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Molecular Mechanism behind the Therapeutic Effect of Magnesium on Vascular Calcification

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Summary

Two types of pathology exist in arteriosclerosis, namely, atherosclerosis and vascular calcification. In atherosclerosis, low-density lipoprotein (LDL) or 'bad' cholesterol has been established as a therapeutic target. In contrast, no such therapeutic target has been identified in vascular calcification. However, recent studies suggest that calciprotein particles (CPPs), colloidal particles composed of calcium-phosphate dispersed in the blood, may be a causative agent that induces vascular damage and chronic inflammation, and thus can be a therapeutic target for vascular calcification. The aim of this project is to determine whether vascular calcification can be treated with reagents that lower serum CPP levels in animal studies. We used Klotho-deficient mice as a model for vascular calcification associated with elevated serum CPP levels.

Because magnesium inhibited formation of CPPs *in vitro*, we placed Klotho-deficient mice on high magnesium diet (containing 0.18% magnesium) at weaning and asked if vascular calcification might be ameliorated. Unexpectedly, the majority of Klotho-deficient mice failed to adapt themselves to the high magnesium diet and died within a week. We analyzed aortas from a few survivors and observed decrease in expression of osteopontin, a marker of calcification, when compared with those from Klotho-deficient mice fed normal diet (containing 0.06% magnesium). To avoid death from maladaptation to the high magnesium diet, we are planning to compare between Klotho-deficient mice fed the normal diet and those fed low magnesium diet (containing 0.02% diet).

We identified two types of CPPs with different physical properties, namely, high-density CPPs (H-CPPs) and low-density CPPs (L-CPPs). L-CPPs were found in the blood from both normal individuals and dialysis patients with severe vascular calcification. In contrast, H-CPPs exist only in the blood from dialysis patients. Similarly, H-CPPs exist only in Klotho-deficient mice, but L-CPPs were found in both wild-type mice and Klotho-deficient mice, implying that H-CPPs may be primarily responsible for vascular calcification. In future studies, it will be necessary to determine potential effects of magnesium not only on serum levels but also on physical properties of CPPs (e.g. ratio of H-CPPs to L-CPPs).