

Review Article

Hepatocarcinogenesis: From Chronic Liver Injury to Hepatocellular Malignancy

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Abstract

Hepatocarcinogenesis is a complex, multistep biological process through which chronic liver injury progresses to malignant transformation, most commonly resulting in hepatocellular carcinoma (HCC). Unlike many cancers that arise from a single dominant genetic event, liver carcinogenesis involves the interaction of chronic inflammation, hepatocyte death and regeneration, genomic instability, epigenetic alterations, metabolic disturbances, oxidative stress, and changes in the tumor microenvironment. Persistent liver injury caused by chronic viral hepatitis, alcohol-associated liver disease, metabolic dysfunction-associated steatotic liver disease, and other chronic hepatic disorders promotes fibrosis and cirrhosis, creating a microenvironment favorable for malignant transformation. During this process, hepatocytes accumulate genetic and epigenetic abnormalities affecting pathways responsible for cell proliferation, differentiation, apoptosis, DNA repair, and immune regulation. Important molecular pathways implicated in hepatocarcinogenesis include Wnt/ β -catenin, RAS/MAPK, PI3K/AKT/mTOR, TGF- β , JAK/STAT, and Hippo/YAP signaling. Epigenetic dysregulation, altered metabolism, immune-cell interactions, angiogenesis, and cancer stem-cell characteristics further contribute to tumor initiation and progression. Understanding these mechanisms has improved the identification of individuals at high risk and has provided a foundation for the development of targeted therapies and immunotherapeutic strategies. This review summarizes the major cellular, molecular, and environmental mechanisms involved in hepatocarcinogenesis and highlights their implications for prevention, early detection, and treatment of HCC.

Introduction

Hepatocellular carcinoma is the most common primary malignant tumor of the liver and represents a major global health challenge. Its development is strongly associated with chronic liver disease and prolonged hepatic injury. Hepatocarcinogenesis refers to the biological process by which normal hepatocytes or hepatic progenitor cells acquire malignant characteristics through a series of molecular and cellular changes.

The liver has a remarkable capacity for regeneration. Following injury, surviving hepatocytes proliferate to restore hepatic tissue. However, when injury becomes persistent, repeated cycles of hepatocyte death and regeneration can promote genomic damage, chronic inflammation, fibrosis, and ultimately malignant transformation.

Chronic Viral Hepatitis

Chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) is an important cause of HCC worldwide. HBV can contribute to carcinogenesis through both indirect and direct mechanisms. Persistent viral infection produces chronic inflammation and hepatocyte destruction. In addition, HBV DNA can integrate into the host genome, potentially causing genomic instability and altering the expression of cellular genes.

Alcohol-Associated Liver Disease

Long-term excessive alcohol consumption can cause steatosis, alcoholic hepatitis, fibrosis, and cirrhosis. Alcohol metabolism generates toxic metabolites and

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reactive oxygen species that can damage cellular proteins, lipids, and DNA

Persistent alcohol-induced inflammation and oxidative stress create conditions that favor genomic alterations and malignant transformation

Metabolic Dysfunction-Associated Steatotic Liver Disease

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become an increasingly important risk factor for HCC. Obesity, insulin resistance, type 2 diabetes, dyslipidemia, and metabolic abnormalities can cause hepatic steatosis and progressive liver injury. Lipotoxicity, oxidative stress, mitochondrial dysfunction, chronic inflammation, and altered insulin signaling contribute to hepatocarcinogenesis. Importantly, HCC can occasionally develop in patients with metabolic liver disease even without advanced cirrhosis.

Chronic Inflammation and Hepatocyte Injury

Chronic inflammation is a central component of hepatocarcinogenesis

Persistent liver injury results in the release of inflammatory mediators, cytokines, and growth factors. Kupffer cells, hepatic stellate cells, infiltrating macrophages, lymphocytes, and other immune cells participate in this inflammatory environment.

Inflammatory signaling can promote:

- Hepatocyte proliferation
- DNA damage
- Oxidative stress
- Fibrogenesis
- Angiogenesis
- Resistance to apoptosis
- Immune evasion

Repeated hepatocyte destruction followed by regeneration increases the probability that cells carrying DNA damage will survive and proliferate.

Thus, chronic inflammation can create a pro-tumorigenic environment in which genetically altered hepatocytes gain a selective growth advantage.

Role of the Tumor Microenvironment

The liver tumor microenvironment consists of malignant cells together with immune cells, fibroblasts, endothelial cells, extracellular matrix, and signaling molecules.

Hepatic stellate cells are particularly important because their activation contributes to fibrosis and extracellular-matrix remodeling

Tumor-associated macrophages and other immune cells can produce cytokines and growth factors that support tumor growth. At the same time, malignant cells can develop mechanisms that suppress effective antitumor immunity.

Conclusion

Hepatocarcinogenesis is a dynamic and multifactorial process resulting from the interaction of chronic liver injury, inflammation, oxidative stress, genetic and epigenetic alterations, metabolic dysfunction, immune escape, and tumor-microenvironment remodeling. Chronic viral hepatitis, alcohol-associated liver disease, metabolic dysfunction-associated steatotic liver disease, and environmental carcinogens can initiate or accelerate this process. The transformation from an injured hepatocyte to an invasive malignant cell occurs through the progressive accumulation of molecular abnormalities that alter cellular proliferation, survival, differentiation, and genomic stability

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