2 Oxidative Damage and Carcinogenesis

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2.1 Introduction

Substantial evidence has suggested that free radicals, particularly oxygen radicals, play an important role in several stages of carcinogenesis. Oxidants are ubiquitous in our natural environment but they can also be formed in the tissue by endogenous cellular mechanisms (Cerutti 1985; Kozumbo et al. 1985; Cerutti and Trump 1991). Oxidants can introduce structural damage to DNA, leading to chromosomal aberrations and point mutations. Point mutations in cancer-related genes such

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as the ras-family protooncogenes (Bos 1989) and the p53 tumor suppressor gene (Hollstein et al. 1991; de Fromentel and Sassi 1992) represent the most frequent genetic changes in human malignancies and at least part of them may be caused by oxidants. Besides these “genotoxic” effects, oxidants activate signal transduction pathways which lead to the modulation of the expression of growth- and differentiation-related genes (Crawford et al. 1988; Shibanuma et al. 1988; Cerutti et al. 1990). However, unlike growth factors oxidants always induce macromolecular damage, cytotoxicity, and cell killing. The effect of oxidants are influenced by the cellular antioxidant defenses (Cerutti et al. 1988; Amstad and Cerutti 1990) which consist of low-molecular-weight antioxidants and several antioxidant enzymes. The biological consequences of the exposure to an oxidant carcinogen may vary with the dose, the type of oxidant, and the tissue because it is the result of the superposition of effects on multiple cellular targets.

Chronic tissue injury by physical and chemical irritants frequently results in inflammation which is accompanied by the infiltration of phagocytic leukocytes (Creasia and Nettesheim 1974; Mass et al. 1985; Alexander-Williams 1976; Argyris and Slaga 1981). Phagocytic leukocytes produce a highly complex mixture of growth and differentiation factors as well as biologically active arachidonic acid metabolites (Edginton et al. 1987). In addition, they have the capacity to release large amounts of active oxygen (AO) in an oxidative burst (Badwey and Karnovsky 1990). Current evidence suggests that AO and arachidonic acid metabolites are important in tumorigenesis. Low-molecular-weight antioxidants, antioxidant enzymes, and anti-inflammatory agents that inhibit arachidonic acid metabolism are anticarcinogenic in several experimental systems (Slaga et al. 1983; Viaje et al. 1977; Kensler et al. 1983). The hypothesis that AO from phagocytes may be an important carcinogen is supported by the finding that an extracellular burst of AO produced by xanthine/xanthine oxidase (X/XO) is a potent promoter for initiated mouse embryo 10T1/2 fibroblasts and mouse epidermal JB6 cells (Zimmerman and Cerutti 1984; Muehlematter et al. 1988). While \( \text{H}_2\text{O}_2 \) itself is a weak promoter for initiated mouse skin, several xenobiotic organic endo- and hydroperoxides possess considerable potential as promoters and progressors (Slaga et al. 1983; Gindhart et al. 1985; O’Connell et al. 1986).