OPEN ACCESS Freely available online

ISSN: 2167-0889
Journal of Liver

Commentary

Molecular Pathways Involved in Hepatic Oxidative Injury

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DESCRIPTION

Non-alcoholic fatty liver disease has emerged as one of the most widespread chronic liver conditions worldwide, affecting individuals across a wide range of ages and lifestyles. It is characterized by the excessive accumulation of lipids within hepatocytes in the absence of significant alcohol consumption. This accumulation begins as simple steatosis and may progress toward steatohepatitis, fibrosis, cirrhosis, and even hepatocellular carcinoma. At the center of this progression lies oxidative stress, a biochemical imbalance between the production of reactive oxygen species and the capacity of antioxidant systems to neutralize them. As lipid droplets build up inside liver cells, the burden on mitochondrial and peroxisomal metabolism increases, resulting in excessive generation of reactive oxygen species. These reactive molecules interact with cellular macromolecules such as lipids, proteins and DNA, leading to structural and functional disturbances that define disease advancement.

Beyond mitochondrial impairment, oxidative stress also arises from endoplasmic reticulum stress. The endoplasmic reticulum has the responsibility of protein folding and lipid synthesis. When lipid accumulation alters the structure of its membrane and increases unfolded protein load, the unfolded protein response is activated. While initially this response aims to restore normal function, prolonged activation contributes to reactive oxygen species generation. Calcium release from the endoplasmic reticulum into the cytosol further disturbs mitochondrial function, creating a cycle of oxidative damage and metabolic shutdown.

Kupffer cells, the resident macrophages of the liver, amplify oxidative damage by releasing pro-inflammatory cytokines and producing reactive oxygen species. As hepatocytes become injured, they release damage-associated molecular patterns that activate these immune cells. Activated Kupffer cells stimulate the recruitment of circulating immune cells that further increase inflammation through additional cytokine release. This inflammatory environment encourages fibrogenesis through the activation of hepatic stellate cells, which begin producing excess collagen and extracellular matrix components. As fibrosis advances, oxygen diffusion in liver tissue becomes limited, worsening hypoxic stress and promoting more reactive oxygen species formation.

The management of oxidative stress in non-alcoholic fatty liver disease requires a multifaceted therapeutic approach that addresses both the cause and the biochemical consequences of lipid accumulation. Lifestyle interventions remain a mainstay in reducing oxidative load. Weight reduction through caloric moderation decreases hepatic fat content, while regular physical activity improves insulin sensitivity and reduces free fatty acid inflow into the liver. Exercise upregulates endogenous antioxidant enzymes and enhances mitochondrial biogenesis, which improves metabolic resilience within hepatocytes. The reduction of processed sugar and saturated fat intake decreases de novo lipogenesis, while diets rich in polyphenols and unsaturated fatty acids support antioxidant defenses.

Nutritional compounds have gained attention for their ability to reduce oxidative stress in the liver. Vitamin E, a lipid-soluble antioxidant, has been studied for its ability to interrupt lipid peroxidation chain reactions in cellular membranes. Supplementation has shown beneficial effects on liver enzyme levels and histological features in selected patients. Polyphenols such as resveratrol, quercetin and curcumin exhibit antioxidant and anti-inflammatory properties. These compounds scavenge reactive oxygen species and regulate signaling pathways related to inflammation and apoptosis. Omega-3 fatty acids also help modulate lipid metabolism and reduce oxidative damage by improving membrane composition and reducing inflammatory mediators.

Gut microbiota also influences oxidative stress in the liver. Dysbiosis increases intestinal permeability, allowing endotoxins to enter the portal circulation and activate inflammatory responses in the liver. These responses increase oxidative stress through immune activation and cytokine production. Probiotics, prebiotics and dietary fiber may support a healthier microbial population, reducing systemic inflammation and decreasing oxidative load on hepatocytes. Short-chain fatty acids produced

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Received: 29-Aug-2025, Manuscript No. JLR-25-30450; **Editor assigned:** 01-Sep-2025, PreQC No. JLR-25-30450 (PQ); **Reviewed:** 15-Sep-2025, QC No. JLR-25-30450; **Revised:** 22-Sep-2025, Manuscript No. JLR-25-30450 (R); **Published:** 29-Sep-2025, DOI: 10.35248/2167-0889.25.14.264

Citation: Magin F (2025). Molecular Pathways Involved in Hepatic Oxidative Injury. J Liver. 14:264.

by beneficial bacteria support anti-inflammatory responses and enhance cellular energy metabolism.

While the underlying mechanisms are complex, the common thread in disease progression is the persistent imbalance between oxidant production and antioxidant defenses. Addressing this imbalance through metabolic correction, nutritional modulation, pharmacological therapy and microbiota regulation provides a comprehensive strategy for managing non-alcoholic fatty liver disease. Continued exploration of cellular redox mechanisms will lead to improved preventive and therapeutic approaches that minimize liver injury and reduce the burden of chronic liver disease in global populations.

Oxidative stress remains a central driving force in the development and progression of non-alcoholic fatty liver disease. Its impact extends from molecular alterations to whole-organ dysfunction. By targeting the sources of reactive oxygen species, strengthening intrinsic antioxidant systems and reversing contributing metabolic disturbances, it is possible to slow disease advancement and support hepatic recovery. A comprehensive and integrated strategy remains essential for effective intervention and long-term liver health.