SIGNIFICANCE STATEMENT

Elucidating the mechanisms that mediate injury in early diabetic nephropathy is necessary for development of novel preventive and therapeutic measures. Aided by the proteomic analysis of an experimental rodent model of DN, the authors have identified protein S as a highly expressed protein in early DN, but not in late DN. Protein S is a well studied plasma glycoprotein that serves as an essential cofactor in pathways that regulate coagulation. The study demonstrates that this temporal increase in protein S signal transduction through Tyro3 receptor thwarts DN progression and that the eventual loss of protein S results in worsened DN outcome. The findings reveal a previously unrecognized role of protein S in kidney cells and suggest that approaches to elevate protein S signaling may have therapeutic benefit against DN progression.