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Intranasal Administration of Resveratrol Successfully Prevents Lung Cancer in A/J Mice

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Introduction: Resveratrol, a phytoalexin found in various foods such as grapes, is one of the most studied natural products. It displayed several biological activities including cancer chemoprevention. However, the low bioavailability of resveratrol often limited the translation of the *in vitro* activities to *in vivo* studies. For example, oral administration of resveratrol effectively inhibited carcinogenesis in the digestive tract, but failed to protect mice from chemically-induced lung carcinogenesis [1,2]. This failure was attributed in part to the metabolism that undergoes resveratrol when taken orally. Therefore, other non-invasive administration routes must be considered to bring sufficient doses to the lungs, and the pulmonary route seems the best one.

Aim: The aim of this work was to investigate intranasal instillation of resveratrol in lung cancer chemo-prevention in A/J mice.

Methods: In order to overcome the low hydrosolubility of resveratrol, a human transposable formulation was designed using 200 mM hydroxypropyl-beta-dex in saline solution. After demonstrating the efficacy of both this formulation and the intranasal administration route in delivering a high amount of resveratrol into the lungs, this formulation was administered 3 times a week during 26 weeks to A/J mice having 4-[methyl(nitroso)amino]-1-(3-pyridinyl)-1-butanone (NNK)-induced lung carcinogenesis. After sacrifice, lungs were harvested, tumor were counted and measured under a dissecting microscope. *In vitro* experiments were conducted on A549 cells in the hope of understanding the mechanism of action of RES.

Results: Resveratrol-treated mice showed a 27% decrease in lung tumor multiplicity, with smaller tumors, resulting in 45% decrease in tumor load. Resveratrol administration also reduced by 57% the incidence of spontaneous tumors in non-NNK treated mice. Further *in vitro* investigations revealed a dose dependent increase in NNK-induced-H₂AX phosphorylation after resveratrol treatment, highlighting DNA repair modifications as a possible mechanism of action.

Conclusions: The present results lead to the hypothesis that resveratrol low oral bioavailability may be responsible for the lack of activity observed in former studies. Overall, this study supports the interest in intrapulmonary administration of resveratrol for further clinical development in lung cancer chemo-prevention.

Keywords: resveratrol, lung cancer, chemoprevention, intranasal instillation.

References:

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- [2] Hecht SS et al. Cancer Lett. 1999; 137 (2): 123-30.