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Effects of antioxidant supplementation on cancer progression

Akademisk avhandling

Som för avläggande av medicinsk doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Medicinaregatan 3, den 8:e Juni, klockan 13.00

av Kristell Le Gal Beneroso

Fakultetsopponent:
Professor Massimo Santoro
Università di Padova, Italien

Avhandlingen baseras på följande delarbeten

I. **Le Gal K**, Ibrahim MX, Wiel C, Sayin VI, Akula MK, Karlsson C, Dalin MG, Akyürek LM, Lindahl P, Nilsson JA, Bergo MO. Antioxidants can increase melanoma metastasis in mice. *Sci. Transl. Med.* **7**: 308re8

II. **Le Gal K***, Wiel C*, Ibrahim MX, Jonsson J, Ståhlman M, Sayin VI, Bergo MO. Mitochondria-targeted antioxidants do not influence malignant melanoma and lung cancer progression in mice. *Manuscript*.

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Effects of antioxidant supplementation on cancer progression

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Abstract

Popular wisdom holds that antioxidants protect against cancer because they neutralize reactive oxygen species (ROS) and other free radicals which can otherwise cause cancer by damaging DNA. This has been the rationale behind many clinical trials with antioxidants, which in most cases failed to show a beneficial effect and in others even increased cancer incidence. Our group believes that these inconsistencies can be explained by the idea that antioxidants have opposite effects on tumor initiation and progression, and that tumor cells benefit from low ROS levels which is facilitated by antioxidant supplementation. In this thesis we describe the effects of two widespread antioxidants, N-acetylcysteine and vitamin E, on malignant melanoma progression, a cancer known to be sensitive to redox alterations, using a transgenic mouse model and a panel of human cell lines. Because strong evidence links mitochondria-associated ROS to tumor progression, we also define the impact of targeting mitochondrial ROS on malignant melanoma and lung cancer progression. The results show that dietary antioxidant supplementation increases metastasis in malignant melanoma, and that this is dependent on new glutathione synthesis and activated RHOA. The data also indicates that mitochondria-targeted antioxidants do not inhibit cancer progression. These results suggest that cancer patients and people with high risk of developing cancer should avoid the use of antioxidant supplements.

Keywords: Antioxidants, ROS, cancer, metastasis

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