THE ROLE OF NRF2 ACTIVATION ON HUMAN NEUROBLASTOMA CELLS TREATED WITH RETINOIC ACID.

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INTRODUCTION: Retinoic acid (RA), the most biologically active derivate of Vitamin A, is well known for its importance on tissues development and cells differentiation. This molecule has been used in different kinds of therapies, since neurodegenerative disorders until some types of cancer such as promyelocytic leukaemia and neuroblastoma. However, most of the pathways responsible for RA effects remain unknown. A usual model used to investigate this effects is the human neuroblastoma cells SH-SY5Y that, when treated with low doses of RA, can represent the initial stages of neuronal differentiation. Some works have shown that reactive species (RS) production and oxidative stress (OS) have a major importance for some subsequently effects of RA treatment on these cells. Also the nuclear factor erythroid 2 (NF-E2]-related factor 2 (Nrf2) pathway, an important redox-sensitive signaling mechanism, revealed to have great influence on the cell response. Thus, this work aims to understand the regulation of Nrf2 pathway in SH-SY5Y cells leading to a better understanding of the RS role under RA treatments, and proposing new targets to optimize RA therapies. MATERIALS AND METHODS: To measure the Nrf2 activation by RA treatment we used a Cignal Antioxidant Response (ARE) Reporter Assay (luciferase) Kit. The intracellular RS production was indirectly quantified by the oxidation of 2′,7′-Dichlorofluorescin (DCFH). Cell viability was measured by the Sulforhodamine B assay. RESULTS AND CONCLUSIONS: N-acetyl-cysteine (NAC) and bovine catalase pre-treatments attenuated Nrf2 activation by RA treatment, differently from Trolox®, suggesting a specific RS signalization. In addition, the ERK 1/2 and PI3K/AKT pathway revealed to be equally necessary. Nrf2 knockdown influenced SH-SY5Y cells viability not only when exposed to RA treatment but also on proliferative cells, suggesting that this pathway has a major importance for its physiology. These results suggests that Nrf2 pathway can be a important target to modulate RA therapies response.

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Key words: Nrf2, retinoic acid, human neuroblastoma.