Nat Struct Mol Biol, 2020. **27**(7): p. 660-667.
24. Meier, D.T., et al., *The S20G substitution in hIAPP is more amyloidogenic and cytotoxic than wild-type hIAPP in mouse islets.* Diabetologia, 2016. **59**(10): p. 2166-71.
25. Gallardo, R., et al., *Fibril structures of diabetes-related amylin variants reveal a basis for surface-templated assembly.* Nat Struct Mol Biol, 2020. **27**(11): p. 1048-1056.
26. Zhang, Y., et al., *Subacute to chronic Alzheimer-like alterations after controlled cortical impact in human tau transgenic mice.* Sci Rep, 2019. **9**(1): p. 3789.
27. Schweighauser, M., et al., *Structures of alpha-synuclein filaments from multiple system atrophy.* Nature, 2020. **585**(7825): p. 464-469.
28. Elkins, M.R., et al., *Structural Polymorphism of Alzheimer's beta-Amyloid Fibrils as Controlled by an E22 Switch: A Solid-State NMR Study.* J Am Chem Soc, 2016. **138**(31): p. 9840-52.
29. Fichou, Y., et al., *Tau-Cofactor Complexes as Building Blocks of Tau Fibrils.* Front Neurosci, 2019. **13**: p. 1339.
30. Lei, P., et al., *Prevention and promotion effects of apolipoprotein E4 on amylin aggregation.* Biochem Biophys Res Commun, 2008. **368**(2): p. 414-8.
31. Mo, X.D., et al., *Lipid accelerating the fibril of islet amyloid polypeptide aggravated the pancreatic islet injury in vitro and in vivo.* Lipids Health Dis, 2018. **17**(1): p. 42.
32. Ivanova, M.I., et al., *Biophysical processes underlying cross-seeding in amyloid aggregation and implications in amyloid pathology.* Biophys Chem, 2021. **269**: p. 106507.
33. Martinez-Valbuena, I., et al., *Amylin as a potential link between type 2 diabetes and alzheimer disease.* Ann Neurol, 2019. **86**(4): p. 539-551.
34. Jackson, K., et al., *Amylin deposition in the brain: A second amyloid in Alzheimer disease?* Ann Neurol, 2013. **74**(4): p. 517-26.
35. Martinez-Valbuena, I., et al., *Interaction of amyloidogenic proteins in pancreatic beta cells from subjects with synucleinopathies.* Acta Neuropathol, 2018. **135**(6): p. 877-886.
36. Steneberg, P., et al., *The type 2 diabetes-associated gene ide is required for insulin secretion and suppression of alpha-synuclein levels in beta-cells.* Diabetes, 2013. **62**(6): p. 2004-14.
37. Ueda, K., T. Saitoh, and H. Mori, *Tissue-dependent alternative splicing of mRNA for NACP, the precursor of non-A beta component of Alzheimer's disease amyloid.* Biochem Biophys Res Commun, 1994. **205**(2): p. 1366-72.
38. Moreno-Gonzalez, I., et al., *Molecular interaction between type 2 diabetes and Alzheimer's disease through cross-seeding of protein misfolding.* Mol Psychiatry, 2017. **22**(9): p. 1327-1334.
39. Barbiellini Amidei, C., et al., *Association Between Age at Diabetes Onset and Subsequent Risk of Dementia.* JAMA, 2021. **325**(16): p. 1640-1649.
40. Casagrande, S.S., et al., *Cognitive function among older adults with diabetes and prediabetes, NHANES 2011-2014.* Diabetes Res Clin Pract, 2021. **178**: p. 108939.
41. Cheong, J.L.Y., et al., *The Association Between Type 2 Diabetes Mellitus and Parkinson's Disease.* J Parkinsons Dis, 2020. **10**(3): p. 775-789.
42. De Pablo-Fernandez, E., et al., *Association between diabetes and subsequent Parkinson disease: A record-linkage cohort study.* Neurology, 2018. **91**(2): p. e139-e142.
43. Khemtemourian, L., et al., *Low pH acts as inhibitor of membrane damage induced by human islet amyloid polypeptide.* J Am Chem Soc, 2011. **133**(39): p. 15598-604.
44. Susa, A.C., et al., *Defining the molecular basis of amyloid inhibitors: human islet amyloid polypeptide-insulin interactions.* J Am Chem Soc, 2014. **136**(37): p. 12912-9.
45. Baram, M., et al., *Mechanistic perspective and functional activity of insulin in amylin aggregation.* Chem Sci, 2018. **9**(18): p. 4244-4252.
46. Ermert, D. and A.M. Blom, *C4b-binding protein: The good, the bad and the deadly. Novel functions of an old friend.* Immunol Lett, 2016. **169**: p. 82-92.

