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Endoplasmic Reticulum: An Interface Between the Immune System and Metabolism

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COMMENTARY

Endoplasmic reticulum (ER) is a busy cell organelle that participates in many important cellular tasks. It has been established that ER is involved in protein and lipid biosynthesis, calcium regulation, redox regulation, cell signaling, and cell death. Given the many vital and complex functions of ER, there is little wonder that its failure can trigger a range of diseases. Recent genetic and clinical evidence indicates that inherited or acquired dysregulation of ER homeostasis can give rise to genetic diseases, including Wolfram syndrome (which is characterized by juvenile-onset diabetes and neurodegeneration) and a number of common metabolic diseases including diabetes and atherosclerosis. Accelerating interest in the role of ER in metabolic disease has been fueled by recent reports showing pathways that link ER to inflammation. The role of ER as an interface between the immune system and metabolism is an emerging concept (Fig. 1). However, currently there is no treatment targeting ER for combating immunometabolic diseases. To fulfill this unmet medical need, we need to identify pathways and molecules that link the immune system to metabolism at ER.

ER dysfunction has been a suspect as a major pathogenic component of human chronic diseases, such as diabetes, atherosclerosis, and Wolfram syndrome (1–10). However, the precise role of ER in the etiology of these diseases is not clear. It has been recognized that inflammation plays a central role in chronic metabolic diseases, raising the possibility that ER is at the intersection of inflammation and metabolism (7,11–14). Over the past several years, this concept has been supported by genetic, experimental, and clinical evidence (10,15). One of the unmet scientific needs in this emerging field is to identify the pathways linking ER to production of inflammatory cytokines. Two molecular pathways linking ER to production of interleukin (IL)-1β, a major player in inflammation, have been recently identified. These are activating transcription factor (ATF) 5 and miR-17 (16,17). Both molecules are regulated by key regulators of the ER stress response, Perk and Ire1α.

In this issue, Iwasaki et al. (18) describe the molecular pathway linking ER to IL-6 production. Using DNA microarray and network analyses of macrophages, they show compelling evidence that ATF4, which is involved in the ER stress response, plays an essential role in IL-6 expression induced by various metabolic stresses, including ER stress. Furthermore, they reveal that the ATF4 pathway has a synergistic effect on the Toll-like receptor-4 signaling pathway, enhancing IL-6 expression. IL-6 has been shown to play crucial roles in insulin resistance and type 2 diabetes (19), raising the possibility that ATF4 signaling is a novel target for the treatment of metabolic diseases. The new findings from Iwasaki et al. (18) also suggest that ER-stressed macrophages may trigger autoimmune diseases through IL-6 production.

Compelling evidence indicates that ER is at the intersection of inflammation and metabolism and is therefore an attractive target for immunometabolic diseases. For example, recent evidence strongly suggests that ER dysfunction in antigen-presenting macrophages and β-cells triggers autoimmunity during the onset and progression of type 1 diabetes (20,21). Despite the underlying importance of ER dysfunction in these diseases, no current therapies target ER. The unmet scientific and medical need in the field of ER immunometabolism is to target the common molecular processes that are altered in ER diseases as a novel therapeutic discovery strategy. The strategy of performing clinical studies using drugs previously known to target ER, such as glucagon-like peptide 1 agonists and vitamin D, on patients with immunometabolic diseases should be explored (22,23).

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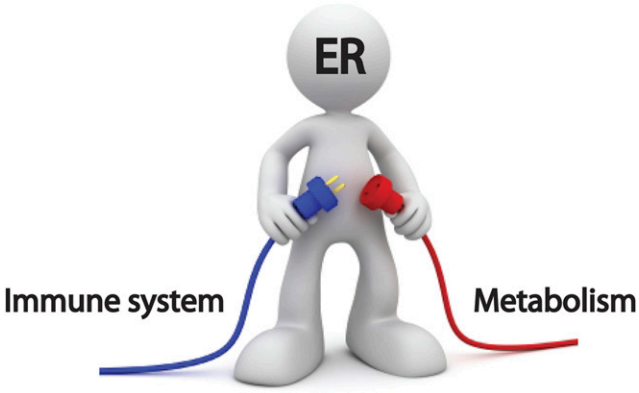

Figure 1—ER is an interface between the immune system and metabolism. ER is an intersection between inflammation and metabolism and an attractive target for immunometabolic diseases, including type 1 and type 2 diabetes, atherosclerosis, and Wolfram syndrome.

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