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ISCHAEMIC DISORDERS

Nanotherapeutic delivers clot-busting drug

STOCKBYTE

The formation of a vascular blood clot — thrombosis — can disrupt normal blood flow to major organs and is a leading cause of death worldwide. Although agents capable of dissolving such clots are available, their use is limited by a narrow therapeutic window and bleeding risk. Now, writing in *Science*, Korin and colleagues report the use of shear-activated nanotherapeutics (SA-NTs) to effectively and safely deliver thrombolytic drugs specifically to the site of vascular occlusion, enabling rapid clot dissolution and an increase in survival in mouse models of thrombosis.

When blood vessels become obstructed, fluid shear stress is dramatically increased, which locally activates normal circulating platelets, causing them to rapidly adhere to the adjacent surface lining of the narrowed vessel. In an attempt to address the limitations of clot-busting drugs, Korin and colleagues set out to exploit this natural mechanism of platelet targeting by using high shear stress to deliver drugs directly to sites of vascular obstruction.

First, the authors spray-dried solutions of multiple small nanoparticles (NPs) composed of poly(lactic-co-glycolic acid) to form aggregates similar in size to natural platelets. *In vitro* and three-dimensional microfluidic studies showed that when flowing in blood under physiological flow conditions, these hydrophobic aggregates were stable, but when exposed to high local shear stress, the attractive forces holding the NPs together was overcome, which caused them to disperse and adhere to the adjacent blood vessel wall. They termed these NP aggregates SA-NTs.

Next, they evaluated the therapeutic potential of SA-NTs by treating mouse thrombosis models with SA-NTs carrying 50 ng per ml of the thrombolytic drug tissue plasminogen activator (tPA-SA-NTs). Notably, this dose is 100 times lower than the equivalent therapeutic dose commonly used in humans.

When tPA-SA-NTs were intravenously injected into a mouse arterial thrombus model (in which clot formation is triggered by vessel wall insults) 8 minutes after injury, the dispersed NPs accumulated in the regions of clot formation and occlusions were cleared within 5 minutes. Furthermore, the SA-NTs reopened the obstructed mesenteric arteries and significantly delayed the time to full vascular occlusion in injured vessels in this model. By contrast, the same dose of soluble free tPA, pre-dissociated tPA-NPs or heat-fused tPA-NP microaggregates (which do not dissociate upon shear stress) did not delay thrombosis. Similarly, in a mouse model of pulmonary embolism, tPA-SA-NTs reduced both total clot area and clot number by more than 60% and 30% when administered immediately or 30 minutes after injection of emboli, respectively. Finally, 86% of mice with life-threatening acute massive embolism that received immediate infusion of tPA-SA-NTs for 45 minutes survived with no visible symptoms of respiratory stress, whereas all control animals died within 1 hour.

> “[they used] high shear stress to deliver drugs directly to sites of vascular obstruction”

In summary, this novel drug-targeting strategy has the potential to lower the required dose and eliminate systemic side effects associated with thrombolytic agents. Moreover, it may allow for the immediate administration of clot-busting drugs to patients prior to reaching the hospital.

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ORIGINAL RESEARCH PAPER Korin, N. *et al.* Shear-activated nanotherapeutics for drug targeting to obstructed blood vessels. *Science* 5 Jul 2012 (doi:10.1126/science.1217815)