47. Sjolander, J., et al., *C4b-binding Protein Protects beta-Cells from Islet Amyloid Polypeptide-induced Cytotoxicity.* J Biol Chem, 2016. **291**(41): p. 21644-21655.
48. Caillon, L., et al., *Molecular Structure, Membrane Interactions, and Toxicity of the Islet Amyloid Polypeptide in Type 2 Diabetes Mellitus.* J Diabetes Res, 2016. **2016**: p. 5639875.
49. Huynh, M.B., et al., *Glycosaminoglycans from Alzheimer's disease hippocampus have altered capacities to bind and regulate growth factors activities and to bind tau.* PLoS One, 2019. **14**(1): p. e0209573.
50. Mehra, S., et al., *Glycosaminoglycans have variable effects on alpha-synuclein aggregation and differentially affect the activities of the resulting amyloid fibrils.* J Biol Chem, 2018. **293**(34): p. 12975-12991.
51. Nguyen, P.T., et al., *Mechanistic Contributions of Biological Cofactors in Islet Amyloid Polypeptide Amyloidogenesis.* J Diabetes Res, 2015. **2015**: p. 515307.
52. Sebastiao, M., et al., *Glycosaminoglycans Induce Amyloid Self-Assembly of a Peptide Hormone by Concerted Secondary and Quaternary Conformational Transitions.* Biochemistry, 2019. **58**(9): p. 1214-1225.
53. Trikha, S. and A.M. Jeremic, *Distinct internalization pathways of human amylin monomers and its cytotoxic oligomers in pancreatic cells.* PLoS One, 2013. **8**(9): p. e73080.
54. Gingell, J.J., E.R. Burns, and D.L. Hay, *Activity of pramlintide, rat and human amylin but not Abeta1-42 at human amylin receptors.* Endocrinology, 2014. **155**(1): p. 21-6.
55. Fu, W., et al., *Amylin Receptor: A Potential Therapeutic Target for Alzheimer's Disease.* Trends Mol Med, 2017. **23**(8): p. 709-720.
56. Soudy, R., et al., *Cyclic AC253, a novel amylin receptor antagonist, improves cognitive deficits in a mouse model of Alzheimer's disease.* Alzheimers Dement (N Y), 2017. **3**(1): p. 44-56.
57. Abedini, A., et al., *RAGE binds preamyloid IAPP intermediates and mediates pancreatic beta cell proteotoxicity.* J Clin Invest, 2018. **128**(2): p. 682-698.
58. Alquezar, C., S. Arya, and A.W. Kao, *Tau Post-translational Modifications: Dynamic Transformers of Tau Function, Degradation, and Aggregation.* Front Neurol, 2020. **11**: p. 595532.
59. Emendato, A., et al., *Glycation affects fibril formation of Abeta peptides.* J Biol Chem, 2018. **293**(34): p. 13100-13111.
60. Milordini, G., et al., *The Role of Glycation on the Aggregation Properties of IAPP.* Front Mol Biosci, 2020. **7**: p. 104.
61. Vicente Miranda, H., et al., *Hsp27 reduces glycation-induced toxicity and aggregation of alpha-synuclein.* FASEB J, 2020. **34**(5): p. 6718-6728.
62. Rauch, J.N., et al., *LRP1 is a master regulator of tau uptake and spread.* Nature, 2020. **580**(7803): p. 381-385.
63. Levine, P.M., et al., *alpha-Synuclein O-GlcNAcylation alters aggregation and toxicity, revealing certain residues as potential inhibitors of Parkinson's disease.* Proc Natl Acad Sci U S A, 2019. **116**(5): p. 1511-1519.
64. Park, J., et al., *O-GlcNAcylation ameliorates the pathological manifestations of Alzheimer's disease by inhibiting necroptosis.* Sci Adv, 2021. **7**(3).
65. Khemtemourian, L., et al., *The role of the disulfide bond in the interaction of islet amyloid polypeptide with membranes.* Eur Biophys J, 2010. **39**(9): p. 1359-64.
66. Roberts, A.N., et al., *Molecular and functional characterization of amylin, a peptide associated with type 2 diabetes mellitus.* Proc Natl Acad Sci U S A, 1989. **86**(24): p. 9662-6.
67. Hernandez, M.G., et al., *Pancreatic beta cells overexpressing hIAPP impaired mitophagy and unbalanced mitochondrial dynamics.* Cell Death Dis, 2018. **9**(5): p. 481.
68. Gotz, J., L.M. Ittner, and Y.A. Lim, *Common features between diabetes mellitus and Alzheimer's disease.* Cell Mol Life Sci, 2009. **66**(8): p. 1321-5.
69. Patti, M.E. and S. Corvera, *The role of mitochondria in the pathogenesis of type 2 diabetes.* Endocr Rev, 2010. **31**(3): p. 364-95.

70. Guan, H., et al., *The Mitochondrial Peptidase Pitrilysin Degrades Islet Amyloid Polypeptide in Beta-Cells.* PLoS One, 2015. **10**(7): p. e0133263.
71. Montemurro, C., et al., *IAPP toxicity activates HIF1alpha/PFKFB3 signaling delaying beta-cell loss at the expense of beta-cell function.* Nat Commun, 2019. **10**(1): p. 2679.
72. Saisho, Y., et al., *beta-cell mass and turnover in humans: effects of obesity and aging.* Diabetes Care, 2013. **36**(1): p. 111-7.
73. Cosentino, C. and R. Regazzi, *Crosstalk between Macrophages and Pancreatic beta-Cells in Islet Development, Homeostasis and Disease.* Int J Mol Sci, 2021. **22**(4).
74. Masters, S.L., et al., *Activation of the NLRP3 inflammasome by islet amyloid polypeptide provides a mechanism for enhanced IL-1beta in type 2 diabetes.* Nat Immunol, 2010. **11**(10): p. 897-904.
75. Templin, A.T., et al., *Low concentration IL-1beta promotes islet amyloid formation by increasing hIAPP release from humanised mouse islets in vitro.* Diabetologia, 2020. **63**(11): p. 2385-2395.
76. Kragl, M. and E. Lammert, *Basement membrane in pancreatic islet function.* Adv Exp Med Biol, 2010. **654**: p. 217-34.
77. Franko, A., et al., *Epigallocatechin gallate (EGCG) reduces the intensity of pancreatic amyloid fibrils in human islet amyloid polypeptide (hIAPP) transgenic mice.* Sci Rep, 2018. **8**(1): p. 1116.
78. Saravanan, M.S., et al., *The small molecule inhibitor anle145c thermodynamically traps human islet amyloid peptide in the form of non-cytotoxic oligomers.* Sci Rep, 2019. **9**(1): p. 19023.
79. Cabaleiro-Lago, C., et al., *Inhibition of APP and IAPP(20-29) fibrillation by polymeric nanoparticles.* Langmuir, 2010. **26**(5): p. 3453-61.
80. Nedumpully-Govindan, P., et al., *Graphene oxide inhibits hIAPP amyloid fibrillation and toxicity in insulin-producing NIT-1 cells.* Phys Chem Chem Phys, 2016. **18**(1): p. 94-100.
81. Ke, P.C., et al., *Mitigation of Amyloidosis with Nanomaterials.* Adv Mater, 2020. **32**(18): p. e1901690.
82. Andrieux, K. and P. Couvreur, *Nanomedicine as a promising approach for the treatment and diagnosis of brain diseases: the example of Alzheimer's disease.* Ann Pharm Fr, 2013. **71**(4): p. 225-33.
83. Wang, H., et al., *Analysis of the ability of pramlintide to inhibit amyloid formation by human islet amyloid polypeptide reveals a balance between optimal recognition and reduced amyloidogenicity.* Biochemistry, 2015. **54**(44): p. 6704-11.
84. Avgerinos, I., et al., *Comparative efficacy and safety of glucose-lowering drugs as adjunctive therapy for adults with type 1 diabetes: A systematic review and network meta-analysis.* Diabetes Obes Metab, 2021. **23**(3): p. 822-831.
85. Cao, P., et al., *Islet amyloid: from fundamental biophysics to mechanisms of cytotoxicity.* FEBS Lett, 2013. **587**(8): p. 1106-18.
86. Khemtemourian, L., et al., *Residue specific effects of human islet polypeptide amyloid on self-assembly and on cell toxicity.* Biochimie, 2017. **142**: p. 22-30.
87. Yan, L.M., et al., *Design of a mimic of nonamyloidogenic and bioactive human islet amyloid polypeptide (IAPP) as nanomolar affinity inhibitor of IAPP cytotoxic fibrillogenesis.* Proc Natl Acad Sci U S A, 2006. **103**(7): p. 2046-51.
88. Aftabizadeh, M., et al., *Blocking Inflammasome Activation Caused by beta-Amyloid Peptide (Abeta) and Islet Amyloid Polypeptide (IAPP) through an IAPP Mimic.* ACS Chem Neurosci, 2019. **10**(8): p. 3703-3717.
89. Lesma, J., et al., *beta-Hairpin Peptide Mimics Decrease Human Islet Amyloid Polypeptide (hIAPP) Aggregation.* Front Cell Dev Biol, 2021. **9**: p. 729001.
90. Kaffy, J., et al., *Helical gamma-Peptide Foldamers as Dual Inhibitors of Amyloid-beta Peptide and Islet Amyloid Polypeptide Oligomerization and Fibrillization.* Chemistry, 2020. **26**(64): p. 14612-14622.

