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Elucidating the Mechanism of Magnesium-Mediated Attenuation of Kidney Disease Progression with a Focus on Calciprotein Particle (CPP) and Megalin.

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Summary

With the increase in the elderly population and the prolonged duration of lifestyle-related diseases, the number of patients with chronic kidney disease (CKD) and those undergoing dialysis has been increasing yearly, making it a pressing issue both medically and socially. Hyperphosphatemia is a promoting factor for vascular calcification, and its health hazards have long been a concern for CKD patients. It was reported that increasing phosphate (P) excretion from the kidney tubules through a high P diet leads to the formation of fine calcium P crystals (calciprotein particles, CPPs) within the tubules, causing tubule damage. Meanwhile, epidemiological studies suggest that magnesium (Mg) intake reduces the risk of CKD and cardiovascular diseases, although the mechanism remains unclear. I have studied the impact of aging and lifestyle-related diseases on the autophagy and its role. Notably, it was found that under high P load, autophagy protects the kidney via mitochondrial quality control but also causes late-stage autophagy stagnation, nullifying its protective effects. On the other hand, megalin, an endocytosis receptor expressed on the apical membrane of proximal tubules, is involved in the reabsorption, metabolism, and intracellular signaling of various proteins and drugs filtered by the glomerulus.

In this study, we hypothesize that "Mg can mitigate high P nephrotoxicity by either inhibiting the formation of pathogenic CPPs or regulating the function of megalin as an entry point." We have aimed to elucidate the effects of P-Mg balance and Fetuin-A localization on CPP formation and megalin function, explore CPP formation inhibitors (Mg and Fetuin-A), and megalin antagonistic drugs (cilastatin as a candidate). The results showed:1) Tubular damage in the high P, low Mg diet group with CPP-like substances observed in the tubular lumen and cells under electron microscopy was improved by Mg supplementation. Inflammasome activation was also observed in the high P, low Mg diet group; 2) Tamoxifen-induced proximal tubule-specific megalin knockout mice (iMegKO) exhibited significantly reduced albumin uptake; 3) The survival rate and weight loss of iMegKO mice worsened under high P and low Mg diet load; 4) No significant difference in kidney damage and fibrosis was observed between iMegKO mice and control mice under high P and low Mg diet load. These findings offer a new perspective and potential for urgent CKD countermeasures, directly linking diet and health.