mTOR dysregulation disrupts RNA-processing networks in Alzheimer's disease cerebrovasculature

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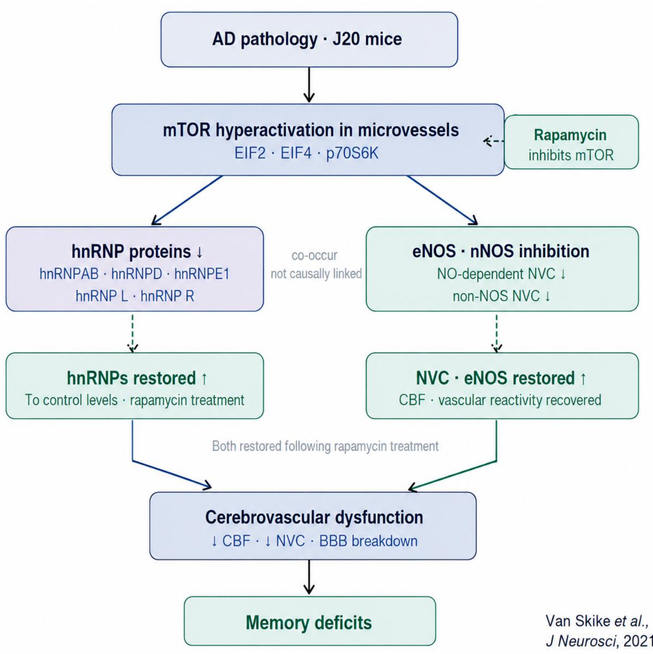
Abstract

Cerebrovascular dysfunction is increasingly recognized as a central contributor to the initiation and progression of Alzheimer's disease (AD). The mechanistic target of rapamycin (mTOR) pathway has emerged as a key driver of AD-related vascular dysfunction. Consistent with this, attenuation of mTOR signaling improves various aspects of cerebrovascular function in AD models, including vascular density, cerebral blood flow, vascular reactivity, and neurovascular coupling. However, the downstream molecular mechanisms linking mTOR dysregulation to cerebrovascular dysfunction remain poorly understood.

Here, we performed unbiased quantitative proteomic profiling of cerebral microvessels to identify molecular pathways involved in mTOR-driven vascular dysfunction in AD. Proteomic analysis revealed significant remodeling of the microvascular proteome in AD mice, dysregulation of EIF2 signaling, EIF4, and p70s6K pathways, as well as other mTOR-associated networks. mTOR inhibition by rapamycin restored proteins involved in canonical microvascular pathways, such as tight-junction signaling and nitric oxide-dependent pathways, to levels indistinguishable from controls. Across two independent mouse cohorts with different rapamycin dosing regimens, mTOR attenuation also coordinated the restoration of RNA-processing and translation regulation networks. Among the most impacted proteins by mTOR activity were members of the heterogeneous nuclear ribonucleoprotein (hnRNP) family of RNA-binding proteins. Chronic mTOR attenuation with rapamycin restored several hnRNP proteins, including hnRNPAB, hnRNPD (AUF1), and hnRNPE1 (PCBP1), as well as proteins involved in vascular regulatory pathways such as tight junction signaling and nitric oxide-dependent signaling. Importantly, we found that hnRNPE1 (PCBP1), hnRNP L, and hnRNP R levels were inversely correlated with the progression of AD pathology. Together, these findings identify a previously unrecognized mTOR-dependent RNA regulatory program in the cerebrovasculature that contributes to neurovascular dysfunction in AD. This new, reversible molecular pathway linking mTOR to RNA regulation in the brain microvasculature may provide new targets for interventions in AD.

Working model



mTOR-driven cerebrovascular dysfunction in hAPP(J20) mice. mTOR hyperactivation suppresses hnRNP RNA-binding proteins and inhibits eNOS/nNOS-dependent neurovascular coupling (Van Skike et al., 2021). Both are restored following rapamycin treatment. Dashed lines indicate co-occurrence without demonstrated causality.