91. Caillon, L., et al., *Cholesterol modulates the interaction of the islet amyloid polypeptide with membranes.* Mol Membr Biol, 2014. **31**(7-8): p. 239-49.
92. Pingale, T.D. and G.L. Gupta, *Novel therapeutic approaches for Parkinson's disease by targeting brain cholesterol homeostasis.* J Pharm Pharmacol, 2021.
93. Pytowski, L., et al., *Liquid-liquid phase separation of type II diabetes-associated IAPP initiates hydrogelation and aggregation.* Proc Natl Acad Sci U S A, 2020. **117**(22): p. 12050-12061.
94. Chua, S.W., M. Kassiou, and L.M. Ittner, *The translocator protein as a drug target in Alzheimer's disease.* Expert Rev Neurother, 2014. **14**(4): p. 439-48.
95. Trincavelli, M.L., et al., *Upregulation of mitochondrial peripheral benzodiazepine receptor expression by cytokine-induced damage of human pancreatic islets.* J Cell Biochem, 2002. **84**(3): p. 636-44.
96. Issop, L., et al., *Translocator Protein-Mediated Stabilization of Mitochondrial Architecture during Inflammation Stress in Colonic Cells.* PLoS One, 2016. **11**(4): p. e0152919.
97. Grimm, A., et al., *Mitochondria modulatory effects of new TSPO ligands in a cellular model of tauopathies.* J Neuroendocrinol, 2020. **32**(1): p. e12796.
98. Riban, V., et al., *In Vitro and In Vivo Neuroprotective Effects of Etifoxine in beta-Amyloidinduced Toxicity Models.* CNS Neurol Disord Drug Targets, 2020. **19**(3): p. 227-240.
99. Matveyenko, A.V., J.D. Veldhuis, and P.C. Butler, *Mechanisms of impaired fasting glucose and glucose intolerance induced by an approximate 50% pancreatectomy.* Diabetes, 2006. **55**(8): p. 2347-56.
100. Oliveira, L.T., et al., *Exogenous beta-amyloid peptide interferes with GLUT4 localization in neurons.* Brain Res, 2015. **1615**: p. 42-50.
101. Qiao, H., et al., *Alpha-synuclein induces microglial migration via PKM2-dependent glycolysis.* Int J Biol Macromol, 2019. **129**: p. 601-607.
102. Wijesekara, N., et al., *Tau ablation in mice leads to pancreatic beta cell dysfunction and glucose intolerance.* FASEB J, 2018. **32**(6): p. 3166-3173.
103. Tsakmaki, A., P. Fonseca Pedro, and G.A. Bewick, *Diabetes through a 3D lens: organoid models.* Diabetologia, 2020. **63**(6): p. 1093-1102.
104. Papoz, A., et al., *[Generating pancreatic islets organoids: Langerhanoids].* Med Sci (Paris), 2022. **38**(1): p. 52-58.
105. Wassmer, C.H., et al., *Bio-Engineering of Pre-Vascularized Islet Organoids for the Treatment of Type 1 Diabetes.* Transpl Int, 2021. **35**: p. 10214.
106. Young, A., *Tissue expression and secretion of amylin.* Adv Pharmacol, 2005. **52**: p. 19-45.
107. Haukedal, H. and K.K. Freude, *Implications of Glycosylation in Alzheimer's Disease.* Front Neurosci, 2020. **14**: p. 625348.
108. Condello, C., et al., *Structural heterogeneity and intersubject variability of Abeta in familial and sporadic Alzheimer's disease.* Proc Natl Acad Sci U S A, 2018. **115**(4): p. E782-E791.
109. Morales, R., et al., *Infusion of blood from mice displaying cerebral amyloidosis accelerates amyloid pathology in animal models of Alzheimer's disease.* Acta Neuropathol Commun, 2020. **8**(1): p. 213.
110. Mandrekar, S., et al., *Microglia mediate the clearance of soluble Abeta through fluid phase macropinocytosis.* J Neurosci, 2009. **29**(13): p. 4252-62.
111. Buee, L., et al., *Tau protein isoforms, phosphorylation and role in neurodegenerative disorders.* Brain Res Brain Res Rev, 2000. **33**(1): p. 95-130.
112. Chai, X., J.L. Dage, and M. Citron, *Constitutive secretion of tau protein by an unconventional mechanism.* Neurobiol Dis, 2012. **48**(3): p. 356-66.
113. Merezhko, M., et al., *Secretion of Tau via an Unconventional Non-vesicular Mechanism.* Cell Rep, 2018. **25**(8): p. 2027-2035 e4.
114. Mattsson, N., et al., *Plasma tau in Alzheimer disease.* Neurology, 2016. **87**(17): p. 1827-1835.
115. Holmes, B.B., et al., *Heparan sulfate proteoglycans mediate internalization and propagation of specific proteopathic seeds.* Proc Natl Acad Sci U S A, 2013. **110**(33): p. E3138-47.

