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Review

Targeting Insulin-Degrading Enzyme to Treat Type 2 Diabetes Mellitus

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Insulin-degrading enzyme (IDE) selectively degrades peptides, such as insulin, amylin, and amyloid β (Aβ) that form toxic aggregates, to maintain proteostasis. IDE defects are linked to the development of type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD). Structural and biochemical analyses revealed the molecular basis for IDE-mediated destruction of amyloidogenic peptides and this information has been exploited to develop promising inhibitors of IDE to improve glucose homeostasis. However, the inhibition of IDE can also lead to glucose intolerance. In this review, I focus on recent advances regarding our understanding of the structure and function of IDE and the discovery of IDE inhibitors, as well as challenges in developing IDE-based therapy for human diseases, particularly T2DM.

Trends

IDE is involved in the process of cellular protein homeostasis (proteostasis) by degrading the monomeric forms of many amyloidogenic peptides to prevent the formation of toxic aggregates and amyloid fibrils.

Consistent with the role of IDE in the clearance of insulin, amylin, and glucagon, three hormones that are vital for glucose homeostasis, IDE defects lead to age-dependent glucose intolerance and are associated with T2DM.

IDE represents a promising therapeutic target for the treatment of T2DM because IDE inhibitors that do not bind the IDE catalytic cleft improve glucose tolerance.

Understanding the catalytic cycle of IDE provides a roadmap toward designing substrate-selective inhibitors for IDE.

Introduction

IDE (EC 3.4.24.56) is an evolutionarily conserved zinc metalloprotease that cleaves and inactivates several bioactive peptides with diverse sequences and structures, thus preventing the formation of peptide aggregates in many subcellular compartments (reviewed in [1–5]). IDE was initially discovered and named based on its ability to bind **insulin** (see Glossary) with high affinity (~10 nM) and rapidly cleave it (K_{cat} = 0.5–2/s) into fragments, causing its inactivation [6,7]. IDE was subsequently found to degrade other bioactive peptides, such as **glucagon**, **amylin**, and **Aβ**. Thus, IDE has been implicated in diverse physiological and pathological functions.

Cellular Regulation of IDE

IDE is expressed in all tissues and its levels can be modulated by many signals, including cellular stress, glucagon, and free fatty acids [4,8,9]. It is localized in the cytosol and growing evidence indicates that its proteolytic activity is subjected to complicated regulation inside cells. IDE readily dimerizes [10,11] and mutational analyses reveal that IDE dimerization allosterically regulates its catalytic activity [12,13]. ATP can enhance the activity of IDE against short peptides, such as bradykinin, but not against large substrates, such as insulin and Aβ [14]. IDE comprises approximately 55-kDa homologous N- and C-domains (IDE-N and IDE-C, respectively) that are connected by a short linker to form the final 110-kDa protein (Figure 1A) [15]. The triphosphate moiety of ATP binds the highly positively charged surface of IDE-C to induce conformational changes in IDE [16,17]. IDE also binds cellular proteins, including components of the cytoskeleton (vimentin and nestin) [18]. These interactions enhance its ability to degrade short peptides but suppress its ability to degrade insulin. Together, IDE dimerization and its binding with ATP and cytoskeletal proteins ensure that the enzyme preferentially degrades short peptides. Physical association of IDE with the 26S proteasome may also contribute to such a preference [1,19].

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IDE exists in various subcellular compartments, including the cytosol, intracellular vesicles, plasma membrane, mitochondria, and extracellular milieu [3,20–22]. Its secretion is mediated by an autophagy-based nonconventional secretory mechanism and can be regulated by both extracellular calcium levels, via the calcium channel, calcium homeostasis modulator protein 1 (CALHM1), and cholesterol-lowering drugs, such as statins [21,22,83]. A sequence motif near its C terminus has been shown to contribute to nonconventional translocation [23]. Similar to intracellular IDE, the catalytic activity of IDE in compartments outside the cytosol might also be regulated by its dimerization and surrounding cellular factors, but less is known about such regulation (see Outstanding Questions).

IDE Substrates and Functions

Insulin, a biologically relevant IDE substrate, has pleiotropic functions, including the regulation of metabolism of sugars, lipids, and amino acids; aberrant levels of insulin and improper responses to insulin and other hormones that control glucose levels are the primary causes of **T2DM** [24]. Insulin has a short half-life in circulation, presumably due to the highly efficient action of the clearance mechanism, such as receptor-mediated internalization and degradation by IDE [25–27]. Insulin has two chains (A and B) held together by disulfide bonds (monomeric insulin). Upon synthesis and processing by pancreatic β cells, insulin oligomerizes to a hexamer and is secreted. As an oligomer, insulin is protected from degradation by IDE, because IDE only cleaves monomeric insulin [7]. IDE cuts both A and B chains once in a processive manner (without breaking the disulfide bonds) to generate nonfunctional insulin fragments [7]. Substantial *in vitro* and *in cyto* evidence supports the role of IDE in the clearance of insulin [1]. Furthermore, IDE-null mutants, gene knockout, and pharmacological inhibition in rodents all result in elevated blood insulin levels (hyperinsulinemia) [5,25,26,28,29].

