

Multi-omics discovery of novel molecular pathways in cardiovascular calcification

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5 Social Impact

CVD is the primary cause of mortality worldwide, accounting for approximately one-third of deaths globally. Projections predict a burden of 23.3 million deaths by 2030². This rising prevalence of CVD is associated with a substantial economic, social, and health care expenditure. Only in Europe is estimated that CVD costs €210 billion a year. This cost splits into 53% (€111 billion) for health care costs, 26% (€54 billion) for productivity losses, and 21% (€45 billion) for the informal care of people with CVD²⁷². A major comorbidity in CVD patients is T2DM, in which vascular calcification represents a contributing risk factor. Figures from the International Diabetes Federation state that around 415 million patients had diabetes in 2015 – a scenario projected to rise to 642 million by 2040²⁷³. The median annual cost per T2DM patient with CVD is 112% higher than those without CVD. The yearly economic burden of coronary artery calcification in the elderly population of the USA alone (aged ≥65 years) is estimated \$1.3 billion²⁷⁴.

As CVD prevalence rises, proper control and treatment of associated risk factors such as vascular calcification and T2DM are integral to curbing poor clinical outcomes. Accordingly, the focus has increased on the joint management of CVD with vascular calcification and T2DM. Despite progress in treatment and diagnosis of CVD in the past few decades, vascular calcification persists without a pharmacological therapy to either inhibit or halt its progression. This, and my work, illustrates the high promise of vascular calcification as a new target for intervention in CVD.

Therefore, research in CVD can be considered an investment in increased welfare, productivity, and economic growth. New CVD medications in the 38 countries members of the Organization for Economic Co-operation and Development are estimated to have reduced hospitalization costs by 70% between 1993 and 2005²⁷⁵. Now, the advances in omics investigative tools present an opportunity to explore novel molecular networks for further therapeutical targets in vascular calcification.

First, this thesis established an effective use of bioinformatics tools in cardiovascular calcification omics analysis using publicly available multi-omics data sets in CAVD. The multi-omics data integration proposed a novel multi-omics layered network in CAVD that was linked to the formation of amyloid structures, such as those present in Alzheimer's disease or cardiac amyloidosis. Identifying these novel pathways in this thesis provides a rationale for future mechanistic studies to better understand the

pathophysiology of CAVD, which paves the way for the development of therapeutic strategies.

Secondly, the transcriptomics analysis of CaP-induced calcification in VSMCs extended the current knowledge of vascular calcification molecular mechanisms by providing a gene signature that served as a discovery platform for novel mechanistic investigations. The newly generated hypotheses based on gene expression suggest potential cellular and molecular targets for pharmacological intervention in CaP-induced vascular calcification related to mitochondrial energy metabolism and glycolysis in VSMCs. Furthermore, a drug repurposing analysis suggested a differential role of protein kinase C as a therapeutical option to be further explored in vascular calcification.

Thirdly, this thesis investigated the mechanism by which T2DM promoted vascular calcification through a hyperglycemic in vitro model of calcified VSMC. The study confirmed in the employed in vitro system that glucose promotes ECM mineralization; surprisingly, the absence of glucose inhibited this process. A multi-omics analysis using untargeted transcriptomics and metabolomics was employed to explore the mechanistic pathways from hyperglycemia-induced vascular calcification. This thesis presents the first multi-omics study in hyperglycemia-induced vascular calcification in VSMCs, contributing and adding on to the current knowledge. After multi-omics data integration, key players from the hypotaurine/taurine metabolic pathway were identified as central hubs of a novel reconstructed network. Hypotaurine was one of the most regulated metabolites by glucose, secreted in a dose-dependent manner. In hyperglycemia-calcified VSMCs, blocking hypotaurine production increased ECM mineralization while hypotaurine treatment prevented calcification. This work suggests that hypotaurine may exert its effect through proliferation- and oxidative stress-mediated mechanisms.

The results presented in this thesis were disseminated and shared in national and international conferences, symposiums, and other meetings through oral presentations and posters. Moreover, part of the results was published in a peer-reviewed journal.

In summary, this thesis emphasizes the potential of omics techniques in unveiling novel molecular mechanisms in CVD. It also puts forward hyperglycemia as an important risk factor for intervention in vascular calcification. The added power of multi-omics integration provided evidence of the dysregulation of the hypotaurine/taurine

metabolic pathway in hyperglycemia-induced vascular calcification. Those molecular alterations suggest potential novel therapeutic targets that warrant further investigation in vascular calcification.