Impact of ER Protein Homeostasis on Metabolism
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Proper regulation of protein homeostasis in a cell is critical for the health of the organism. Proteins, intracellular or secreted, need to be produced and maintained at the right quantity, folded into their three-dimensional conformation with necessary posttranslational modifications, targeted to their correct destinations to insure their optimal function, and degraded efficiently and disposed when needed. The overall process is tightly regulated at many levels to increase or decrease the rate of the synthesis and breakdown of polypeptides. In most cases, failure to properly regulate any one of these control points leads to a dysfunction at the cellular and organismic level resulting in disease.

The endoplasmic reticulum (ER) is a cellular organelle consisting of a vast tubular network, where about one-third of all proteins are synthesized. Proteins secreted to extracellular environment, membrane proteins, and proteins that reside inside the ER lumen are all synthesized and folded into their native conformation in this organelle. Later, most of the posttranslational modifications are completed in the Golgi compartment. Similar to cytoplasmic protein synthesis machinery, ER-mediated protein synthesis involves a complex molecular apparatus to insure the quality and quantity of synthesized proteins (1). ER-mediated protein synthesis and folding represent unique challenges compared with its cytoplasmic counterpart due to the high oxidative environment and high calcium concentrations of the ER lumen (2). Problems arising at the synthesis and folding stages lead to the appearance and accumulation of unfolded proteins in the ER lumen that have to be efficiently cleared using the primary protein degradation machine, the 26S proteasome, which mediates degradation of most of the ER resident as well as cytoplasmic proteins (3). Misfolded proteins, as well as the organelle itself, can also be removed through autophagy (4). Synthesis and degradation machinery interact with each other closely, and it is widely accepted that dysfunction of either of these processes compromises the efficiency of the other. If unfolded proteins appear in the lumen, a cellular adaptation program named the unfolded protein response (UPR) is triggered to increase the folding and degradation capacity of the ER. Once the burden of unfolded proteins is removed, UPR response is silenced to its initial basal state. Prolonged or inappropriate UPR responses are causally linked to various pathologies including neurodegenerative diseases, obesity, and diabetes (5,6).

Degradation and removal of unfolded proteins from the ER system are specifically named as ER-associated degradation (ERAD). Defects in ERAD are associated with an increasing number of human diseases, including metabolic diseases (7). One plausible mechanism linking ERAD dysfunction to pathological states involves chronic UPR responses resulting from the negative impact of a defective ERAD on the protein synthesis and folding machinery. Consistent with this hypothesis, a large number of ER chaperones, which normally assist protein folding, were shown to be involved in targeting unfolded proteins to ERAD pathway, providing further support that the two processes are simultaneously controlled (8,9).

New evidence of ERAD dysfunction leading to diabetes emerged from a study by Otoda et al. (10), which is reported in this issue of Diabetes. The initial leads that prompted Otoda et al. to investigate the involvement of protein degradation dysfunction in obesity and related metabolic diseases came from expression profiling of obese and diabetic human patients. As previously reported in obese liver tissue in mouse models (11), the expression of several members of proteasome-mediated degradation machinery was increased. Interestingly, however, the authors detected a significant decrease in the activity of the proteasome accompanied by the accumulation of ubiquinated proteins in liver tissue in various mouse models of diabetes. The authors suggest that increased expression of components of the proteasome system is a result of feedback cellular adaptation to the decreased proteasome activity.

Otoda et al. next generated a genetic mouse model lacking all three isoforms of the PA28A family of proteasome activator genes to test whether compromised protein degradation is causal to metabolic disease. Deletion of PA28A genes did, in fact, resulted in significantly decreased proteasome activity and accumulation of ubiquinated proteins in liver tissue lysates. Importantly, this state was accompanied by increased hepatic glucose production even in the presence of high levels of insulin. Experiments, in vivo, also provided support to the presence of hepatic insulin resistance, despite the fact that liver tissue analysis appeared normal except for a rather mild increase in lipid accumulation. However, a more detailed examination of human hepatocytes by electron microscopy revealed unusual expansion and disorganization of ER membranes in cells lacking PA28A subunits α, β, and γ. This observation prompted the investigators to hypothesize that ER stress maybe the mechanistic link between proteasome dysfunction, insulin resistance, and abnormal glucose metabolism. This is a sound postulate as many independent studies have firmly established that there is chronic ER stress in liver tissue both in experimental models and in humans with obesity and type 2 diabetes (12–14). Furthermore, proteasome dysfunction induced by specific inhibition of hepatic Cyp3a has been shown to trigger UPR response in cultured rat hepatocytes (15). Consistently, PA28A-deficient animals displayed increased UPR response, evident by elevated expression of several ER stress indicators such as PERK,
IRE1α, and eIF2α phosphorylation, GRP78 and CHOP accumulation, JNK activation, and the consequential decrease in insulin-induced Akt phosphorylation. These results demonstrate that experimentally induced defects in proteasome activity can be sufficient to cause ER stress and lead to insulin resistance.

Several important questions are raised from these observations. One is whether the effects of Otoda et al. are specific to hepatocytes or whether they are more broadly applicable to other organs. This is an important consideration given the diverse roles that the proteasome plays in various tissues and cell types. Another question is the potential for metabolic interventions to improve proteasomal function. Metabolic interventions such as dietary changes or pharmacological treatments may offer strategies to mitigate the effects of proteasomal dysfunction.

In conclusion, the study by Otoda et al. provides new insights into the complex interplay between proteasome activity and ER stress. The findings highlight the importance of proteasomal function in maintaining protein homeostasis and suggest potential therapeutic targets for conditions associated with proteasomal dysfunction.