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Perspectives

PERSPECTIVES

Megalin as a Metabolic Modulator in the Kidney and Beyond

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A Perspective on "Megalin Knockout Reduces SGLT2 Expression and Sensitizes to Western Diet-induced Kidney Injury"

The highly metabolic proximal tubule epithelium is critical for maintaining kidney function and metabolic homeostasis. Central to this function is glucose reabsorption through the apical sodium-glucose transporters, SGLT1 and SGLT2, and the basolateral GLUT2 glucose transporter. SGLT2 inhibition provides significant clinical benefits in the treatment of diabetes, heart failure, and chronic kidney disease—effects that extend beyond glucose disposal.[1] The proximal tubule additionally expresses the multi-ligand receptors megalin and cubilin, which recover proteins from the primary glomerular filtrate. The Weisz group has previously characterized additional roles of megalin in governing endocytic flux and influencing proximal tubule gene expression.[2, 3] Specifically, megalin knockout in proximal tubule cells impairs endocytic trafficking[3] and substantially remodels gene expression of pathways involved in metabolism and inflammation.[2]

In their most recent study in *Function*,[4] the Weisz group explores the complex role of megalin in kidney disease and systemic metabolism, demonstrating that kidney-specific *Lrp2* (encoding megalin) knockout mice exhibited improved glucose tolerance and resistance to fat accumulation and weight gain on a Western diet, correlating with reduced SGLT2 expression. Despite these salutary effects on metabolic health, knockout mice suffered significant kidney fibrosis and inflammation under the same dietary conditions. Female *Lrp2* knockout mice also displayed improved glucose tolerance when challenged with Western diet, but were less susceptible to kidney injury than males, although histological kidney injury scoring was still significantly greater than control females.

The Weisz group previously demonstrated that proximal tubule endocytosis and transcription are intricately linked.[2, 3] In particular, *Lrp2* knockout in highly differentiated cultured proximal tubule cells led to the differential expression of over 400 genes.[2] Notably, the transcriptional response to megalin knockout was much more robust compared to that observed with the endocytic adaptor protein, Dab2, or cubilin knockout,[2] highlighting the importance of spatial distribution and signaling within these pathways. Disruptions in endocytosis are reported to affect gene expression through various mechanisms, including altered receptor-mediated signaling, trafficking, and localization; faulty nuclear import of transcription factors; and potential impacts on epigenetic signaling and chromatin remodeling.[5] For example, the unique transcriptional response to *Lrp2* knockout could be related to the reported accumulation of clathrin, a protein that forms signaling platforms facilitating selective endocytosis, at the apical surface of *Lrp2* knockout cells, which was not reported with cubilin or Dab2 knockout.[2]

Expression of *Slc5a2*, encoding SGLT2, was decreased ~80% in *Lrp2* knockout cells.[2] Kidney-specific *Lrp2* knockout mice also display decreased gene expression (~25%) and protein abundance (~13%) of SGLT2, although to a lesser extent than knockout cells,[2, 4] an effect of the mixed cell population in tissue or perhaps suggesting inter-organ homeostatic mechanisms in vivo. *Slc5a2* transcriptional regulation has not been extensively studied, although it is reportedly influenced by factors such

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as HNF-1α, mTOR activity, nucleosome positioning, and hormonal signaling (eg, insulin, glucagon).[6] As SGLT2 is the target of the nephro- and cardioprotective "gliflozin" pharmaceuticals, identification of megalin as a novel regulator of *Slc5a2* expression is a compelling finding with implications for numerous cardio-kidney-metabolic conditions. Further investigation into SGLT2 expression and activity in the context of megalin knockout and reciprocal changes in megalin function with SGLT2 inhibition could reveal novel cellular processes underlying proximal tubule glucose metabolism.

Consistent with decreased SGLT2 expression in *Lrp2* knockout mice, both male and female knockout mice exhibited improved glucose tolerance when maintained on normal chow or a Western diet. Knockout mice were also resistant to weight gain on a Western diet, linking proximal tubule megalin expression to systemic metabolism. Notably, despite modest reductions in SGLT2 protein expression, *Lrp2* knockout mice exhibited comparable glycemic protection to that of mice with SGLT2 knockout or inhibition,[7, 8] suggesting that additional factors may contribute to the observed glycemic protection. These phenomena warrant further study, as lifestyle factors including the Western diet have been linked to metabolic dysregulation and subsequent kidney tubule injury. The pronounced resistance to diet-induced glucose intolerance with *Lrp2* knockout could reveal unexplored means by which proximal tubule endocytic flux may influence whole-body glycemic regulation.

In addition to exciting implications for renal and systemic metabolism, the Weisz group's findings of increased susceptibility to kidney dysfunction, inflammation, and fibrosis in *Lrp2* knockout mice challenged with Western diet feeding highlights the complexity of megalin's context-dependent role in kidney physiology and disease. Megalin knockout or genetic defects are characterized by urinary excretion of low molecular weight proteins, due to their impaired reabsorption in the proximal tubule.[9] Accordingly, megalin knockout mice exhibit protection against various nephrotoxins. Megalin knockout has also shown protective effects in high-fat-diet-induced kidney injury, attributed to decreased uptake of lipotoxic albumin-bound lipids, which impair proximal tubule autophagy and induce fibrosis and inflammation.[10] In the present study, however, *Lrp2* KO mice exhibited significant fibrosis, inflammation, and kidney dysfunction when challenged with a Western diet. The opposing outcomes in mice challenged with high-fat and Western diets, both laden in saturated fats but differing in carbohydrate content, suggest that the high sucrose burden of the Western diet might be a differentiating factor. Notably, *Lrp2* knockout modulated carbohydrate-responsive element-binding protein expression in proximal tubule cells, potentially implicating megalin in the regulation of fructose metabolism and pathogenic downstream signaling pathways.[2]

The findings of Weisz and colleagues reveal much about the role of megalin in renal and metabolic health while raising further questions on the influence of megalin in (1) proximal tubule function and metabolism, (2) systemic glycemic control, and (3) diet- and sex-divergent responses to kidney injury. Loss of SGLT2 typically affords both metabolic and renal benefits; however, megalin knockout mice dichotomously displayed worsened kidney injury, even in the presence of metabolic benefits. As the severity of kidney injury was largely diet-dependent, further study into the consequences of megalin knockout could unlock mechanisms by which (1) SGLT2 inhibition confers nephroprotection and (2) the combination of high fat and high sucrose in the Western diet leads to kidney injury—both critical clinical questions. Indeed, this study confirms an important role of megalin in maintaining homeostasis within the kidney and beyond, particularly under metabolic stress.

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Conflict of Interest

No conflicts of interest, financial or otherwise, are declared by the authors.

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