Acknowledgment

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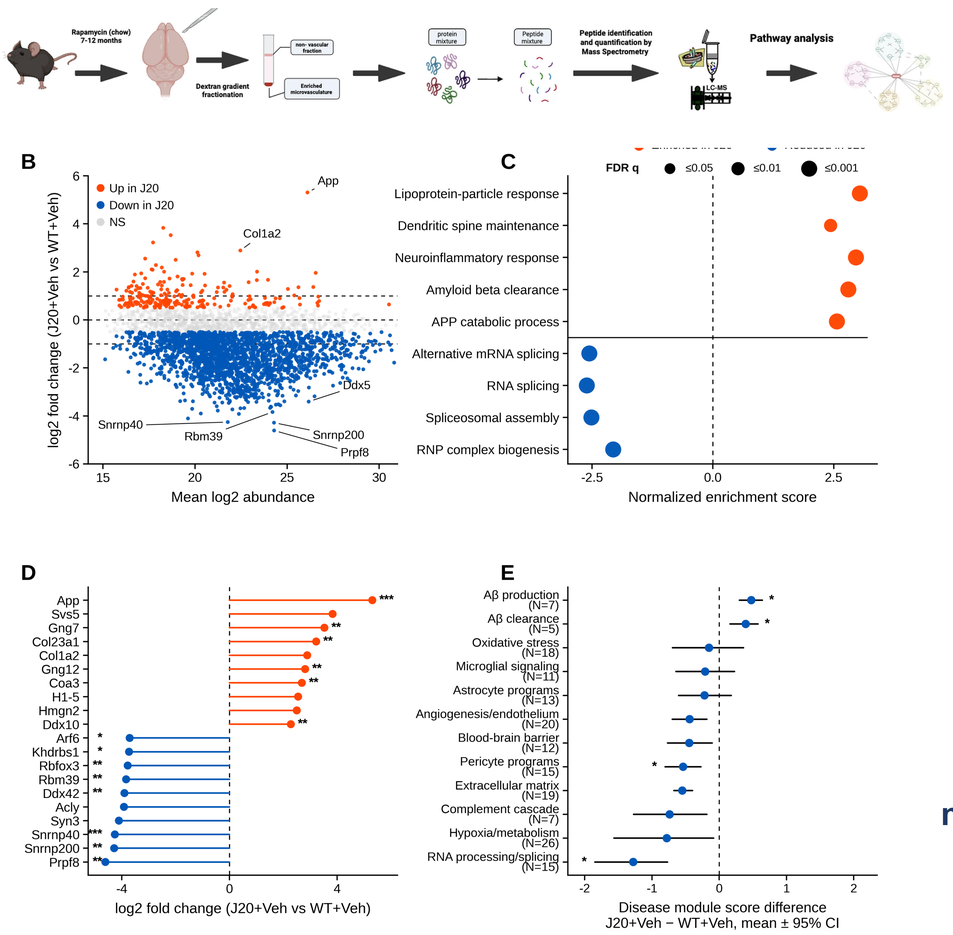
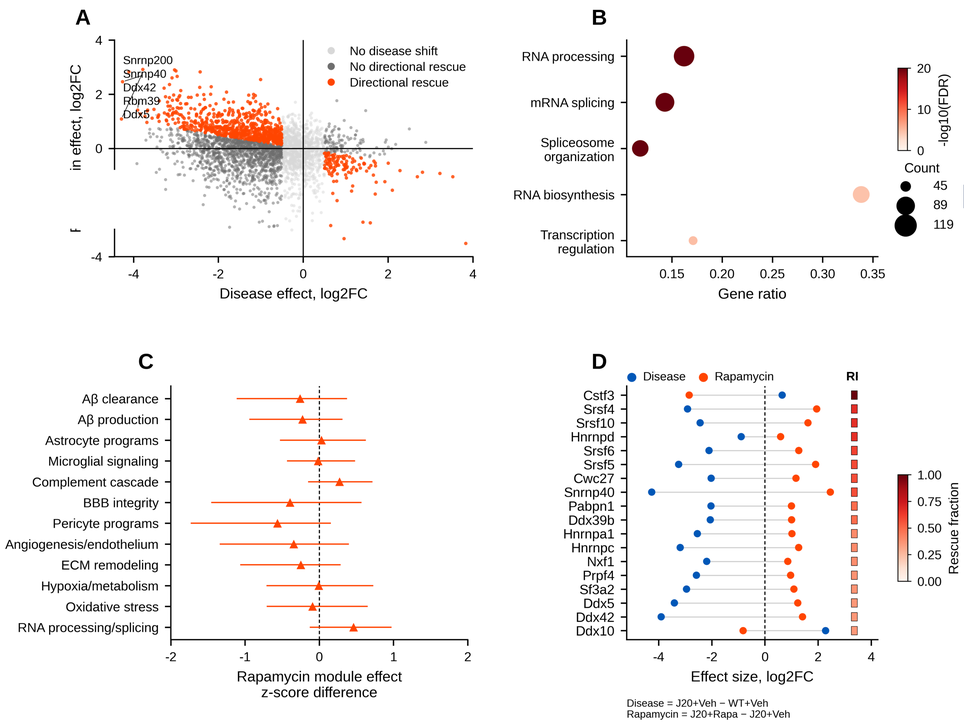
Results

Disease-associated proteomic alterations in the cerebral vasculature of hAPP(J20) mice



Rapamycin counteracts disease-associated vascular proteomic remodeling in hAPP(J20) mice



