Reactive Oxygen Species

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Reactive oxygen species (ROS) can directly activate HSCs or induce inflammation or programmed cell death, especially pyroptosis, in hepatocytes, which in turn activates HSCs and fibroblasts to produce ECM proteins.

Keywords: NRF2-KEAP1 ; inflammation ; NF-κB ; NLRP3 inflammasome ; extracellular matrix ; hepatic stellate cells ; ROS ; liver damage.

1. Introduction

Free radicals are atoms or molecules that possess unpaired electrons and are frequently unstable and highly reactive [1]. Two types of free radicals are present in biological systems: reactive oxygen species (ROS), which are radicals derived from oxygen, and reactive nitrogen species (RNS), which are derived from nitrogen. ROS can be divided into non-radicals, including hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$), and radicals, such as superoxide anion ($O_2^{\bullet -}$), hydroxyl radical ($^{\bullet}OH$), alkoxyl radical ($RO^{\bullet}$), and peroxyl radical ($ROO^{\bullet}$). Injury to cells can be mediated by free-radical-induced lipid peroxidation, DNA strand breaks, and oxidized proteins[2][3]. ROS and RNS exhibit important physiological effects at certain levels; therefore, living organisms can regulate ROS and RNS levels via antioxidants consumed in the diet, endogenous antioxidant production, and systems specifically designed to inactivate excess radicals, to maintain a balance between antioxidants and ROS/RNS, allowing for the normal function of the organism. An imbalance favoring the accumulation of ROS/RNS is defined as oxidative/nitrosative stress. Oxidative/nitrosative stress has been demonstrated to be involved in several pathologies, including hepatic diseases[4].

2. Sources of ROS

Oxidative stress is a causative factor in various types of pathologies, such as cancer, diabetes, neurological disease, and liver illness[5][6][7]. However, ROS play dual roles because, at low concentrations, ROS participate in the maturation processes of cellular structures, act as second messengers in signaling pathways, and attack pathogens[7][8]. ROS can be produced in the mitochondria, where molecular oxygen (O_2) is reduced to $O_2^{\bullet -}$ by reduced nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2) in a single e^- reduction process by complexes I and III. In addition, monoamine oxidase, α-ketoglutarate dehydrogenase, and glycerol phosphatase dehydrogenase, which are present in mitochondria, further contribute to the generation of $O_2^{\bullet -}$ [7][9][10]. However, quantitatively, the endoplasmic reticulum and peroxisomes have a greater capacity to produce ROS than mitochondria in the liver[9]. Indeed, peroxisomes, microsomes, and the endoplasmic reticulum are important for the production of various kinds of ROS[9]. $O_2^{\bullet -}$ can react with other molecules, to produce new, highly reactive molecules such as $^{\bullet}OH$, perhydroxyl radical ($HO_2^{\bullet}$), H_2O_2, and $^1O_2$ [11]. Moreover, the endoplasmic reticulum can produce ROS inside the cell [12]. In addition to ROS generation in organelles, several enzymes, including cytochrome P450 (CYP) 2E1, NADPH oxidase (NOX), cyclooxygenases, xanthine oxidase, and lipoxygenases in the plasma membrane and cytosol, produce ROS[13][14]. Interestingly, NOX directly generates H_2O_2 or $O_2^{\bullet -}$ in Kupffer cells, hepatocytes, and HSCs[15][16].

In particular, CYP enzymes play an important role in the generation of ROS in the liver [17]. These enzymes are very important in phase I metabolism of approximately three-quarters of xenobiotic metabolism reactions in humans[18]. The metabolism of drugs and other xenobiotics by CYP enzymes in the liver generates ROS and bioactivated intermediates, thus leading to oxidative stress and contributing to hepatic diseases, including alcoholic liver disease and drug-induced liver injury and cancer [12]. For a detailed review of the generation of ROS by CYP P540 enzymes, the reader is referred to References[17][19][20].

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