Mesenchymal stem cells - Key players in vascular calcification of chronic kidney disease patients?

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Abstract

Vascular calcification in chronic kidney disease (CKD) patients has emerged as a tightly regulated, coordinated and osteoblastic process resembling bone morphogenesis. The current study is based on the hypothesis that mesenchymal stem cells (MSC) constitute critical cells for pro-calcific ECM remodeling in CKD patients. Human MSC were cultured in media supplemented with pooled sera from either healthy or uremic patients (20%). Exposure to uremic serum enhanced the proliferation of MSC (cell counting, BrdU incorporation) whereas apoptosis and necrosis were not affected (annexin V and 7-AAD staining). Uremic serum exposed MSC recapitulated osteogenesis by matrix calcification and expression of bone-related genes (BMP2-receptor, ALP, osteopontin, Runx2) within 35 days. The uremic serum-induced osteogenesis was shown to be BMP2/4 dependent and was completely blocked by a BMP2/4 neutralizing antibody or its natural antagonist NOGGIN. Calcification and matrix remodelling were further analysed in a collagen-embedded osteogenesis model recapitulating the vascular collagen I/III environment.

The uremic serum induced calcification was shown to occur along collagen fibres as shown by SEM, energy-dispersive X-ray spectroscopy and von Kossa staining and was accompanied by extensive matrix remodelling.

MSC acquired a myofibroblastic phenotype, contracted the collagenous matrix and extensively remodelled the collagenous matrix by producing components of the ECM.

These changes in the artificial vascular wall were comparable to remodelling process observed in arteries of CKD patients (n=12) compared to vessels of young children (n=10).

Concluding, uremic serum induced in a BMP2/4-dependent manner an osteoblast-like phenotype in MSC accompanied by matrix remodelling and calcification comparable to the remodelling and calcification in CKD patients' arteries.