Menaquinone-4 accelerates calcification of human aortic valve interstitial cells in high-phosphate medium through PXR

Kazuhiko Seya[1], Wei Yang[2], Zaiqiang Yu[2], Mari Chiyoya[2], Kazuyuki Daitoku[2], Shigeru Motomura[3], Tadaastu Imaizumi[1], Ikuo Fukuda[2], Ken-Ichi Furukawa[3]

[1]Dept. Vascul. Biol., Hirosaki Univ. Grad. Sch. Med., [2]Dept. Thorac. Cardiovasc. Surg., Hirosaki Univ. Grad. Sch. Med., [3]Dept. Pharmacol., Hirosaki Univ. Grad. Sch. Med.

Recently, we confirmed that menaquinone-4 (MK-4), the most common form of vitamin K_2 in animals, induced the calcification of human aortic valve interstitial cells (HAVICs) isolated from aortic valve stenosis (AVS) patients in high inorganic phosphate (high-Pi) medium via BMP2-ALP pathway. However, the mechanism of MK-4-induced BMP2 expression is unclear. There is a report that MK-4 can enhance collagen accumulation through pregnane X receptor (PXR) resulting in bone formation. So, the involvement of PXR in MK-4-induced calcification of HAVICs and BMP2 gene expression was investigated. HAVICs from AVS patients were cultured in α-MEM containing 10% FBS, and when the cells reached 80% confluence, they were further cultured in the presence or absence of MK-4 for 7 days in high-Pi medium (3.2 mM Pi). MK-4 dose-dependently accelerated PXR activity (EC_{50} 6.2 nM). MK-4-induced calcification was potently suppressed by two PXR inhibitors, ketoconazole and coumestrol. In physiological-Pi medium, MK-4 alone also increased BMP2 gene expression, which was significantly suppressed by coumestrol. These results suggested that MK-4 accelerates the calcification of HAVICs from AVS patients through the PXR-BMP2-ALP pathway.