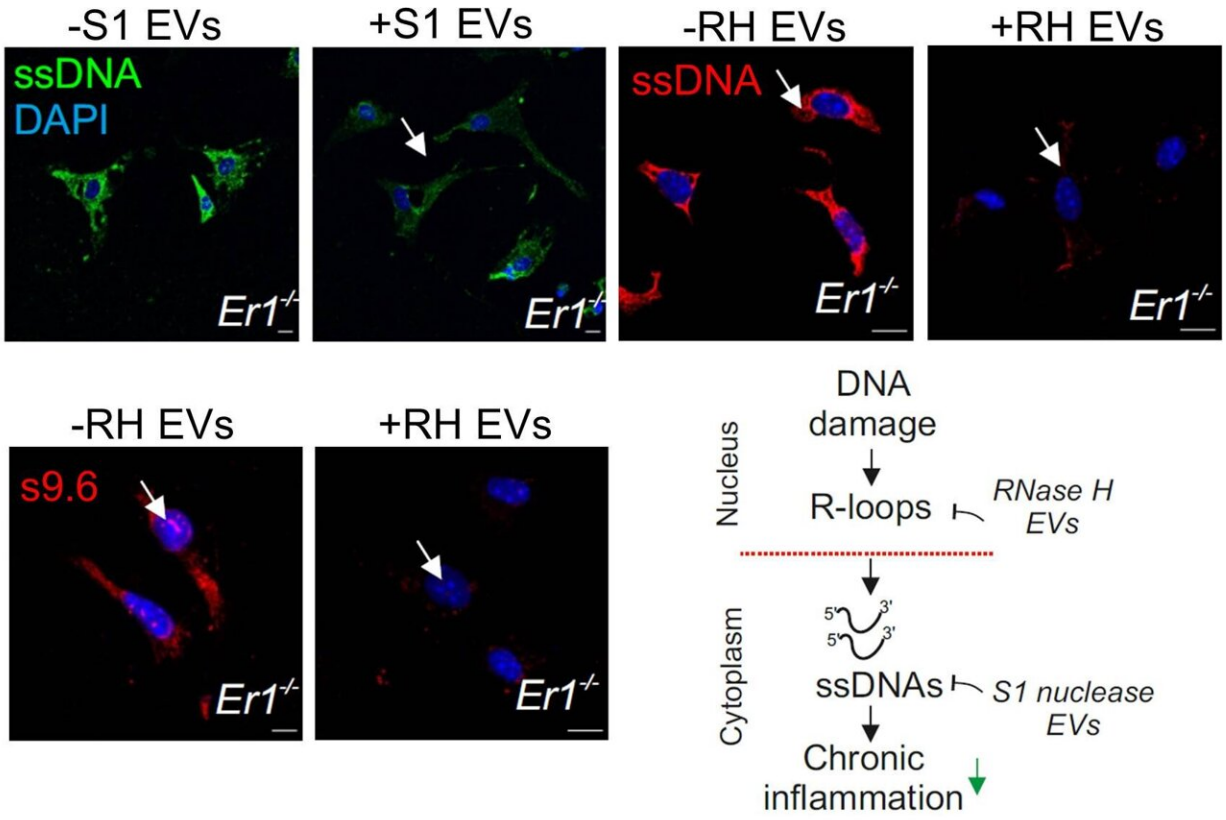
DNA damage in tissue-infiltrating macrophages triggers an exosome-based metabolic reprogram

November 26 2021



An extracellular vesicle (EV)-based strategy to deliver recombinant S1 or ribonuclease H nucleases in inflamed Ercc1−/− pancreatic cells. Treatment of Ercc1−/− animals with the EV-delivered nuclease cargo eliminates DNA damage-induced R-loops and cytoplasmic ssDNAs alleviating chronic inflammation. Credit: Foundation for Research and Technology - Hellas

Research carried out at the Institute of Molecular Biology and Biotechnology (IMBB) of FORTH, provides evidence that persistent DNA damage triggers an exosome-based, metabolic reprogramming that leads to chronic inflammation and tissue pathology in DNA repair-deficient progeroid syndromes and likely also during aging.

Inborn defects in DNA repair mechanisms are associated with cancer and aging but also with complex metabolic and endocrine disorders whose causal mechanisms are not well understood. Using animals with a DNA repair, the IMBB researchers provide a novel mechanism by which DNA damage leads to cellular senescence, fibrosis, loss of tissue architecture and chronic pancreatitis in mice. These findings led the team to propose a new therapeutic strategy, aimed at combating chronic inflammation and tissue damage associated with aging. The findings pave the way for novel rationalized intervention strategies against age-related chronic inflammatory disorders.

Using ERCC1-defective animal models of the human progeroid syndrome XFE, the researchers revealed that the gradual accumulation of irreparable DNA lesions leads to the premature onset of chronic pancreatitis in the DNA repair-deficient animals. Further work on cells from these animals revealed that DNA damage triggers the formation of RNA: DNA hybrids called "R-loops" causally contributed to the release and build-up of single-stranded DNA fragments in the cytoplasm of cells. In turn, the cytoplasmic DNA fragments stimulated a viral-like immune response in the pancreas of DNA repair-defective and naturally aged mice. To reduce the proinflammatory load, the researchers developed an extracellular vesicle (EV)-based strategy to deliver recombinant RNase H or S1 nuclease in inflamed *Ercc1*$^{-/-}$ pancreatic cells *in vitro* and *in vivo*. Using this novel strategy, they found that treatment with the EV-delivered nuclease cargo rapidly removes R-loops and the ssDNA moieties in the cytoplasm of pancreatic cells, thereby reducing the proinflammatory response seen in the DNA repair deficient

mice.

The findings support the notion that the development of EV-based therapeutic regimens against DNA damage-driven cytoplasmic ssDNAs is a promising therapeutic strategy against chronic inflammation and tissue degeneration associated with aging.

More information: Ourania Chatzidoukaki et al, R-loops trigger the release of cytoplasmic ssDNAs leading to chronic inflammation upon DNA damage, *Science Advances* (2021). DOI: 10.1126/sciadv.abj5769

Provided by Foundation for Research and Technology - Hellas