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Non-Canonical Role of MK-7 in Vascular Smooth Muscle Cells—Promoting Energy and Inhibiting of Oxidative Stress †

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Abstract: Background: The sequential processes that lead to pathological cardiovascular remodeling is unclear. From the multiple components that constitute the cardiovascular system, it is believed that vascular smooth muscle cells (SMCs) play a central role. SMCs have the ability to differentiate into a proliferative and migratory phenotype which supports vessel homeostasis. These synthetic SMCs display increased oxidative stress, secrete extracellular vesicles, and promote vascular calcification. SMC driven calcification is regulated by vitamin K-dependent matrix Gla protein (MGP). Since vitamin K promotes energy to bacteria, and vitamin K can scavenge free radicals and reduce oxidative stress, we reasoned that vitamin K can have non-canonical functions to decrease vascular calcification. Aim: We investigated the potential of vitamin K to reduce oxidative stress and support ATP synthesis in SMCs. Methods: Primary SMCs were cultured in M199 medium containing 20% FBS and 1% P/S. Warfarin (vitamin K antagonist; 10 microM) and MK-7 (10 microM) were added and ATP (luminescence), oxidative stress (DCFDA) and extracellular vesicles (EV: CD63-CD81-PE bead-assay) were measured. Results: We show that SMCs take up MK-7 very efficiently. Interference with vitamin K metabolism, using warfarin resulted in increased intracellular oxidative stress (4 fold; $p < 0.005$) and EV release (2.5 fold; $p < 0.01$). The addition of MK-7 counteracts intracellular oxidative stress, both under normal conditions (2 fold; $p < 0.05$) as well as under warfarin induced oxidative stress conditions (4 fold; $p < 0.001$). Additionally, chronic hypoxia induced by the HIF1a stabilizing cobalt chloride induced increased oxidative stress (2.5 fold; $p < 0.01$), and MK-7 could counteract oxidative stress, indicative for improved mitochondrial activity. Finally, MK-7 increased ATP production as compared to vehicle (15%; $p < 0.05$), even in the presence of warfarin. Conclusion: Our experiments show that in primary human SMCs, MK-7 lowers oxidative stress and EV release and increases ATP production. This pathway points to a non-canonical role of MK-7 in the prevention of vascular calcification, unrelated to its canonical role as cofactor for the posttranslational modification of MGP.**Keywords:** NAFLD; Intrahepatic Fat Content; oxidative stress; inflammation; biomarkers

Keywords: vitamin K; MK-7; vascular smooth muscle cells; oxidative stress; vascular calcification

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