Lipocalin-2 derived from adipose tissue mediates aldosterone-induced renal injury

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Increased lipocalin-2 levels are not only the sensitive biomarkers but also causally contribute to the pathogenesis of acute and chronic renal injuries. Mice without lipocalin-2 are protected from the development of chronic kidney diseases. However, the source of lipocalin-2 contributing to the pathological elevation of this molecule in blood and urine during renal injury remain largely unknown. The present study demonstrated that adipose tissue-derived lipocalin-2 represented a major pathological form of this molecule causing inflammatory and fibrotic damages in kidney of mice treated with aldosterone. Compared to sham controls, wild type mice subjected to four-week treatment with aldosterone/uninephrectomy/salt (ANS) showed elevated circulating and urinary lipocalin-2, accompanied by glomerular and tubular injuries in kidney. The same treatment was not able to augment the circulating levels of lipocalin-2 in mice with selective depletion of the Lcn2 alleles in adipose tissues (Adipo-LKO). Despite the increased Lcn2 mRNA expression in kidney and lipocalin-2 protein levels in urine, Adipo-LKO mice were protected from ANS-induced tubular injuries and fibrotic renal damages. Data from acute studies confirmed that aldosterone treatment mainly promoted the urinary excretion of lipocalin-2 originated from adipose tissue; the latter acted to inhibit glomerular expression of Wilms tumor-1 (Wt-1) and enhanced the mRNA levels of clusterin (Clu) and kidney injury marker (KIM)-1. In the presence of aldosterone, acute treatment with recombinant lipocalin-2 variants significantly induced the mRNA expressions of both Clu and kidney injury molecule-1 (Kim-1). Moreover, chronic treatment with R81E, a variant form of lipocalin-2, led to renal injuries in mice lacking the Lcn2 alleles, resembling those observed in wild type mice treated with ANS. Collectively, the results demonstrated that lipocalin-2 derived from adipose tissue caused ANS-induced renal injuries.