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AUTHOR'S VIEWS

Extracellular vesicles as potential tools for regenerative therapy

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ABSTRACT

Small extracellular vesicles released by fibroblasts from young human donors diminish lipid peroxidation in senescent cells and in different old mice organs due to their enrichment in Glutathione-S-transferase Mu lipid antioxidant activity.

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Aging is characterized by a progressive decline in the physiological function efficiency and by an increased susceptibility to disease. This decline is in part mediated by the activation of the cellular phenotype named senescence. Cellular senescence is characterized by a cell-cycle arrest, and by the senescence-associated secretory phenotype, or SASP, that includes the secretion of small extracellular vesicles (sEVs), soluble factors, and matrix remodeling enzymes.[1]

We recently showed that sEVs secreted by cells isolated from young human healthy individuals (sEV-Y) can ameliorate the senescence phenotype in old cells and in old mice by reducing lipo-oxidative stress.[2]

In vitro, different cell types (fibroblasts from old human donors, fibroblasts obtained from Hutchison-Gilford progeria patients, and young fibroblasts induced to senesce by over-expression of *H-RAS* oncogene) were used as old cells to determine the ability of sEV-Y to counteract senescence. Treatment of old cells with sEV-Y (but not with extracellular vesicles from young individuals (EV-Y) larger than 200 nm) reduced the levels of senescence markers and revert the proliferation arrest of fibroblasts. One of the most widely used biomarkers for senescent cells is the β-Galactosidase staining. We could observe that sEV-Y treatment in old mice reduced the levels of β-Galactosidase staining in tissue sections of different organs like liver, kidney, lung, and brown adipose tissue. Similarly, we found a decreased mRNA expression of SASP factors in the liver and kidney when old mice were treated with sEV-Y.[2,3]

Previous work from the O´Loghlen lab characterized the differential proteomic composition of proliferating versus senescent cells sEVs allowed us to identify enzymes of the glutathione antioxidant system enriched in sEV-Y.[3] In particular, Glutathione-S-Transferase Mu 2 (encoded by the *GSTM2* gene) enzyme counteracts lipid oxidation and it decreases with age in mice and humans. The oxidation of lipids generates highly reactive products such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) reactive aldehydes that accumulate in senescence, aging, and age-related diseases. We observed a decrease in their levels in the liver and serum of aged mice after the treatment with sEV-Y enriched in antioxidant enzymes.[2] Accordingly, Yoshida et al. described that extracellular nicotinamide phosphoribosyltransferase enriched in EVs enhances Nicotinamide adenine dinucleotide (NAD^+) biosynthesis once the vesicles are internalized by cells, improving motor activity and extending lifespan in old mice.[4] Therefore, additional components within sEV-Ys can also contribute to the observed reversion of certain characteristics of senescence and aging.

More experimental data are needed to affirm that sEV-Y have the ability to rejuvenate young tissues and counteract age-related pathologies as happens with cellular reprogramming.[5] We need longer-term experiments, more behavioral and physiological data. In spite of the mounting evidence supporting a protective and antioxidant role of sEVs in old individuals, we must be cautious before starting to use sEVs in clinical trials to counteract aging. EVs are implicated in the development of neurodegenerative and cardiovascular diseases, and participate in the progress of carcinomas. The sEV composition (ribonucleic acids, proteins, lipids, etc.) depends not only on the age of the donor cell, but also on the cell type, physiological condition, isolation methodology, etc. Cancer, and different stem and immune cells secrete sEVs that can influence physiological and pathological processes.[6-8]

However, in our experiments, sEV-Ys are helping aged cells and tissues to repair. Therefore, it will be interesting to perform long-term experiments, try different administration routes,

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and test sEV-Y therapeutic capacity in pathological models to demonstrate their repairing and rejuvenating abilities.

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