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Mechanisms of Vascular Calcification in Atherosclerosis in Mouse Model of Chronic Renal Failure

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Objectives:

Accelerated atherosclerosis and cardiovascular calcification contribute to mortality in patients with end-stage renal failure. Proteolytic enzymes promote atherosclerotic plaque progression, extracellular matrix breakdown and calcification. However, mechanisms underlying accelerated calcification in chronic renal failure (CRF) remain obscure. We hypothesized that elastolytic proteinase cathepsin S contributes to atherosclerotic/intimal and medial calcification using optical molecular imaging of atherosclerosis mouse model with CRF.

Method:

High-cholesterol fed apoE^{-/-} (n=12) and apoE^{-/-}/catS^{-/-} (n=12) mice were randomly assigned to CRF and control groups. We used a two-step procedure to create CRF: left renal hemi-nephrectomy followed by total right nephrectomy. At 12 weeks after surgery, we employed dual-channel, intravital fluorescence microscopy to image catS and microcalcifications. To detect calcification, we administered a biphosphonate-NIRF agent (OsteoSense-680) via intravenous injections 24 hours before imaging. Elastolytic activity was visualized using a catS-activatable imaging agent.

Results:

Intravital microscopy revealed co-localization and increased osteogenic and elastolytic signal intensity in CRF apoE^{-/-} mice. In contrast, CRF apoE^{-/-}/catS^{-/-} mice had lower osteogenic signal and negligible elastolytic activity. Histological evaluation demonstrated increased calcification in CRF apoE^{-/-} mouse aorta compared to CRF apoE^{-/-}/catS^{-/-} mice detected by von Kossa and alkaline phosphatase activity corroborating imaging findings. We also found catS expression in osteoblast-like cells and higher degree of elastin fiber disruption associated with catS expression in CRF apoE^{-/-} mice compared to CRF apoE^{-/-}/catS^{-/-} mice.

Conclusions:

Mice with CRF lacking catS have delayed development of aortic calcification, supporting the hypothesis that elastolytic catS activity accelerates calcification in CRF.