Chapter 20
Antioxidants Reduce Consequences of Radiation Exposure

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Abstract Antioxidants have been studied for their capacity to reduce the cytotoxic effects of radiation in normal tissues for at least 50 years. Early research identified sulfur-containing antioxidants as those with the most beneficial therapeutic ratio, even though these compounds have substantial toxicity when given in-vivo. Other antioxidant molecules (small molecules and enzymatic) have been studied for their capacity to prevent radiation toxicity both with regard to reduction of radiation-related cytotoxicity and for reduction of indirect radiation effects including long-term oxidative damage. Finally, categories of radiation protectors that are not primarily antioxidants, including those that act through acceleration of cell proliferation (e.g. growth factors), prevention of apoptosis, other cellular signaling effects (e.g. cytokine signal modifiers), or augmentation of DNA repair, all have direct or indirect effects on cellular redox state and levels of endogenous antioxidants. In this review we discuss what is known about the radioprotective properties of antioxidants, and what those properties tell us about the DNA and other cellular targets of radiation.

20.1 Introduction

There are many types of radiation damage to normal tissues. The types of damage depend on the cells and organs being irradiated, the dose and dose rate of the exposure, and the time after exposure that is being assayed for a radiation effect. Many of the types of damage seen after irradiation can be ameliorated by antioxidants. This review will outline a number of radiation-related toxicological processes and discuss the role antioxidants might play in affecting these processes in terms of the likely cellular types or compartments in

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which an antioxidant is employed. The role that different combinations of antioxidants might play in preventing each of these individual effects will also be explored.

## 20.2 Cell Components

Exposure of a cell to ionizing radiation results in the formation of free radicals within the cell, leading to damage of cellular components. Here we will provide some examples of how antioxidants reduce or prevent the damaging effects of radiation at three sensitive targets in the cell, the nucleus, cellular membranes and mitochondria.

### 20.2.1 Nucleus

#### 20.2.1.1 Immediate Effects by Antioxidants

Radiation-induced DNA damage is the best studied effect of radiation. An oxygen enhancement ratio (OER) of 2.5 to 3 in the yield of DNA damage is observed in the presence of oxygen tensions of 5 mmHg or higher compared to maximally hypoxic conditions (<1 mmHg). In accordance with this difference in DNA damage, there is a 3-fold difference in cell reproductive survival measured by clonogenic assays in the presence of oxygen which is generally independent of the phase of the cell cycle [1]. Prevention of immediate radiation-induced genotoxicity requires that an antioxidant be present at the time of irradiation [2]. To be maximally effective the antioxidant must be present near the DNA and thus must have access to the nucleus. It must be able to either, 1) react with all the oxygen-related free radicals and detoxify them to radicals that are not themselves genotoxic and/or 2) effectively compete with oxygen to repair damage to the DNA chemically through reactions with free radicals on the DNA. Thiol-based compounds are especially good antioxidants because these compounds are capable of both scavenging oxygen radicals and affecting chemical repair of some forms of DNA damage with the subsequent formation of sulfur-based radicals, which are not reactive with DNA [3]. Incorporating one or more positive charges on the thiol-based antioxidant has the effect of changing the proximity of the compound to the DNA [4,5]. The resulting counter-ion condensation between the positive charge of the thiol and the negatively charged sugar-phosphate backbone of the DNA binds the thiol close to the DNA, facilitating the competition of the thiol with oxygen in reactions with DNA radicals, thereby, reducing DNA damage and increasing cell survival [5,6].

Like the synthetic antioxidants (e.g., amifostine, captopril, and NAC), antioxidants derived from natural sources also exhibit dose-modifying effects on DNA damage and cell survival when present at the time of irradiation. This