

GATA6

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Arterial calcification is a hallmark of vascular pathology in the elderly and in individuals with chronic kidney disease (CKD). Vascular smooth muscle cells (VSMCs), after attaining a senescent phenotype, are implicated in the calcifying process. However, the underlying mechanism remains to be elucidated. Here, we reveal an aberrant upregulation of transcriptional factor GATA6 in the calcified aortas of humans, mice with CKD and mice subjected to vitamin D3 injection. Knockdown of GATA6, via recombinant adeno-associated virus carrying GATA6 shRNA, inhibited the development of arterial calcification in mice with CKD. Further gain- and loss-of function experiments in vitro verified the contribution of GATA6 in osteogenic differentiation of VSMCs. Samples of human aorta exhibited a positive relationship between age and GATA6 expression and GATA6 was also elevated in the aortas of old as compared to young mice. Calcified aortas displayed senescent features with VSMCs undergoing premature senescence, blunted by GATA6 downregulation. Notably, abnormal induction of GATA6 in senescent and calcified aortas was rescued in Sirtuin 6 (SIRT6)-transgenic mice, a well-established longevity mouse model. Suppression of GATA6 accounted for the favorable effect of SIRT6 on VSMCs senescence prevention. Mechanistically, SIRT6 inhibited the transcription of GATA6 by deacetylation and increased degradation of transcription factor Nkx2.5. Moreover, GATA6 was induced by DNA damage stress during arterial calcification and subsequently impeded the Ataxia-telangiectasia mutated (ATM)-mediated DNA damage repair process, leading to accelerated VSMCs senescence and osteogenic differentiation. Thus, GATA6 is a novel regulator in VSMCs senescence. Our findings provide novel insight in arterial calcification and a potential new target for intervention.