

Retinoic acid downregulates thiol antioxidant defences and homologous recombination while promotes A549 cells sensitization to cisplatin

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Abstract

Recent studies have investigated the use of retinoic acid (RA) molecule in combined chemotherapies to cancer cells as an attempt to increase treatment efficiency and circumvent cell resistance. Positive results were obtained in clinical trials from lung cancer patients treated with RA and cisplatin. Meanwhile, the signalling process that results from the interaction of both molecules remains unclear. One of the pathways that RA is able to modulate is the activity of NRF2 transcription factor, which is highly associated with tumour progression and resistance. Therefore, the aim of this work was to investigate molecular mechanism of RA and cisplatin co-treatment in A549 cells, focusing in NRF2 pathway. To this end, we investigated NRF2 and NRF2-target genes expression, cellular redox status, cisplatin-induced apoptosis, autophagy and DNA repair through homologous recombination. RA demonstrated to have an inhibitory effect over NRF2 activation, which regulates the expression of thiol antioxidant enzymes. Moreover, RA increased reactive species production associated with increased oxidation of thiol groups within the cells. The expression of proteins associated with DNA repair through homologous recombination was also suppressed by RA pre-treatment. All combined, these effects appear to create a more sensitive cellular environment to cisplatin treatment, increasing apoptosis frequency. Interestingly, autophagy was also increased by combination therapy, suggesting a resistance mechanism by A549 cells. In conclusion, these results provided new information about molecular mechanisms of RA and cisplatin treatment contributing to chemotherapy optimization.

Keywords: Retinoic acid, Cisplatin, A549 cells, NRF2, Antioxidants systems, Homologous recombination