Targeting the vessel wall in cardiovascular prevention
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Citation for published version (APA):

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Part 1

The endothelial glycocalyx
Initial steps in testing a promising concept

Nothing will ever be attempted if all possible objections must be first overcome. (Samuel Johnson)

Part 1 deals with the endothelial glycocalyx. The glycocalyx is a gel-like layer covering the inside of the vessel wall. The idea that the endothelial glycocalyx is an important barrier against cardiovascular disease is a promising and exciting concept. Our research consists mainly of small, exploratory studies that form part of the initial steps toward possible use of the glycocalyx as biomarker and potential target for therapy.
INTRODUCTION

An aspect of the vessel wall that is often unknown, denied or simply forgotten is the endothelial glycocalyx. However, the term glycocalyx, together with an invitation prompting further research, was already introduced in 1963 by Bennett with the following words:

‘By now we have established the point that many plant and animal cells possess an extracellular coating rich in polysaccharides. … I deem it desirable to assign a single, general, inclusive term to this extracellular, sugary coating, wherever it may be found. The ancient Greeks had no word for sugar, but they had one for sweet - a taste which we often associate with sugars. I propose … that we choose to speak generally of this polysaccharide-rich coating of cells as the ‘glycocalyx’. This word means ‘sweet husk’. We know of very many kinds of plant, animal, bacterial and other cells which possess a glycocalyx. Do all cells possess one? Is a glycocalyx a general feature of cells, as is the plasma membrane? We do not know. … I hope my speculations and suggestions may stimulate new research and new experiments.’ (1)

Since then many research efforts followed, often complicated by technical hurdles. Standard histological techniques, using dead tissue and aggressive fixation, did not adequately preserve the glycocalyx. Eventually, especially intravital microscopy, imaging the microcirculation of living animals, enhanced our knowledge of this layer.

The endothelial glycocalyx is a complex, highly hydrated mesh of proteoglycans, glycosaminoglycans and plasma proteins that is anchored to the endothelial plasma membrane (2). It separates endothelial cells from the flowing blood, enabling blood cells to gently ‘snowboard’ along the surface (3). Its size of approximately 0.5 μm exceeds that of an endothelial cell and that of adhesion molecules on its surface. The endothelial glycocalyx exerts a wide array of anti-atherogenic effects. These include limiting of transendothelial leakage of lipids, mediating nitric oxide (NO) release, and modulating coagulation as well as leukocyte and platelet adhesion (4).

Just recently, our group developed new methodologies to study glycocalyx synthesis in cultured cells, glycocalyx dimension and function in mouse models, as well as glycocalyx dimension in humans. Although these techniques are still not infallible, initial results have already demonstrated accelerated degradation of glycocalyx in cultured endothelium exposed to risk factors, smaller glycocalyx size at specific arterial sites in mice (5) and a dramatic reduction of systemic glycocalyx volume in humans with induced hyperglycemia and type 1 diabetes mellitus (6, 7).
HYPOTHESIS

We hypothesize that an intact endothelial glycocalyx contributes to endothelial barrier function and protects against the development of atherosclerosis, whereas disruption of the glycocalyx promotes vascular permeability and atherogenesis. Moreover, we propose that restoration of the endothelial glycocalyx is an attractive novel target for prevention of cardiovascular disease.

OUTLINE

In chapter 1, we review the cumulating evidence underlying our hypothesis that the endothelial glycocalyx protects the vessel wall, whereas damage increases vascular vulnerability. Chapter 2 introduces two novel techniques to estimate glycocalyx dimension in humans. We applied these methods in chapter 4 to 6, in which we studied the effect of different atherogenic stimuli, i.e. diabetes mellitus, inflammation and hypercholesterolemia, on glycocalyx dimension in humans. Subsequently, we explored the possibilities of glycocalyx restoration. The effect of sulodexide, a drug consisting of glycocalyx components, was also studied in cell cultures (chapter 3). To provide additional, more direct proof of our hypothesis, we studied the effect of chronic degradation of the glycocalyx component hyaluronan by hyaluronidase infusion on permeability and atherosclerosis progression in mice (chapter 7).

REFERENCES