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PROTECTION AGAINST STROKE THROUGH PRESERVATION OF VASCULAR INTEGRITY BY ANGIOPOIETIN-LIKE 4 (ANGPTL4)

Poster Contributions
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Background: Timely recanalization of the occluded artery is the treatment for ischemic stroke, but has limited application. ANGPTL4 has vasculoprotective effects in myocardial infarction by counteracting VEGF-induced permeability. Given the impact of vascular leakage and edema formation in tissue damage during stroke, we hypothesized that ANGPTL4 might exert cerebral protection in stroke.

Methods and Results: In a mouse model of transient ischemic stroke, injection of ANGPTL4 at ischemia led to a decreased infarct size, as assessed by TTC staining ($p<0.0008$) and cerebral MRI ($p<0.03$). Brain edema was decreased in the ANGPTL4 treated group ($p<0.002$). Using PECAM staining we showed that vascular network was preserved in ANGPTL4-treated mice (vascular density $p< 0.0007$ and branching points $p<0.002$). We then assessed integrity of tight and adherens junctions using VE-cadherin and Claudin-5 immunostainings, and showed a significant increase in VE-cadherin and Claudin 5 areas in ANGPTL4-treated mice. Thus ANGPTL4 protects from global vascular damage, and also from junctions disruption. ANGPTL4 protective effect on junctions was further assessed in vitro using microvascular endothelial cells treated with VEGF±ANGPTL4 and stained with VE-Cadherin antibody. The straight and tight VE-Cadherin junctions observed in basal conditions were severely affected by VEGF, but were restored by ANGPTL4 co-treatment: thus ANGPTL4 counteracts the effect of VEGF on junctions breakdown. Mechanistically, using VEGFR2 co-immunoprecipitation experiments, we showed that ANGPTL4 counteracts VEGFR2-induced Src signaling and protects VE-Cadherin junctions from Src dependent disassembly. Moreover, ANGPTL4 protected neuronal loss after stroke, as assessed by the increased number of NeuN-positive cells (neurons) in treated mice ($p<0.001$). Finally, mouse behaviour was also significantly improved in treated mice ($p<0.01$).

Conclusions: ANGPTL4 treatment counteracts the loss of vascular integrity in a mouse model of ischemic stroke, by restricting Src kinase recruitment downstream VEGFR2. Consequently, ANGPTL4 reduces edema, infarct size, neuronal loss and finally improves mouse behavior.