Prion-Like Protein Aggregates and Type 2 Diabetes

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Type 2 diabetes (T2D) is a highly prevalent metabolic disease characterized by chronic insulin resistance and β-cell dysfunction and loss, leading to impaired insulin release and hyperglycemia. Although the mechanism responsible for β-cell dysfunction and death is not completely understood, recent findings suggest that the accumulation of misfolded aggregates of the islet amyloid polypeptide (IAPP) in the islets of Langerhans may play an important role in pancreatic damage. Misfolding and aggregation of diverse proteins and their accumulation as amyloid in different organs is the hallmark feature in a group of chronic, degenerative diseases termed protein misfolding disorders (PMDs). PMDs include highly prevalent human illnesses such as Alzheimer’s and Parkinson’s disease, as well as more than 25 rarer disorders. Among them, prion diseases are unique because the pathology can be transmitted by a proteinaceous infectious agent, termed a prion, which induces disease by propagating protein misfolding and aggregation. This phenomenon has a striking resemblance to the process of protein misfolding and aggregation in all of the PMDs, suggesting that misfolded aggregates have an intrinsic potential to be transmissible. Indeed, recent studies have shown that the pathological hallmarks of various PMDs can be induced in vivo under experimental conditions by inoculating tissue extracts containing protein aggregates into animal models. In this review, we describe our current understanding of the molecular mechanism underlying the prion-like transmission of protein aggregates and its possible role in T2D.

Protein misfolding disorders (PMDs) are a group of diseases in which at least one protein or peptide has been shown to misfold, aggregate, and accumulate in tissues, leading to cellular damage and organ dysfunction. There are at least 25 different diseases in the PMD group, including several neurodegenerative disorders such as Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease (HD), the transmissible spongiform encephalopathies (TSEs), and amyotrophic lateral sclerosis (ALS), as well as diverse systemic disorders such as familial amyloid polyneuropathy, type 2 diabetes (T2D), secondary amyloidosis, and dialysis-related amyloidosis (Soto 2003). Early postmortem histopathological studies linked the accumulation of protein deposits composed of different proteins (such as Aβ and tau in AD, α-synuclein in PD, polyglutamine [polyQ] extended huntingtin in HD, islet amyloid poly-
peptide [IAPP] in T2D, and prion protein [PrP] in TSEs) with disease pathology (Soto 2003). Genetic studies have shown that mutations in the genes encoding the proteins that predominantly compose the aggregates are associated with inherited transmission of many PMDs (Hardy and Gwinn-Hardy 1998; Soto 2003). Vertical transmission of these mutations resulted in an extensive burden of protein aggregates, earlier disease onset, and increased disease severity compared with sporadic cases (Hardy and Gwinn-Hardy 1998). Finally, transgenic expression of disease-specific human genes harboring the associated mutations in animal models reproduced several clinical and pathological characteristics of PMDs, supporting the key contribution of protein aggregates in these diseases (Moreno-Gonzalez and Soto 2012). Among PMDs, prion diseases are considered unique because misfolded prions transmit disease through an infectious route (Prusiner 1998). Aggregates of misfolded prion protein transmit disease by seeding the aggregation of the host prion protein, resulting in the accumulation of large quantities of these toxic aggregates in the brain (Prusiner 1998; Soto et al. 2006; Soto 2012). Interestingly, we and others have recently demonstrated that several amyloid pathologies can be experimentally transmitted by a prion-like mechanism in various cellular and animal models of diverse diseases (Desplats et al. 2009; Frost et al. 2009; Ren et al. 2009; Brundin et al. 2010; Westermark and Westermark 2010; Jucker and Walker 2011; Prusiner 2012; Soto 2012). Furthermore, the prion-like propagation of aggregates appears to significantly contribute to the spatiotemporal spreading of disease pathology in affected individuals. In this review, we discuss the role of protein misfolding in T2D and the possibility of prion-like transmission of T2D-associated protein aggregates.

