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Review

Toxicological and pathophysiological roles of reactive oxygen and nitrogen species

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ABSTRACT

'*Oxidative and Nitrative Stress in Toxicology and Disease*' was the subject of a symposium held at the EUROTOX meeting in Dresden 15th September 2009. Reactive oxygen (ROS) and reactive nitrogen species (RNS) produced during tissue pathogenesis and in response to viral or chemical toxicants, induce a complex series of downstream adaptive and reparative events driven by the associated oxidative and nitrative stress. As highlighted by all the speakers, ROS and RNS can promote diverse biological responses associated with a spectrum of disorders including neurodegenerative/neuropsychiatric and cardiovascular diseases. Similar pathways are implicated during the process of liver and skin carcinogenesis. Mechanistically, reactive oxygen and nitrogen species drive sustained cell proliferation, cell death including both apoptosis and necrosis, formation of nuclear and mitochondrial DNA mutations, and in some cases stimulation of a pro-angiogenic environment. Here we illustrate the pivotal role played by oxidative and nitrative stress in cell death, inflammation and pain and its consequences for toxicology and disease pathogenesis. Examples are presented from five different perspectives ranging from *in vitro* model systems through to *in vivo* animal model systems and clinical outcomes.

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1. Introduction

A symposium was held at the EUROTOX meeting in Dresden September 2009 entitled 'Oxidative and Nitrative Stress in Toxicology and Disease'. In this lively and well-attended session, inflammation and the role of reactive oxygen and reactive nitrogen species (ROS and RNS) were discussed initially followed by illustrative examples from diverse tissue and model systems. The concept behind the session was to seek cross-fertilisation between the different illustrative examples, revealing common themes.

Inflammation begins when tissues react to a local irritation usually caused by a physical injury, by infection or by exposure to a toxicant. Fluid and accompanying white blood cells traverse the vascular barrier leading to swelling, erythema, further inflammation and attraction of further white blood cells (Fig. 1). The resolution phase of inflammation involves repair and cell proliferation ultimately leading to tissue regeneration. During the inflammatory phase, there is a burst of respiration leading to the creation and release of free radicals, including production of both reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS and RNS utilize three main pathways of signalling which results in damage to DNA, proteins and lipids. Lipid peroxidation triggers the arachidonic-acid cascade, with the production of cell proliferation-stimulating eicosanoids. While free radicals induce DNA damage directly, by-products of the arachidonic-acid pathway such as malondialdehyde (MDA) and 4-hydroxynonenol (4-HNE) also are DNA-damaging agents. Free radicals can also modify enzyme systems involved in DNA repair and alter cell death signalling by modification of caspases and modulation of cell survival pathways regulated by key molecules such as JNK and p38 MAP kinase (reviewed in Aslan et al., 2008; Roberts et al., 2009a,b).

Although inflammation and the associated generation of free radicals can have a deleterious effect on the host, these processes also play a normal physiological role, especially in the elimination of invading pathogenic organisms. Since free radicals are ubiquitous in our body and are generated during normal physiological processes, mutiple defense systems have evolved to protect our cells from these potentially damaging free radicals. Antioxidant enzymes and scavenger systems serve to remove free radicals, whereas DNA repair pathways are triggered to repair damage to DNA after it has occurred.

It is clear that in certain situations of toxicant exposure or disease, the generation of ROS and RNS and the associated oxidative and nitrative stress are key mediators of inflammation, cell proliferation and cell death. In this review, evidence is presented in diverse tissues including the liver, brain, heart and skin in order to highlight common themes.

2. Oxidative and nitrative stress: role in the response to liver toxicants (Roberts)

The liver is the front line of defence and is therefore a target organ for many toxicants. Persistent inflammation plays a pivotal role in the response of liver to both chemical and viral damage, ranging from transient liver injury and repair through to hepatocarcinogenesis (Fig. 2).

There is a major drive to understand the mechanisms of toxicant and viral-induced liver disease to facilitate prevention and treatment and also to understand the molecular basis of individual susceptibility. WHO mortality data for the Americas (WHO, 2003) show liver cirrhosis as responsible for 4% of deaths in the 45–64 age group, making it the 3rd most common cause of death. As illustrated by these figures, cirrhosis itself is a major health issue which is exacerbated by the association of chronic cirrhosis with quite frequent progression to hepatocellular adenoma and carcinoma.

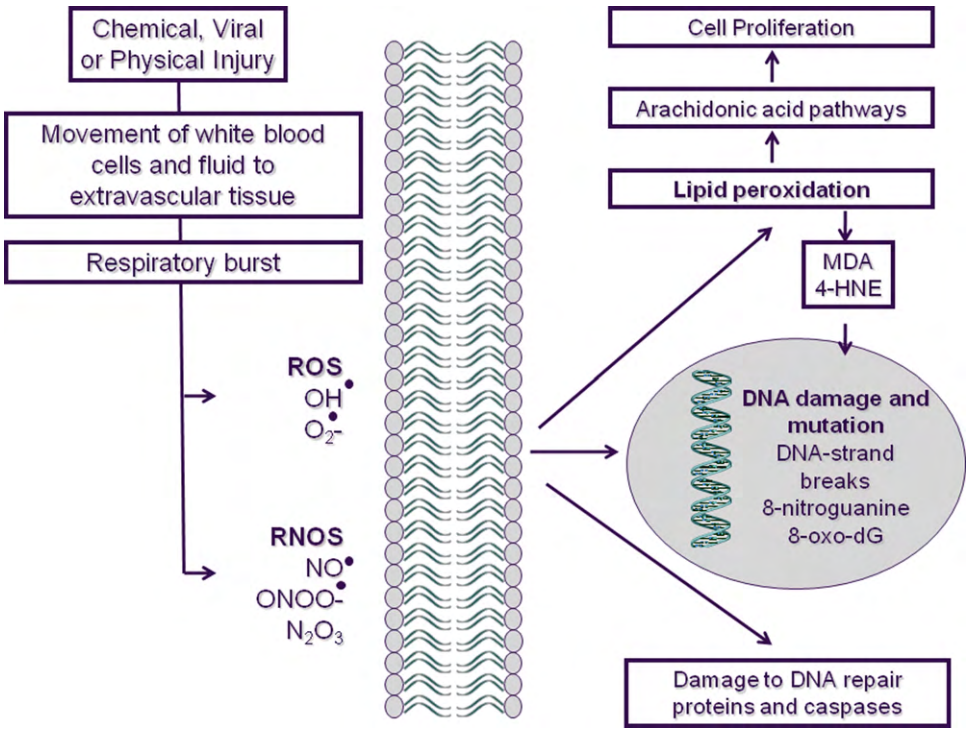

Fig. 1. Inflammation and the role of ROS and RNS in tissue damage. Inflammation begins with a reaction to an irritant or infection that is characterized by movement of fluid and white blood cells into extravascular tissue. This is followed by tissue repair and regeneration and involves cell proliferation. Associated with these processes are the release of free radicals, such as reactive oxide species (ROS) and reactive nitrogen species (RNS). This can activate a process called lipid peroxidation and the arachidonic-acid cascade, with the production of cell proliferation-stimulating eicosanoids. Also, DNA-damaging agents, such as malondialdehyde (MDA) and 4-hydroxynonenol (4-HNE), are by-products of the arachidonic-acid cascade. The free radicals can also damage DNA and modify the structure and function of cancer-related proteins. OH•, hydroxyl radical; O_2^-, superoxide; NO, nitric oxide; $ONOO^-$, peroxynitrite; N_2O_3, nitrous anhydride.

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