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Cellular Oxidative Stress and Antioxidant Enzymes

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Oxidative stress is the damage that results from the interaction of free radicals, molecules or molecular fragments with one or more unpaired electrons, with living cells. This damage not only affects the cell immediately, but also can cause enough damage to affect future cells and subsequently the entire organism. Additionally, damaged caused to DNA affects future cell generations as well as future offspring of the organism. Fortunately, cells and organelles contain some means of battling the damage that can be caused by internal and environmental free radicals. Studies into antioxidants as a means to combat the negative effects of oxidative stress are ongoing however it is still unclear whether the use of antioxidants is entirely beneficial or possibly harmful

Introduction

Organisms living in an aerobic environment cannot help but be subject to reactive oxygen species (ROS), which have higher reactivities than molecular oxygen. Although the fleeting fluctuations of ROS serve important regulatory functions, sustained high levels are known to cause severe damage to the affected cells (Martindale & Holbrook, 2002).These O_2^- molecules, also referred to as free radicals, are the result of a partial reduction of O_2 and can cause serious damage to the membrane lipids, connective tissues, and nucleic acids of cells (Harris, 1992).Within cells, ROS are the product of normal cellular metabolism. Under normal circumstances, leakage from electron transport chains, such as those in the mitochondria and endoplasmic reticulum, is not uncommon. Oxygen occupies the final position in the electron transport chain within mitochondria which leaves it susceptible to react with any 'leaked electrons' (Valko *et al.*, 2004). Cells have however developed mechanisms to combat low levels of ROS to prevent cellular damage.As part of the cell's defense mechanisms against damage, quenchers are produced that act as "sacrificial molecules" to combat the output from redox cycles or they may produce specific enzymes to act directly upon the oxygen radical. These processes allow the cell to turn oxygen radicals into less harmful products (Harris, 1992).When these mechanisms are overwhelmed beyond their capabilities, oxidative stress is the result. Cellular reactions to oxidative stress can range from proliferation, to growth arrest, to senescence to cell death and vary even further depending on the type of cell being affected. Due to the variety of intracellular stress signaling pathways and the different activations resulting from different stresses, some pathways are linked to enhanced survival while others result in cell death(Martindale & Holbrook, 2002).

Recent Progress

DNA and Cellular Damage

Estimates as to how often one human cell is exposed to free radicals and other oxidative damage are around 10^5 hits per day. Despite the antioxidant defense systems employed by cells, free radical damage to DNA and proteins occurs."All ROS have the potential to interact with the cellular components including DNA bases or the deoxyribosyl backbone of DNA to produce damaged

bases or strand breaks. Oxygen radicals can also oxidize lipids or proteins thus generating intermediates that react with DNA by forming adducts" (Valko *et al.*, 2004).Since ROS are normal byproducts of cellular metabolisms, they are a potential source of chronic and persistent DNA damage.Two mechanisms that play a role in oxidative stress are the modulation of gene expression and genetic alterations. Gene expression is affected through chromosomal rearrangements resulting from strand breakage misrepair which affects signal transduction pathways. Gene alterations, such as mutations and chromosomal rearrangements, can block DNA replication and cause wide cytotoxicity (Valko *et al.*, 2004).

Due to the critical nature of nuclear DNA, a number of DNA repair systems have evolved to address the threat of ROS upon cellular and organismal function. These repair functions can occur through nonhomologous end-joining, homologous recombination pathways, base excision repair, or nucleotide excision repair depending on the type of damage. Oxidative stresses resulting in permanent modification are the first step involved in mutagenesis. "DNA alterations caused by radicals are removed by specific and non-specific repair mechanisms. Repair of DNA base damage is thought to occur mainly by base-excision. However, misrepair of DNA damage could result in mutations such as base substitution and deletion….Mutagenic potential is directly proportional to the number of oxidative DNA lesions that escape repair" (Valko *et al.*, 2004).

"While major attention has focused on direct DNA damage by free radicals because of the genetic consequences of such damage, reactive radical species may also cause damage to other cellular components" (Valko *et al.*, 2004). Other cellular aspects such as cell walls, cytoplasm, mitochondria, ribosomes, etc. can all be affected by ROS rendering the cell damaged and in danger of replicating mutated material thus risking the overall functionality of the entire organism.

Antioxidants

The classification for the group of organic substances thought to be effective at deactivating free radicals is called antioxidants. This group includes vitamins E, C, and A (which is converted from β-carotene), selenium, and carotenoids (β-carotene being the most prevalent).

Vitamin E is a generic descriptor for all tocol and tocotrienol and it is a fat-soluble vitamin that exists in eight different forms (α-tocopherol is the most active in humans). It is an effective antioxidant that protects cells against the potentially hazardous free radical byproducts that can result from the actions of the cell's metabolism. In humans, α-tocopherol is employed by the cell wall to protect against lipid peroxidation.It does this by donating a readily available hydrogen to a lipid or lipid peroxyl radical. This results in α-tocopherol becoming an energetically stable radical, forming a product that is less offensive, which then poses no threat to the integrity of the cell. "Recent evidence suggests that α-tocopherol and ascorbic acid function in a cyclic-type reaction." Ascorbic acid acts as a reducing agent for α-tocopherol as well as acting as an effective scavenger of ROS.(Valko *et al.*, 2004).

Vitamin C's major role involves the production of collagen which is the main protein that holds connective tissues together in the body. It is also critical responsible for producing certain nerve transmitting substances as well as the absorption and utilization of other nutrients. Vitamin C, which is represented chemically as $AscH^-$ is a donor antioxidant. When it comes in contact with an oxidizing radical, it donates a hydrogen atom to produce a stabilized resonance and in doing so, stabilizes the free radical. Vitamin C has also been shown to cooperate with vitamin E to regenerate the above mentioned α-tocopherol from its radical state in membranes and lipoproteins (Valko *et al.*, 2004).

The carotenoid group (CAR) are not synthesized by animals, but they are present in plants and microorganisms. CAR are an effective antioxidant due to their conjugated double bond structure which allows it to easily localize any unpaired electrons. β-Carotene has the ability to stabilize O_2^- without risking degradation as well as having the ability to stabilize other free radicals. Unfortunately, β-carotene in larger doses has been shown in some studies to increase oxidation, also known as 'pro-oxidant activity. This has the effect of increasing the total radical yield of a particular system thus increasing the cellular damage (Valko *et al.*, 2004).

Discussion

Although oxidative stresses are present within cells, increasing exposure from outside sources has the potential to overwhelm the internal measures that are in place to address oxidation of tissues. The structural integrity of DNA and cell structure as well as functionality are important to the overall success of a particular organism.Study and understanding of the repair mechanisms employed by cells and cell systems are important because they can be employed in the curing and prevention of diseases that attack or disable DNA or infect cells. Study into the subject is ongoing although progress is being made regarding the additive and antagonistic pathways and the contexts in which they

operate which are determined by the oxidative stress being applied and the type of tissue being affected.

A large part of a cell or tissue's response to oxidative stress is the employment of antioxidant enzymes. Most antioxidants are already present in the human (vitamin C being a large exception) and are used to convert free radicals into a more stable form that is no longer harmful. Studies into the positive, and sometimes negative, effects of antioxidants is also ongoing. The enzymatic nature of antioxidants makes them a powerful response to threats, however it is also possible for antioxidants to enhance the negative effects of oxidative stress by actually driving the oxidative process.

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