TYPE 2 DIABETES AND IAPP AGGREGATES

T2D, also known as non-insulin-dependent diabetes (NIDDM), is a widespread metabolic disease. It is most prevalent in adults over the age of 40 and accounts for 90%–95% of the total number of diabetic patients. Currently, 285 million people worldwide are affected by T2D, and the number is predicted to increase progressively in future years, reaching as many as 438 million by 2030 (Shamseddeen et al. 2011). Clinico-pathologically, T2D is characterized by chronic insulin resistance, progressive loss of β-cell function (Kahn 2003), and β-cell mass (Butler et al. 2003), leading to impaired insulin release and hyperglycemia. In healthy individuals, insulin, which is secreted by β-cells in pancreatic islets, plays a major role in maintaining a normal blood sugar level (euglycemia). During insulin resistance, when normal levels of insulin fail to maintain euglycemia, there is a compensatory increase in insulin secretion from β-cells. However, genetic and environmental factors are believed to predispose some individuals (~20% of the population) to β-cell failure under chronic insulin resistance (Kahn et al. 2014). Both dysfunction and loss of β-cells are frequently ascribed to be consequences of glucolipotoxicity (Poitout and Robertson 2002; El-Assaad et al. 2003), islet cholesterol accumulation (Brunham et al. 2010), and islet inflammation (Donath and Shoelson 2011). However, accumulating evidence suggests that toxic aggregates of IAPP, a neuroendocrine polypeptide hormone (Westermark et al. 1987), or amylin (Cooper et al. 1988) may substantially contribute to β-cell dysfunction and loss (Hull et al. 2004; Haataja et al. 2008).

IAPP is predominantly expressed by β-cells as 89-amino-acid pre-pro-IAPP. After processing in the endoplasmic reticulum (ER)–Golgi network (Wang et al. 2001; Marzban et al. 2004, 2005), the 37-amino-acid-long IAPP is stored in secretory granules with insulin, awaiting stimulus for secretion. Although the exact role of IAPP in diabetes is not fully understood, its proposed functions include inhibition of insulin secretion, delay in gastric emptying, diminishing appetite, suppression of glucagon release (for review, see Westermark et al. 2011), and suppression of tumorigenesis (Venkatanarayan et al. 2015).

IAPP amyloid accumulation was initially observed more than 100 years ago (Opie 1901). However, the clinical significance of this observation remained unappreciated because not all
of the T2D patients manifested islet amyloid. Also, low levels of islet amyloid were found in healthy individuals (Ludwig and Heitner 1967; Westmark 1972; Westmark and Wilander 1978). Further studies established that islet amyloid deposits can be found in >90% of T2D patients (Westmark 1972; Clark et al. 1988; Betsholtz et al. 1989b; Johnson et al. 1989; Jurgens et al. 2011). Eventually, studies of other PMDs (such as AD or PD) showed that aged, healthy individuals, presumably in the process of developing the disease, may show a substantial accumulation of protein aggregates (Pike et al. 2007; Chételat et al. 2013). Several studies linked IAPP aggregation with β-cell loss and the progression of T2D. Pancreatic β-cell mass is determined by a balance between individual β-cell size, proliferation, neogenesis, and apoptosis. Autopsy studies from T2D patients suggested that IAPP aggregates are associated with increasing β-cell apoptosis, leading to loss of β-cell mass (Clark et al. 1988; Butler et al. 2003; Jurgens et al. 2011). Similarly, IAPP aggregation was suggested to be a crucial determinant of declining β-cell function in clinically transplanted islets (Westmark et al. 2005). Mutation in the IAPP gene, which enhances its amyloid forming propensity (Sakagashira et al. 2000; Ma et al. 2001), was associated with early induction of T2D (Janson et al. 1996; Matveyenko and Butler 2006). In a recent review, we summarized the mechanism of IAPP aggregate formation and toxicity and established a detailed comparison with other protein aggregates associated with PMDs of the central nervous system (CNS), such as amyloid-β (Aβ) and tau in AD, α-synuclein in PD, or prions in prion diseases (Mukherjee et al. 2015). Here, we will focus on the possibility of prion-like propagation of IAPP aggregates and their putative role in T2D.

