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The Summer Undergraduate Research Fellowship (SURF) Symposium
6 August 2015
Purdue University, West Lafayette, Indiana, USA

Proteoglycan Mimic of the Glycocalyx to Treat Endothelial Dysfunction

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ABSTRACT

Patients with kidney failure usually undergo hemodialysis, a process by which toxins produced by the body are filtered from the blood, in order to survive. The preferred form for vascular access is called an arteriovenousfistula (AVF), a surgically created connection between an artery and vein that is utilized to undergo dialysis. However, AVFs have a failure rate of 50-60%. One of the contributions to AVF failure is endothelial cell dysfunction and loss of glycocalyx, which allows neutrophils and other native cells into the media of the vessel, which causes an inflammatory response. Our lab addresses endothelial dysfunction by mimicking the function of the glycocalyx to prevent transmigration of inflammatory cells and ultimately create a healthier vessel for hemodialysis. We have synthesized several glycocalyx mimics consisting of a dermatan sulfate backbone with multiple selectin and ICAM-binding peptides attached. Initial testing involved determining the ability of the variants to bind to inflamed endothelial cells. We also cultured human promyelocytic leukemia cells (HL60) and used retinoic acid to differentiate them into neutrophils. These cells would then test the glycocalyx mimics ability to prevent migration of neutrophils. Thus far, we have seen that the glycocalyx mimics binding to endothelial cells and that this binding is dependent upon the type of selectin and/or ICAM-binding peptides as well as how many peptides are present per dermatan sulfate backbone. We have also shown that proliferation occurs 10 days after seeding, and that rentinoic acid (RA) differentiates HL60 cells into neutrophils. We have developed a protocol for differentiation of HL60 cells to neutrophils, a promising set of glycocalyx mimics, and culturing method for HL60 cells.

KEYWORDS

Kidney Failure, Glycocalyx, Proteoglycan Biomimic, Arteriovenous Fistula, Endothelial Cell Dysfunction, Chronic Kidney Disease, End Stage Renal Disease, Vascular Access