

Arc at the virus–synapse interface: A domesticated capsid that writes memory and disseminates neurodegeneration

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ARC AS A NEURONAL CARGO-TRANSFER SYSTEM

Arc no longer fits comfortably within the usual category of immediate-early gene products. Nor is it merely an evolutionary relic with an intriguing viral ancestry. It is better viewed as a domesticated cargo-transfer system whose activity has been woven into neuronal plasticity. In a recent study, Tyagi and colleagues place this unusual biology directly in the path of tau propagation by showing that Arc associates with tau and promotes its loading into extracellular vesicles (EVs).¹ Their findings expose an evolutionary trade-off: machinery evolved to package and exchange neuronal information can also be co-opted to export proteotoxic material in Alzheimer's disease (AD). Such export may briefly relieve the donor neuron, but it shifts the burden outward, from a single cell to the surrounding circuit.¹

VIRAL ANCESTRY AND CAPSID-LIKE FUNCTIONS OF ARC

Arc is, in several respects, almost preadapted for this role. Tetrapod Arc arose from a Ty3/gypsy retrotransposon Gag lineage and retained the ability to oligomerize, bind RNA, form capsid-like assemblies and enter EVs.² Drosophila Arc genes emerged independently from a different Ty3/gypsy lineage, yet converged on related particle-forming and cargo-transfer functions.³ Whether this convergence extends to tau or other aggregation-prone protein cargoes remains unresolved.

The evolutionary logic of Arc is striking. Arc has lost its *Pol* genes (which encode reverse transcriptase and integrase) and the long terminal repeats needed for retrotransposition or viral replication, so it can no longer replicate on its own. Instead, the remaining Gag-like capsid structure has been co-opted for new functions, such as activity-dependent assembly, RNA packaging, and intercellular RNA transfer, rather than for self-propagation. The value of the selectively retained Gag-like fold was not infection in any meaningful sense. It was the ability to assemble conditionally, protect molecular cargo and move that cargo across membranes.

This is particularly well matched to the constraints of neurons. These cells are highly polarized, exceptionally long-lived and dependent on communication across large distances. They often need to move transient molecular signals without altering the genome or sustaining prolonged transcriptional responses. A capsid-like carrier offers a reversible and physically protected means of transfer. Because Arc expression is coupled to neuronal activity, the same assembly machinery can be recruited only when and where it is needed. One plausible interpretation is that Arc acts as a molecular thresholding device: weak activity favors soluble or low-order assemblies, whereas higher local concentrations of Arc and RNA support larger complexes and EV-associated export. An ancestral selfish element may thus have been converted into a host-regulated system that filters molecular noise and amplifies biologically salient activity.

ARC-DEPENDENT TRANSMISSION OF TAU

Tyagi *et al.* now extend this framework by showing that Arc-dependent communication also governs tau traffic. Arc directly associates with tau. Loss of Arc reduces tau selectively within neuronal and brain-derived EVs, without producing a comparable suppression of vesicle-free tau release. The authors further show that Arc and tau interact directly in a dynamic, structurally heterogeneous complex and associate with IIRSp53, a membrane-curvature factor implicated in Arc-EV biogenesis. In rTg4510 mice expressing mutant human tau, Arc deletion lowers EV-associated tau and reduces the seeding

activity of isolated brain EVs. Arc and tau are co-packaged in EVs from both mouse and human brain, and EV-associated Arc correlates with phosphorylated tau in AD samples. Most strikingly, intercellular tau transmission is almost absent in Arc-deficient experimental systems.¹ Taken together, these results move Arc well beyond the status of a bystander cargo. It appears to participate directly in tau sorting, export and propagation.

DONOR-CELL RELIEF, NETWORK-LEVEL COST OF ARC-DEPENDENT TAU TRANSFER

The more unsettling finding is what happens inside the donor neuron when Arc is removed. Arc deficiency leads to intracellular tau accumulation and a modest increase in early neuronal toxicity.¹ This observation argues against describing Arc as a simple disease-promoting protein. Arc-dependent secretion may instead represent a form of neuronal triage: export lowers intracellular proteostatic pressure, at least temporarily, but the released tau remains competent to seed aggregation elsewhere. The same process can therefore be protective at the level of the individual neuron and harmful at the level of the network (Figure 1). The apparent conflict is not intentional choice; it follows from a neuron's limited capacity to manage proteotoxic stress and its reliance on secretion as one coping mechanism.

STRUCTURAL EVIDENCE FOR SELECTIVE EV CARGO HANDLING

Cryo-electron tomography of EVs isolated from human AD brain lends further support to this view. Fowler and colleagues identified predominantly short, truncated tau filaments enclosed within endolysosomal EVs and observed contacts that tethered the filaments to the vesicle-limiting membrane.⁴ Such organization argues against random extracellular contamination. Tau appears to be selectively handled within a membrane-bound compartment. Arc may therefore serve as one of the molecular links that converts intracellular proteostatic stress into ordered, transmissible cargo.

A PROVISIONAL ACTIVITY-ARC-TAU FEEDBACK MODEL

The study also raises the possibility that Arc helps connect neuronal activity to tau dissemination. Neuronal activity induces Arc and has independently been linked to enhanced tau release and spread.⁵ A feed-forward scheme is therefore conceivable: network hyperactivity increases Arc expression; Arc promotes EV-associated tau export; tau seeding further destabilizes synapses and circuits; and the resulting disinhibition drives additional Arc expression. This is an attractive unifying model, but it remains provisional.