116. Zhao, J., H. Wu, and X.Q. Tang, *Tau internalization: A complex step in tau propagation.* Ageing Res Rev, 2021. **67**: p. 101272.
117. He, Z., et al., *Transmission of tauopathy strains is independent of their isoform composition.* Nat Commun, 2020. **11**(1): p. 7.
118. Horvath, I. and P. Wittung-Stafshede, *Cross-talk between amyloidogenic proteins in type-2 diabetes and Parkinson's disease.* Proc Natl Acad Sci U S A, 2016. **113**(44): p. 12473-12477.
119. Vinnakota, R.L., et al., *Identification of an Alternatively Spliced alpha-Synuclein Isoform That Generates a 41-Amino Acid N-Terminal Truncated Peptide, 41-syn: Role in Dopamine Homeostasis.* ACS Chem Neurosci, 2018. **9**(12): p. 2948-2958.
120. Bras, I.C., et al., *Synucleinopathies: Where we are and where we need to go.* J Neurochem, 2020. **153**(4): p. 433-454.
121. Foulds, P.G., et al., *A longitudinal study on alpha-synuclein in blood plasma as a biomarker for Parkinson's disease.* Sci Rep, 2013. **3**: p. 2540.
122. Lau, A., et al., *alpha-Synuclein strains target distinct brain regions and cell types.* Nat Neurosci, 2020. **23**(1): p. 21-31.
123. Shahnawaz, M., et al., *Discriminating alpha-synuclein strains in Parkinson's disease and multiple system atrophy.* Nature, 2020. **578**(7794): p. 273-277.
124. Ashok, A. and N. Singh, *Prion protein modulates glucose homeostasis by altering intracellular iron.* Sci Rep, 2018. **8**(1): p. 6556.
125. Strom, A., et al., *Pronounced cytosolic aggregation of cellular prion protein in pancreatic beta-cells in response to hyperglycemia.* Lab Invest, 2007. **87**(2): p. 139-49.
126. Pan, I., N. Roitenberg, and E. Cohen, *Vesicle-mediated secretion of misfolded prion protein molecules from cyclosporin A-treated cells.* FASEB J, 2018. **32**(3): p. 1479-1492.
127. Katorcha, E., et al., *Cross-seeding of prions by aggregated alpha-synuclein leads to transmissible spongiform encephalopathy.* PLoS Pathog, 2017. **13**(8): p. e1006563.
128. Morales, R., *Prion strains in mammals: Different conformations leading to disease.* PLoS Pathog, 2017. **13**(7): p. e1006323.
129. Rodriguez Camargo, D.C., et al., *The redox environment triggers conformational changes and aggregation of hIAPP in Type II Diabetes.* Sci Rep, 2017. **7**: p. 44041.
130. Nanga, R.P., et al., *Structure and membrane orientation of IAPP in its natively amidated form at physiological pH in a membrane environment.* Biochim Biophys Acta, 2011. **1808**(10): p. 2337-42.
131. Patil, S.M., et al., *Dynamic alpha-helix structure of micelle-bound human amylin.* J Biol Chem, 2009. **284**(18): p. 11982-91.
132. Mirecka, E.A., et al., *Beta-Hairpin of Islet Amyloid Polypeptide Bound to an Aggregation Inhibitor.* Sci Rep, 2016. **6**: p. 33474.
133. Coles, M., et al., *Solution structure of amyloid beta-peptide(1-40) in a water-micelle environment. Is the membrane-spanning domain where we think it is?* Biochemistry, 1998. **37**(31): p. 11064-77.
134. Watson, A.A., D.P. Fairlie, and D.J. Craik, *Solution structure of methionine-oxidized amyloid beta-peptide (1-40). Does oxidation affect conformational switching?* Biochemistry, 1998. **37**(37): p. 12700-6.
135. Hoyer, W., et al., *Stabilization of a beta-hairpin in monomeric Alzheimer's amyloid-beta peptide inhibits amyloid formation.* Proc Natl Acad Sci U S A, 2008. **105**(13): p. 5099-104.
136. Gremer, L., et al., *Fibril structure of amyloid-beta(1-42) by cryo-electron microscopy.* Science, 2017. **358**(6359): p. 116-119.
137. McKnelly, K.J., et al., *Effects of Familial Alzheimer's Disease Mutations on the Assembly of a beta-Hairpin Peptide Derived from Abeta16-36.* Biochemistry, 2022. **61**(6): p. 446-454.
138. Ono, K., et al., *Cross-seeding effects of amyloid beta-protein and alpha-synuclein.* J Neurochem, 2012. **122**(5): p. 883-90.

139. Vasconcelos, B., et al., *Heterotypic seeding of Tau fibrillization by pre-aggregated Abeta provides potent seeds for prion-like seeding and propagation of Tau-pathology in vivo.* Acta Neuropathol, 2016. **131**(4): p. 549-69.
140. Morales, R., et al., *Molecular cross talk between misfolded proteins in animal models of Alzheimer's and prion diseases.* J Neurosci, 2010. **30**(13): p. 4528-35.
141. Bibow, S., et al., *The dynamic structure of filamentous tau.* Angew Chem Int Ed Engl, 2011. **50**(48): p. 11520-4.
142. Fitzpatrick, A.W.P., et al., *Cryo-EM structures of tau filaments from Alzheimer's disease.* Nature, 2017. **547**(7662): p. 185-190.
143. Zhang, W., et al., *Heparin-induced tau filaments are polymorphic and differ from those in Alzheimer's and Pick's diseases.* Elife, 2019. **8**.
144. Waxman, E.A. and B.I. Giasson, *Induction of intracellular tau aggregation is promoted by alpha-synuclein seeds and provides novel insights into the hyperphosphorylation of tau.* J Neurosci, 2011. **31**(21): p. 7604-18.
145. Rao, J.N., et al., *A combinatorial NMR and EPR approach for evaluating the structural ensemble of partially folded proteins.* J Am Chem Soc, 2010. **132**(25): p. 8657-68.
146. Ulmer, T.S., et al., *Structure and dynamics of micelle-bound human alpha-synuclein.* J Biol Chem, 2005. **280**(10): p. 9595-603.
147. Mirecka, E.A., et al., *Sequestration of a beta-hairpin for control of alpha-synuclein aggregation.* Angew Chem Int Ed Engl, 2014. **53**(15): p. 4227-30.
148. Guerrero-Ferreira, R., et al., *Cryo-EM structure of alpha-synuclein fibrils.* Elife, 2018. **7**.
149. Tuttle, M.D., et al., *Solid-state NMR structure of a pathogenic fibril of full-length human alpha-synuclein.* Nat Struct Mol Biol, 2016. **23**(5): p. 409-15.
150. Petkova, A.T., et al., *A structural model for Alzheimer's beta -amyloid fibrils based on experimental constraints from solid state NMR.* Proc Natl Acad Sci U S A, 2002. **99**(26): p. 16742-7.
151. Zahn, R., et al., *NMR solution structure of the human prion protein.* Proc Natl Acad Sci U S A, 2000. **97**(1): p. 145-50.
152. Knaus, K.J., et al., *Crystal structure of the human prion protein reveals a mechanism for oligomerization.* Nat Struct Biol, 2001. **8**(9): p. 770-4.
153. Wang, L.Q., et al., *Cryo-EM structure of an amyloid fibril formed by full-length human prion protein.* Nat Struct Mol Biol, 2020. **27**(6): p. 598-602.
154. Apostol, M.I., et al., *Crystallographic studies of prion protein (PrP) segments suggest how structural changes encoded by polymorphism at residue 129 modulate susceptibility to human prion disease.* J Biol Chem, 2010. **285**(39): p. 29671-5.
155. Biljan, I., et al., *Structural basis for the protective effect of the human prion protein carrying the dominant-negative E219K polymorphism.* Biochem J, 2012. **446**(2): p. 243-51.
156. Weirich, F., et al., *Structural Characterization of Fibrils from Recombinant Human Islet Amyloid Polypeptide by Solid-State NMR: The Central FGAILS Segment Is Part of the beta-Sheet Core.* PLoS One, 2016. **11**(9): p. e0161243.
157. Alexandrescu, A.T., *Amide proton solvent protection in amylin fibrils probed by quenched hydrogen exchange NMR.* PLoS One, 2013. **8**(2): p. e56467.
158. Bedrood, S., et al., *Fibril structure of human islet amyloid polypeptide.* J Biol Chem, 2012. **287**(8): p. 5235-41.

