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EDITORIAL

Protein Lysine Acetylation

An Unexpected Mediator in Pancreatitis

The factors that contribute to acute pancreatitis development and modulate its severity continue to be described. In addition to acute injury, chronic cell injury and inflammation, such as seen in chronic pancreatitis, increases the risk of developing pancreatic cancer. To meet its major physiologic functions to produce, store, and release digestive enzymes, the pancreatic acinar cell has exceptionally high rates of protein synthesis. This makes it particularly susceptible to endoplasmic stress responses, a process that can contribute to the pathogenesis of pancreatitis and pancreatic cancer. The study by Cooley et al[1] in this issue of *Cellular and Molecular Gastroenterology and Hepatology* highlights how important acetylation of lysine resides on nascent proteins is to acinar function and its links to ER stress. Although the work is done in the context of pancreatic acinar cell responses, the findings likely have relevance to other gastrointestinal tissues.

During synthesis, nascent secretory proteins are translocated into the lumen of the endoplasmic reticulum (ER) and there undergo an exquisitely orchestrated process of modification and folding that results in a preprotein or mature protein. This time- and energy-dependent process is monitored by a family of ER quality control proteins that sense proper protein folding; if that is the case, the protein is then allowed to advance in the secretory pathway. If not, responses are first activated that work to globally improve protein folding; if this fails, an ER stress response is triggered that can lead to cell injury, elaboration of inflammatory mediators, and even cell death. Protein misfolding can occur for many reasons including defects in amino acid sequences, failure to properly form disulfide bonds, and changes in the milieu of the ER including its energetics and calcium levels.

Several major cotranslational and post-translational modifications of nascent protein, such as phosphorylation and ubiquitylation, are frequently needed for functionality. Such modifications can have a range of biologic effects that include cellular targeting, biologic activity, protein stability, and protein-protein interactions. Although described more than 50 years ago, the functional and cellular effects of protein acetylation on surface exposed lysine residues of nascent proteins has been much less studied and is the topic examined by Cooley et al.[1]

The importance of this study is that it highlights a previously undescribed role for protein acetylation in acinar cell physiology and disease and makes several key observations. First, mRNA levels of a key modulator of protein acetylation, AT-1, which mediates the transport of acetyl-CoA into the ER lumen, are regulated (upregulated with physiologic stimulation of acinar cells, and downregulated during pancreatitis). Others have found that AT-1 levels determine the degree of protein acetylation and that both increased and decreased levels can result in cell pathology.[2] That the levels of AT-1 can be dynamically regulated is an important insight that should prompt the examination of this pathway in many systems and a more detailed examination in the pancreas. Second, global reduction of AT-1 activity or targeted deletion of AT-1 in the acinar cell produced ER stress followed by fibrosis and inflammation. Furthermore, mice with acinar-targeted deletion of AT-1 display an advanced chronic pancreatitis phenotype that includes loss of acinar cell mass when pancreatitis is induced by cerulein, an orthologue of cholecystokinin that can drive complex events in the acinar cell that culminate in pancreatitis.[3]

Although the read-out for the effects of decreased AT-1 levels are pancreatitis and activation of the ER stress response, the primary effect of reducing protein acetylation in the acinar cell is unclear. Protein acetylation can occur on ER resident proteins involved in quality control. Potentially relevant to the ER stress phenotype, BiP, calnexin, calreticulin, and ERAD E3 ligase, all proteins with roles in ER quality control, can be acetylated.[4] Defective acetylation can also affect proteins that have only transient association with the ER; such changes can prominently impact mitochondrial and lysosomal function and carbohydrate, amino acid, and lipid metabolism. Some of the effects on lipid metabolism are likely ER-mediated and include fatty acid elongation and generating lipid complexes. Additionally, increasing or decreasing AT-1 expression significantly impacts the availability of acetyl-CoA in the cytosol, thereby impacting the acetylation of proteins in the cytosol and nucleus.[2] Potential effects of changing protein acetylation on disrupting mitochondrial energy generation may be relevant because that can induce ER stress. Finally, changes in protein acetylation can stimulate ER autophagy (reticulophagy) and thus indirectly limit protein synthesis and processing and thereby contribute to ER stress.

The contribution by Cooley et al[1] should lead to additional studies. Confirming that AT-1 mRNA levels correspond to protein content and documenting that the responses are conserved in human acinar cells are important. Understanding the factors that dynamically modulate the levels of AT-1 mRNA and protein in acute and chronic pancreatitis is needed. Although AT-1 regulates acetyl-CoA entry into the ER, other enzymes regulate acetyl-group addition and its removal from target proteins; their role in organ homeostasis and during disease

is essential to explore. Because the effects of protein acetylation can extend well beyond the ER, it is of value to determine how the changes identified in this study impact organellar communication, mitochondrial function, and cellular energy metabolism. Although inactivating mutations in AT-1 in humans lead to profound disease, whether AT-1 variants might modulate pancreatitis phenotypes deserves exploration. Finally, it seems likely that protein acetylation will be dynamically regulated in other forms of cell injury and should be broadly investigated in other gastrointestinal diseases.

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