MISFOLDED PROTEIN AGGREGATES AS INFECTIOUS AGENTS: THE PRION STORY

Prion diseases are a group of fatal neurodegenerative diseases that affect humans, cattle, and several other mammals (Soto 2011). The hallmark event in prion disease is the conversion of the native prion protein (PrP\(^\text{C}\)) into a misfolded, aggregated, and protease-resistant conformation called PrP\(^{\text{Sc}}\), followed by its accumulation in the brain (Prusiner 1998). Clinically, prion diseases are characterized by a long presymptomatic phase in which PrP\(^{\text{Sc}}\) accumulates silently and progressively. This phase is followed by an aggressive and usually short symptomatic phase that leads inevitably to death (Prusiner 1998). Prion diseases can be transmitted from
animal to animal, animal to human, or human to human by an unorthodox infectious agent (devoid of nucleic acids) thought to be solely composed of the misfolded prion protein (Prusiner 1998). At the molecular level, the mechanism of prion transmission is best explained by the seeding/nucleation model of protein aggregation. This model is characterized by an initial lag phase in which the protein misfolds and self-associates, forming small oligomers that act as nuclei or seeds to catalyze further polymerization. Once the seed is formed, it can nucleate/seed aggregation of large amounts of monomers, forming aggregates comprising a dynamic range of sizes. Large aggregates can be fragmented to produce more seeds, leading to a vicious cycle (Jarrett and Lansbury 1993; Soto et al. 2006). Prion infectivity depends on the ability of misfolded prion protein aggregates to nucleate the misfolding and aggregation of the host prion protein (Soto 2012). In cases of prion disease in both mammals and humans, it has been shown that infection can be initiated by exposure to PrPSc-contaminated materials (i.e., tissue, blood, and surgical materials). The acquisition of these exogenous seeds transmits the disease by inducing the conversion of the endogenous prion protein, resulting in a large accumulation of toxic PrPSc in the brain (Prusiner 1998; Soto 2012).

### SPREADING OF PROTEIN AGGREGATES WITHIN AFFECTED TISSUE AND ITS POSSIBLE ROLE IN T2D PATHOLOGY

Interestingly, the formation of misfolded aggregates in all other PMDs follows the same seeding/nucleation principle responsible for prion replication (Soto 2012), suggesting that other PMDs may also be transmissible in a similar manner as prions (Soto et al. 2006; Soto 2012). The possibility that other protein aggregates may be transmissible has been supported by a large collection of recent studies demonstrating prion-like propagation of protein aggregates associated with AD, PD, HD, and ALS (Danzer et al. 2009; Frost et al. 2009; Ren et al. 2009). In fact, cell-to-cell propagation of protein aggregates has been suggested to play a key role in the spatiotemporal progression of the pathology within the affected tissues (Guo and Lee 2014). Propagation of the protein aggregates from cell to cell appears to depend on the extracellular release of the aggregates and their internalization by their neighboring cells. Death of aggregate-laden cells or shuttling exosomes has been shown to contribute to the release of aggregates to the extracellular space (Fevrier et al. 2004; Rajendran et al. 2006; Aguzzi and Rajendran 2009). Endocytosis, pinocytosis, or simple diffusion through membranes between adjacent cells has been proposed as the mechanism of cellular internalization of these aggregates in various PMDs (Burück et al. 1997; Sung et al. 2001; Nagele et al. 2002; Frost et al. 2009). It is also possible that aggregates are transferred directly from cell to cell without the need to move through the extracellular space, for example, by transsynaptic connections or tunneling nanotubes (Liu et al. 2012; Costanzo et al. 2013).