Table 1: Biological characteristics of the main amyloid forming proteins described in this review. For each of the amyloid forming protein, their expression sites, size of the propeptide and matured peptide, secretion mechanisms, circulation, internalization mechanisms, fibrillation properties and the associated pathologies are given in the first to seventh column, respectively.

	Expressed in	Amino Acid Number of Propeptide > peptide	Secretion mechanism	Circulates	Internalization (species and mechanism)	Fibrils In vivo	Pathology
hIAPP (amylin)	pancreatic β-cells, enteroendocrine cells (G cells) [106]	89 > 37 [106]	Vesicles [106]	through blood [106]	Monomer & oligomer Several pathways including direct entry and/or endocytose with receptors [53]	fibrils alone & cross fibrils with Aβ, αsynuclein or Tau [33, 35]	T2DM [5, 13] Only one strain
Amyloid-beta (Aβ)	Neurons & astrocyte [107]	695 (APP in brain) > 42 Several cleavage leading to many Isoforms 40/42 1-14,1-15,1-16 [108]	Released from transmembrane precursor after cleavage by Beta and gamma secretase [107]	through blood [109]	Monomer & oligomers Endocytose with apoE Receptors (LRP1, VLDLR) [110]	fibrils alone and Glycated [59] Cross fibrils with hIAPP, Tau & αsynuclein [32]	Alzheimer [68] Various stains [108]
Tau	Neurons, Glial cells, Pancreatic β-cells [33]	441 to 352 5 adult isoforms splicing variant & 1 fetal [111]	Free & vesicle/exosome [112, 113]	from neuron to neuron [62] Through blood when phosphorylated [114]	Monomers & oligomers Several pathways including Endocytose controlled by LRP1 & amyloids precursors [62, 115, 116]	Ser/Thr-Pro Phosphorylated forms [58] Request cofactor (such as heparin, RNA) [29] Cross fibrils with hIAPP, Aβ & α-synuclein [32, 33, 35]	Tauopathies [110] (among which Alzheimer linked to different conformations of Tau protein = strains) Various stains [117]
Alpha synuclein (α-synuclein)	Neurons (in brain & intestine) & pancreatic β-cells [118]	14[illegible] 5 Isoforms splicing variant (140,126,112,98,41) [119]	Free, vesicles & tunnelling nanotubes [120]	along axone, In Cerebro Spinal Fluid and blood [121]	Oligomers Several pathways including pore, endocytose, receptor (EGF), interaction with heparane sulfate [120]	fibrils alone and glycated Cross fibrils with hIAPP, Aβ & Tau [32, 33, 35]	Parkinson, Lewy bodies Disease, Multiple Systems Atrophy Various stains with brain region specificity [122, 123]
Prion	Neurons & Pancreatic β-cells [124, 125]	254 > 234 (ovin) ou 231 (human, mouse) several cleavage sites isoforms	Vesicles [126]	through lymphatic system [126]	Monomer & oligomer Endocytose via Clatherin and Calveolin	fibrils alone [32] Cross fibrils with alpha synuclein [32, 127]	Kuru, Creutzfeldt Jakob disease, GSS Gerstmann-Sträussler-Scheinker, FFI Fatal familial insomnia Various stains [128]Interspecies transmission

Table 2: Physicochemical properties of the main amyloid forming proteins described in this review. For each of the amyloid forming protein, their amino acid composition, structure of monomer, fibrils, cross-fibrils in vivo and in vitro are given in the first to fifth column, respectively.

	Amino Acid number	Structures monomer	Structures fibrils	Structure Cross Fibrils	Cross Fibrils In vitro
hIAPP (amylin)	37	NMR non-folded in solution (PDB ID: 5MGQ) [129] NMR in membrane-like micelles (PDB ID: 2KB8, 2L86) [130, 131] NMR complexed in solution (PDB ID : 5K5G) [132]	Cryo-EM (PDB ID: 6Y1A) [23] Cryo-EM with SUMO tag (PDB ID: 6VW2) [21] Solid state NMR (no PDB) [22] Polymorphs (PDB ID: 7M61, 7M62, 7M64, 7M65) [20]	hIAPP-α-synuclein (AFM) [118] No structural data for hIAPP with Aβ, Tau or PrP	IAPP-Aβ [32] hIAPP- α-synuclein [118]
Amyloid-beta (Aβ)	42	NMR Aβ40 in SDS micelles (PDB ID: 1BA4) [133] NMR Aβ40 in solution (PDB ID: 1BA6) [134] NMR Aβ42 complexed in solution (PDB ID : 2OTK) [135]	Cryo-EM Aβ42 (PDB ID: 5OQV) [136] Solid state NMR Aβ42 (no PDB) [132] Polymorphs (PDB ID:2MVX) [28] Fragments mutant (PDB ID:7JQK, 7JQU) [137]	No structural data for Aβ with hIAPP, α-synuclein, Tau or PrP	Aβ-hIAPP [28] Aβ-α-synuclein [138] Aβ-tau [139] Aβ-PrP [140]
Tau	441	NMR in solution Full length tau 1 structure RMN (no PDB) [141]	No full length structure Paired helical and straight filaments (PDB ID: 5O3L) [142] Pronase-treated paired helical filament (PDB ID: 5O3O) [142] Straight filament (PDB ID: 5O3T) [142] Polymorphs (PDB ID:6QJH,6QJM,6QJP,6QJQ) [143]	No structural data for Tau with hIAPP, Aβ, α-synuclein or PrP	Tau-Aβ [139] Tau- α-synuclein [144]
Alpha synuclein (α-synuclein)	140	NMR full length in micelle (PDB ID: 1XQ8 and 2KKW) [145, 146] NMR full length in solution complexed (PDB ID : 4BXL) [147]	Cryo-EM (PDB ID: 6H6B) [148] Solid state NMR (PDB ID: 2N0A) [149] Polymorphs (PDB ID: 6XYO,6XYP,6XYQ) [27]	No structural data for α-synuclein with hIAPP, Aβ, Tau or PrP	α-synuclein –hIAPP [148] α-synuclein-Aβ [150] α-synuclein –Tau [144]
Prion	253	Domain 23-230 by NMR (PDB ID: 1QLX, 1QLZ, 1QM0, 1QM1, 1QM2 and 1QM3) [151] Domain 90-231 by X-Ray at pH 8 (PDB ID: 1I4M) [152]	Cryo-EM (PDB ID: 6LNI) [153] Polymorphs of fragments (PDB ID:2LFT;3NHC,3NHD) [154, 155]	No structural data for prion with hIAPP, Aβ, Tau or α-synuclein	PrP- α-synuclein [127] PrP-Aβ [140]

Figures legend

Figure 1: Maturation of hIAPP. The pre-propeptide (of 89 amino acids) is expressed in the endoplasmic reticulum (ER) from a nuclear gene located on the short arm of chromosome 12. The signal peptide cleavage in position 22 takes place in the ER. The propeptide is further cleaved by two endoproteases prohormone convertase (PC1/3 and PC2) in the trans-golgi network. This pH-dependent process involves the PC2 on the N-terminus side whereas the PC1/3 acts on the C-terminus side. The carboxypeptidase E (CPE) removes the carboxyterminal dibasic aminoacids (KK) and the peptidyl amidating monooxygenase (PAM) cleaves the glycine and amidates the tyrosine. Finally, a disulfide bond is formed between cysteins 2 and 7 of the mature hIAPP of 37 amino acids.

