Soluble RAGE inhibits disease progression in Autosomal Dominant Polycystic Kidney Disease by blockade of cell proliferation

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Introduction: Autosomal polycystic kidney disease (ADPKD) is one of the common genetic renal diseases in which epithelial-lining fluid-filled cysts appear in kidneys. It is accompanied by hyper-activation of cell proliferation, interstitial inflammation and fibrosis around the cyst lining cells, finally reaching end-stage renal disease (ESRD). Previously, we found high expression of ligands stimulating the receptor for advanced glycation endproducts (RAGE) in ADPKD mice. Furthermore, gene silencing of RAGE was revealed to reduce cystogenesis via down-regulation of cell proliferation in vitro, while intravenous administration of anti-RAGE adenovirus in vivo also displayed alleviation of the disease. Objectives: Here, we attempted to identify the role of soluble RAGE (sRAGE) in inhibiting the progression of ADPKD, in vivo.

Materials and Methods: Using either mice primary cells or human ADPKD cell line WT9-12, both sRAGE treatment and over-expression of sRAGE with cloned construct we established herein were tested, in vitro. In addition, in vivo test via intraperitoneal injection using ADPKD mice model jck, and confirmed the in vitro results in in vivo systems.

Discussion and Results: sRAGE is an endogenously expressed form of RAGE which has no membrane-anchoring domain, thereby being able to neutralize the ligands that stimulate RAGE signals. Both over-expression of sRAGE and sRAGE treatment blocked RAGE-mediated cell proliferation in vitro. In addition, sRAGE-injected ADPKD mice showed reduced cysts accompanied by enhanced renal function, inhibition of cell proliferation, inflammation and fibrosis. Conclusions: These positive therapeutic effects of sRAGE displayed little liver toxicity, suggesting it as a new potential therapeutic target of ADPKD with low side effects.