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The endothelial glycocalyx: from hemodynamic hypothesis to clinical risk predictor

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Short summary:

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Although the endothelial cell glycocalyx is nowadays broadly accepted as an important structure that is essential for endothelial function and microvascular health, I would like to revisit some of the earlier studies on several apparent capillary hemodynamic discrepancies that led to the original glycocalyx hypothesis.

These studies include observations of very low and variable capillary tube hematocrit (Klitzman and Duling, 1979), discrepancies between estimates of capillary blood flow with measurements of total muscle flow (Duling, Sarelius and Jackson, 1982),

measurements of capillary discharge hematocrit (Desjardins and Duling, 1987), the impact of heparinase treatment on capillary hematocrit (Desjardins and Duling, 1990), and the first direct observation of distinct luminal domains for plasma macromolecules and erythrocytes within mammalian capillaries (Vink and Duling, 1996).

Based on the observation that a healthy glycocalyx keeps flowing red blood cells at a considerable distance from the endothelial cell surface, the GlycoCheck system was developed to assess glycocalyx damage noninvasively in both experimental as well as clinical settings, resulting in the publication of more than 120 peer-reviewed papers that not only confirm that breakdown of the glycocalyx correlates with patients' complications in a wide range of diseases, but also that assessment of glycocalyx damage in healthy individuals predicts future risk of adverse cardiovascular events (Ikonomidis, 2022).

In conclusion, after more than 4 decades of glycocalyx research, it is beyond question that the endothelial glycocalyx is essential for microvascular health, and that identification of glycocalyx damage can identify (early) cardiovascular risk in patients and healthy individuals. Finally, recent development of specific glycocalyx therapeutics show great potential for improvement of microvascular health, and ongoing clinical trials are currently testing its potential impact on cardiovascular risk in a variety of clinical conditions.

Inflammation plays a critical role in the pathogenesis of various diseases by promoting the acquisition of new functional traits by different cell types. Shared risk factors between cardiovascular disease and cancer, including smoking, obesity, diabetes, high-fat diet, low physical activity, and alcohol consumption, contribute to inflammation linked to platelet activation. Platelets contribute to an inflammatory state by activating various normal cells, such as fibroblasts, immune cells, and vascular cells. This activation is achieved by releasing diverse molecules from platelets, including lipids (eicosanoids), growth and angiogenic factors, and extracellular vesicles(EVs) rich in various RNA species. Antiplatelet agents like low-dose aspirin can prevent cardiovascular disease and cancer by inhibiting platelet functions beyond the antithrombotic action. Notably, platelets induce the epithelial-mesenchymal transition(EMT) in tumor cells, enhancing their metastatic potential. Two platelet eicosanoids, PGE_2 (generated as a minor product of COX-1) and 12S-

hydroxyeicosatetraenoic acid(HETE) [derived from the platelet-type 12-lipoxygenase(LOX)], contribute to EMT. In addition to the pharmacological inhibition of eicosanoid biosynthesis, a potential strategy for mitigating platelet-induced metastasis might encompass the inhibition of direct interactions between platelets and cancer cells. New antiplatelet drugs, such as revacept and selective 12-LOX inhibitors, currently under clinical development, are of interest due to their low risk of bleeding. Platelets and EVs carry important clinical information because they contain specific proteins and RNAs associated with disease conditions. Their analysis can improve the accuracy of liquid biopsies for early disease detection, monitoring progression, and assessing drug response.

In the current era of precision medicine, developing treatment protocols involving the safe utilization of antiplatelet agents to prevent cancer and cardiovascular disease necessitates adopting a systems biology approach. This strategy entails a comprehensive analysis of heterogeneous datasets, including genomics, epigenomics, proteomics, lipidomics, and clinical data, at the level of the individual patient. This procedure involves dynamic systems modeling to identify candidate pathways contributing to aspirin's benefits and harms and possibly other antiplatelet agents. Additionally, this strategy will help identify susceptibility profiles for disease, verifying whether platelet- and EV-based liquid biopsy can predict the onset and recurrence of cancer and atherothrombosis.

Biosketch:

Hans Vink received his physics degree in 1989 at the University of Amsterdam. After receiving his PhD in Medicine in 1994 and a post-doctoral fellowship at the dept. Molecular Physiology and Biological Physics, University of Virginia, Charlottesville, VA, USA, he returned to the University of Amsterdam and developed a research program on the endothelial glycocalyx, supported by grants from the Netherlands Organization for Scientific Research (NWO 1997 – 1999) and a fellowship from the Royal Netherlands Academy of Sciences (KNAW 2000 – 2005). In 2006 he was awarded an Established Investigatorship by the Netherlands Heart Foundation and moved to the University of Maastricht as a Principal Investigator at the Cardiovascular Research Institute of Maastricht, and he was appointed professor of Circulatory Physics at the University in Amsterdam in 2008. His research on the endothelial glycocalyx progresses towards clinically applicable tools for early diagnosis of cardiovascular risk

and new therapeutic approaches to protect the vascular wall against atherogenic challenges and is supported by program grants from the Center for Translational Molecular Medicine, The Netherlands Heart Foundation, The Dutch Diabetes Research Foundation and the Netherlands Kidney Foundation. He founded several companies such as GlycoCheck BV, GlycoCheck US and the GlycoCalyx Research Institute (www.glycocalyx.com) for development of a non-invasive biomedical device to measure the health of the endothelial glycocalyx (the GlycoCheck device) and several glycocalyx specific therapeutics. He has published more than 100 scientific publications and supervised 10 PhD projects. His Hirsh factor is 54.

Relevant publications:

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