Extracellular vesicle engineering to counteract age-related cognitive declines

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Innovative medical advances have increased the average lifespan but, unfortunately, these improvements have not been satisfactorily accompanied with advances in healthspan, particularly with respect to brain health and cognition.

Physical activity is increasingly recognized to play a role in maintaining brain health. Exercise attenuates age-related cognitive declines, including loss of brain volume, impaired neurogenesis, decreased attention and learning. These benefits are attributed, at least in part, to the function of skeletal muscle: muscle contractile activity is critical for the secretion of myokines into the bloodstream, and these myokines work in a hormone-like fashion to influence the health and function of distal organs, including the brain. Identification of these exercise-induced factors can aid in the development of novel therapeutics to promote brain health with aging.

Findings from our laboratory suggest that circulating extracellular vesicles (EVs) play a major role in the non-cell-autonomous regulation of tissue aging. EVs are a broad class of membrane-bound nanoparticles that can target and reprogram cells to regulate physiological functions or pathological processes. EVs are particularly promising for central nervous system therapies because they can cross the blood–brain barrier.

We have shown that blood serum from young donors enhances muscle regeneration and cognition in aged animals. However, this effect is diminished when the serum is depleted of EVs, suggesting that circulating EVs play a central role in in this process (Figure). Our work further suggests that exercise may promote more youthful cargoes in aged circulating extracellular vesicles.

Building on these studies, we are developing novel EV engineering approaches designed to counteract the effect of aging on cognitive health. Specifically, our focus is on identifying age- and exercise-responsive EV cargoes critical for enhancing brain vitality. This work will allow us to engineer autologous EVs to express and deliver these optimized cargoes across the blood–brain barrier to neural tissues.

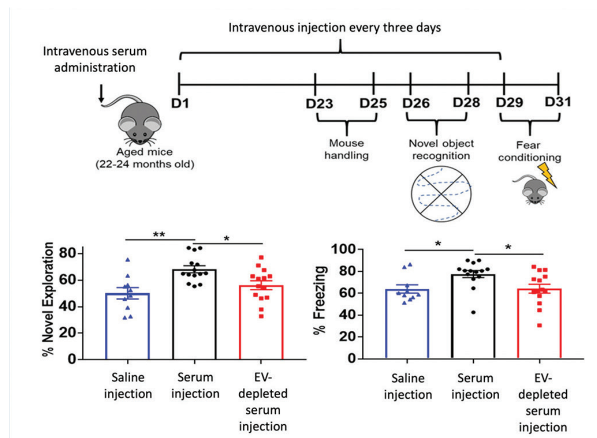

Fig. Circulating extracellular vesicles contribute to the beneficial effect of young serum on cognitive function in aged mice. (Top) Schematic of the experimental paradigm for cognitive testing in aged mice following intravenous injections of saline, young serum, or young serum depleted of EVs. (Left bottom) Quantification of % novel exploration memory test across the three groups. (Right bottom) Quantification of % freezing memory test across the three groups.