Hypothesis as to How a Common Missense Mutation in COL4A3 May Confer Protection against Diabetic Kidney Disease

In the September issue of *JASN*, Salem *et al.*[1] carried out a genome-wide association study of diabetic kidney disease (DKD) reporting that the variant with the strongest association is a common missense mutation in the collagen type IV α 3 chain (COL4A3) gene. The authors report that this rs55703767 minor allele (Asp326Tyr) in COL4A3 is found to be protective against several definitions of DKD, including albuminuria and ESKD. This protective effect was found to be strongest in patients with glycemia. The authors offer two hypotheses to explain this protective effect: (*1*) the variant confers tensile strength or flexibility to the glomerular basement membrane (GBM), making it robust to the glomerular hypertension associated with DKD; or (*2*) the variant on COL4A3 regulates the rates of production and/or turnover of other GBM components, affecting GBM width changes in diabetes. The authors did not hypothesize as to how these effects might confer protection in a manner dependent on ambient glucose concentrations. Indeed, this protective effect of a COL4A3 mutation, which is otherwise implicated in heritable nephropathies such as thin basement membrane nephropathy (TBMN) and Alport syndrome, is very interesting and paves the way for understanding the complex molecular mechanisms of COL4A3 mutations on kidney pathology. I would therefore like to propose an alternative hypothesis by which the COL4A3 missense mutation could provide a defense mechanism against DKD in patients with diabetes.

In our paper published in *JASN* in 2014,[2] we described how a missense mutation in the COL4A3 chain can evoke the unfolded protein response (UPR) pathway in human and mouse podocytes. UPR is an adaptive response aiming at maintenance of endoplasmic reticulum (ER) homeostasis. Nonetheless, ER stress, when in excess, can eventually activate the proapoptotic branch of the UPR, triggering cell apoptosis and loss of function. Because the level of UPR activation is linked directly to the duration and severity of the ER stress experienced by the cell, this could vary between different COL4A3 mutations, leading to diverse clinical outcomes. The (COL4A3):c.976G>T (p.Asp326Tyr) single nucleotide polymorphism is characterized as "benign" or "likely benign" by the ClinVar database (accession number VCV000255010.1). Notably, mild triggering of the UPR pathway can induce tolerance to subsequent cellular stressors (a form of cellular "readiness" or preconditioning) which has been shown to have a paradoxic protective effect against further cellular damage.[3] Inagi *et al.*,[4] for example, were able to show that mild chemical UPR preconditioning ameliorates mesangioproliferative GN in the anti-Thy1 model in rats. Therefore, I propose that the inheritable presence of the minor allele (Asp326Tyr) in COL4A3 could result in mild ER perturbation and a constant activation of the cyto-protective (adaptive) branch of the UPR pathway in the podocytes of patients with diabetes, acting as a form of "natural preconditioning" to the cells. In this way, this specific mutation could provide a "mild genetic challenge" to the podocyte that is then ready to withstand further ER stress caused by diabetes. This hypothesis is in line with the fact that the COL4A3-variant effect on DKD risk is amplified by poor glycemic control. It is known that hyperglycemia triggers the UPR mechanism,[5] so if the COL4A3 mutation causes a cellular readiness to the glycemic ER stress, then this protection would be more relevant to the patients whose blood glucose level is uncontrolled. Absence of the variant would result in a lack of preconditioning, which could rapidly set the glycemia-induced UPR pathway toward the proapoptotic branch, consistent with podocyte and GBM pathology observed in DKD.

If this hypothesis was to be verified then it would be, to my knowledge, the first time that an inherent mutation would result in a "natural UPR preconditioning situation," something worth pursuing further experimentally.

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DISCLOSURES

None.

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