SENESCENT FIBROBLASTS HAVE DECREASED ACETYL-COA CARBOXYASE LEVELS SUGGESTING COORDINATE REGULATION OF LIPID SYNTHESIS AND PROLIFERATION

Marmisolle I.¹; Martínez J.¹; Quijano C.¹

Center for Free Radical and Biomedical Research and Departmento de Bioquímica, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay

Introduction and objectives: Cell proliferation and metabolism are tightly linked in mammalian cells; pathways such as glycolysis, are differentially regulated in proliferating and non-proliferating cells and in coordination with the cell cycle. Herein we assessed the fatty acid synthesis pathway in proliferating primary human lung fibroblasts and in arrested cells after the induction of replicative senescence and premature senescence.

Methods: We obtained primary human lung fibroblasts (IMR-90) with different cumulative population doublings, (cPD) by sub cultivating early passage cells. Premature senescence was achieved by exposure to the topoisomerase inhibitor doxorubicin (0.2 μM) or the oxidant hydrogen peroxide (H₂O₂, 600 μM, two-additions).

Results: For replicative senescent cells we observed that as cPD increased, the percentage of senescence associated β-Galactosidase (SA- β-Gal) positive cells in the culture increased, achieving approximately 80% when proliferation had totally ceased. A decline in de novo lipid synthesis, assessed as [¹⁴C]-acetate incorporation to the cell lipids, was observed as cells underwent replicative senescence; that correlated with a reduction in the protein levels of Acetyl CoA Carboxylase (ACC1) and fatty acid synthase (FAS). Exposure to doxorubicin or to H₂O₂ triggered the phosphorylation of the DNA Damage Response sensor Ataxia Telangiectasia Mutated kinase (ATM), hypophosphorylation of the retinoblastoma protein (pRb) and proliferation arrest. SA- β-Gal positive cells reached 90 ± 2 % in doxorubicin treated cells and 65 ± 9 % in H₂O₂ treated cells, while SA- β-Gal levels in control cells were ≤ 22 ± 2%. Incubation with both doxorubicin and H₂O₂ lead to an immediate decrease in ACC1 protein levels, and the decay paralleled the phosphorylation of ATM and the hypophosphorylation of the pRb.

Conclusions Together, our results point to the existence of a coordinated regulation between proliferation and lipid synthesis in senescence.

Key Words: Acetyl CoA carboxylase, senescence, quiescence