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Key role for VSMCs in vascular remodeling and calcification

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Chapter 10

Valorization

Valorization, the utilization of academic research. Or the process of value creation out of knowledge and make it available for economic or societal purposes. Eventually so that it can be translated into products, service or other processes regarding industry.

In my thesis we studied the vascular smooth muscle cell (VSMC), a pivotal player in vascular health and the development of cardiovascular disease (CVD). In more detail we focused on its action in vascular remodeling processes that lead to the development of CVD and vascular calcification. CVD is still the number one cause of death in the world. And understanding the mechanisms of CVD is important, but does not help society directly. However, it can help in the development of new treatments strategies and earlier detection. Most clinical tools that are currently available diagnose CVD at a too late stage. Especially, vascular calcification is diagnosed overdue, when only treatment is focused around resolving the symptoms rather than curing the disease. The valorization part of my thesis focusses on the effect of medial remodeling processes that affect vascular calcification and CVD.

Chapter 2 elaborates on the role of VSMCs in arterial remodeling processes, with a focus on calcification-related processes. In this chapter the role of VSMCs in CVD is discussed from a fundamental, translational and clinical point of view. Chapter 3 investigates the effect of medial calcification on atherosclerosis development. We believe that medial degradation precedes the pathological build-up of plaques. This concept is already old, but recent literature investigates atherosclerosis mostly from a lipid point of view. The research in **chapter 3** confirms that medial degeneration, induced as medial calcification by vitamin K antagonists (VKAs), leads to extensive extracellular medial remodeling with subsequent atherosclerosis induction. We believe it is important to disseminate this view with clinicians to change the way of treating CVD. Additionally, big pharmaceutical companies should change their focus on CVD drug discovery from relieving symptoms towards disease prevention. Another important finding in chapter 3 is that VKAs induce accelerated vascular calcification. VKAs are regularly prescribed to patients suffering from CVD, but clinicians are often not aware of the detrimental effects VKAs have on established atherosclerotic plaques. For example, numerous studies have shown that chronic kidney disease (CKD) patients display extreme vascular calcification after VKA use.

In **chapter 4** we focused on the role of VSMCs apoptosis on the development of atherosclerosis. Our results indicate that VSMC apoptosis in the vessel media results in larger and more vulnerable atherosclerotic plaques. Furthermore, recent literature indicates that most cells that reside inside atherosclerotic plaques are derived from VSMC origin. These findings might have a great impact on the clinical situation. The most well-known treatments of atherosclerosis involve lipid lowering, by-pass surgery and stenting. It is pivotal to include the VSMC into current treatment, as an important contributor to the development and progression of atherosclerosis. Future treatment strategies should focus more on changing the phenotype from synthetic, excreting and proliferative VSMCs towards a contractile phenotype in which the proliferative and secretory nature is decreased.

Chapter 5 describes a novel method to measure calcification propensity using patient serum or plasma, and its susceptibility to develop vascular calcification. Current methods for calcification determination are unrefined and there is no consensus on how

the calcification assays are performed. With our assay we are able to measure calcification kinetics and evaluate patient specific responses while restricting to optimal calcification conditions. The BioHybrid assay might potentially be used in future academic research as golden standard. Thereby, normalising and improving the current end-point assays that are available. Moreover, the BioHybrid platform can be expanded by more in vitro assays to cover a wide range of biological read-out parameters. This in combination with the use of several primary cell types provides a platform that is currently unique and non-existing, with the potential to not only combat vascular calcification but other diseases as well. Additionally, the BioHybrid platform is expected to be fully translatable into animal and healthy volunteer phase, making it a patentable solution that can be commercialized.

The concept of a biohybrid platform is appealing but should not attenuate research to new biomarkers. In **chapter 6** we investigate the biomarker potential of matrix Gla protein (MGP). We found that MGP is an independent predictor of both intimal and medial vascular calcification is a specific cohort of CKD patients. Biomarker research is valuable for the clinic as they can directly be used to interpret parameters of patients. The most inactive variant of MGP (dephosphorylated-uncarboxylatedMGP; dp-ucMGP) reflects a patient' Vitamin K status. Vitamin K is key in the activation of Vitamin K dependent proteins (VKDP) that are known to be important in the coagulation cascade. However, other VKDP, such as MGP, are involved in the inhibition of mineralization. We found that dp-ucMGP plasma levels associate with local protein and mRNA expression and also medial calcification. Targeting MGP, and especially its activation, might prove a novel therapeutic target as it can inhibit or prevent local tissue mineralization at a much earlier stage of the disease. One strategy to activate MGP is to supplement Vitamin K to patients. Although critical care should be taken when supplementing Vitamin K to patients that require anticoagulation. Currently, several clinical trials are being conducted to study the beneficial effects of Vitamin K in CVD and specifically vascular calcification prevention.

Taken together, the data described in my thesis provide a new angle for the development of therapeutic strategies to target vascular calcification and atherosclerosis. Ideally, treatment shifts towards earlier stages of the disease in which regression or prevention is still possible. Treating patients earlier is advantageous but clinical detection should develop along. To aid detection, we build the BioHybrid platform which is based on a VSMC readout to patients' plasma or serum. Clinically treatment that prevents or regresses calcification would be greatly appreciated as it is a benefit for CVD mortality/ morbidity and expensive treatments costs. In conclusion this thesis, covers the whole spectra of research from fundamental to translational and clinical. Thereby some of the findings can be valuable for the interpretation of a different therapeutic approach or can be translated into products and services that can be commercialized.