

Passive Gold Nanoparticle Delivery to Plaque-prone Blood Vessel Regions

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Introduction

Cardiovascular disease caused by atherosclerosis is a leading cause of death in the world, killing more than 17 million people annually.¹ One of the initial causes of atherosclerosis is the increased uptake of low-density lipoproteins through the layer of endothelial cells that lines and protects the blood vessel walls. Clinical data, showing shed glycocalyx components in blood samples of atherosclerotic patients, suggest a link between atherosclerotic development and integrity of the endothelium extracellular matrix. This matrix, called glycocalyx, is comprised of membrane proteins and sugar chains in a brush-like configuration². It is proposed that the breakdown of glycocalyx leads to a weakening in endothelium barrier against lipoprotein uptake and atherosclerosis. We hypothesize that compromised glycocalyx can be passively targeted with the use of nanoscale particles, for improved drug delivery to better address atherosclerosis. Many treatment options available for patients have detrimental side effects and high failure rates. Thus, the ability to target atherosclerosis-prone areas via dysfunctional glycocalyx allows for improved measures against cardiovascular disease.

Materials and Methods

To test our hypothesis, rat fat pad endothelial cells (RFPEC) were cultured and grown into a monolayer on glass coverslips. The endothelial cells were then subjected to several treatments to simulate glycocalyx condition, including healthy, collapsed (low serum treatment), shed (HepIII treatment), and recovered models (HepIII + HS treatment). Red fluorescent, polymer-coated gold nanoparticles measuring 10 nm in diameter³ were incubated with RFPEC at each condition for 16 hours to observe their uptake into the monolayer. The RFPEC were then fixed with aldehydes and stained with green fluorescent markers to quantify the thickness and coverage of the heparan sulfate (HS) component of the glycocalyx under confocal microscopy. The nanoparticle fluorescence was used to identify the localization of the nanoparticles within the monolayer, giving a quantitative measurement of nanoparticle uptake and glycocalyx permeability.

Results and Discussion

Healthy RFPEC cultures exhibited a robust glycocalyx, specifically the HS component of the matrix. This glycocalyx state coincided with minimal uptake of the gold nanoparticles. When the glycocalyx was

weakened from collapse or shedding, the thicknesses and coverage decreased by an average of 35% and 90%, respectively. This glycocalyx weakness coincided with a significant increase of gold nanoparticle uptake of more than six-fold (Fig 1A). Glycocalyx recovery (partial) lowered the uptake of gold nanoparticles back to baseline levels. The large difference in nanoparticle uptake seen between the investigated glycocalyx conditions suggests that glycocalyx integrity is important in modulating endothelium permeability and nanoparticle drug delivery specificity for more targeted delivery of therapeutics to treat atherosclerosis.

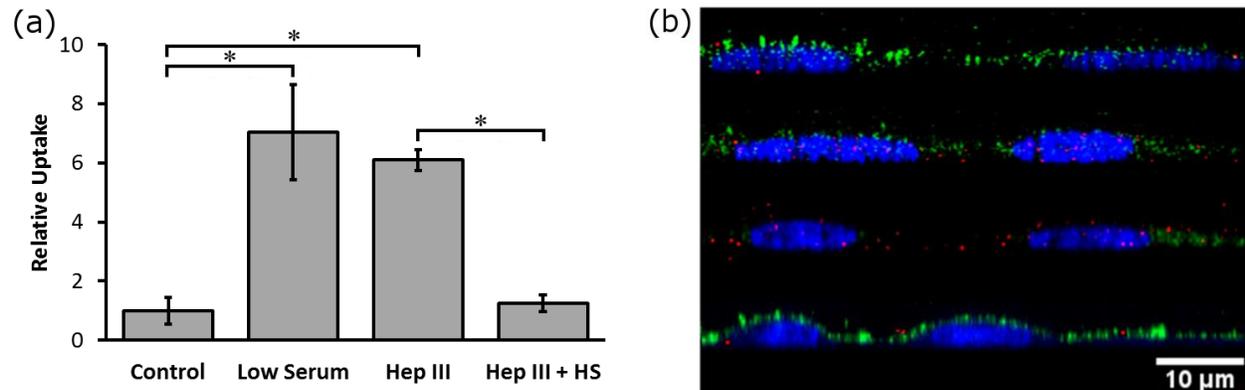


Figure 1: (a) The relative uptake of gold nanoparticles by the RFPEC monolayer under each condition. Low serum and Hep III-induced collapse and shedding of glycocalyx caused a significant increase in the uptake of the gold nanoparticles. Recovery of glycocalyx by treatment with HepIII + HS lowered the uptake significantly. (b) Cross-sectional confocal images of RFPEC monolayer. From the top: Control (healthy), low serum (collapsed), HepIII (shed), and HepIII + HS (recovered) treatments. Blue shows the cell nucleus, green indicates heparan sulfate sugar chains, and red is the nanoparticles trapped within the culture.⁴

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