Activation of NF-κB by Vitamin A (Retinol) in Human Lung Cancer Cells Downregulates RAGE Expression

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INTRODUCTION: As an essential component of the diet, retinol supplementation is often considered harmless and its application is poorly controlled. However, recent works demonstrated that retinol may induce a wide array of deleterious effects, especially when doses used are elevated. These include the increase in reactive species production and the modulation of the expression of the receptor for advanced glycation end-products (RAGE). In lungs, RAGE is constitutively expressed and changes in its expression were observed to be related to lung cancer.

MATERIAL AND METHODS: We used the A549 non-small lung cancer cell line as a cellular model. These cells were incubated with retinol from 2 µM to 20 µM and the expression of RAGE was evaluated by western blot and RT-PCR. To determine the involvement of NF-κB in the modulation of RAGE expression, A549 cells were incubated with the NF-κB inhibitor SN50 (100 µg/ml) and also transfected with siRNA to p65. In these conditions, RAGE expression was evaluated by western blot, RT-PCR and NF-κB activation was assessed by EMSA and nuclear detection of p65 by confocal immunohistochemistry and western blot.

RESULTS AND DISCUSSION: Retinol at 10 µM downregulated RAGE expression and caused activation of NF-κB. Antioxidant co-treatment with Trolox, a hydrophilic analogue of α-tocopherol, reversed the effects of retinol on RAGE expression and NF-κB activation, indicating the involvement of reactive oxygen species. Blockade of NF-κB activity or expression inhibited RAGE downregulation by retinol.

CONCLUSION: These results indicate that retinol induces the activation of NF-κB by a redox-dependent mechanism, and this effect results in the down-regulation of RAGE expression in A549 cells.

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