SUPEROXIDE-HYDROGEN PEROXIDE IMBALANCE INTERFERES ON CELLULAR VIABILITY, PROLIFERATION AND OXALIPLATIN RESPONSE OF COLORECTAL CANCER CELLS

Assmann, C.E.¹; Azzolin, V.F.¹; Machado, A.K.¹; Cadoná, F.C.¹; Barbisan, F.¹; Dornelles, E. B.¹; Rosa, B. S.¹; Cruz, I.B.M.¹

¹Departmento de Morfologia, Universidade Federal de Santa Maria, Rio Grande do Sul, Brazil

Introduction and objectives: Tumor response to radiochemotherapy is highly variable among patients. A previous investigation of potential genetic markers has evaluated 128 single nucleotide polymorphisms (SNPs) and found significant association between SOD 2 (Superoxide Dismutase 2) SNP (rs4880) and radiochemotherapy resistance. This polymorphism, with the change of a valine (V) to an alanine (A) (Ala16Val-SOD2), has been associated with the risk of several cancer types. The homozygous genotypes present different SOD2 efficacies causing increase in superoxide anion ($O_2^{-}$) levels (VV) or hydrogen peroxide ($H_2O_2$) levels (AA). Cellular control of superoxide anion and hydrogen peroxide concentrations is considered crucial to the cell. At low concentrations, reactive oxygen species (ROS) can function as intracellular signalling molecules related to homeostatic regulation, while at high levels they can cause cellular dysfunction and senescence. We evaluated if an in vitro superoxide-hydrogen peroxide (S-HP) imbalance could influence the response of colorectal cancer cells (HT-29) resistant to oxaliplatin. Materials and methods: HT-29 cells (ATCC) were cultured in standard conditions and exposed to different concentrations of methylviologen (superoxide anion donator) as well as porphyrin (SOD2-like molecule), with and without oxaliplatin. The effects on viability, cell proliferation and cell cycle were evaluated by MTT assay. Apoptosis analysis were performed by annexin V quantification using flow cytometry detection. Apoptosis pathway genes modulation (p53, Bax/Bcl-2, caspases 3 and 8) was determined by qRT-PCR. Results and conclusions: The results showed that S-HP imbalance was able to increase cell cytotoxicity and apoptosis induction of colorectal cancer cells independent of oxaliplatin treatment. Methylviologen has also potencialized the oxaliplatin cytotoxic and antiproliferative effects by increase of apoptosis events, arrestment of cell cycle in S and M/G2 phases. The results corroborate the potential pharmacogenetic relevance of this polymorphism on colorectal cancer treatment.

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