In the case of IAPP, evidence shows that IAPP oligomerization begins intracellularly, perhaps in secretory granules of islet β-cells (Guo et al. 2010). Degenerating β-cells may release these aggregates, which subsequently accumulate extracellularly as large amyloid deposits, a process that occurs in several other systemic amyloid diseases. Indeed, it has been reported that the number of β-cells is selectively decreased in islets containing IAPP aggregates (Jurgens et al. 2011). It is interesting to note that our own studies have shown that large amyloid fibrils are able to release oligomers capable of forming seeds under physiological conditions (Shahnavaz and Soto 2012). Based on the findings obtained in other PMDs, it seems possible that IAPP aggregates may be able to propagate from β-cell to β-cell and perhaps even from islet to islet. The proximity among β-cells and the fact that IAPP aggregates appear to be released from cells to the extracellular space supports cell-to-cell transmission. A crucial question is whether IAPP aggregates can propagate from one islet to another by a prion-like mechanism. Although there is no direct evidence, studies of pancreatic tissue from T2D patients have shown that amyloid formation...
initiates in one or a few islets; then at least in some cases, it gradually spreads to other islets in the pancreas (Westermark 1972; Westermark et al. 2011). Similar results were obtained from a longitudinal study in baboons in which islet amyloids were found, initially in 0%–50% of islets without significant change in the total amyloid load. In the second stage, both amyloid severity and prevalence (percentage of islet containing amyloid) increased (9.5%–47.3% and 50%–95%, respectively), followed by a significant increase in amyloid severity (47.3%–68.9%) in the third stage (Guardado-Mendoza et al. 2009). It is important to consider that islets in the pancreas are not physically connected. Therefore, spreading of IAPP aggregates within the pancreas requires a specific route (Fig. 1). The most obvious candidate is by blood circulation because islets are highly vascularized. IAPP aggregates were found between β-cells and adjacent capillaries in both human and rodent models of T2D (de Koning et al. 1994). It is

Figure 1. A schematic model of the possible mechanisms of islet amyloid polypeptide (IAPP) aggregate propagation from islet to islet and spreading into other tissues. IAPP aggregates in individuals with type 2 diabetes (T2D) are mostly located in the pancreas but have also been reported in other organs, including the kidney, heart, and brain. The figure shows how aggregates might spread through the circulation or peripheral nervous system. In the insets, two islets are shown with the vasculature and innervation. The top panel displays massive amounts of IAPP aggregates, both in the form of small, intracellular species as well as large, extracellular deposits, located mostly between β-cells and adjacent capillaries. The axonal innervations from sympathetic, parasympathetic, and sensory nerves are shown in green. In the bottom panel, a similar islet is shown without IAPP aggregates. IAPP aggregates can hypothetically spread from islet to islet using both the circulation and the peripheral nervous system. The dotted black arrows indicate possible routes of IAPP aggregate spreading. For the sake of simplicity, only β-cells are shown in the islets. The diagram is not drawn to scale.
important to highlight that the capillaries in the islets are highly fenestrated and permeable compared with those in the exocrine part of the pancreas (Henderson and Moss 1985). However, there is no direct evidence that IAPP aggregates can leak into the islet capillaries and spread to other islets through circulation. Interestingly, a recent study demonstrated that intravenous injection of synthetic IAPP aggregates can accelerate IAPP aggregate formation in islets in a rodent model of T2D (Oskarsson et al. 2015). Although the amount of IAPP injected in this study is substantially higher than the physiological level of IAPP found in the blood, these results strongly suggest that blood can be an effective route for spreading of IAPP aggregates from islet to islet. Furthermore, IAPP deposits positively stained with Congo red were found in blood vessels of the brain from individuals affected by T2D, suggesting that IAPP aggregates might be present in the circulation (Jackson et al. 2013). It is generally believed that islets are highly innervated by parasympathetic, sympathetic, and sensory projections (Ahren 2000). Protein aggregates related to many PMDs of the CNS have been shown to be efficiently transferred through transsynaptic connections, both anterogradely and retrogradely (for review, see Guo and Lee 2014). In fact, transsynaptic spreading of protein aggregates was recently found to play a key role in the spatiotemporal progress of the disease lesions in models of AD, PD, ALS, and dementia with Lewy bodies. Whether IAPP aggregates are able to spread from islet to islet via innervating axons and the autonomic ganglia is unknown. It is also important to consider that the architecture of the islets, including β-cell arrangement by the capillaries and the extent of innervation, can be significantly different in different species (Bosco et al. 2010; Rodriguez-Diaz et al. 2011).

