Stressed podocytes fail to fold: a potential new role of ER in FSGS

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FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS) has been attributed to both acquired and genetic causes. Although FSGS, at least in some cases, appears to be a systemic process that recurs in transplants, the precise pathobiology at the glomerulus is poorly elucidated. Research in the field supports a significant involvement of the glomerular epithelial cell, or podocyte, in the disease process (6, 7). Understanding the actual glomerular epithelial cell biology and the sequence of events that leads to podocyte dysfunction in FSGS is a critical step on the path toward targeted therapy.

A novel and relevant feature of glomerular epithelial cell “health” involves the endoplasmic reticulum (ER) (2). This cellular organelle is involved in diverse processes, including protein synthesis, synthesis and metabolism of sterols, fatty acid synthesis, drug metabolism, and the regulation of intracellular calcium concentrations. As implied by the diversity of function, the ER integrates and adapts to many different internal and external stimuli. Changing microenvironmental states and certain genetic conditions can place limitations on the cellular ability to properly synthesize and process protein, resulting in a state called ER stress. In response, cells either adapt and optimize protein production by the unfolded protein response and survive, or succumb to the cellular stress and undergo apoptosis.

In their article in an issue of the American Journal of Physiology-Renal Physiology, Cybulsky and colleagues (1) focused on a fundamental feature of FSGS, extracellular matrix alterations, and questioned whether extracellular matrix changes might affect ER function in podocytes. Specifically, they used the ability of the cell to properly fold newly synthesized proteins as a measure of ER function and a surrogate of cellular health. A key finding presented by Cybulsky is that glomerular epithelial cells, grown on matrix, compared with those grown on plastic, exhibit a decreased requirement for the unfolded protein response. This was a unique finding to glomerular epithelial cells because this change in ER stress was not noted in several other cell types. While the fact that cellular growth on a more physiological substrate would reduce ER stress is not entirely surprising, these findings raise the possibility that ER stress-related signaling may be at play in FSGS.

The authors extended their cell-based experimentation by observing the effects of exacerbating ER stress in a unique murine model of FSGS. In this model, they found that the experimental FSGS appeared to upregulate markers of ER stress. This finding raised the possibility that the podocyte response to the induced disease process may involve ER stress and that, in some settings, such stress may drive podocyte dysfunction and apoptosis and thus cause or exacerbate disease.

Whether this model faithfully phenocopies human FSGS does not detract from the important scientific findings presented by the authors. The ability to understand FSGS, and other glomerular diseases in general, at the cellular level provides a significant opportunity to move the diagnosis from a histologically descriptive term into possibly a mechanistic classification of disease. An important step will be determining whether podocytes in the human disease counterpart experience significant ER stress.

The findings presented by Cybulsky and colleagues appear to be the foundation for additional research that may more fully elucidate the significance of podocyte ER stress as a novel and potentially targetable pathway in human FSGS. This could manifest clinically by screening the drugs a patient may be receiving, and specifically avoiding drugs that have the potential to exacerbate podocyte ER stress. With this pathway in mind, future genetic studies may identify patients that exhibit a decreased threshold that places them at increased risk for glomerular disease based on the unique ability of their cells to handle ER stress.

Targeted therapeutic strategies also may be realized. Current work using animal models supports this possibility. For example, efforts to modulate mesangioproliferative glomerulonephritis by using tunicamycin preconditioning have had promising results (1a). Approaches that increase critical ER proteins (3), or that use chemical chaperones like 4-phenylbutyrate (4, 5) to reduce ER stress also have shown promise. Therapeutic approaches in humans may involve these potential avenues, but also could be expanded to strategies that limit the ER oxidative stress or even reduce protein synthesis by modulating the mTORC1 pathway. Although such therapies may enhance podocyte survival and in some settings be curative, they also have the capacity to limit podocyte loss while other definitive curative therapies could be used. While these possibilities are speculative, the work presented by Cybulsky and colleagues (1) offers the promise that understanding glomerular disease at the cellular level may result in new and exciting therapeutic opportunities.

REFERENCES


