Cytoskeleton Dynamics and Extracellular Vesicles in Arterial Remodeling

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Recent epidemiological data illustrate that cardiovascular diseases remain the leading cause of death worldwide. Vascular calcification, defined as the pathological calcification of arteries, has emerged as a strong predictor of and contributor to cardiovascular morbidity and mortality. This fibro-calcific remodeling of highly flexible cardiovascular tissues disrupts the normal biomechanical function, leading to complications like heart failure, myocardial infarction, and stroke. Prevention of VC is a high unmet clinical need, particularly among high-risk patients with impaired kidney function. However, the molecular mechanisms underlying accelerated VC are poorly understood.

We demonstrated that calcifying extracellular vesicles (calEVs) released by vascular smooth muscle cells (SMC) actively contribute to the initiation of vascular calcification. Their payload and trafficking, as well as detailed physiochemical characterization, are, however, elusive. Our preliminary findings indicate that calcifying SMCs have a different tubulin and actin cytoskeleton, and that inhibiting actin polymerization prevents SMC calcification. Moreover, we recently discovered a distinct microRNA (miRNA) profile in calcified human arteries that are known to be enriched in EV cargo.

This project, therefore, aims to understand (i) the role of actin dynamics in EV-mediated vascular calcification by characterizing the intracellular trafficking dynamics of calcifying EVs and (ii) the implication of the miRNA cargo. **We hypothesize that cytoskeleton dynamics regulated by key actin-proteins play a central role in the development of vascular calcification via the biogenesis and intracellular trafficking of calcifying EVs and subsequent cargo loading, including miRNAs that directly regulate cell mineralization.**

To achieve our objectives, we will utilize established in vitro and in vivo calcification models in combination with loss-of and gain-of-function experiments as well as molecular imaging to i) characterize the EV subpopulation that drives SMC calcification, (ii) investigate the functional role of cytoskeleton dynamics in EV-mediated SMC, and (iii) determine the role of calcifying EVs and EV-loaded miRNAs in SMC calcification and intercellular communication within the atherosclerotic plaque.

This research program will contribute to a better understanding of the biogenesis and the resulting functional consequences of calcifying EVs and thereby to the understanding of early mechanism of vascular calcification laying the foundation for new therapeutic strategies to prevent pathological mineral deposits in patients and thus limit their harmful effects on vascular dysfunction.

Preferred Course of Study/Expertise of Candidate: Biology, molecular biology, cell biology, biochemistry, biomedicine

Further reading:

Hutcheson JD, Goettsch C. Cardiovascular Calcification heterogeneity in chronic kidney disease. Circ Res 2023;132: 993-1012. doi: 10.1161/CIRCRESAHA.

Iqbal F, Schlotter F, Becker-Greene D, Goettsch C, Hutcheson JD, Rogers MA, Halu A, Lee LL, Blaser MC, Mlynarchik A, Hagita S, Kuraoka S, Chen HY, Engert JC, Passos LS, Jha P, Osborn E, Jaffer F, Body, SC, Robson SC, Thanassoulis G, Aikawa M, Singh SA, Sonawana AR, Aikawa E. Sortilin enhances fibrosis and calcification in aortic valve disease by inducing interstitial cell heterogeneity. Eur Heart J 2023;44:885-898. doi: 10.1093/eurheartj/ehac818.

Jankowski V, Saritas T, Kjolby MF, Hermann J, Speer T, Himmelsbach A, Mahr K, Heuschkel M, Schunk SJ, Thirup S, Winther S, Bottcher M, Nyegard M, Nykjaer A, Kramann R, Kaesler N, Jankowski J, Floege J, Marx N, Goettsch C. Carbamylated sortilin associates with cardiovascular calcification in patients with chronic kidney disease. Kidney Int 2022;101:574-584. doi: 10.1016/j.kint.2021.10.018

Goettsch C, Hutcheson JD, Aikawa M, Iwata H, Pham T, Nykjaer A, Kjolby M, Rogers M, Michel T, Shibasaki M, Hagita S, Kramann R, Rader DJ, Libby P, Singh SA, Aikawa E[#]. Sortilin mediates vascular calcification via its recruitment into extracellular vesicles. J Clin Invest 2016; 126:1323-36. doi: 10.1172/JCI80851.