PRION-LIKE TRANSMISSION OF PROTEIN AGGREGATES IN “REAL LIFE” AND ITS POSSIBLE ROLE IN THE ETIOLOGY OF T2D

As discussed above, a series of recent studies has shown that inoculation of tissue homogenate containing disease-specific protein aggregates or aggregates made of pure proteins can induce or accelerate amyloid pathology in mouse models by a prion-like mechanism of transmission. However, prions are currently the only protein aggregates that have been convincingly demonstrated to be transmissible between individuals under “real life” conditions. The potential for protein aggregates to become infectious depends not only on their ability to convert host protein but also on the stability of the aggregates in the biological system and the bioavailability in the tissue of interest (for a detailed discussion on this topic, see Soto 2012). Because the brain is heavily insulated from the rest of the body, it may be difficult for protein aggregates acquired along systemic routes to reach the brain in sufficient quantities to initiate infection. Here lies a unique feature of prions, which exhibit an extremely high resistance to cellular and physiological clearance mechanisms and are known to self-replicate in peripheral tissues, such as in the lymphatic organs (Aguzzi et al. 2013). It is likely that prions acquired by peripheral routes are substantially amplified before reaching the brain in large quantities. If this argument is correct, other PMDs of the CNS might not be transmissible in real life. This argument would also suggest that systemic PMDs might have a better chance to be transmissible under natural conditions. Supporting this view, the only other case of a PMD shown to be naturally transmissible between individuals is amyloid-A amyloidosis in captive cheetahs (Zhang et al. 2008). A similar transmission of amyloid-A amyloidosis has also been suggested to cause an epidemic of avian amyloidosis (Murakami et al. 2014). There are no epidemiological studies that specifically consider whether T2D could be transmissible from individual to individual. Nevertheless, several studies suggest an infectious-like pandemic increase of T2D incidence. This is mostly attributed to changes in lifestyle and increase in obesity (Matthews and Matthews 2011). Interestingly, several reports indicate increased risk of diabetes after organ transplant (Kasiske et al. 2003; Carey et al. 2012) and blood transfusion (Chern et al. 2001). New-onset diabetes after organ transplant (NODT), such as kidney transplant, is frequently ob-
served in recipients (Kasiske et al. 2003; Carey et al. 2012). This is generally attributed to the use of immunosuppressant drugs by the recipients. It is important to highlight that a recent study reported the presence of IAPP aggregates in the kidney of 48.3% of patients with T2D nephropathy (Gong et al. 2007). Individuals with diabetic nephropathy would likely not be considered as kidney donors; however, it is likely that IAPP aggregates could begin to accumulate in the kidney before the appearance of any clinical symptoms of T2D. In fact, longitudinal studies in nonhuman primates suggest that IAPP accumulation in the pancreas begins well before the appearance of any impairment in glucose metabolism (Guardado-Mendoza et al. 2009). Moreover, a recent report indicates that diseased hearts from obese, prediabetic individuals exhibit oligomeric IAPP, suggesting that the process of IAPP accumulation may begin decades before the onset of overt T2D (Despa et al. 2012). Increased risk of developing impairment in glucose metabolism and diabetes has also been noted in individuals who have received chronic blood transfusion (Chern et al. 2001; Shamshirsaz et al. 2003). Iron-overload-mediated toxicity in the endocrine system is believed to be the underlying cause. Conversely, a recent study reported the presence of oligomeric IAPP in the blood of diabetic rats (Srodulski et al. 2014). However, further studies are required to validate this claim. Although controversial, several studies have reported increased maternal inheritance of T2D in offspring (Alcolado and Alcolado 1991; Young et al. 1995; Arfa et al. 2007). Gestational diabetes in mothers has also been shown to increase the risk of offspring developing diabetes (Damm 2009). Furthermore, a study reported that the offspring of women who were diabetic during pregnancy were more likely to develop T2D than the offspring of women who developed diabetes after giving birth (Pettitt et al. 1988). Mutations in the mitochondrial genome, genetic factors responsible for birth weight, and the intrauterine environment are believed to explain the excess maternal inheritance of T2D (Lin et al. 1994; McCance et al. 1994; Moses et al. 1997). Insulin resistance, which is one of the characteristics of gestational diabetes, may be a prerequisite for pancreatic IAPP accumulation in a mouse model (Couce et al. 1996). Nevertheless, whether pancreatic IAPP aggregates are present in individuals suffering from gestational diabetes is unknown. It is crucial to understand that all of this anecdotal evidence does not imply that T2D is transmissible. However, it does warrant more specific epidemiological studies to fully investigate the possibility. It is also important to highlight that epidemiological tracking of an infectious origin for diseases transmitted by prion-like agents might be very difficult considering the unorthodox rules of transmission for protein-based agents (Soto 2012), as well as the variable and extended time between exposure to the misfolded aggregates and the onset of clinical symptoms (Collinge et al. 2006).

