KSN 2017 Abstract

Premature Ageing Drives Vascular Calcification in Chronic Kidney Disease

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Vascular calcification is a ubiquitous feature in the ageing population and is accelerated in patients with chronic kidney disease (CKD) where it is associated with increased mortality, morbidity and surgical intervention. Medial calcification is most prevalent in CKD and ageing and accumulating evidence suggests that calcification is driven by vascular smooth muscle cell (VSMC) dysfunction leading to activation of osteogenic processes in the vessel wall. VSMCs lose expression/function of calcification inhibitors (Matrix Gla protein (MGP)) and circulating levels of key inhibitors (fetuin-A) are also reduced. VSMCs undergo osteo/chondrogenic differentiation characterized by upregulation of a number of mineralization-regulating proteins and ECM components normally expressed in bone. The most important of these is the master bone regulatory transcription factor (TF) Runx2. Other key events in the induction of calcification are apoptosis as well as release of membrane bound vesicles which have an essential role in promoting calcification by forming the first nidus for mineralization. Studies focussing on the specific factors that induce a 'calcific milieu' in patients as well as factors that may be targeted for intervention such as (1) increasing inhibitor function and (2) blocking the maladaptive signalling that promotes osteogenic differentiation, are now key to ameliorating this disease process.

The physiological environment in patients with CKD and particularly those on dialysis is exceedingly 'pro-calcific'. Dysregulated mineral metabolism resulting in chronically high circulating levels of phosphate as well as transient bouts of hypercalcemia potently induce VSMCs to undergo specific phenotypic changes that promote calcification. Importantly, emerging evidence suggests that calcification is an indicator of a 'prematurely aged' vasculature and that dysregulated mineral metabolism maybe a key driver of accelerated ageing. Our studies show that VSMCs from children on dialysis accumulate prelamin A, a novel biomarker of VSMC ageing, and this toxic protein promotes accelerated VSMC senescence and activation of the senescence associated secretory phenotype (SASP) that acts to promote VSMC osteogenic differentiation and calcification.