Role of RNase L in Kidney Function

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ABSTRACT

Renal diseases have continued to be a prevalent problem. The data released by the US Renal Data System show increasing of the incidence of acute kidney injury (AKI) at a rate of 14 % since 2001. AKI severity results in patient morbidity and mortality. 1% of patients admitted to the hospital are diagnosed initially with acute kidney injury (AKI), while about 2-5% of hospitalized patients develop AKI secondarily. Clinical studies documented the contribution of epidermal growth factor (EGF)/EGFR activation to the development and progression of renal through mechanisms involved in induction of tubular atrophy, overproduction of inflammatory factors, and/or promotion of glomerular and vascular injury. In this study, we showed that RNase L, an interferon inducible enzyme, involves in kidney function and recovery from AKI by using RNase L wild type and null cells and mice. Proteomic analyses of urine protein excretion discovered that lack of RNase L exclusively blocked EGF excretion. Interestingly, we found that RNase L deficiency enhanced kidney recovery after AKI. The lack of RNase L exclusively blocked EGF excretion into urine and affected the activation of its receptor EGFR, which is important for promoting kidney recovery. However, the lack of RNase L enhanced EGFR phosphorylation which might contribute to kidney recovery after AKI. Moreover, the level of serum creatinine in RNase L null mice significantly decreased. This study suggests that RNase L may play an important role in the kidney function, which is a novel target for AKI treatment.

METHODS

1. Animal model of wild type and RNase L mice used to elucidate the role of RNase L in kidney
2. To assess the kidney function, urine samples were collected under normal and pathological conditions and subjected to SDS-PAGE
3. The different bands were dissected and enzymatically digested with trypsin and introduced to mass spectrometer to be identified.

RESULTS

• Lack of RNase L blocks EGF excretion into urine

• RNase L regulates the shedding of EGF and excretion into urine by affecting the maturation of ADAM10

• Level of serum creatinine in RNase L null mice significantly decreased

• Lack of RNase L enhanced kidney recovery from AKI by increasing EGFR phosphorylation

BACKGROUND

Interferons (IFNs) are a family of cytokines participating in innate immunity against a wide range of viruses and other microbial pathogens. IFNs also have anti-tumor activities due to their antiproliferative, immunoregulatory, and apoptotic properties. When viruses trigger the IFN system, hundreds of interferon-stimulated genes (ISGs) are produced and some of them are with antiviral function; 2-5A-dependent RNase L (RNase L) is one of such ISGs. RNase L is one of the key enzymes in the 2-5A system of IFN action against viral infection and cellular proliferation. Interferons (IFNs) are a family of cytokines participating in innate immunity against a wide range of viruses and other microbial pathogens. IFNs also have anti-tumor activities due to their antiproliferative, immunoregulatory, and apoptotic properties. When viruses trigger the IFN system, hundreds of interferon-stimulated genes (ISGs) are produced and some of them are with antiviral function; 2-5A-dependent RNase L (RNase L) is one of such ISGs. RNase L is one of the key enzymes in the 2-5A system of IFN action against viral infection and cellular proliferation. Most recently, it has been reported that RNase L mediates innate immunity through regulating the expression of IFN and proinflammatory genes. In our preliminary study we found that RNase L-deficient mice exclusively blocked the excretion of EGF into urine, suggesting that RNase L may contribute to the function of the kidney.