Role of vascular remodeling in atherosclerosis and aortic aneurysm

Valorisation

Aortic aneurysm is a life-threatening, pathological condition characterized by permanent dilation of the aorta. Aortic aneurysm is associated with male gender, advanced age, hypertension, genetic diseases and lifestyle factors such as smoking. Because of lack of understanding of the pathology underlying aneurysm formation, no pharmacotherapy is yet recommended to reduce risk of aortic aneurysm progression and rupture. Current management of aneurysms relies exclusively on surgical repair in order to prevent rupture. Decision for the type of repair requires careful assessment of rupture risk, specific feature or anatomy, life-expectancy, and patient's preference. Although medical advancement enables less invasive surgical treatments such as Endovascular aneurysm repair (EVAR) over the previous decade. EVAR comes with higher reintervention rate and cost.

Better knowledge of basic mechanisms underlying aortic aneurysm will open up novel avenues for intervention and disease management. Key areas which offer great opportunities to advance knowledge regarding aneurysm formation have been proposed by medical experts in the field and include the following topics: 1. definition of etiologic factors responsible for development of aortic aneurysm, with an emphasis on elucidating biological mechanisms by which specific risk factors might act to promote aortic disease such as atherosclerosis and hypertension; 2. elucidation of genetic loci for an inherited predisposition; 3. better definition of the cellular and molecular pathophysiology of aneurysms, with emphasis on the mechanisms underlying progressive destruction of aortic wall. This includes the role of specific proteinases, nature of immune response, and better understanding of the role of VSMC in disease initiation and progression.[5]

The research described in this thesis aims to unravel mechanisms underlying aortic aneurysm formation. We characterized VSMCs from aortic aneurysm tissue with specific focus on the involvement of vascular calcification in the pathogenesis of abdominal aortic aneurysm. Moreover, we studied the effect of smoking, the strongest life-style risk factor for development of aneurysm, on VSMCs and explored the role of vitamin K as potential anti-calcific and antioxidant therapy in vascular pathologies.

Current implications of vitamin K and vitamin K dependent proteins in cardiovascular diseases are described in Chapter 2. The importance of VSMCs in vascular pathologies, with a focus on aortic aneurysm, is emphasized in Chapter 3. In this chapter, we extended on current knowledge by providing an insight in the involvement of vitamin K-dependent processes in

aortic aneurysm and shed light on potential treatment mechanisms with the nutraceutical vitamin K to prevent vascular calcification induced aortic aneurysm formation and progression.

In **Chapter 4**, we characterized VSMCs from aneurysm patients and compared apparently healthy VSMCs and VSMCs from the abdominal aneurysm of the same patient. Understanding the basic pathologies of aortic aneurysm promote emergence of new approaches that would result in a better disease management. The findings in this chapter extend the current knowledge of aneurysmal VSMCs characteristic and morphology which has mainly been described based on studies in animal models. Importantly, we report that aneurysmal VSMCs are less contractile, increase extracellular vesicle release, and calcified more than control VSMCs. Our findings emphasize the importance of VSMCs in aortic aneurysm and its significant role in mediating vascular microcalcification which is observed during aortic aneurysm progression. Indeed, use of ^{18}F-NaF to detect microcalcification recently became a promising additive tool to predict aneurysm progression and clinical events. It is particularly useful for patients in which the decision to intervene is challenging. We put forward (micro) calcification as an important risk factor amendable for intervention in AAA. Thus, targeting of VSMCs and extracellular vesicles may prevent vascular microcalcification and thus reduce aggravation of aortic diseases.

In a pilot study, we showed that aneurysmal tissue is positive for (inactive) ucMGP, a marker used for indication of vascular vitamin K deficiency. Vascular vitamin K deficiency is associated with increased vascular calcification. Future studies in aneurysm patients measuring plasma inactive ucMGP as biomarker might provide insight on aortic aneurysm risk, hence provide a novel treatment area using vitamin K to improve vitamin K status.

Nicotine is known for its devastating effects on the vasculature. It increases risk of atherosclerotic calcification and abdominal aortic aneurysm. In **Chapter 5** we investigated the molecular mechanisms how nicotine potentially affects the vasculature. We revealed that smoking is associated with higher degree of microcalcification in atherosclerotic plaques and unravel a potential mechanism by which nicotine affects VSMC via Nox5-mediated pro-calcific processes. We demonstrated the involvement of α3 and α7 nicotine acetylcholine receptor in nicotine-induced VSMC pathologies which thus serve as potential targets for pharmacological intervention. Moreover, we show that downstream of nicotine binding to the nAChr induces oxidative stress and causes extracellular vesicle mediated calcification. Our data contribute to the understanding of how nicotine not only affects atherosclerotic plaque calcification, but possibly also other VSMC-mediated vascular diseases, such as hypertension and aortic aneurysm. Because nicotine is the primary agent in both cigarettes and e-cigarettes,

our findings also add to the current knowledge that vaping may not be a better and healthier choice for vascular health.

In **chapter 5**, we provide evidence that vitamin K2, besides being a cofactor for the carboxylation of matrix Gla-protein to inhibit vascular calcification, is an effective antioxidant ameliorating nicotine-induced oxidative stress and extracellular vesicle release, subsequently inhibiting calcification of VSMCs. Vitamin K2 is naturally present in fermented food and is also available as supplement. The use of vitamin K2 is an easy, safe and cost-effective way to maintain vascular health and prevent vascular disease. **In chapter 6**, we further provide evidence on cardiovascular promoting effects of vitamin K2 *in vivo*. Using an animal model of atherosclerosis, we show that discontinuation of VKA and switch to supplementation with vitamin K2 prevents vascular calcification and reduces atherosclerotic plaque progression. Our findings emphasized an adequate status of vitamin K2 for vascular health and put forward clinical implications of vitamin K2 supplementation to treat cardiovascular diseases.

Reference

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