Small extracellular vesicles combat senescence

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CELL SENESCENCE

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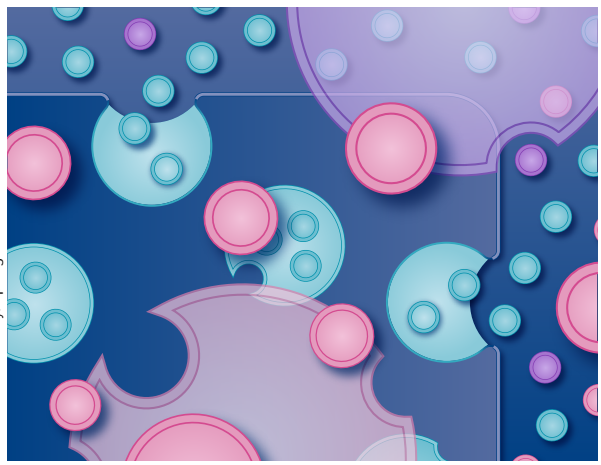
> … sEVs secreted by cells of young individuals can ameliorate senescence in cells of old individuals …

Cellular senescence is a hallmark of ageing characterized by cell cycle exit and by a secretory phenotype, which includes the secretion of small extracellular vesicles (sEVs). Fafián-Labora et al. report that sEVs secreted by cells of young individuals can ameliorate senescence in cells of old individuals by reducing oxidative stress.

Previous research from the group showed that sEVs secreted from cells of old individuals ('old cells') can mediate features of senescence to proliferating cells from young individuals ('young cells') in a paracrine manner. To determine whether sEVs from young cells can ameliorate senescence-related phenotypes in old cells, the authors studied in vitro three cell types: old fibroblasts, young fibroblasts induced to senesce by *H-RAS* oncogene overexpression (iRAS cells) and fibroblasts obtained from individuals with the premature-ageing Hutchison-Gilford progeria syndrome (HGPS).



Credit: V. Summersby/Springer Nature Limited

The authors obtained conditioned medium from young (Y) human donor fibroblasts and separated it into fractions containing small and large extracellular vesicles (sEV-Ys and lEV-Ys, respectively). Treatment of old fibroblasts with sEV-Ys, but not with lEV-Ys, prevented proliferation arrest of old fibroblasts, and the number of old cells expressing senescence markers was reduced. Similar results were obtained following treatment of HGPS fibroblasts with sEV-Ys.

Previous proteomic analysis of sEVs by the group had identified proteins whose expression levels change upon induction of iRAS cells. Network analysis revealed an association between some of these proteins and the glutathione conjugation pathway, which counteracts the senescence-inducing effects of reactive oxygen species (ROS). Specifically, the expression of glutathione S-transferase Mu 2 (GSTM2) was considerably reduced in iRAS-sEVs; conversely, GSTM2 was enriched in sEV-Ys compared with HGPS-sEVs.

Addition of sEV-Ys to culture medium inhibited ROS accumulation and DNA damage in old cells, owing to the transmission of GST activity from the sEV-Ys to the old cells, leading to reduction in oxidative stress. Furthermore, transfection of sEVs from old cells with GSTM2 and subsequent treatment of old cells with these sEVs decreased the expression of senescence markers.

In agreement with these in vitro results, intraperitoneal injection of sEV-Ys in old mice led to a decrease in senescence markers in the liver, kidney, brown adipose tissue and serum, and to a lesser extent in the lungs. ROS levels were reduced, and GSTM2 activity, which is typically low in old mice, was increased to levels seen in young mice in the tissues tested. Finally, treatment of old mice with sEV-Ys resulted in a decrease of markers of lipid peroxidation in various tissues, in agreement with the fact that lipid peroxidation products are endogenous substrates of GSTM2.

In summary, this study illuminates the potential of sEVs from young individuals to ameliorate senescence-related cell damage. Longer-term experiments are needed to establish the rejuvenating potential of such sEVs.

Anna Melidoni, Editor, BMC Series

ORIGINAL ARTICLE Fafián-Labora, J. A. et al. Small extracellular vesicles have GST activity and ameliorate senescence-related tissue damage. *Cell Metab.* **32**, 71–86 (2020)
RELATED ARTICLE O'Brien, K. et al. RNA delivery by extracellular vesicles in mammalian cells and its applications. *Nat. Rev. Mol. Cell Biol.* https://doi.org/10.1038/s41580-020-0251-y (2020)