TRB3: an oxidant stress-induced pseudokinase with a potential to negatively modulate MCP-1 cytokine in diabetic nephropathy

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TRB3 belongs to a family of kinase-like proteins that lack an ATP-binding site (GXGXXG) and the catalytic DFG (Asp-Phe-Gly) motif, and thus they are devoid of kinase activity. Such proteins are traditionally known as pseudokinases, and members of this particular family include TRB1, TRB2, and TRB3 (tribbles homolog) (4). They are ubiquitously expressed, including in the kidney; but their relevance in renal diseases has been explored to a limited extent. TRB1 expression has been described to be augmented in chronic antibody-mediated rejection in renal transplants (1). TRB2 is expressed in the metanephric mesenchyme during development, but gene deletion studies did not yield any overt phenotype, indicating its minimal role in renal organogenesis (17, 18). The Drosophila homolog of TRB3, tribbles, was first described a decade ago, and it has been shown to regulate cell cycle progression by modulating the expression of phosphatase, CDC25 (8, 16) and degradation/ubiquitination of transcription factor, C/EBP, thus implicating its role in early development (oogenesis/gastrulation) of fruit fly (15).

Over the years, TRB3 has been regarded as Novel Kinase-like Gene induced during hypoxia and programmed cell death in various normal and tumor cells, and it has been referred to by several different abbreviated names, such as NIPK, C5fw, C8fw, SKIP3, and SINK (3, 10, 19, 21, 22). The landmark study on insulin resistance by Montminy’s group (4) captured the interest of TRB3, where they demonstrated that it negatively regulates the activity of AKT/protein kinase B by blocking its phosphorylation in hepatocytes; and thereby conceivably promoting hyperglycemia and glucose intolerance. Followup in vivo studies revealed that TRB3 expression increased in fasting mice and augmented glucose output (4, 7). Moreover, in human studies a functional polymorphism of TRB3 has been described to be associated with insulin resistance and increased cardiovascular risk, which further highlights the interest in this intriguing pseudokinase (13).

Cunard and colleagues (11) present in a journal issue the expression of TRB3 in the kidney. They reported that TRB3 expression increases in diabetic mouse kidneys—both in low-dose streptozotocin-treated (type 1) and db/db (type 2) mice. Similar increased expression of TRB3 has been described in the liver (4), heart (20), and pancreatic islets (8) of diabetic mice. Further tissue immunofluorescence studies revealed TRB3 expressed in glomerular epithelial cells, and the remaining focus of the investigation was confined to the delineation of the mechanisms of expression and functions of TRB3 in the podocytes utilizing a well-established culture cell line.

Intriguingly, in the current study, the high-glucose ambience did not increase TRB3 in podocytes, a finding similar to that observed in cardiac myocytes (2). The hyperglycemia in diabetes or high-glucose ambience in cell culture systems are known to be associated with high levels of reactive oxygen species (ROS) (5). Thus, relevance of ROS in the biology of TRB3 was investigated. Both hydrogen peroxide and ROS synthesized via the xanthine oxidase reaction augmented the TRB3 expression. Similarly, palmitate, a dominant circulating free fatty acid (FFA) in diabetes and the metabolic syndrome, generated in response to ROS stress, also augmented the TRB3 expression. This finding is novel and would be of great interest, and it reconciles with the observations of Montminy’s group (14) that TRB3 stimulates lipolysis by promoting the degradation of acetyl-coenzyme A carboxylase, the rate-limiting enzyme of fatty acid synthesis. Along these lines, Liew et al. (8) also reported recently that palmitate upregulates TRB3 expression in human and mouse islets. These perplexing observations led Cunard’s group to suggest that TRB3 upregulation may be involved in a negative feedback loop that augments the oxidation of FFAs. This hypothesis is appealing but it would necessitate further investigations to assess its applicability in classic insulin-sensitive tissues.

Nevertheless, the authors delineated certain other mechanisms by which TRB3 is upregulated and how the increased expression could dampen the renal injury in diabetes. They devoted their efforts to study the stress in the Endoplasmic Reticulum (ER); the latter folds and modifies cellular proteins. When cells are stressed by ROS, nutrient deprivation, and hypoxia, unfolded proteins accumulate in the ER and activate the Unfolded Protein Response (UPR). The UPR is a signaling pathway that functions to restore normal ER activity and it is characterized by the expression of a classic group of proteins including transcription factors, such as ATF4, C/EBP homologous protein (CHOP), BiP/GRP78, and XBP; and earlier work by Ord and Ord (12) suggested that TRB3 interacts with ATF4. Thus, the TRB3 is now considered as an ER-stress regulated protein. In the current work, the link between ER stress and TRB3 is strengthened as CHOP was shown to regulate TRB3 expression in podocytes, which is augmented by ROS and FFA. The CHOP has been considered proapoptotic, and further studies are needed to evaluate whether CHOP and TRB3 induce cellular apoptosis and effacement of glomerular podocytes.

The punch line of the studies by Cunard’s group is exploration of the mechanism(s) by which TRB3 conceivably can serve as a protective agent against the inflammatory renal injury induced largely by monocyte chemoattractant protein-1 (MCP-1) in diabetic nephropathy (11). The TRB3 has been shown to alter signaling pathways including those involving AKT and mitogen-activated protein kinases (MAPK) (6), and it also acts as a transcriptional inhibitor of NF-kB (22). The NF-kB modulates the activity of MCP-1, the latter cytokine has emerged as an important mediator of inflammation in many kidney diseases, including in diabetic nephropathy. The dem-
onstration that TRB3 specifically inhibits MCP-1 expression in podocytes, most likely by modulating the signaling cascade of AKT-MAPK-NF-κB, highlights the value of TRB3 as a potential therapeutic agent for dampening the hyperglycemic injury in diabetic nephropathy. As to whether TRB3 inhibits other inflammatory cytokines in different cell types of the kidney and whether it promotes or reduces cellular survival would be a matter of future investigations.

REFERENCES


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