IDE also degrades and inactivates amylin and glucagon, additional peptides that are crucial to regulating blood glucose levels [5,7,15]. Amylin, also produced by pancreatic β cells, complements the action of insulin by slowing gastric emptying, regulating postprandial glucagon secretion, and reducing food intake [30]. Glucagon, secreted by pancreatic ∝ cells, opposes the action of insulin, particularly in the liver [31]. Glucagon promotes the release of glucose from glycogen, stimulates gluconeogenesis, and triggers the release of fatty acids from stored triglycerides [31]. Glucagon can also enhance the response to stress [32]. Consistent with the role of IDE in the clearance of amylin and glucagon, administration of IDE inhibitors in mice leads to elevated levels of amylin and glucagon and modulates signaling by these hormones [5]. Given that glucose homeostasis is dependent on a complex interplay between many hormones, such as insulin, amylin, and glucagon, the effects of an IDE defect *in vivo* are expected to be complicated. Glucose intolerance is one of hallmarks for T2DM. IDE-knockout (IDE-KO) mice exhibit age-dependent glucose intolerance, likely due to the hyperinsulinemia-associated onset of insulin resistance [25,33]. However, the precise mechanism remains unresolved.

IDE also degrades Aβ, an approximately 4-kDa peptide derived from the cleavage of amyloid precursor protein and the primary component of plaques in the brains of patients with AD [34]. Aβ has a high propensity to form various types of oligomer and amyloid fibril that disrupt communications between neurons and cause cell death [35]. IDE degrades monomeric Aβ, thus preventing formation of oligomers and aggregates. Indeed, mice carrying an IDE inactivation mutation have increased Aβ accumulation and AD phenotypes [25,28]. Conversely, overexpression of IDE in mouse brains leads to reduced Aβ accumulation and retarded progression of AD [36].

While rodent studies clearly show the role of IDE in the degradation of insulin, glucagon, amylin, and Aβ, the clear link of defect in *IDE* gene or activities with T2DM or AD in humans has been elusive. This is due to the complicated factors involved in the progression of these two chronic

Glossary

Amylin: a 37-residue peptide hormone co-secreted with insulin by pancreatic β cells. Amylin works together with insulin to lower blood glucose levels; thus, amylin analogs have been developed to treat diabetes. Human amylin contributes to the formation of islet amyloid, which is associated with the loss of pancreatic β cells and T2DM.
Amyloid β (Aβ): the proteolytic product of amyloid precursor protein that is diverse in size and post-translational modifications. Aβ can readily form aggregates and amyloid fibrils, which are toxic to neurons. Extracellular plaque deposits of Aβ are one of two hallmarks of Alzheimer's disease (the other being intracellular neurofibrillary tangles of protein tau).
Amyloidogenic peptides: small proteins that typically exist as a soluble monomeric precursor but have a high propensity to undergo irreversible conformational changes to form nanometer-size fibrils. Such amyloid fibrils and the intermediate aggregates are usually highly cytotoxic. Aβ, insulin, and human amylin are well-known examples.
Glucagon: a 29-residue peptide hormone that is secreted by pancreatic ∝ cells to elevate blood glucose levels. Glucagon has been formulated for medical uses, such as treating hypoglycemia, β-blocker overdose, and anaphylaxis.
Insulin: a hormone produced by β cells. It is initially synthesized as preproinsulin. Upon entry into the endoplasmic reticulum, preproinsulin is further processed into A and B chains that are held together by disulfide bonds. Insulin lowers glucose levels in circulation and, thus, is administered to manage T1DM and late-stage T2DM, characterized by diminished insulin production.
Proteostasis (protein homeostasis): the process that cells use to control the abundance and folding of the proteome. The regulation of gene expression and various signaling pathways, as well as the action of molecular chaperones and protein degradation systems, are key mechanisms that maintain proteostasis.
Type 2 diabetes mellitus (T2DM): a metabolic disorder in which the human body cannot properly respond to insulin (insulin resistance), leading to hyperglycemia. T2DM is the most common form of diabetes mellitus.