

KSN 2017 Abstract

KSN-17-O093

Sirt1-induced hypoxia-inducible factor-1 deacetylation attenuates tubular damage in aged kidney

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Objectives : Aging is associated with chronic hypoxia and aged kidney shows increased vulnerability to hypoxic challenges. Although it is well known that the expression and activity of Sirt-1 are decreased in the aged kidney, the role of interaction between Sirt-1 and hypoxia-inducible factor (HIF)-1, which is activated in chronic hypoxic condition, is largely unknown. Here, we investigated whether HIF-1 could be a deacetylation target of Sirt-1 and the effect of their interaction on age-associated renal tubular injury.

Methods : Six-week-old (young) and 24-month-old (old) male C57BL/6 mice were assessed for their age-associated changes. To identify the underlying mechanisms, HK-2 cells were used for in vitro analyses.

Results : Aged mice showed significantly higher body weight, kidney to body weight ratio, and urinary albumin to creatinine ratio. Serum creatinine tended to be higher in aged mice compared to young mice without statistical significance. Kidney from aged mice showed increased infiltration of CD68 positive macrophages and collagen deposition. Type I and IV collagen and fibronectin expression levels and apoptosis were significantly higher in renal cortices from aged mice than in young controls. Compared with control, aged kidney showed decreased protein expression of Sirt-1 and increased acetylated HIF-1 as well as its total protein expression. Bcl-2/adenovirus E1B 19 kDa-interacting protein (BNIP) 3 level, which is regulated by HIF-1, was significantly higher in aged mice suggesting that HIF-1 activity is increased. In HK-2 cells, Sirt-1 inhibitor sirtinol enhanced protein expression of cleaved caspase 3, cleaved poly-ADP ribose polymerase (PARP), and type I and IV collagen, and similar observations were made following siRNA-mediated knock-down of Sirt1. In contrast, Sirt1 over-expression significantly reduced these protein levels. During hypoxia, Sirt-1 was down-regulated, which allowed the acetylation and activation of HIF-1 assessed by HIF-1 luciferase activity and mRNA levels of BNIP3 and carbonic anhydrase (CA) 9. Resveratrol, a Sirt1 activator, effectively prevented all of these changes. We confirmed the interaction of Sirt-1 and HIF-1 in HK-2 cells using c-terminal mutated HIF-1.

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Conclusions : Our data suggest that Sirt-1-induced deacetylation of HIF-1 may have protective effects against tubular damage in aged kidney.

Keywords : Age, Sirt-1, HIF-1, deacetylation