Figure 2: hIAPP fibrils description. TEM image of multiple (A) and unique (B) fibril(s). Three-dimensional model of fibril generated from cryo-EM images (C). hIAPP amino acids forming β-sheets and involved in fibril formation in various experimental conditions (D). Comparison of hIAPP structures obtained by solid state NMR (dark green [22] and green [150]), by proton exchanged NMR (light green [157]), by EPR (grey [158]), by liquid NMR in a protein complex (brown [132]), by cryo-EM (yellow and orange for wild type [23] and fused proteins [21], respectively). Cryo-EM of hIAPP fibrils seeded by patient-extracted fibrils, 4 polymorphs: light blue to dark blue [20-23]. (E) Cryo-EM of hIAPP S20G fibrils (3 polymorphs: dark purple, purple and pink/striped pink [25].

Figure 3: Amyloid peptide synthesis, circulation between pancreas and brain, and cross fibril formation. hIAPP is synthesized in the pancreas and circulates to the brain where it participates in the formation of cross fibrils with Aβ, Tau and α-synuclein in neurons and glial cells. Tau, PrP and α-synuclein are also synthesized in the pancreas, but it is not unknown if the observed cross fibrils within the β-cells are due to this local synthesis or to the circulation of these proteins from the brain. Concerning Aβ synthesized in the brain, its circulation to the pancreas leads to the formation of cross fibrils with hIAPP at the surface of the islets (green, red and blue circles correspond to alpha, beta and delta cells, respectively).

Figure 4: Three-dimensional models of the main human amyloid fibrils gained from cryo-EM images. hIAPP (PDB ID: 6Y1A), Tau (PDB ID: 5O3L), Aβ (PDB ID: 5OQV), α-synuclein (PDB ID: 6H6B) and prion (PDB ID: 6LNI). (A) Top line shows the side views of the fibrils whereas (B) shows top views and reveals monomer packing. The stacking of hIAPP monomers that have a “S” shape lead to various interactions within the fibril, whereas the stacking of Tau monomers with a “L” shape have reduced number of interactions within the fibril. Aβ monomers have a mixed “LS” shape which “S” part have structural features similar to hIAPP (in agreement with the sequence similarities). This part is involved in the “heart” of the fibril. The α-synuclein monomer has a more complex structure and its stacking in the fibril exhibits a large interface between the monomers. Finally, the prion monomers have an elongated shape and short contact region within the fibril involving charged residues. (C) shows the protofilament interface with residues involved shown as spheres. (D) hot spot sequence of the interface with residues in interaction written as big letters.

Figure 5: hIAPP from synthesis and physiology to cellular toxicity. hIAPP is produced and matured in granules within the pancreatic β-cell (1). Once secreted (2) hIAPP may enter the blood circulation (3) and is targeted to other organs. hIAPP can also act in a paracrine way (4). hIAPP interacts with membrane lipids (5), oligomerizes and damages the membrane by different mechanisms such as pore formation (6). hIAPP interacts with the membrane leading to endocytosis (7). hIAPP also

interacts with the AMY receptor complex (8). At low concentration, it activates cAMP dependent pathway and regulates insulin. At high concentration, hIAPP enters β-cell through a membrane receptor. hIAPP can also interact with RAGE activating caspase3 leading to cell apoptosis (9). hIAPP oligomers can be trapped by soluble RAGE (sRAGE) inhibiting fibril formation and cell toxicity (10). Within the cell, hIAPP can form fibrils targeting mitochondria (11), inducing ROS production, which increases fibril formation damaging mitochondria and leading to cell death. hIAPP interacts with macrophages (12).

Figure 6: Proposed targets to prevent hIAPP fibril formation and cellular toxicity. (1) Prevent the loss of granular balance to avoid hIAPP liberation in the non-acidic cytoplasm that favors fibrillation. (2) After its secretion, hIAPP can form toxic species (oligomers, protofibrils) which formation can be targeted developing various classes of inhibitors. (3) Targeting membrane cholesterol content could prevent hIAPP interaction with the membrane and thus, pore formation and/or hIAPP internalization. (4,5) Deciphering the interactions of hIAPP with receptors (AMY, RAGE) is a key for the development of specific antagonists. (6) Characterization of the intracellular mechanisms leading to the fibril formation could help in the development of regulators and novel inhibitors. (7) Regulation of ROS production could be targeted, especially, among others, those from mitochondria through TSPO regulation.

Figure 1.

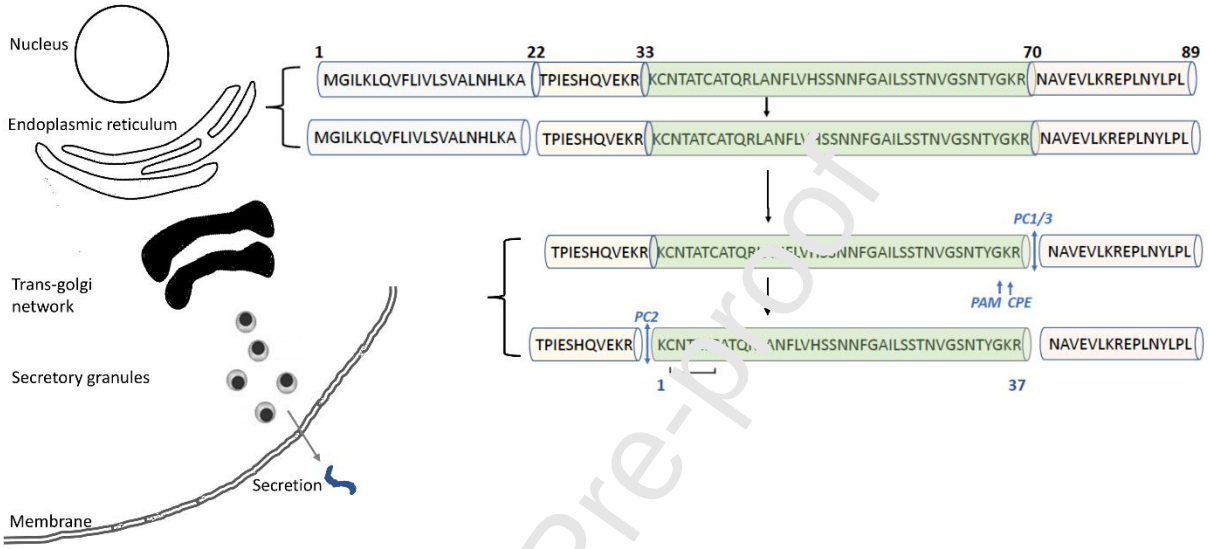


Figure 2.

