

ANTI-OXIDANTS AND LUNG CANCER

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Number of clinical studies indicates that antioxidants increase the risk of some malignancies, particularly lung cancer (1, 2). Additionally, study published by Sayin *et al*, suggested that treatment with NAC or vitamin-E accelerated tumour growth in mice with lung cancer caused by a *Ras* gene mutation, although it reduced oxidative stress and DNA damage as would be predicted causing decrease in the activity of the p53 protein associated with the suppression of oxidative stress (3). N-acetylcysteine (NAC), an antioxidant is frequently recommended in chronic respiratory disorders including chronic obstructive pulmonary disease (COPD), due to its anti-inflammatory properties (4). However, the therapeutic efficacy of these treatments has yet to be proven. An expected benefit of antioxidants is their ability to reduce the risk of cancer, by decreasing DNA damage and mutations induced by reactive oxygen species (ROS) (4). A limitation of these studies is the development of experimental animal model of lung cancer induced by the *Ras* mutation, which makes it possible to study the therapeutic impact of antioxidants on tumor progression, however, not on the initiation of tumor. Thus, the potential effect of antioxidants, particularly NAC, on tumor induction and the

emergence of lung cancer remained unknown. However, given that NAC is already prescribed to patients with chronic bronchitis, smokers with or without COPD, and particularly those who are at risk of developing lung cancer, this question seems to be of important clinical interest.

Senescence is usually considered as a protection against cancer progression (5). Indeed, the activation of onco-suppressive proteins p53, p21, or p16 is a key step in the engagement of cells in the process of senescence. Thus, senescence in response to a specific stress, such as oncogenic stress, protects against tumor initiation by stopping cell proliferation and promoting their elimination by the immune system. Nevertheless, chronic senescence induced by oxidative stress (6), such as that occurring during aging or that induced by cigarette smoke (6), could have pro-cancerous effects, in particular via the secretory phenotype of senescent cells (senescence associated secretory phenotype, SASP). It is well known, that the majority of human cancers are linked to an escape from senescence, which is due to the inactivation of the onco-suppressive proteins p53, p21, or p16 (5). For most cells, p53 inactivation, bypassing the senescence process, leads to cell death due to excessive replication causing telomere shortening and resulting in genomic instability (5). However, some of these cells can survive, thus escaping senescence and having passed a stage of genetic instability with possible DNA mutations in their key genes, are particularly likely to transform into cancerous cells. This mechanism is relevant to lung cancer because, in the majority of cases, the development of this cancer is linked to one or more specific mutations in the *p53* gene that result in the protein's loss of function.

A major cause of concern is how these observations may be interpreted in the context of persistent oxidative stress, such as that caused by cigarette smoking. This question has considerable clinical significance given the efficacy of NAC treatment in smoking individuals with chronic bronchitis or COPD who are at risk of developing lung cancer. Indeed, it has been shown that the pathogenesis of respiratory diseases like COPD heavily depends on cellular senescence (7). The lungs of these patients are the site

of an accumulation of senescent cells which may become the reason of increase levels of SASP ultimately leading to the development of pulmonary fibrosis, distortion of lung parenchyma causing irreversible damage hence developing pulmonary emphysema, and pulmonary inflammation. Eliminating senescent cell or blocking the mechanism behind cellular senescence, therefore represents a real therapeutic option, which is currently the subject of intense research activity. The use of antioxidants is often cited as one of the possible therapeutic approaches, both preventive as well as curative. However, further research is warranted to confirm its actual role.

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