

CHARACTERIZATION OF A RENOPROTECTIVE AATF PEPTIDE IN MODELS OF DIABETIC NEPHROPATHY

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Inflammation and cell death play central roles in diabetic kidney complications. Identification of novel renoprotective molecules is essential for developing new therapies. We have identified an unconventional extrinsic renoprotective pathway mediated by a 12-amino acid peptide (SAP-12) derived from extracellularly secreted AATF (apoptosis antagonizing transcription factor) in blocking renal damage in models of diabetic nephropathy (DN). SAP-12 (secreted AATF peptide of 12 amino acids, SALKNSHKALKA) is conserved among human, mouse, and rat AATF proteins, and confers potent renoprotective properties at femtomolar concentrations with a broad effective range in renal tubular epithelial cells (RTECs) following exposure to high levels of glucose. We reported previously that AATF was highly effective in protecting against renal damage and it rescues renal tubular epithelial cells from both apoptotic and necrotic death. The rationale for the current study was based on our recent observation that the renoprotective actions of AATF seemed to be accomplished in a highly unusual manner in diabetic kidneys. As a transcription factor, AATF often functions as an intracellular protein located in cytoplasmic and/or nuclear compartments. However, we have unexpectedly noted that a significant amount of intracellular AATF protein was secreted extracellularly by RTECs under diabetic conditions. Furthermore, secreted AATF (sAATF) functions, at least in part, as a specific ligand and antagonist of the cell surface receptor TLR4 (Toll-like receptor-4). Of importance, TLR4-mediated signaling has been shown to be critically involved in the inflammation and cell death in DN. A region corresponding to the amino acid sequence between AATF179 and AATF279 was responsible for interacting with TLR-4. Based on these observations, several small AATF core peptides derived from this region of AATF were synthesized and tested for their renoprotective properties and their ability to interact with TLR4. One of these peptides, SAP-12, was identified at the interface of AATF/TLR4 interaction. Surprisingly, SAP-12 had a much greater potency and broader effective dose range than the full length sAATF in protecting RTECs in models of diabetic nephropathy. The extrinsic pathway mediated by sAATF and SAP-12 provides strong support for the existence of non-classical secretory pathways where cytoplasmic and nuclear proteins can be secreted extracellularly without a classical N-terminal signal peptide. The region(s) in the extracellular ectodomain of TLR4 involved in interacting with SAP-12 and the potential therapeutic applications of SAP-12 in DN will be discussed. By studying the structure-activity relationships of SAP-12, it may also be possible to develop additional novel versatile peptides with even greater renoprotective capacity and specificity. This study is therefore highly innovative and significant.

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