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STROKE

Opening the therapeutic window

Current approaches to treat stroke — which aim to restore blood flow to limit neuronal death — are limited by their narrow therapeutic window and lack of effect on cerebral inflammation. Writing in *Sci. Transl Med.*, Tomlinson and colleagues now demonstrate in mice that inhibition of complement activation in the ischaemic area of the brain, up to 24 hours after stroke, protects neurons and inhibits neuroinflammation, thereby improving long-term motor and cognitive recovery.

Pathological activation of complement occurs in the ischaemic brain, leading to deposition of complement opsonins and release of complement anaphylatoxins. In mouse models of stroke, complement activation is triggered by the binding of self-reactive natural immunoglobulin M (IgM) antibodies to neoepitopes expressed on the surface of stressed and dying cells. Tomlinson and colleagues therefore set out to exploit this recognition system to inhibit complement activation in the ischaemic brains of mice.

> “These findings demonstrate the potential of complement inhibition in the ischaemic area of the brain”

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To do this, the authors generated a fusion construct comprised of a single chain antibody derived from an IgM monoclonal antibody (mAb) that recognizes a post-stroke modified annexin IV neoepitope (B4) linked to murine CRRY, an orthologue of human complement receptor 1 that inhibits all complement pathways at the C3 activation step. The fusion construct was termed B4Crry.

In the transient middle cerebral artery occlusion (MCAO) mouse model of stroke, a single systemic dose of B4Crry, administered 2 hours after MCAO, specifically and transiently inhibited complement activation in the ipsilateral cortex and hippocampus of the post-ischaemic brain. B4Crry exhibited a short circulatory half-life ensuring minimal impact on systemic complement activity. B4Crry-treated mice all showed reduced C3d deposition in the post-ischaemic brain, improvement in neurological deficits and reduced infarct volume 24 hours after stroke compared with vehicle-treated mice.

Next, mice were followed through 15 days of recovery, after intravenous administration of B4Crry at either 2 or 6 hours following MCAO. Mice treated with B4Crry showed a greater improvement in recovery of initial deficit and were protected from secondary astrogliosis in the hippocampus, which was associated with improvements in motor and cognitive dysfunction.

The neuroprotective effects of B4Crry in mice were maintained across gender, age and different ischaemia times, with benefits evident over a 30-day period. Importantly, B4Crry was also effective when treatment was delayed to 24 hours after MCAO in adult mice, reducing neurological deficits and forearm laterality, improving memory retention and reducing infarct volume compared with control mice.

Mechanistically, complement activation in the MCAO mouse model was found to promote neuronal stress and trigger phagocytosis of stressed neurons (tagged by C3d) by inflammatory microglia, effects that were prevented by B4Crry treatment. Importantly, these inhibitory effects of B4Crry were sustained, thereby limiting the propogation of chronic neuroinflammation and neurodegeneration that occurs post-stroke.

Finally, analysis of postmortem brain sections from patients who had died from acute stroke showed extensive binding of B4Crry in the ischaemic penumbra, but not in the contralateral tissue.

These findings demonstrate the potential of complement inhibition in the ischaemic area of the brain as a novel therapeutic option for the treatment of stroke, which may present significant advantages over currently approved stroke therapy, the clinical window for which is just a few hours. The lead author of the study has co-founded a company, Admirx, which aims to develop targeted complement therapeutics.

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ORIGINAL ARTICLE Alawieh, A. et al. Targeted complement inhibition salvages stressed neurons and inhibits neuroinflammation after stroke in mice. *Sci. Transl Med.* **10**, eaao6459 (2018)