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Oxidative stress in carcinogenesis

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Abstract

Carcinogenesis is a multistep process involving both mutation of critical genes and increased cell proliferation. Over production of oxygen species (ROS) occurs from endogenous and/or exogenous sources. Endogenous sources include both intracellular organelles as well as inflammatory sources. Exogenous sources include xenobiotics, pharmaceuticals and radiation. Important to carcinogenesis, the resulting oxidative stress can induce mutations in critical cellular genes under inhibited antioxidant defense pathways and DNA repair mechanisms. In addition, ROS can activate a number of signal transduction pathways such as HIF1a, Nrf2, AP-1, and NF-kB that transcript cell growth regulatory genes. It is clear that oxidative stress and damage participate in all stages of the cancer process. Oxidative stress has also been linked to a number of human cancers both as causing and modulating factor. Further, the susceptibility to human cancers can be modified by polymorphisms in oxidative DNA repair genes and antioxidant genes.

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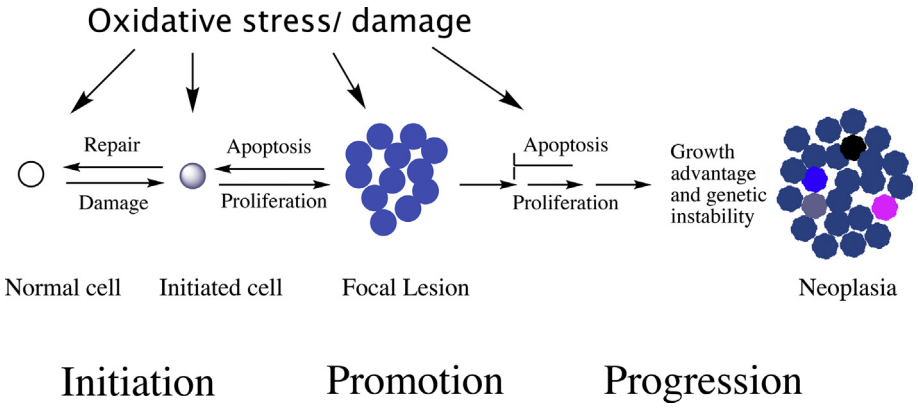
Oxidative stress, ROS, Multistage carcinogenesis, DNA damage, Proliferation, Polymorphism.

1. Introduction

The formation of a neoplasia is a multistep process. In its basic form this process involves genetic modification of genomic DNA (formation of a mutated cell) followed by the selective growth of the mutated cell. This growth can be stimulated by either an increase in the cell division rate of the mutated cell and/or a decrease in the death rate (apoptosis) of the mutated cell. As the mutated cell further divides, additional epigenetic and genetic changes occur in the newly formed lesion. Previous investigations characterized the changes that occur in tumorigenesis leading to the designations of initiation, promotion and progression to describe cellular and pathological demonstrable stages [1]. Initiation involves the formation of a mutated, preneoplastic cell from a genotoxic event. The formation of the preneoplastic, initiated cell is an irreversible, but dose-dependent process. Promotion involves the selective clonal expansion of the initiated cell through an increase in cell growth through either an increase in cell proliferation and/or a decrease in apoptosis in the target cell population [2]. The events of this stage are dose dependent and reversible upon removal of the tumor promotion stimulus. Progression, the third stage, involves cellular and molecular changes that occur from the preneoplastic to the neoplastic state. This stage is irreversible, involves genetic instability, changes in nuclear ploidy, and disruption of chromosome integrity. Subsequent investigations have shown that carcinogenesis is much more complicated, however utilization of the three-stage process is useful in understating where and how modifiers of the cancer process function. Based on our knowledge of multistage carcinogenesis. It is apparent that chemicals that induce cancer can function at all stages of the process (complete carcinogens) or at selective stages (initiation stage (tumor initiators)) and the promotion stage (tumor promoters) [3] (Fig. 1).

