A Catechol-Based Intravascular Adhesive can be Implanted on the Inside and Outside of Blood Vessels and Reduce Inflammation in Atherosclerotic Plaques

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Introduction:

The rupture of atherosclerotic plaques and the subsequent formation of blood clots is the major cause of strokes and heart attacks. Developing therapies that locally treat plaques and make them less vulnerable to rupture is an important goal for preventing heart attack and stroke. Current clinical techniques for implanting drug-eluting devices, such as stenting, rely on mechanical forces to implant materials in vessels, which can permanently damage the vessel. The question that is addressed in this talk is: Can adhesive forces be used to permanently implant materials onto blood vessel walls? The hypothesis that was tested was that by mimicking the adhesive chemistry that marine mussels use to adhere under water, synthetic gels can be permanently coated on the inside surface of blood vessels when delivered via cardiovascular catheter. The objectives were to measure the adhesion of catechol-based gels to endothelial surfaces *in vitro* and to the carotid arteries of mice, and test if the gels could be used to deliver therapeutics to atherosclerotic plaques in mice.

Materials and Methods:

The mussel-mimicking adhesive gel was synthesized by functionalizing alginate and hyaluronan with a catechol moiety. Adhesion was measured *in vitro* in blood-vessel mimicking microfluidic devices and by measuring the shear strength of the materials to excised bovine carotid arteries using a mechanical analyzer. Adhesion was measured *in vivo* by depositing the material in the carotid arteries of mice using intravascular catheters and monitoring the amount of gel present on the wall over one month using live-animal fluorescence imaging. The biological response of the vessels to the material was assessed using vascular histology and systemic measurement of cytokine production and liver toxicity. The ability of the gel to treat atherosclerotic plaques was tested in a mouse model of atherosclerosis ($ApoE^{-/-}$ mice fed a high-cholesterol diet). Efficacy was tested by releasing an anti-inflammatory steroid from the gel and analyzing the expression of the inflammatory markers VCAM-1, NF-kB, MCP-1, and MMP-9 using histology and RT-qPCR. Experimental protocols were approved by the MIT Committee on Animal Care, and the Massachusetts General Hospital Subcommittee on Research Animal Care and Institutional Animal Care and Use Committee, and the University of British Columbia Animal Care Committee.

Results:

The intravascular gel locally and durably adhered onto the inside surface of the carotid arteries of mice. *In vitro*, the adhesive shear strength of the material to endothelial surfaces was over 2 KPa, which is 1000 times higher than physiological shear stress. In arteries of mice, the gel, delivered via catheter, adhered for over a month and controllably released small molecules into the local vasculature. The material did not elicit a chronic inflammatory response, but instead was encapsulated by a thin layer of endothelial and smooth muscle cells. In mice with atherosclerosis, inflamed plaques treated with steroid-eluting adhesive gels had reduced inflammation and had protective fibrous caps covering the plaque core. In treated mice, the concentrations of VCAM-1, NF-kB, MCP-1, and MMP-9 were all significantly lower in gel-coated arteries. The adhesive gel

could also coat the tunica externa (the outer layer of the blood vessel) for over a week when deposited onto surgically exposed carotid arteries.

Discussion:

Locally depositing catechol-based adhesive gels onto blood vessels provides a general strategy for implanting materials in the vasculature. This work shows that adhesive forces, rather than mechanical forces, can be used to implant drug-depots without causing the substantial vascular damage associated with mechanical intravascular devices. Intravascular adhesives that release therapeutics can be used to pacify atherosclerotic plaques. In the future, these materials may become useful for locally delivering therapeutics to aneurisms, arteriovenous malformations, and other regions of diseased vasculature, such as the vasculature around tumors.

References:

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