

## Prevention of fibroblast senescence by hyaluronic acid and clinical application to chemoradiation-induced oral mucositis

Nicola Cirillo

The University of Melbourne, Australia

**Purpose:** Virtually all patients receiving radio and chemotherapy for head and neck cancer develop oralmucositis (1), a severe and highly debilitating condition. Because the onset of mucositis is related to the production of reactive oxygen species (ROS) (2), here we investigated a possible protective effect of sodiumhyaluronate enriched with aminoacids (Mucosamin®) in the damage induced by oxidative stress both in vitro and in vivo.

**Methods:** Normaloralstromalfibroblasts (NOF) and keratinocytes (NOK) were used for the in vitro study. Oxidative stress was induced with H<sub>2</sub>O<sub>2</sub> and senescence markers were investigated by Western blot (p16), immunofluorescence (SA-bgal), and senescence-associated secretory (SAS) molecules. Metabolic effect on NOK was studied by MTT test. The clinical study was a case-series of 11 patients undergoing chemotherapy, radiotherapy, or both. Sodiumhyaluronate spray (Mucosamin®) was used for this study.

**Results:** Whilst H<sub>2</sub>O<sub>2</sub> was toxic to NOK and induced cell death in vitro, exposure of NOF to H<sub>2</sub>O<sub>2</sub> led to long term senescence, as demonstrated by sustained increase in the levels of p16 and Sab-gal and expression of SAS phenotype. Conditioned media from senescent NOF induced detrimental effects on NOK, as shown by MTT. Pre-treatment with Mucosamin® could prevent both H<sub>2</sub>O<sub>2</sub>-induced fibroblast senescence and reduction of metabolic activity of NOK exposed to the conditioned media. The data from case-series of 11 patients undergoing radio/chemotherapy demonstrated that prophylactic use of Mucosamin® prevented oral mucositis in 9 out of 11 patients; the remaining 2 showed low grade transient mucositis; 10 out of 11 patients developed radiodermatitis.

**Conclusion:** SH preparations can prevent cellular senescence in NOF undergoing oxidative stress in vitro. Clinically, prophylactic use of SH virtually abrogates the incidence of oral mucositis secondary to chemoradiation, providing a safe and approachable intervention for this most debilitating condition.

[nicola.cirillo@unimelb.edu.au](mailto:nicola.cirillo@unimelb.edu.au)