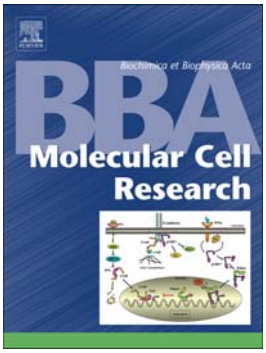

ATM-ROS-iNOS axis regulates nitric oxide mediated cellular senescence

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Running title: NO mediated cellular senescence

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Highlights

Exposure to elevated levels of nitric oxide generated internally or provided externally causes DNA damage and cellular aging similar to ROS. The viability of aged cells is regulated by ATM kinase, ROS and iNOS axis.

Abstract

Cellular senescence is an outcome of the accumulation of DNA damage which induces the growth arrest in cells. Physiologically, it is presumed to be mediated by accumulation of reactive oxygen species (ROS). Here, we show that another free radical, nitric oxide (NO) produced during inflammation or present as environmental pollutant can also induce cellular senescence. In primary cells and various immortalized cell lines, exposure to chronic NO, through external addition or internally generated by iNOS expression, leads to the activation of DNA damage response and causes cellular senescence. The phenotype generated by NO includes robust growth arrest, increase in the levels of the DNA damage foci, ROS, SAβ-gal staining, and inflammatory cytokines like IL-6 and IL-8, all hallmarks of cellular senescence similar to replicative senescence. Mechanistically, inhibitor and knockdown analysis revealed that NO mediates senescence through ATM kinase activation and the viability of cells is dependent on both ROS and ATM kinase involving the ATM - ROS - iNOS axis. Overall, we demonstrate that nitric oxide mediates cellular senescence through a novel free radical dependent genotoxic stress pathway.

Keywords: Cellular senescence; free radicals; ATM kinase; iNOS; Nitric oxide; DNA damage response.