CHEMOTHERAPY-INDUCED SENESCENCE PROMOTES A METABOLIC REPROGRAMMING IN MELANOMA

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Introduction: Melanoma mortality has increased in recent years due to the lack of an effective treatment. Chemotherapy using alkylating agents, such as temozolomide (TMZ), alone or associated with immunotherapy is currently the preferred treatment for metastatic melanoma. Unfortunately, the response to these agents is low and temporary, mainly due to the resistance to apoptosis.

Objectives: To characterize the phenotypic and metabolic alterations of a melanoma cell line exposed to TMZ in order to better understand the molecular mechanisms involved in melanoma resistance to alkylating chemotherapeutics.

Methods: We performed qRT-PCR to evaluate cytokine transcription; western blot and immunocytochemistry to assess the activation of the DNA damage response and proliferation. The metabolic studies were performed in a Seahorse XFe Analyzer.

Results and discussion: We observed that exposure of the mouse melanoma cell line B16-F1 to TMZ (200 µM, 2 doses) induced an arrest in proliferation, activation of the DNA damage response (evidenced as phosphorylation of ATM, p53 and H2AX), acquisition of an enlarged and flattened morphology, increased senescence associated β-galactosidase activity and increased transcription of pro-inflammatory factors, including IL6, CCL2, CXCL9, CXCL10, IL18, TGF-β. These changes were consistent with the induction of premature senescence in approximately 60% of the cell culture. The induction of senescence in melanoma cells resulted in substantial modification of mitochondrial function. Maximal oxygen consumption (determined after the addition of an uncoupler) was 2 to 3-fold higher in TMZ treated cells than in control cells, indicative of increased number or activity of the respiratory chain complexes. Besides, senescent cells had lower extracellular acidification rates than control cells, suggestive of decreased lactate production.

Conclusion: Our results indicate that the induction of senescence by chemotherapy promotes the synthesis of many cytokines and that is also accompanied by a substantial metabolic reprogramming.

Key words: Mitochondria, Melanoma, Senescence.

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