Using the rodent liver model as an example, the mechanisms of action by which carcinogens induce hepatic cancer can be categorized based upon molecular targets and cellular effects that include genotoxic (DNA reactive) and nongenotoxic (epigenetic) mechanisms [3]. Genotoxic agents usually refer to chemicals that directly damage genomic DNA, which in turn can result in mutation and/or clastogenic changes. Chemicals in this category are frequently activated in the target cell and produce a dose-dependent increase in neoplasm formation. A second category of carcinogenic compounds (nongenotoxic) appear to function through non-DNA reactive or indirect DNA reactive mechanisms. Nongenotoxic carcinogens, they modulate cell growth and cell death. Changes in gene expression and cell growth parameters are paramount in the action of nongenotoxic carcinogens. These agents frequently function during the promotion stage of the cancer process [4,5]. Increased replicative DNA synthesis and subsequent cell division is important in each of the stages of carcinogenesis [4,6]. Two possible mechanisms have been proposed for the induction of cancer by nongenotoxic agents. In one, an increase in DNA synthesis and cell proliferation by a nongenotoxic carcinogens may induce mutations in dividing cells through misrepair. With continual cell division, mutations will

Fig. 1



Role of Oxidative Stress and Damage in Multistate Carcinogenesis. Diagram showing the multistage process of carcinogenesis using the three general stage designations. Oxidative stress and resulting oxidative damage can occur at multiple steps of the cancer process from the formation of the mutated cell (initiation) to the promotion of the mutated cell (cell proliferation; epigenetic effects) and eventual formation of the neoplasm (progression).

result in an initiated preneoplastic cell that may clonally expand to a neoplasm. In addition, nongenotoxic agents may serve to stimulate the selective clonal growth of already "spontaneously initiated cells [7].

A number of studies have shown an important role for reactive oxygen species (ROS) in tumor development [8]. ROS can be produced from endogenous sources (mitochondria, peroxisomes, and inflammatory cell activation) [9] as well as exogenous sources (environmental agents, radiation, pharmaceuticals, and industrial chemicals) (Fig. 2). Oxidative stress may in turn lead to genetic mutation and/or alterations in cell growth. A linkage between an increase in reactive oxygen radicals and cancer formation has been established. During neoplasm formation, reactive oxidants can be generated from both endogenous and exogenous sources. In addition, chemical carcinogens have been shown to override of the cellular antioxidant systems and/or the DNA repair systems Endogenous sources of reactive oxidant species include both intracellular (peroxisomes, mitochondria, and cytochrome P450) and extracellular (inflammatory cells). Exogenous sources of reactive oxygen include radiation, metals, pathogens, chemotherapeutic agents and other xenobiotic chemicals. Both endogenous and exogenous sources of ROS can interact and modify all stages of the cancer process (Fig. 1).

2. Oxidative DNA damage

Oxidative DNA damage is a major source of mutations. Estimates of 10,000 (human) to 100,000 (mouse) oxidative lesions are formed per day in normal cells [10–12], with an estimated frequency of resulting oxidative DNA damage in human cells to be 10^4 lesions/cell/day [13]. Being highly reactive, the hydroxyl radical is the predominant ROS that targets DNA [13]. Cell death, DNA mutation, replication errors, and genomic instability can occur if the oxidative DNA damage is not repaired prior to DNA replication [9,14]. The most extensively studied and most abundant oxidative DNA lesion produced is 8-hydroxydeoxy guanosine (8-OHdG), which is mutagenic in bacterial and mammalian cells [15]. While most of the oxidative DNA lesions are in the form of OH8dG, additional oxidative DNA adducts have been identified [16,17]. 8-OHdG levels are elevated in various human cancers [18–20] and in animal models of tumors [21].

Central to the induction of cancer is the production of unrepairable DNA damage in the target cell that, after a round of DNA replication, results in a mutated cell. Reactive oxygen species are able to induce both single- or double-stranded DNA breaks, DNA cross links and base modification. While several can form oxidized bases, the hydroxyl radical has been studied extensively for its oxidized DNA lesions [22]. Oxidation of guanine at the C8 position results in the formation of 8-hydroxydeoxyguanosine (OH8dG), probably the most studied oxidative DNA adduct. The OH8dG DNA lesion results in site-specific mutagenesis in bacterial and mammalian cells. OH8dG also produces dose-related increases in cellular transformation [23]. Reactive oxygen species can also interact with the nucleotide pool, specifically dGTP to produce OH8dG. OH8dG in the nucleotide pool can therefore be incorporated into DNA during replication resulting in A:T to C:G transversions [15,17]. Besides OH8dG, other oxidative DNA lesions and uracil analogs have been shown to be mutagenic [24,25]. In addition to reactive oxygen species, reactive nitrogen species, such as peroxynitrites and nitrogen oxides, have also been implicated in carcinogenesis [26]. Peroxynitrite has been shown to react with guanine producing a 8-nitroguanine adduct