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Pathophysiologic Mechanisms of Vascular Calcification in CKD

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Age is the dominant risk factor for cardiovascular disease and medial vascular calcification is a prevalent, age-associated pathology. Medial vascular calcification is also a prominent pathology in patients with chronic kidney disease (CKD) and progresses rapidly in patients on dialysis. Significantly, even children and adolescents on dialysis develop vascular calcification and have a vastly elevated risk for cardiovascular mortality when compared to the normal age matched population. The clear association between ageing and vascular calcification in the general population has led to the suggestion that CKD patients may exhibit accelerated vascular ageing. Recent evidence has confirmed this notion and studies have shown that both adults, and more significantly children with CKD on dialysis, have increased measures of cellular ageing. Importantly changes in cell phenotype and signalling in response to ageing are emerging as key drivers of vascular calcification.

Vascular calcification is a cell mediated process regulated by vascular smooth muscle cells (VSMCs). In response to dysregulated mineral metabolism VSMCs undergo maladaptive osteogenic differentiation and act to orchestrate the mineralization process. Aged or senescent VSMCs show enhanced osteogenic differentiation and calcification potential. Using VSMCs from young children on dialysis we have shown that dysregulated mineral metabolism can promote premature vascular ageing and induce persistent DNA damage via the induction of oxidative stress. Importantly cells with persistent DNA damage display the senescence associated secretory phenotype (SASP) which is characterized by the secretion of an array of proinflammatory cytokines and chemokines as well as proteases that can act in a paracrine manner to modify the cellular environment. A number of these factors are pro-osteogenic for VSMCs including BMP2, IL6 and OPG. Our data shows that blocking the SASP by treating VSMCs with drugs targeting the DNA damage response can delay calcification *in vitro*. Moreover, in children on dialysis clinical measures of vascular stiffness and calcification correlate with circulating levels of these pro-osteogenic SASP factors implicating them in calcification *in vivo*.

Further work using animal models of CKD as well as vessel rings from patients with CKD cultured ex vivo has shown that blocking key DNA damage signalling with drug inhibitors can ameliorate calcification in vascular tissues. Mechanistically, in addition to accelerating senescence and promoting the inflammatory SASP, the DNA damage response acts to stabilise Runx2, a bone-associated transcription factor that is a key driver of osteogenic differentiation in VSMCs. A by-product of this reaction can also act to form a nidus for mineralisation in the vessel wall. Taken together this data strongly implicates premature VSMC ageing in the process of vascular calcification via multiple mechanisms including the induction of 'inflammaging' and identifies novel targets for treatment of this devastating condition.