Disease = J20+Veh − WT+Veh
Rapamycin = J20+Rapa − J20+Veh

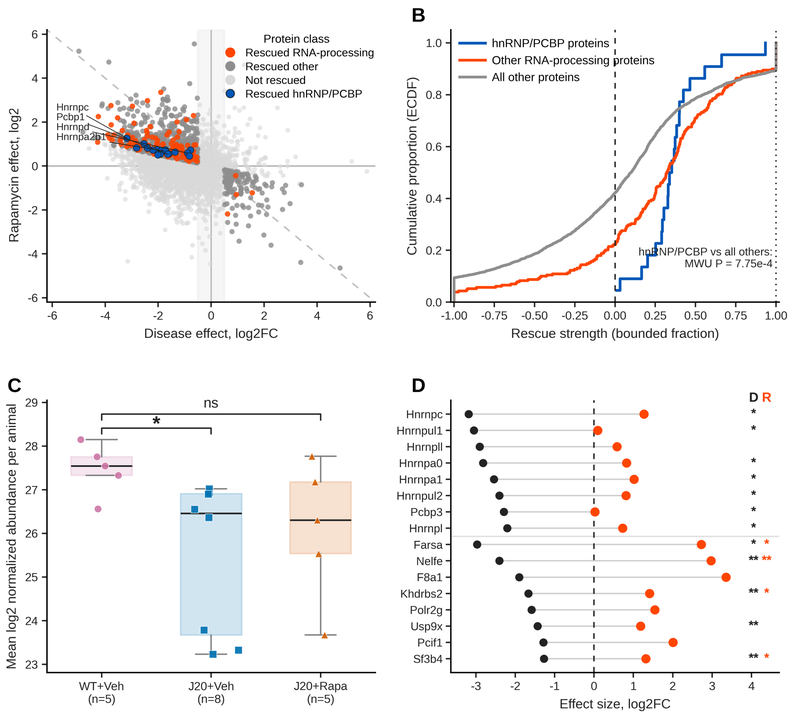
Conclusions

Aβ-associated cerebrovascular dysfunction is linked to mTOR-dependent remodeling of RNA-processing networks.

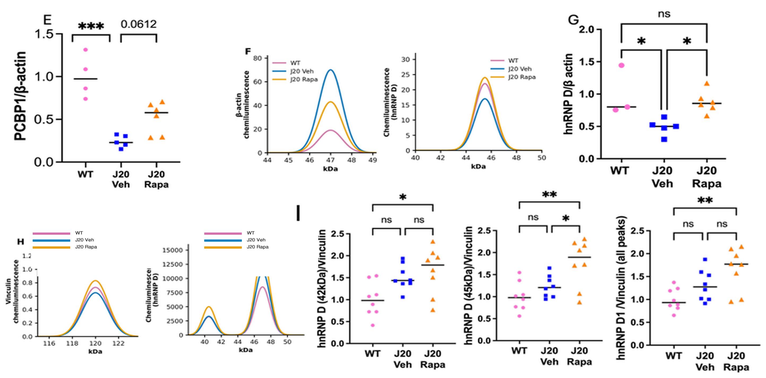
✓hAPP(J20) mice show cerebrovascular proteomic remodeling.
✓Rapamycin counteracts selected disease-associated vascular proteomic changes.
✓RNA-processing and hnRNP networks emerge as prominent rapamycin-responsive pathways.
✓These vascular molecular changes link mTOR dysregulation to neurovascular dysfunction.

Results

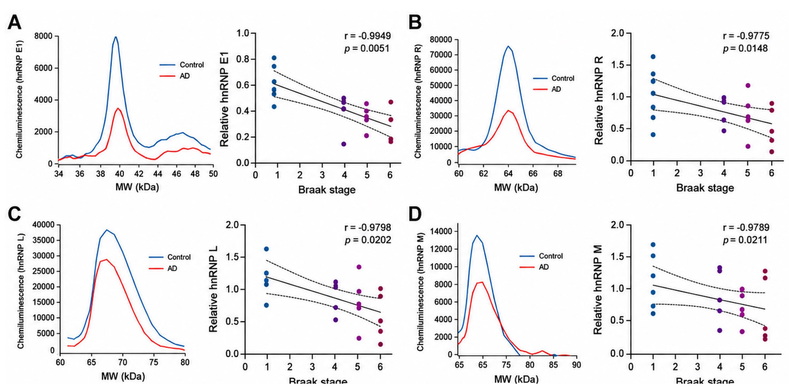
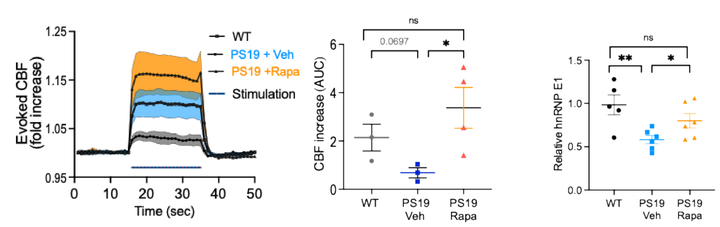
Rapamycin preferentially rescues RNA-processing proteins and hnRNP networks in the hAPP(J20)



mTOR-dependent reduction of microvascular hnRNP D1 and hnRNP E1 in hAPP(J20) mice



Progressive decline of selected hnRNP family members across Braak stage in Alzheimer's disease



Rapamycin improves cerebrovascular functional responses in the PS19 tauopathy model