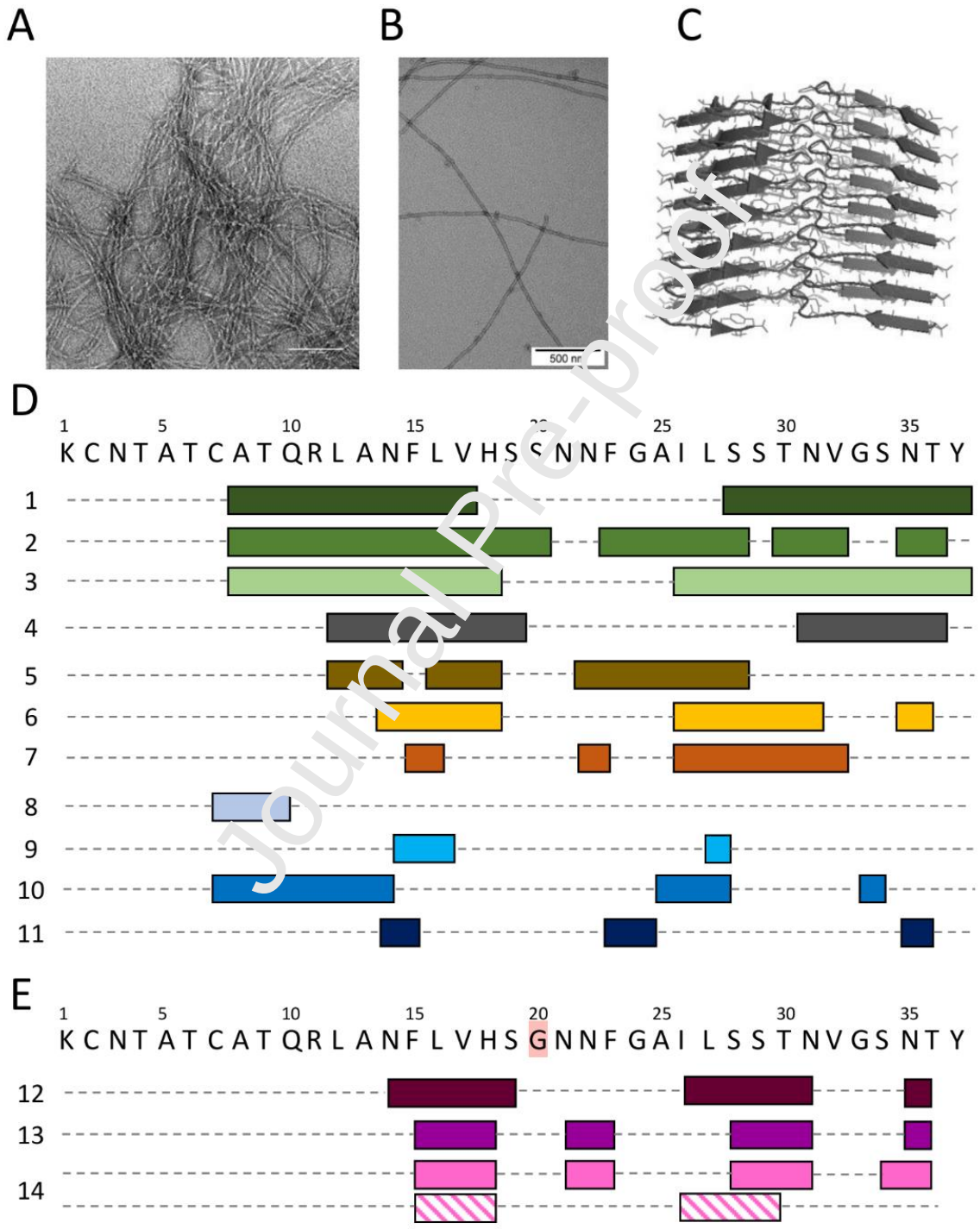


Figure 3.

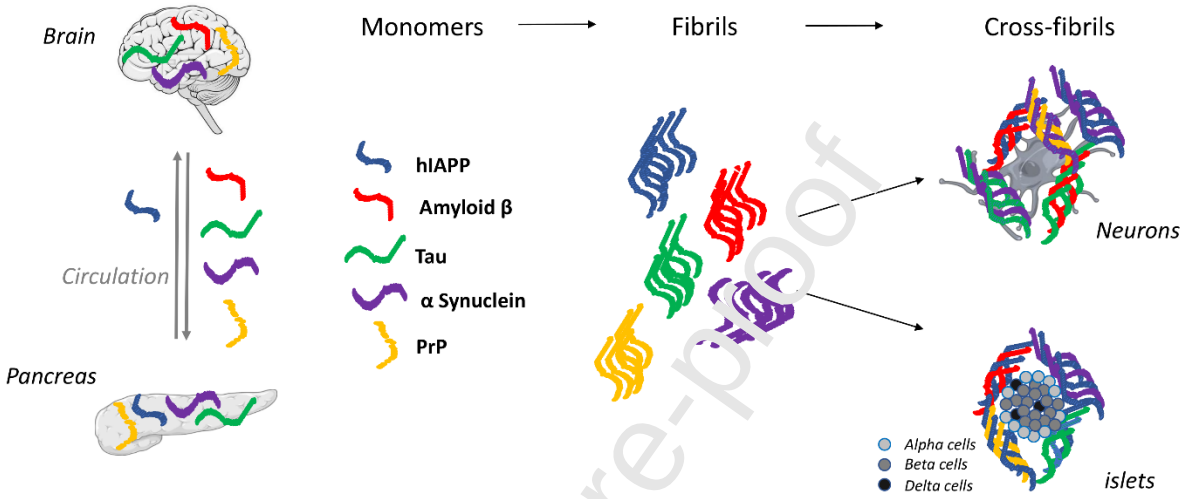


Figure 4.