THERAPEUTIC IMPLICATIONS

The translational implications are also complex. The current findings make Arc tempting as a therapeutic target, but global inhibition would likely be counterproductive. Arc is deeply involved in memory formation, synaptic scaling and AMPA-receptor trafficking. Suppressing it broadly could impair cognition while worsening intracellular tau retention. The more credible objective is to uncouple Arc's physiological functions from its pathological interaction with tau. One route would be to disrupt the Arc-tau binding interface while preserving Arc-dependent synaptic plasticity and RNA transport. Another would leave donor-cell export intact but prevent uptake, endosomal escape or cytosolic seeding of Arc-tau EVs in recipient neurons. A third possibility would pair inhibition of pathological EV release with enhanced lysosomal or autophagic tau clearance, thereby avoiding the intracellular

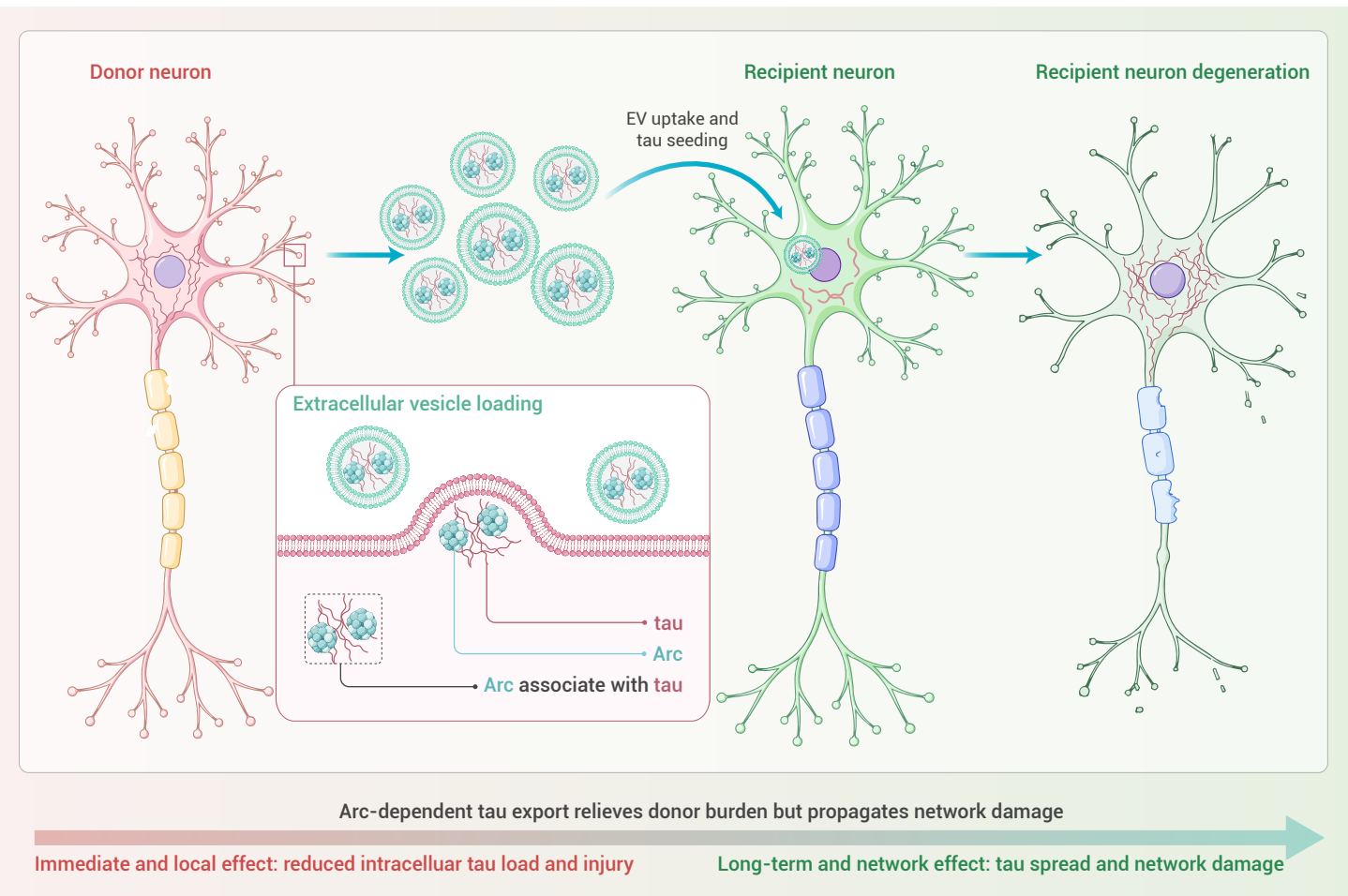


Figure 1. Local and network effects of Arc-dependent tau dissemination Arc associates with tau and promotes its loading into EVs in donor neurons. EV uptake by recipient neurons supports tau seeding and spread, and following neurodegeneration. The schematic depicts a working model based on the findings of Tyagi *et al.*¹

accumulation seen after Arc loss. Each strategy addresses a different stage of the transmission cycle, and they need not be mutually exclusive.

CONCLUSION

In summary, Tyagi *et al.* place Arc at the center of a tractable mechanism for tau dissemination.¹ The broader implication is that neurodegeneration often proceeds not by inventing entirely new machinery, but by misusing systems that normally support brain function. Arc's viral ancestry gave neurons an efficient means of packaging and transferring molecular information. Alzheimer's disease appears capable of hijacking this evolutionary innovation to drive proteopathic spread between neurons. The therapeutic challenge is not to silence Arc, but to preserve its mnemonic role while denying tau access to the neuronal exit route.

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AUTHOR CONTRIBUTIONS

Y.L.: Methodology, Resources, Writing – original draft. Y.Z.: Resources, Writing – original draft. H.Z.: Conceptualization, Funding acquisition, Writing – review & editing. All authors contributed to the manuscript and approved the final version

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.