LRG1 Deficiency in Adolescent Mice Confers Protection Against Diet-Induced Kidney Damage

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Introduction

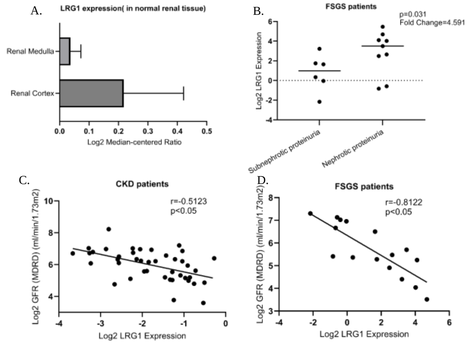
Obesity and diabetes are recognized as pivotal risk factors in the progression of chronic kidney disease (CKD), with close association to lipotoxicity and elevated serum leucine-rich alpha-2-glycoprotein 1 (LRG1) levels, an adipokine up-regulated by high-fat diet (HFD) intake. Recent study have revealed LRG1 binding affinity to various metabolic organs, including the kidney (1). Despite this understanding, the impact of LRG1 and the mechanisms underlying its role in modulating diet-induced lipotoxic kidney injury in CKD remains elusive. In this study, we unveil the influence of LRG1 on renal function and lipid metabolism in adolescent mice.

Experimental Methods

C57BL/6 wild-type (WT) and LRG1 knockout (Lrg1-/-) mice (males at 4-week-old, equivalent to 12-year-old humans) were subjected to either a normal chow (NC) or 45% high-fat diet (HFD) for 26 weeks. Urine was collected one week before euthanasia.

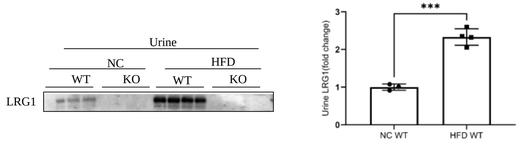
Results

Fig 1. Association Between Elevated LRG1 Gene Expression and Progression of CKD in Humans



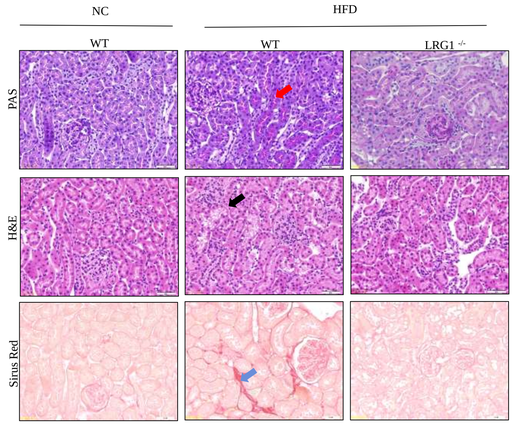
(**A)**The normal distribution of LRG1 mRNA expression in normal human renal tissues based on the study by Higgins (n=5). **(B-D)** The tubular LRG1 mRNA expression dataset and clinical information of corresponding patients were obtained from the Nephroseq Database. The mRNA levels of tubular LRG1 in FSGS patients with subnephrotic proteinuria(n=6) and nephrotic proteinuria(n=9). The tubular LRG1 mRNA levels were found to be negatively correlated with eGFR inpatients with CKD(n=42), FSGS(n=16)

Fig 2. Elevated Levels of Urinary LRG1 Protein in Mice Associated With Nutrient Overload



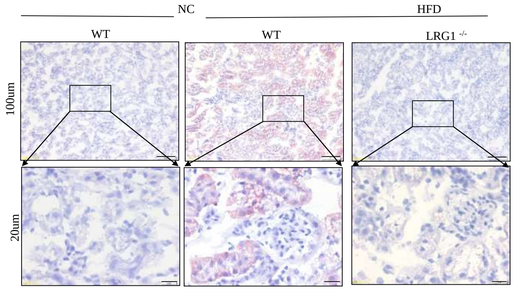
Western blot analysis of urine LRG1, urine samples (0.1 µl/lane) were loaded as indicated.

Fig 3. Protective Role of LRG1 deficiency Against Tubular Injury and Fibrosis Induced by High-Fat Diet in mice



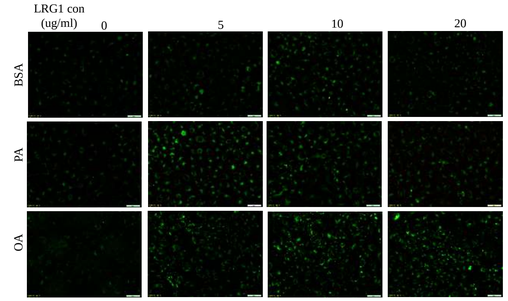
PAS, H&E and Sirus Red staining(Scale bar: 50um) in mouse kidneys. LRG1 deficiency prevented glycogen accumulation (red arrow) and relieved vacuolization (black arrow) and reduced fibrosis (blue arrow) in HFD-induced mice.

Fig 4. Prevention of Lipid Accumulation by LRG1 Deficiency Under High-Fat Diet in Mice



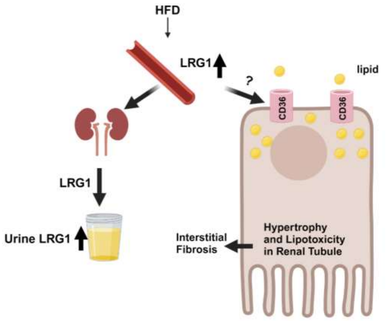
Oil-red O staining in mouse kidneys. LRG1 deficiency prevented renal lipid accumulation in HFD-induced mice.

Fig 5. LRG1 Stimulation Promotes Lipid Deposition in HK-2 Cells



Representative Bodipy staining images of HK-2 cells in different groups(Scale bar: 50 um). HK2 cells were cultured in medium with LRG1 and BSA or 50uM palmitic acid or 50uM oleic acid for 24 h.

Summary



Conclusion and Significance

1. The urinary protein LRG1 demonstrates potential as a biomarker for obesity-induced insulin resistance and chronic kidney disease (CKD) due to its increased presence in urine.
2. Adolescent mice deficient in LRG1 exhibit protection against diet-induced tubular injury, fibrosis, and lipid accumulation.
3. LRG1 stimulation alone is capable of inducing lipid deposition in HK2 cells, and this effect can be enhanced synergistically with co-treatment with lipids.
4. These findings suggest that therapeutic targeting of diet-up-regulated LRG1 could offer a promising strategy to mitigate ectopic fat deposition in the kidney and prevent the worsening of obesity-induced CKD.

Acknowledgments

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Reference

1. He S., et al., LRG1 is an adipokine that mediates obesity-induced hepatosteatosis and insulin resistance. The Journal of Clinical Investigation, 2021. https://www.jci.org/articles/view/148545.