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Review

Proinsulin misfolding and endoplasmic reticulum stress during the development and progression of diabetes ☆

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ABSTRACT

To maintain copious insulin granule stores in the face of ongoing metabolic demand, pancreatic beta cells must produce large quantities of proinsulin, the insulin precursor. Proinsulin biosynthesis can account for up to 30–50% of total cellular protein synthesis of beta cells. This puts pressure on the beta cell secretory pathway, especially the endoplasmic reticulum (ER), where proinsulin undergoes its initial folding, including the formation of three evolutionarily conserved disulfide bonds. In normal beta cells, up to 20% of newly synthesized proinsulin may fail to reach its native conformation, suggesting that proinsulin is a misfolding-prone protein. Misfolded proinsulin molecules can either be refolded to their native structure or degraded through ER associated degradation (ERAD) and autophagy. These degraded molecules decrease proinsulin yield but do not otherwise compromise beta cell function. However, under certain pathological conditions, proinsulin misfolding increases, exceeding the genetically determined threshold of beta cells to handle the misfolded protein load. This results in accumulation of misfolded proinsulin in the ER – a causal factor leading to beta cell failure and diabetes. In patients with Mutant *INS*-gene induced diabetes of Youth (MIDY), increased proinsulin misfolding due to insulin gene mutations is the primary defect operating as a "first hit" to beta cells. Additionally, increased proinsulin misfolding can be secondary to an unfavorable ER folding environment due to genetic and/or environmental factors. Under these conditions, increased wild-type proinsulin misfolding becomes a "second hit" to the ER and beta cells, aggravating beta cell failure and diabetes. In this article, we describe our current understanding of the normal proinsulin folding pathway in the ER, and then review existing links between proinsulin misfolding, ER dysfunction, and beta cell failure in the development and progression of type 2, type 1, and some monogenic forms of diabetes.

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☆ The authors dedicate this review to the memory of the late Donald F. Steiner (University of Chicago), discoverer of proinsulin, and a pioneer in the field of pancreatic beta cell biology.

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Contents

1. Introduction

Insulin is a master hormone that regulates and maintains metabolic homeostasis in the body. In pancreatic ß-cells, insulin is initially synthesized as the precursor molecule, preproinsulin, comprised sequentially of the signal peptide, insulin B domain, C domain flanked by dibasic cleavage sites, and insulin A domain. To make mature bioactive insulin, newly synthesized preproinsulin undergoes co- and post-translational translocation across the membrane of the endoplasmic reticulum (ER), where it is cleaved by signal peptidase to form proinsulin. Proinsulin then folds, forming three disulfide bonds that are conserved among the entire insulin/IGF superfamily. Proinsulin forms noncovalently associated homodimers that undergo intracellular transport from the ER to the Golgi complex and into secretory granules, during which proinsulin forms hexamers and is proteolytically processed to C-peptide and mature insulin that is stored in granules (Dodson and Steiner, 1998; Liu et al., 2014b). Upon stimulation, insulin granule exocytosis rapidly releases insulin to the bloodstream to lower blood glucose.

Although insulin biosynthesis and secretion are both tightly regulated, the glucose concentration thresholds required to trigger insulin release are different from that for proinsulin biosynthesis. Insulin secretion is triggered by glucose concentrations above 5 mM, whereas its biosynthesis is most sensitive to fluctuations of glucose between 2 and 4 mM (Alarcón et al., 1993; Malaisse et al., 1979; Pipeleers et al., 1985; Schuit et al., 1988). Thus, insulin biosynthesis is constantly engaged to replenish insulin granule stores even at normal physiological glucose concentrations. Genetic analysis shows that, on average, approximately one third of total cellular proteins are targeted to the secretory pathway. However, in beta cells, insulin biosynthesis alone accounts for more than 10% of total protein synthesis under basal conditions, and this percentage can further increase up to 50% under stimulated conditions (Scheuner and Kaufman, 2008; Schuit et al., 1988; Van Lommel et al., 2006). Due to this large demand, proinsulin folding in beta cells is very sensitive to changes in the ER environment, and increasing demand for proinsulin synthesis and folding makes the beta cell one of the cell types that is most susceptible to ER stress (Eizirik et al., 2008; Papa, 2012; Vetere et al., 2014).

Over the past years, 30 different insulin gene mutations have been reported to cause a new syndrome named **M**utant ***I****NS*-gene-induced **D**iabetes of **Y**outh (MIDY; for review, Liu et al., 2010b, 2014a; Støy et al., 2010). Most of these mutations lead to proinsulin misfolding in the ER. These misfolded mutant proinsulin molecules generate a "first hit" causing ER stress and a decrease of insulin production that are responsible for the development of diabetes and progression of beta cell failure in MIDY patients. In other cases, even without any *Ins* gene mutation, a defective ER folding environment can generate a "first hit" to beta cells, affecting the folding pathway of wild-type proinsulin, leading to an increase of proinsulin misfolding. At or above a threshold level, these misfolded wild-type proinsulin molecules may further impair the ER folding environment in beta cells, providing a "second hit" that aggravates ER dysfunction and leads to beta cell failure and diabetes. In this article, we review the proinsulin folding pathway in the ER and current literature that focuses on links between proinsulin misfolding, ER dysfunction, and beta cell failure. The roles of proinsulin misfolding and ER stress in the development and progression of type 2 and type 1 diabetes, as well as some monogenic forms of diabetes, are discussed.

2. Proinsulin folding

2.1. Proinsulin disulfide maturation

Upon delivery to the ER lumen, preproinsulin signal peptide is immediately removed by signal peptidase on the luminal side of the ER. The efficiency and fidelity of signal peptide cleavage appear to be very important for subsequent proinsulin folding in the ER. The pathological consequence of a defect in signal peptide cleavage has been demonstrated both clinically and experimentally (Liu et al., 2012a; Stoy et al., 2007). After removal of the signal peptide,

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