

## **ACETYL DEACYLASADISULFIDE, A NATURAL H<sub>2</sub>S DONOR MOLECULE, INHIBITS METASTATIC MELANOMA.**

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Like all body tissues our skin is made up of cells: basal cells, squamous cells and melanocytes. There are three main types of skin cancer that are named after the skin cell in which the cancer develops: basal cell carcinoma, squamous cell carcinoma and melanoma. The latter is the most dangerous form of skin cancer, these cancerous growths develop when unrepaired DNA damage to skin cells triggers mutations that lead the melanocytes to multiply rapidly and form malignant tumors. These tumors originate in the pigment-producing melanocytes in the basal layer of the epidermis. Melanoma is caused mainly by intense, occasional UV exposure, especially in those who are genetically predisposed to the disease. If melanoma is recognized and treated early, it is almost always curable, but if it isn't, the cancer can advance and spread to other parts of the body, where it becomes hard to treat and can be fatal. Given its high mortality, the interest in the search of preventive measures, such as dietary factors, is growing significantly. We have demonstrated that the metabolic pathway l-cysteine/CSE/H<sub>2</sub>S is involved in human melanoma progression<sup>1</sup>. Therefore, the aim of our study was to evaluate the possible anti-tumoral effect of natural H<sub>2</sub>S donor molecule. We tested, in vitro and in vivo, Acetyl deacylasadisulfide (ADA), a vinyl disulfide compound, isolated and purified from asafoetida a foul-smelling oleo gum-resin of dietary and medicinal relevance<sup>2</sup>. Increasing doses of ADA markedly suppressed proliferation of human melanoma cells by inducing apoptosis. The apoptotic machinery can be controlled, at least in part, by NF- $\kappa$ B, which regulates transcription of the Bcl-2 family members<sup>3</sup>. Several reports have shown that in melanoma the constitutive activation of NF- $\kappa$ B confers tumor survival capacity and avoidance of apoptosis<sup>4</sup>. Thus, we have hypothesized that the ADA induction of apoptosis was associated with suppression of NF- $\kappa$ B activation. Western blot analysis proved that treatment of melanoma cells with ADA revealed a time-dependent reduction of nuclear translocation and activation of p65 and decreased the expression of the anti-apoptotic proteins c-FLIP, XIAP, and Bcl-2. In order to better define the mechanism through which this latter effect is achieved, we investigated the possible involvement of the MAPK/ERK and PI3K/AKT pathways, two of the most frequently deregulated pathways in melanoma<sup>5</sup>. Western blot analysis revealed that ADA inhibited the phosphorylation and activation of both AKT and ERK proteins at the time points considered. Invasivity assay carried out on melanoma cells incubated with ADA resulted in a significant inhibition of cell invasion. Finally, to corroborate these results obtained in vitro, we injected B16/F10 mouse melanoma cells into tail veins of C57BL/6 mice to induce lung metastasis. In these mice, the ADA (5-50mg/kg, orally administrated) significantly reduced metastatic foci of lung surface when compared to control group. In conclusion, all these findings suggest that ADA could represent an important lead compound for the development of new anti-metastatic agents in the treatment of human melanoma.

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