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Elucidating the Cellular and Molecular Mechanisms of Magnesium-Mediated Health and Longevity

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Summary

Chronic kidney disease (CKD) is one of the diseases that cause sarcopenia (loss of muscle mass and muscle weakness), as well as lifestyle-related diseases such as hypertension and diabetes, heart failure and malignant tumours. Sarcopenia reduces activities of daily living and is closely related to an increase in falls, fractures, aspiration and cardiovascular diseases, and is a factor that places pressure on the healthcare economy, but its pathophysiology is not well understood, and effective preventive and therapeutic strategies have not yet been established.

Due to the westernization of diets, the increase in lifestyle-related diseases has become a major problem. Almost all of the inorganic phosphate in "ultra-processed foods" is absorbed, and especially in patients with CKD, excessive phosphate intake is a serious problem because elevated phosphate levels are associated with death, cardiovascular disease, vascular calcification, and progression of renal failure. On the other hand, magnesium is lost in the food processing process. As the effects of imbalance of phosphate and magnesium, phosphate toxicity is enhanced by magnesium-deficiency, but the detailed molecular and/or cellular mechanisms are not clear. We have long studied autophagy, one of the major degradation systems in the cell, and found that autophagy gradually stagnates and is unable to combat diseases in aging and obesity, indicating that regulating autophagy through diets is the key to health and longevity.

In this study, we focused on two dietary minerals, phosphate and magnesium, and hypothesized that high phosphate toxicity can be cancelled by modulating autophagy with magnesium. Therefore, we specifically aimed 1) to explore the effects of high phosphate on autophagy-lysosome pathways and Rubicon; 2) to assess their impacts on the pathogenesis of sarcopenia induced by uremia and/or high phosphate diet by using several genetically modified mice; 3) and to investigate the protective effects of magnesium against phosphate toxicity. We found that 1) autophagy activity in skeletal muscle increases and contributes to the maintenance of muscle strength in uremic sarcopenia in CKD patients, 2) high phosphate diet increases Rubicon in various organs throughout the body and causes autophagy impairment, 3) suppression of Rubicon in the whole body prevents muscle weakness induced by high phosphate diet, and 4) a low-magnesium diet exacerbates phosphate toxicity whereas magnesium sufficiency leads to muscle strength maintenance. In conclusion, we elucidated the essential cellular and molecular mechanisms of magnesium-mediated health and longevity focusing on autophagy, Rubicon, and phosphate toxicity. Our findings will provide novel perspectives and possibilities for the urgent task of preventing sarcopenia and achieving healthy longevity in a super-aged society.