CROSS-SEEDING BETWEEN IAPP AND OTHER PROTEIN AGGREGATES AND ITS ROLE IN T2D

Because the intermediate and end products formed during the seeding/nucleation process are similar in all PMDs, seeds composed of one protein may catalyze the polymerization of other proteins by a mechanism known as heterologous seeding or cross-seeding (Morales et al. 2013). The coexistence of multiple protein aggregates has been reported in various PMDs (Morales et al. 2013), and mixed pathology seems to be the rule rather than the exception. The existence of one PMD has also been shown to increase the risk of developing other PMDs (Morales et al. 2013). Whether multiple protein aggregates are present and contribute to T2D pathology has not been studied in great detail. However, epidemiological studies have shown that T2D patients exhibit an increased risk of developing AD compared with age-matched nondiabetic individuals (Biyelles et al. 2006). IAPP deposition has been reported in the gray matter of the temporal lobe in the brains of T2D patients (Jackson et al. 2013). IAPP deposits were also found in both blood vessels and perivascular spaces, suggesting an influx from peripheral circulation (Jackson et al. 2013).
Interestingly, IAPP deposits in AD patient brains co-localized with Aβ amyloid plaques, suggesting a possible interaction between the two proteins. On the other hand, a large percentage of AD patients simultaneously suffer from T2D or impaired fasting glucose (Janson et al. 2004). Furthermore, AD patients show a higher incidence of islet amyloidosis than healthy individuals. The exact mechanism underlying the risk association between AD and T2D is not completely understood. Several hypotheses have been proposed, including alterations in insulin signaling, hypercholesterolemia, and oxidative stress. It is possible that misfolded proteins implicated in AD and T2D may interact with each other, promoting their heterologous seeding and leading to an increased risk of the disease (Morales et al. 2013). In vitro studies report that IAPP and Aβ can cross-seed each other, enhancing amyloid formation (Ono et al. 2014). The presence of Aβ deposits and hyperphosphorylated tau, the hallmark features of AD, is also reported in the islets of T2D patients, as is Aβ co-localized with IAPP aggregates (Miklossy et al. 2010). Furthermore, a recent study suggests that intravenous injection of pure Aβ fibrils can trigger islet amyloid formation in a rodent model (Oskarsson et al. 2015). However, this group did not observe any Aβ immunoreactivity in the pancreas while analyzing a relatively small number (n = 4) of T2D patients. The interaction may not be restricted to AD and T2D proteins. Indeed, the presence of oligomeric α-synuclein was recently reported in islets of T2D patients and was suggested to impair glucose-stimulated insulin release from β-cells (Steneberg et al. 2013). Although there is some scattered evidence, the presence of other protein aggregates in islets and their role in T2D has not yet been thoroughly explored.

