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Translational Insights into Molecular Mechanisms of Chemical Hepatocarcinogenesis for Improved Human Risk Assessment

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Abstract

Background: Hepatocellular carcinoma (HCC) is a prevalent liver cancer with major risk factors being hepatitis viral infections, alcohol, non-alcoholic fatty liver disease, and aflatoxin exposure. Both genotoxic and non-genotoxic agents can induce HCC through mechanisms involving DNA damage, oxidative stress, chronic inflammation, and disrupted signaling pathways like MAPK/ERK, PI3K/AKT, WNT/β-catenin and PPARα. While rodent assays are utilized to detect potential chemical hepatocarcinogens, species differences in pathways like PPARα and CAR/PXR activation impact human risk assessment.

Purpose: This analysis provides an updated, critical examination of species concordance in mechanisms of hepatic carcinogenesis to inform human safety assessment of rodent liver tumor findings.

Main Body: Rodent assays including 2-year bioassays, transgenic models, and short-term studies detect liver tumors through lifetime exposure or early biomarkers. However, rodent-specific PPARα and CAR/PXR activation, along with human risk factors like hepatitis, highlight key interspecies differences. Determining mode of action relevance requires evaluating mechanistic validity and pivotal key events leading to tumors across species. Non-genotoxic compounds eliciting rodent liver tumors can activate PPARα, CAR/PXR, and other pathways triggering increased cell replication; but downstream signaling may differ in human liver. Understanding applicability of these mechanisms in humans as well as incorporating human risk factors into experimental models is critical for accurate risk assessment.

Conclusion: In summary, elucidating conserved versus divergent molecular mechanisms of hepatic carcinogenesis between rodents and humans is essential for appropriately interpreting rodent findings and safeguarding human health through science-based risk assessment frameworks and regulatory decision-making processes around potential chemical hazards.

Keywords: Hepatocellular Carcinoma; Chemical Carcinogenesis; Risk Assessment; Rodent Bioassays; Comparative Mechanistic Analysis

Abbreviations: HCC: Hepatocellular Carcinoma; BCLC: Barcelona Clinic Liver Cancer; MAPK: Mitogen-Activated Protein Kinase; ERK: Extracellular Signal-Regulated Kinase; PI3K: Phosphatidylinositol 3-Kinase; AKT: Protein Kinase B; PPARα: Peroxisome Proliferator Activated Receptor Alpha; CAR: Constitutive Androstane Receptor; PXR: Pregnane X Receptor; ROS: Reactive Oxygen Species; NRF2: Nuclear Factor Erythroid 2-Related Factor 2; AFP: α-Fetoprotein; GST-P: Glutathione S-Transferase Placental Form; CYP - Cytochrome P450; MOA - Mode of Action; ICH - International Conference on Harmonisation.

Introduction

Hepatocellular carcinoma (HCC) is the most common type of liver cancer. Major risk factors include chronic hepatitis B/C viral infections, alcohol-related cirrhosis, non-alcoholic fatty liver disease associated with obesity/diabetes, and aflatoxin exposure. The pathogenesis involves liver injury, inflammation, fibrosis, and ultimately malignant transformation [1-5]. For staging HCC, the Barcelona Clinic Liver Cancer (BCLC) system is commonly used. It incorporates tumor size/spread, liver function, and performance status to guide treatment options and predict prognosis. Early stage tumors that are small and localized have the best prognosis. More advanced stage HCC with vascular invasion or metastases has significantly worse outcomes [6]. Treatment options are expanding for HCC. For early tumors, resection, ablation, or transplant may cure disease. For advanced HCC, sorafenib was the first approved targeted therapy inhibiting tumor angiogenesis. More recent approaches include immunotherapy with checkpoint inhibitors, and other small molecule inhibitors targeting pathways like MAPK or PI3K/AKT. However, advanced HCC still has poor prognosis and high recurrence after surgery [7].

HCC is warranting extensive investigation into mechanisms of chemical-induced liver carcinogenesis and translation from preclinical rodent models to human safety assessment. Both genotoxic agents directly damaging DNA and non-genotoxic compounds disrupting cellular signaling without DNA reactivity can promote hepatocarcinogenesis through increased cell proliferation, decreased apoptosis, oxidative stress, and chronic inflammation [8]. While 2-year rodent bioassays remain the regulatory standard for identifying potential hepatocarcinogens, alternative transgenic and short-term rodent models provide supporting mechanistic evidence. Emerging omics profiling techniques are also enabling more rapid detection of carcinogenic hazard based on biomarker screening. However, the relevance of rodent liver tumor findings to human risk assessment remains a key consideration, requiring detailed mode of action analysis to determine species concordance in key cellular events promoting transformation, such as PPARα or CAR/PXR activation in rodents [9]. Understanding interspecies variability and human-specific risk factors like hepatitis viral infections is critical. As HCC has a poor prognosis at advanced stages, expanded use of molecular classification systems for tumor staging along with development of emerging immunotherapies and molecularly targeted treatments will help combat this aggressive malignancy. Overall, progress in preclinical detection of hepatocarcinogens along with advances in HCC prevention and therapy hinges on elucidating conserved versus species-specific mechanisms in hepatic carcinogenesis [10].

While extensive reviews exist on chemical-induced rodent liver tumors, few have critically examined interspecies concordance in mechanisms of hepatic carcinogenesis to inform human safety assessment. Therefore, we conducted an updated analysis on genotoxic versus non-genotoxic mechanisms in hepatocellular transformation, evaluating mode of action validity across rodent models and human disease through a translational science lens. This focuses specifically on areas of convergence versus divergence across species that impact interpretation of preclinical hepatocarcinogenicity data for human risk evaluation.