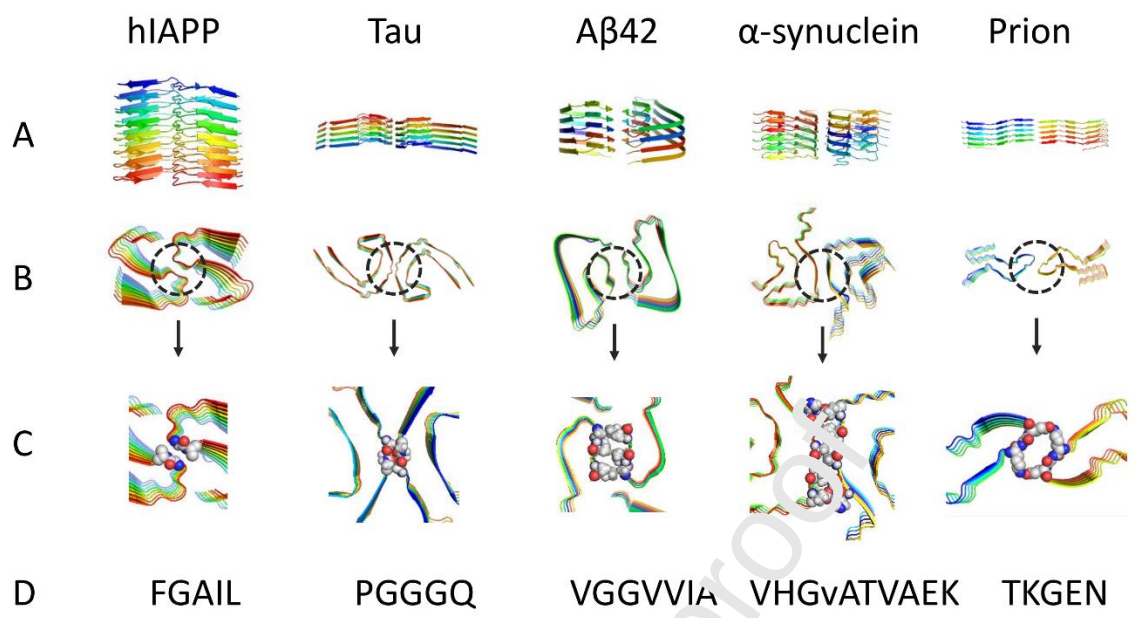
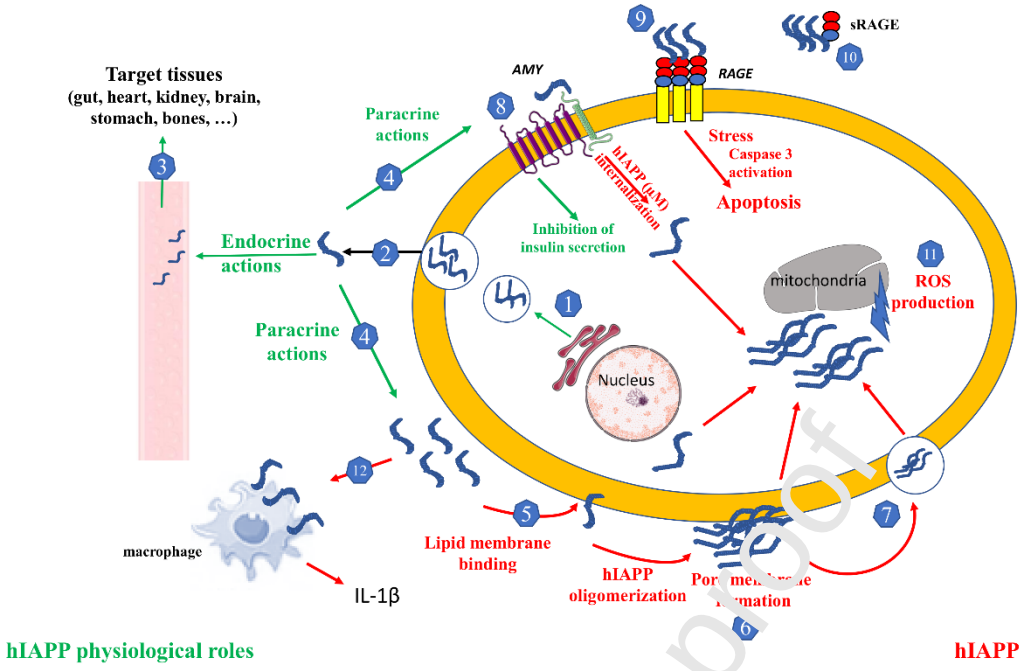


Figure 5.



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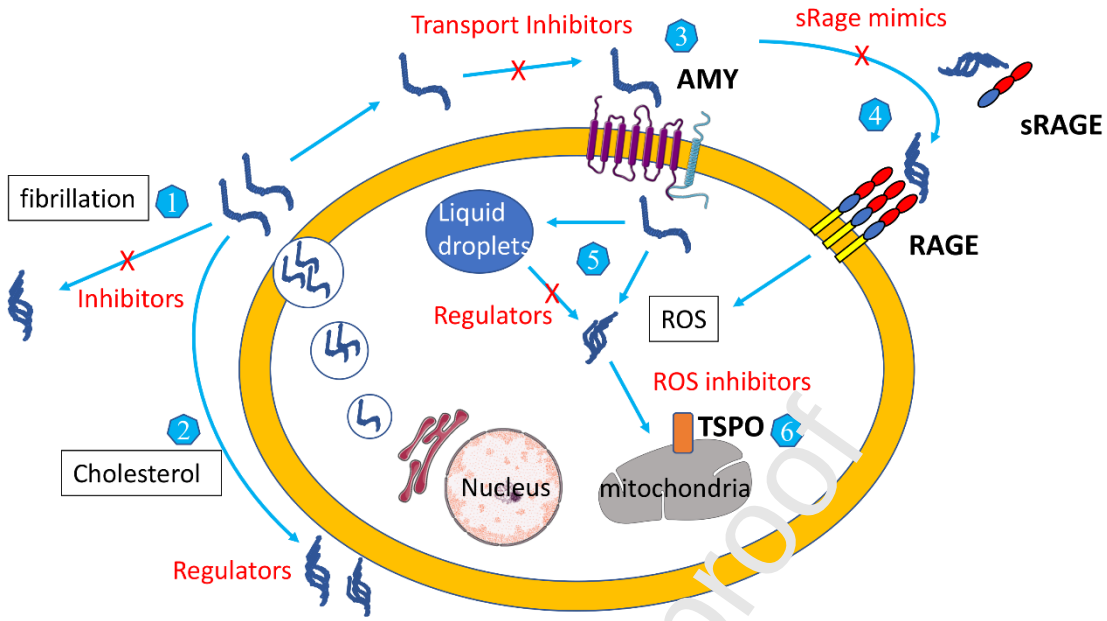
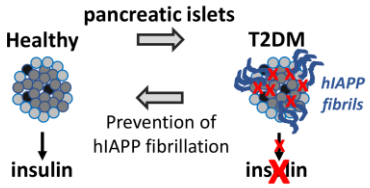


conflict

No conflict of interest to declare

Graphical abstract



Highlights

- How to prevent hIAPP fibrils formation to preserve pancreatic beta cells?
- What do we know about the interacting mechanism of hIAPP with cell proteins/lipids?
- What can we learn from other amyloid proteins to define hIAPP fibrils formation?
- How to use high resolution atomic structures of fibrils to design new inhibitors?
- How to optimize the gap between molecular approaches and therapeutics?