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Blockade of Dickkopf-3 inhibits renal fibrosis and atrophy

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Renal fibrosis is an excessive accumulation of extracellular matrix that can occur in different types of chronic kidney diseases (CKDs). It advances progressively and it is associated with tubular atrophy and renal failure which requires dialysis or renal transplantation. Dickkopf (Dkk) genes comprise an evolutionarily conserved small gene family of four members (Dkk1-4) and a unique Dkk3-related gene, Dkkl1 (soggy). Dkk3 exhibits divergent biological features from the other Dkks likely due to a structural diversity separating it from the other Dkk protein family members. In most studies Dkk1, Dkk2 and Dkk4 share the ability to inhibit canonical Wnt/β-catenin signaling which is not to be seen for Dkk3. The Wnt/β-catenin pathway is involved in fibrosis. Using a Dkk3 reporter mouse (Dkk3-Lch), we could demonstrate the expression of Dkk3 protein in renal tubules during the chronic fibrosing inflammation. Therefore, we postulate that Dkk3 is a relevant component in the induction and progression of fibrosis. In our study, we have been able to reveal that Dkk3-/- mice are protected from renal fibrosis when they are subjected to both UUO and adenine-enriched diet compared to wildtype animals. These results have been further validated by the development of less fibrosis observed in mice injected with Dkk3 antibody. In addition, applying the UUO model on $Pax8^{Cre}Dkk3^{-/-}$ mice, it has been possible to show that the renal tubular epithelial cells are the main Dkk3-producing components. Even though associated with less fibrosis development, $Dkk3^{-/-}$ phenotype showed higher inflammatory cell infiltration, specifically T cells, compared to the wildtype; interestingly, this T cell population has been shown to undergo a Th1 T cell subtype polarization, which has been demonstrated to have an antifibrotic effect. To figure out by which mechanism Dkk3 is able to influence the development of fibrosis and the T cells function, NGS technique has been used to compare $Dkk3^{-/-}$ and wildtype mice in both UUO and steady state condition. The analysis of the NGS data has shown a different activation of some Wnt pathway factors between the two groups of animals, hinting at an up to date unknown interaction between Dkk3 and β-catenin. Furthermore, TCF/LEF-H2B-GFPTr transgenic mice, which report β-catenin activity, have shown lower activation of the Wnt pathway in absence of Dkk3 under fibrotic conditions. Finally, analyses on both mouse and human urine samples have shown the potential of Dkk3 to be used as a biomarker for CKDs. In conclusion Dkk3 seems to play an important role in the kidney fibrosis development, and its action seems to be associated with two profibrotic events: the T cell polarization to the Th2 subtype, and the activation of the Wnt pathway.