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The Effect of Reactive Oxygen Species Threshold on Cancer Cell Fate

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There has been an argument going on for the effectiveness of dietary supplements including various vitamins enriched in antioxidants in cancer treatment and prevention. Several trials have shown that vitamins are unable to suppress cancer progression and may even promote the disease.[1] Some other reports suggest that antioxidants may even accelerate cancer progression, in line with their drug resistance function.[2]

A classical model of carcinogenesis states that free radicals can act as promoters of cancer initiation, promotion and progression phases.[3] In the initiation phase where lethal mutations are absent, free radicals contribute to cell transformation and cancer initiation by generating ROS (reactive oxygen species) such as lipid peroxides that induce mutations and damage DNA.[4] An equilibrium exists between growth and death in normal cells; however, this balance is disturbed in cancer cells and free radicals act in favor of cell survival/growth by abrogating programmed death and tumor suppressing activities.

In the promotion phase that includes clonal expansion, free radicals act as second messengers to control cancer cell proliferation and differentiation. Intracellular concentrations of ROS are critical in this phase as they determine if ROS can induce apoptosis or growth.[5] In the progression phase of carcinogenesis that includes epithelial-to-mesenchymal transition and development of angiogenesis, ROS play important roles by mediating crosstalk between integrins as key players of cell proliferation, survival, and migration on the one hand and many cytokines and growth factors on the other hand.[6]

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The multifactor and dose-dependent contribution of ROS in cancer cell fate consists of DNA modifications and other cellular processes involved in transformation. This implies that the ultimate net effect of ROS on carcinogenesis will depend on their concentration and the redox status of the tumor cell. This dose-dependent effect of ROS constitutes a platform based on which decision is made on the therapeutic utility of either antioxidants or chemotherapy-mediated induction of massive oxidative stress in cancer. Antioxidant therapy would theoretically inhibit transformation and cancer aggression at the initiation stages. Chemotherapy, on the other hand, is based on increased oxidative stress that induces apoptosis.[7]

Reports are accumulating on the mechanisms by which antioxidants actually increase the risk of cancer.[8] In lung cancer, N-acetylcystein (NAC) and vitamin E increase tumor progression by disturbing the ROS-p53 axis.[9] Likewise, NAC has been shown to induce lymph node metastasis in animal models of melanoma and enhances tumor cell migration/invasion without changing its proliferation.[10] This study found a correlation between increased melanoma cell migration and new glutathione synthesis. Antioxidants activate the small guanosinetriphosphatase (GTPase) RHOA which contributes to cell migration/invasion by mediating cytoskeletal changes,[11] and inhibition of downstream RHOA signaling abolished antioxidant-induced migration.[10]

Relevant to breast cancer cells, Davison *et al*. discovered that antioxidant enzymes facilitate cell survival upon ECM-detachment and maintain metabolic activity and anchorage-independent growth in breast cancer cells.[12] These findings imply that strategies based on elimination, instead of administration, of antioxidant activity could effectively render invasive cancer cells susceptible to death.

Based on the reports we summarized above plus

ones, a roadmap can be proposed for intracellular developments in cancer upon exposure to elevated ROS or excessive antioxidants (Figure 1). This roadmap indicates that antioxidants are able to block ROS damages in cancer cells as long as ROS molecules have not increased beyond their toxic levels. However, once their levels cross their upper threshold, antioxidants of endogenous or dietary sources cannot neutralize ROS in order to overcome ROS-mediated intracellular damages.

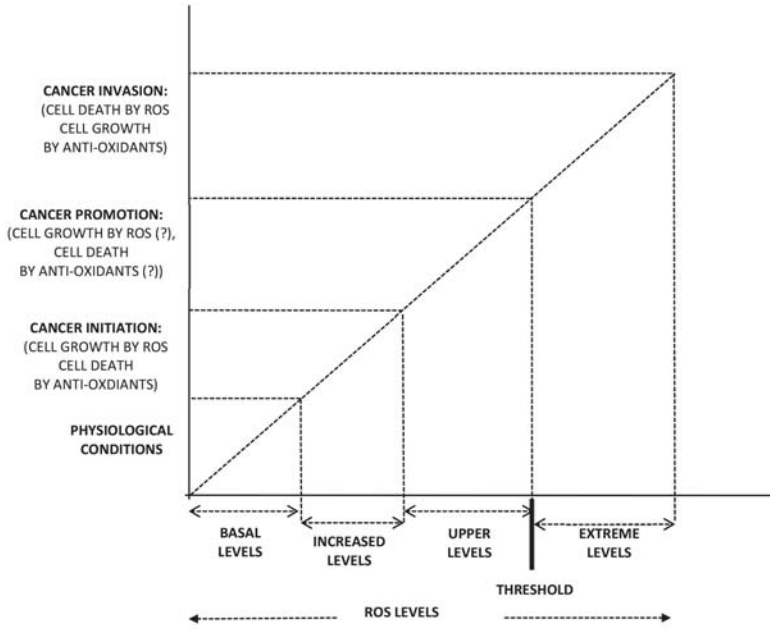

Figure 1. A roadmap for intracellular developments in cancer upon exposure to elevated ROS or excessive antioxidants.

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