The role of alkaline phosphatase in vascular calcification

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Vascular calcification is prevalent in patients with diabetes and nephropathy, and people over 60 years progressively develop mineral deposits. Arterial biomineralization is reminiscent of early stages of matrix mineralization during bone formation. Matrix vesicles are found in medial and intimal calcium deposits. Adaptive cellular processes transforming vascular smooth muscle cells (SMCs) into cells with an osteogenic phenotype were identified and SMCs can be triggered to produce matrix vesicles and mineralization. Elevated phosphate (Pi) transforms SMCs and transdifferentiated SMCs express proteins, critical in mineralization: core binding factor α-, osteocalcin and tissue-nonspecific alkaline phosphatase (TNAP) via runt-related transcription factor-2 (Runx-2) upregulation. Senescence of SMCs enhances calcification, increasing vascular calcifications in the elderly. In renal insufficiency these processes are intensified and calcified arteries contain bone matrix and regulatory proteins. TNAP is critical in bone mineralization as a phosphatase hydrolyzing a major inhibitor of mineralization, i.e. pyrophosphate (PPi). Inhibition of TNAP restores PPi to levels that can inhibit Ca2+ mineralization. TNAP is upregulated during vascular calcification and two recent mouse models of vascular calcification have studied the consequences of selective overexpression of human TNAP in SMCs and endothelial cells. In the first study, extensive vascular calcification was accompanied by high blood pressure and cardiac hypertrophy, and a median life expectancy of 44 days in males, and by upregulated vascular expression of osteoblast and chondrocyte markers vs. decreased expression of SMC markers. In a second model, the ALPL transgene was endothelial cell-specific. Also this model developed generalized arterial calcifications with osteochondrogenesis and conorary lesions expressing Runx2, osteocalcin, osteopontin and collagen II. These models illustrate that TNAP expression in endothelial or vascular smooth muscle cells triggers vascular transdifferentiation and calcification, in intima (atherosclerotic lesions) and media (chronic kidney disease). Therefore, TNAP expression is an integral part of the transdifferentiation process.

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