CEREBROVASCULAR DISEASE

Novel mechanism of cerebral microvascular recanalization demonstrated in mice

A study in mice has revealed a novel mechanism of recanalization in occluded cerebral microvessels.

“The mechanism involves microvascular plasticity,” explains principal investigator Jaime Grutzendler, of Northwestern University Feinberg School of Medicine, Chicago, IL, USA. “Clots or emboli of other material are expelled through the vessel wall into the perivascular space, where they are gradually degraded.”

The occlusion of large blood vessels in the brain can lead to stroke; however, little is known regarding the effects of cerebral microvascular occlusion in terms of injury to the brain. Moreover, the fate of occluded microvessels is incompletely understood. Fibrinolysis and hemodynamic forces are involved in the recanalization of blood vessels of various sizes. The moderately low-flow velocity and small diameter of microvessels, however, probably make these vessels susceptible to occlusion from fibrinolysis-resistant microemboli (such as cholesterol emboli). Whether blood flow is re-established under such circumstances is unclear.

Grutzendler and his group aimed to investigate the effect of occlusion on the cerebral microvasculature and the surrounding tissue. To achieve this goal, the researchers generated fluorescent microemboli (comprising fibrin clots, cholesterol or polystyrene), which were infused into the cerebral circulation of mice. The paths of these emboli were subsequently assessed in fixed tissue by electron or confocal microscopy, or in living animals by time-lapse transcranial two-photon microscopy.

“Our first surprising finding was that only a fraction of the emboli were cleared by the ‘conventional’ clearance mechanisms,” says Grutzendler. Indeed, 2 h after microemboli infusion (over which period fibrinolysis and hemodynamic forces were expected to have acted), the

In vivo time-lapse images showing extravasation of a cholesterol embolus (orange) from a mouse cerebral microvessel (green) at (from left to right) days 1, 3 and 5 postembolization. Permission obtained from Nature Publishing Group © Lam, C. K. *Nature* 465, 478–482 (2010).

researchers noted that many emboli were still present in the lumens of the vessels. Furthermore, 1 day after infusion, most of these retained emboli were observed to be occluding blood flow.

To ascertain the outcome of the observed occlusions, the investigators imaged infused microvessels over periods of up to 8 days. By postembolization day 2, many of the initially retained emboli were no longer present inside the microvessels, and by day 6, nearly all emboli were located outside of these vessels. Moreover, in all vessels where embolus extravasation had occurred, blood flow had been re-established. Notably, microemboli of each material underwent this process.

Using *in vivo* time-lapse imaging, the researchers were able to reveal the steps involved in the extravasation process. “Emboli are engulfed by the adjacent [microvessel] endothelium and extruded through an endothelial opening,” describes Grutzendler. “This is followed by vessel repair and blood-flow re-establishment.”

The investigators went on to examine the vascular and neuronal effects of microvasculature occlusions, and the influence of age on these effects. In young mice (aged 4 months),

polystyrene-microsphere occlusion led to limited hypoxia in tissue close to the occlusion site. Little vascular damage, however, was noted, and an observed reduction in synaptic spine number was reversed on blood-flow re-establishment following extravasation. By contrast, in old mice (aged 22 months), occlusion led to more-severe hypoxia, the development of dystrophic neurites, and a marked increase in the expression of caspase 3 (a marker of apoptosis) in perivascular cells. Notably, the rate of emboli extravasation was markedly lower in old mice than in young animals. “We hypothesize that extravasation failure in aging could be a novel mechanism of neurovascular damage and possibly dementia,” says Grutzendler.

In future studies, the investigators aim to establish whether embolus extravasation occurs in humans, and to determine if this process is affected in models of Alzheimer disease.

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