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Forum Editorial

Redox Considerations in Hepatic Injury and Inflammation

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THE IMPORTANCE OF REACTIVE OXYGEN SPECIES is well recognized in a number of liver diseases, including inflammatory conditions. However, the molecular mechanisms have remained controversial for more than two decades. During the 1980s, reactive oxygen formation was exclusively associated with lipid peroxidation, which was thought to cause cell necrosis. However, more detailed mechanistic studies questioned this concept (5). First, the detoxification capacity for reactive oxygen species in hepatocytes and sinusoidal lining cells is extremely high, even under pathophysiological conditions (5, 11). Second, the amount of reactive oxygen generated *in vivo* is rarely able to cause extensive lipid peroxidation (6). Third, limited lipid peroxidation is not able to cause cell injury directly (6). Because of these inconsistencies, alternative concepts emerged during the last decade. There is increasing support for the hypothesis that reactive oxygen may affect a number of signal transduction pathways, which lead to apoptotic and/or oncotic necrosis in liver cells (7). Furthermore, modulation of redox-sensitive transcription factors by oxidant stress can promote the transcriptional upregulation of pro- and antiinflammatory mediators, enzymes, and stress proteins in all liver cell types (7). Through the formation of these proteins, reactive oxygen can indirectly affect cell injury by promoting inflammation and strengthening defense mechanisms.

The objective of this forum issue on *Redox Considerations in Hepatic Injury and Inflammation* is to provide an overview on current research activities with emphasis on reactive oxygen-modulated signaling mechanisms in apoptotic and oncotic necrosis in hepatocytes and the redox regulation of transcription factors that regulate inflammatory mediator expression and injury. Despite the significant progress in this area, there are still unanswered questions and controversies. In particular, the potency of oxidant stress in directly inducing apoptosis needs to be demonstrated *in vivo*. Furthermore, the molecular targets of reactive oxygen in manipulating signaling mechanisms of cell death or gene transcription need to be elucidated in much more detail.

This forum issue contains a series of review and original articles from leading experts in the field. H. Tsukamoto provides an overview of the redox regulation of nuclear factor-κB activation and proinflammatory cytokine gene expression in Kupffer cells. These events are of critical importance for acute and chronic inflammatory conditions in the liver (12). M. Bauer and I. Bauer discuss the role of reactive oxygen in heme oxygenase-1 gene expression and its pathophysiological function (2). Induction of this enzyme in response to oxidant stress can have profound protective effects. M.J. Czaja summarizes the current knowledge on the mechanisms of oxidant stress-induced apoptotic cell death in hepatocytes (4). This area of investigation is in its early stages and, therefore, many questions are still unanswered. J.J. Lemasters *et al.* review the literature on the role of reactive oxygen in inducing opening of the membrane permeability transition pore in liver mitochondria. Membrane permeability transition pore opening is a central feature of both apoptotic and oncotic cell death pathways (9).

The original research article by B.E. Jones *et al.* describes the paradoxical phenomenon that overexpression of cytochrome P450 2E1, which normally leads to increased intracellular reactive oxygen formation, confers hepatocyte resistance to oxidant stress (8). The cell type-specific and zonal pattern of activation of the redox-sensitive transcription factors activator protein-1 and nuclear factor-κB in hemorrhagic shock was investigated by M. Paxian *et al.* (10). A.P. Bautista reports on the effects of alcohol bingeing and withdrawal on Kupffer cell-induced oxidant stress and chemokine formation during hepatic ischemia–reperfusion (3). M.L. Bajt *et al.* discuss the role of intracellular reactive oxygen in the modulation of tumor necrosis factor or Fas receptor-mediated hepatocellular apoptosis and the potential role of glutathione peroxidase in the process (1).

This forum provides a current summary of research in the area of redox signaling in liver cells. I hope that this stimulates further mechanistic investigations, which can enhance our understanding of the role of reactive oxygen species in liver

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diseases. Ultimately, this will lead to the discovery of more specific and effective therapeutic intervention strategies.

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