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Role of vascular remodeling in atherosclerosis and aortic aneurysm

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Chapter 8

Summary

Chapter 1 provides fundamental knowledge on current understanding of aortic aneurysm and vascular calcification. Abdominal aortic aneurysm is a dilation of the aortic vessel wall and is most commonly found among men, older age population, and smokers. The underlying mechanism how aneurysm is formed has not been elucidated in detail. Current management relies exclusively on surgical repair in order to prevent rupture and there is no pharmacotherapy is yet recommended thus far. Vascular calcification is an active process of calcium-phosphate crystal deposition and is associated with cardiovascular diseases including aortic aneurysm. Numerous processes have been proposed as pathological mechanism for the initiation of vascular calcification including loss of calcification inhibitors and osteochondrogenic-like cells. VSMCs are the major cell type in the vessel and play an important role in vascular pathology and vascular remodeling. VSMC elicits a remarkable phenotypic plasticity and they are important mediators of vascular calcification through differentiation in osteochondrogenic phenotype. Moreover, VSMCs harbor MGP - a vitamin K dependent protein (VKDP) which is an important calcification inhibitor. **Chapter 2** describes the role of vitamin K in depth. Vitamin K is an essential bioactive compound which acts as a cofactor for the carboxylation of hepatic and extrahepatic vitamin K dependent proteins. We elaborated on the different functions and implications in diseases of vitamin K beyond its well-established role in coagulation. There are two naturally occurring vitamin K: Phylloquinone (K1) and Menaquinones (K2), both of which facilitate hepatic VKDPs activation and coagulation processes. Specifically, we highlight the role of vitamin K2 which is more able to redistribute to the circulation and assist extrahepatic VKDPs in maintaining bone hemostasis as well as inhibiting ectopic calcification. Vitamin K2, specifically MK-7, has the longest bioavailability and is most efficiently absorbed. We summarized the current implications of vitamin K in different clinical settings including osteoporosis, atherosclerosis, cancer, and inflammatory diseases.

Chapter 3 elaborates on what is currently known about the role of VSMC phenotypic switching in pathophysiology of aortic aneurysm formation. We highlight that calcification of the vessel wall is involved in the initiation and progression of both thoracic and abdominal aortic aneurysms. Thus, early detection of microcalcification may help to hold aortic aneurysm progression. VSMCs actively mediate changes in aortic wall structure that lead to aneurysm formation and vascular calcification through a process called phenotypic switching. This phenotypic switching can be triggered by various stimuli including oxidative stress which is an important factor underlies the pathology of aortic aneurysm. In our review, we extend on current knowledge by providing an insight of the involvement of vitamin K-dependent

processes in aortic aneurysm. Vitamin K helps decrease vascular calcification through facilitation of MGP, a VKDP which is synthesized by VSMCs. Moreover, vitamin K and vitamin K-oxidoreductase are involved in the regulation of Nox and ROS generation. We shed light on potential treatment mechanisms with vitamin K to prevent vascular calcification induced aortic aneurysm formation and progression.

In **Chapter 4,** we characterized human AAA VSMCs and compared them to VSMCs from a non-aneurysm region of the same patient. AAA VSMCs undergo phenotypic switching, activating several mechanisms leading to vascular calcification. AAA VSMCs lose contractility and assume the synthetic phenotype. This is accompanied by alterations in VSMC oxidative stress and EV release. AAA VSMCs further differentiate towards macrophage-like and osteo/chondrogenic-like VSMCs displaying a SASP phenotype. Pro-inflammatory AAA VSMCs secrete IL6 which induces inflammatory responses in ECs. We hypothesized that these AAA VSMC features, together with an increase in ucMGP (inactive calcification inhibitor), induces microcalcification. Microcalcification is known to cause destructive changes in the surrounding extracellular matrix and leads to weakening of the vessel wall. Macrocalcification develops over time and further aggravates the dilation of the vessel.

In **Chapter 5**, we investigate how smoking affects vascular calcification. Calcification, specifically microcalcification, was found at a higher level in atherosclerotic plaques of smokers compared to non-smokers. We unraveled the mechanism how nicotine initiates VSMC calcification. Nicotine directly affects VSMCs by increasing intracellular calcium, oxidative stress, EV release, and subsequently calcification through binding of α3 and α7 nACh receptor. Binding of nicotine to nAChr resulted in a rapid increase of calcium influx and induced calcium dependent-Nox5 activation generating ROS. We identified Nox5 as a key mediator in inducing pro-calcific processes of VSMCs by nicotine. Finally, we showed that vitamin K2 (MK-7) ameliorates nicotine-induced VSMC pathologies including reduced oxidative stress, EV release and calcification.

In **Chapter 6**, we used a preclinical animal model to demonstrate the effect of vitamin K2 on atherosclerotic plaque development and calcification. We report that discontinuation of VKA prevents vascular calcification in atherosclerotic plaques compared to long-term VKA treatment. Supplementation of vitamin K2 not only prevents vascular intima calcification, but also reduces atherosclerotic plaque progression and improves plaque stability by reducing oxidative stress and increasing collagen content. These findings support a potential use of vitamin K2 supplementation for treatment of atherosclerosis and calcification in the clinical settings.