**FUTURE DIRECTIONS**

Evidence showing that IAPP aggregates play a key role in T2D pathogenesis is compelling and is similar to evidence that has established protein aggregates as the widely accepted cause of various neurodegenerative diseases. However, putative relevance of IAPP aggregates in T2D is generally ignored by those in the diabetes research field, first because IAPP aggregates from islets are generally identified by histological methods, using amyloid binding dyes such as thioflavin or Congo red. A thorough biochemical and biophysical characterization, similar to that reported for the aggregates composed of Aβ or prions, has yet to be performed. Islets constitute merely 1%–2% of the pancreatic mass. Thus, the availability of samples for objective characterization is a limiting condition. Second, there are not sufficient studies to differentiate whether IAPP aggregates are inert bystanders that are the consequence of tissue damage during disease or whether they play a crucial role in pathogenesis. Experiments that aim to induce islet amyloid pathology and at least some diabetes-like alterations, just by induction of IAPP aggregation, might be able to address this issue. Moreover, experiments that aim to inhibit islet pathology by inhibiting IAPP aggregation will also provide crucial information. However, not many studies have been done in this regard. From our extensive experience studying PMDs of the CNS and considering the current evidence that implicates IAPP aggregates in T2D pathology (Mukherjee et al. 2015), we argue that IAPP aggregates (perhaps smaller, soluble oligomers) may play a key role in contributing to T2D. The possibility that IAPP aggregates might propagate from islet to islet or even from individual to individual certainly presents a new area of research. β-cell pathology is closely associated with the presence of IAPP aggregates in the same islets. Thus, prion-like propagation of IAPP aggregates might significantly contribute to the spread of islet lesions within the pancreas. Further research exploring this possibility might lead to the discovery of crucial therapeutic targets that will inhibit the propagation of IAPP aggregates from β-cell to β-cell or from islet to islet, restricting the pathological progress of T2D.

**ACKNOWLEDGMENTS**

This work was supported in part by a grant from the National Institutes of Health (GM100453) to C.S. and a Jean B. Kempner postdoctoral fellowship awarded to A.M.
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A. Mukherjee and C. Soto


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Advanced Online Article. Cite this article as Cold Spring Harb Perspect Med doi: 10.1101/cshperspect.a024315

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*Cold Spring Harb Perspect Med* published online February 3, 2017

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<table>
<thead>
<tr>
<th>Experimental Models of Inherited PrP Prion Diseases</th>
<th>Biological Spectrum of Amyotrophic Lateral Sclerosis Prions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joel C. Watts and Stanley B. Prusiner</td>
<td>Magdalini Polymenidou and Don W. Cleveland</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The Prion-Like Behavior of Assembled Tau in Transgenic Mice</th>
<th>Antibody Therapeutics Targeting Aβ and Tau</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florence Clavaguera, Markus Tolnay and Michel Goedert</td>
<td>Gilbert Gallardo and David M. Holtzman</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biology and Pathobiology of TDP-43 and Emerging Therapeutic Strategies</th>
<th>The Transcellular Propagation and Intracellular Trafficking of α-Synuclein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin Guo and James Shorter</td>
<td>George K. Tofaris, Michel Goedert and Maria Grazia Spillantini</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sporadic and Infectious Human Prion Diseases</th>
<th>Biology and Genetics of PrP Prion Strains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robert G. Will and James W. Ironside</td>
<td>Sina Ghaemmaghami</td>
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<tr>
<th>Clinical Spectrum of Amyotrophic Lateral Sclerosis (ALS)</th>
<th>Huntington's Disease: Mechanisms of Pathogenesis and Therapeutic Strategies</th>
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</thead>
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<table>
<thead>
<tr>
<th>Interactions between Microtubule-Associated Protein Tau (MAPT) and Small Molecules</th>
<th>Genetics of β-Amyloid Precursor Protein in Alzheimer's Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jennifer N. Raucht, Steven H. Olson and Jason E. Gestwicki</td>
<td>Julia TCW and Alison M. Goate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Structural Biology of PrP Prions</th>
<th>Prion-Like Protein Aggregates and Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerald Stubbs and Jan Stöhr</td>
<td>Abhisek Mukherjee and Claudio Soto</td>
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</table>

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<thead>
<tr>
<th>Binding Sites for Amyloid-β Oligomers and Synaptic Toxicity</th>
<th>Developing Therapeutics for PrP Prion Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levi M. Smith and Stephen M. Strittmatter</td>
<td>Kurt Giles, Steven H. Olson and Stanley B. Prusiner</td>
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