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Telomerase at the center of collapsing glomerulopathy

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Abstract

Collapsing glomerulopathy, the classic kidney lesion in HIV-associated nephropathy, is characterized by the closure of glomerular capillary loops and epithelial cell proliferation. A new study shows that upregulation of TERT, the reverse transcriptase component of telomerase, in podocytes, the key filtration cells in the kidney, plays a major part in the development of this condition by activating Wnt signaling (pages 111–119).

The kidney condition collapsing glomerulopathy was first noted in people infected with HIV¹, and was later also shown to occur independently of HIV infection (non-HIV collapsing glomerulopathy)². HIV-associated collapsing glomerulopathy is characterized by the presence of protein in the affected individual's urine (proteinuria) and rapid loss of kidney function. Since the use of antiretroviral therapy became widespread, the incidence of this condition has declined. Nevertheless, it continues to be a substantial cause of morbidity in people with HIV³. The identification⁴ and characterization⁵ of glomerular lesions in transgenic mice that express HIV-1 genes two decades ago brought hope that the pathogenic mechanisms of collapsing glomerulopathy would finally be unraveled. However, despite some progress in this area and the development of additional transgenic models for individual HIV genes, the major mechanisms of this disease have not been elucidated.

In this issue of *Nature Medicine*, Shkreli *et al.*⁶ describe a major breakthrough in understanding the pathogenesis of HIV-associated collapsing glomerulopathy. Using a mouse model in which TERT could be overexpressed in multiple organs in an inducible manner, the authors showed that these mice developed glomerular collapse (Fig. 1) without substantial structural and functional changes in most other organs⁶. Moreover, human kidney tissue samples from individuals with HIV or idiopathic collapsing glomerulopathy showed TERT upregulation. The authors found that TERT overexpression led to activation of Wnt signaling and that the glomerular phenotype could be reversed by switching off the TERT transgene or blocking Wnt signaling⁶, suggesting that targeting the Wnt pathway may be of clinical benefit in people with HIV-associated collapsing glomerulopathy.

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In additional mutant mice that were deficient in TERC, the RNA component of telomerase, or that overexpressed a mutant form of TERT that was catalytically inactive, Shkreli *et al.*⁶ revealed that the TERT-mediated glomerular effect is independent of TERC and the reverse transcriptase activity of TERT. The phenotype of the inducible mice could be reversed after switching off TERT overexpression. Consistent with the observations in mice, biopsies from individuals with HIV-associated and idiopathic collapsing glomerulopathy showed elevated TERT expression in podocytes. By contrast, kidney tissues from people with classic focal and segmental glomerulosclerosis, a glomerular pathology that is not associated with podocyte proliferation, had similar levels of TERT expression to controls without kidney disease.

How does TERT overexpression lead to glomerular pathology? Mature podocytes are normally quiescent, but Shkreli *et al.*⁶ found that overexpression of TERT led to dedifferentiation and proliferation of podocytes. The authors had previously shown that TERT can modulate transcriptional responses regulated by the Wnt pathway⁷. In the current study they found that mouse podocytes overexpressing TERT showed upregulated expression of and increased nuclear localization of the Wnt factor β -catenin, as well as activation of Wnt target genes⁶. The authors also found evidence of Wnt pathway activation in HIV-transgenic mice, and kidney biopsies from patients with HIV and non-HIV collapsing glomerulopathy. Moreover, inhibition of the Wnt pathway in the inducible TERT-transgenic model and in HIV-transgenic mice significantly improved the glomerular phenotype and reduced proteinuria. The parallel changes in TERT and β -catenin expression in human biopsies and in HIV-transgenic mice suggest that the authors' observations in the inducible TERT-transgenic model are clinically relevant.

From a broader perspective, this study shows that podocytes have a reversible phenotype under certain conditions: they can divide and lose differentiation markers under the influence of TERT overexpression and then regain these markers and exit the cell cycle after the stimulus for TERT overexpression is removed. This would suggest that patients with collapsing glomerulopathy may be treated in the future with drugs that inhibit TERT expression or block the Wnt pathway.

The role of TERT's Wnt pathway activation in the pathogenesis of collapsing glomerulopathy, as opposed to its classic reverse transcriptase function, is intriguing. Notably, a recent study showed no effect on Wnt signaling in TERT-knockout mice⁸. However, this study does not negate the conclusions of the work by Shkreli *et al.*⁶, as the outcome of transgenic alteration of gene expression must be interpreted in the context of the baseline expression of these genes and their expression changes during disease. The constitutive expression of TERT in mature podocytes is low, and, therefore, TERT knockout may not affect the Wnt pathway in these cells. By contrast, the study of Shkreli *et al.*⁶ showed changes in Wnt signaling as a consequence of TERT upregulation, and this change was also noted in human and experimental collapsing glomerulopathy. Similar scenarios have been previously reported when examining the effects on the podocyte when knocking out other genes. For example, angiopoietin-like-4 (Angptl4), a major molecular mediator of proteinuria, has low baseline expression in the podocyte, and *Angptl4*^{-/-} mice do not develop proteinuria or changes in podocyte morphology⁹. By contrast, transgenic Angptl4

overexpression in podocytes to mimic the Angptl4 upregulation observed in kidney minimal change disease resulted in the development of proteinuria and the classic morphological changes of minimal change disease⁹.

From the study of Shkreli *et al.*⁶, limited conclusions can be drawn regarding the involvement of TERT in non-HIV collapsing glomerulopathy, as this disease is etiologically heterogeneous, and the clinical details of the individuals with idiopathic collapsing glomerulopathy that the authors studied were not provided. It will be particularly important to determine whether the Wnt pathway is involved in the pathogenesis of non-HIV-associated collapsing glomerulopathy in the subset of people in which this disease is caused by putative circulating factors¹⁰, as Wnt activation could be used to screen and identify these circulating factors in future studies.

Although TERT upregulation seems to be sufficient to induce the structural and functional changes associated with collapsing glomerulopathy, additional pathways may be involved in disease pathogenesis. Hints to this effect have come from a study that characterized mice deficient in a ribonucleotide reductase (*Rrm2b*^{-/-} mice)¹¹ that also develop glomerular capillary loop collapse (Fig. 1). Therefore, better characterization of this knockout mouse and the identification of any potential interactions between *Rrm2b* and TERT, or their downstream pathways, is warranted. In addition, as the upregulation of TERT in the inducible mouse model observed by Shkreli *et al.*⁶ was quantitatively higher than that observed in the human disease, follow-up studies to investigate whether lower levels of TERT upregulation can lead to structural and functional changes in the glomerulus in this model would be appropriate. Also, the mechanism by which HIV induces TERT upregulation will need to be investigated. Finally, from a clinical perspective, the development and testing of less toxic inhibitors of the Wnt pathway may be a potential therapeutic strategy for collapsing glomerulopathy.

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Figure 1.

Pathogenic mechanisms in collapsing glomerulopathy. The study of Shkreli *et al.*⁶ suggests that initial insult due to HIV infection or other causes induces upregulation of TERT, the reverse transcriptase component of telomerase, in podocytes. This activates the Wnt pathway, which causes glomerular epithelial cell proliferation and capillary loop collapse, resulting in collapsing glomerulopathy. Downregulation of the ribonucleotide reductase Rrm2b in mice also causes glomerular capillary loop collapse¹¹, but the relevant mechanisms and potential interaction with TERT or the Wnt pathway have not been defined.