Mechanisms of Chemically-Induced Hepatocarcinogenesis

Chemical agents can induce liver tumors in rodents through both genotoxic and non-genotoxic mechanisms. Genotoxic carcinogens cause direct DNA damage that results in mutations if not properly repaired. As depicted in Figure 1, these mutations can activate oncogenes or inactivate tumor suppressor genes, leading to uncontrolled cell proliferation. Examples of genotoxic hepatacarcinogens include aflatoxin B1, which forms DNA adducts, and vinyl chloride, which causes etheno-DNA adducts [11-12].

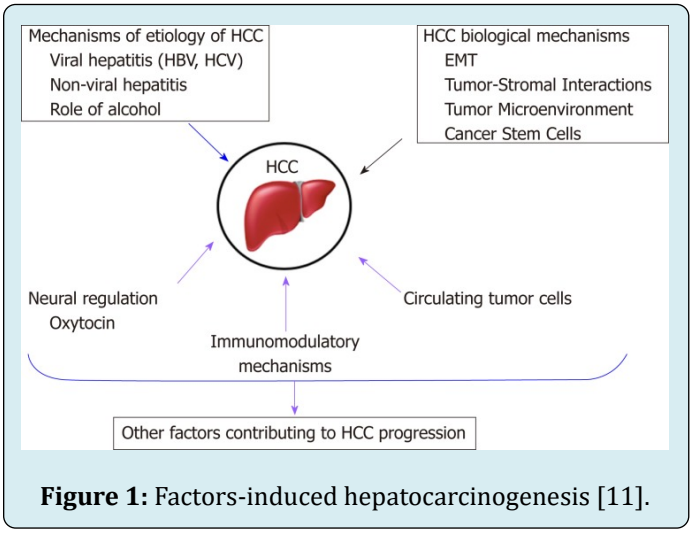

Figure 1: Factors-induced hepatocarcinogenesis [11].

In contrast, non-genotoxic carcinogens induce liver tumors through indirect mechanisms without directly damaging DNA. These include increased cellular proliferation, decreased apoptosis, and induction of epigenetic changes. Some key cellular pathways disrupted by non-genotoxic carcinogens are MAPK/ERK, PI3K/AKT, WNT/β-catenin, and PPARα. For instance, PPARα agonists like WY-14,643 induce liver tumors in rodents by activating PPARα target genes involved in cell proliferation [13-15].

Rodent Models in Safety Assessment of Potential Hepatocarcinogens

The traditional rodent bioassay for identifying chemical carcinogens involves lifetime Exposure of mice and rats to assess increased tumor incidence. These 2-year assays expose animals to maximum tolerated doses of the test agent starting from 6-8 weeks of age. Tumor formation is assessed over the lifespan of the rodents, typically until they reach 104 weeks of age. This long duration and use of adult rodents makes the traditional assays resource-intensive [16-18]. To improve efficiency, alternative rodent models have been developed using transgenic, neonatal, and short-term exposure protocols. Transgenic mouse models with genetic modifications such as Ras activation or p53 knockout allow carcinogenic assessment within 26-52 weeks. Initiating carcinogens can also be detected by exposing rodents during the neonatal period when they are most susceptible. Shorter 6-13 week assays in adult rodents utilize biomarkers, cell proliferation, or preneoplastic lesions to identify potential carcinogenic activity [19-21].

Model	Species	Duration	Key Features	Advantages	Limitations
Traditional 2-year bioassay	Rat, mouse	2 years	Lifetime exposure beginning at adulthood; maximum tolerated dose	Gold standard; detects tumor initiation/promotion	Lengthy, resource intensive
Transgenic	Mouse	6-12 months	Genetic modifications (e.g. p53-/-, ras activation)	Reduced duration; mechanistic insights	Limited genetic contexts
Neonatal	Rat, mouse	Days to weeks	Exposure begins at birth during high susceptibility window	Sensitive detection of tumor initiators	Narrow exposure window
Short-term	Rat, mouse	6-13 weeks	Biomarkers (AFP, GST-P); cell proliferation; preneoplastic lesions	Rapid screening; reduced animal use	Limited to certain pathways/ mechanisms

Table 1: Comparative overview of rodent models utilized in safety assessment of chemical-induced hepatocarcinogenesis.

Early Detection of Potential Hepatocarcinogens

Several approaches have been developed to detect potential hepatocarcinogenic activity earlier than traditional 2-year rodent bioassays. These include biomarker screening, genomic analysis, and omics profiling. Two established biomarkers used for early detection are α-fetoprotein (AFP) and glutathione S-transferase placental form (GST-P). AFP is a fetal protein normally silenced in adult livers that gets reactivated in hepatocellular carcinoma. GST-P is an isozyme not expressed in normal liver but present in preneoplastic lesions. Elevated AFP and GST-P levels can indicate carcinogenic potential within weeks or months [22-28]. Genomic approaches like toxicogenomics measure gene expression changes associated with carcinogens. Computational tools can analyze this data to create gene expression signatures predictive of carcinogenicity. This allows for screening of hepatocarcinogens using short-term in vivo or in vitro assays [29,30]. Emerging omics profiling techniques like glycomics and proteomics provide additional biomarker signatures. Glycomic analysis of serum glycoproteins can detect early liver tumor biomarkers. Proteomic analysis of liver tissue or plasma can also reveal protein patterns indicative of carcinogenic exposure [31-36].

Species Differences in Response to Hepatocarcinogens

Rodent models are important for identifying potential carcinogens, but there are key species differences in response that impact human risk assessment. One example is PPARα agonists, which cause liver tumors in rats and mice but not humans. This is because rodent PPARα activates cell proliferation genes not affected by human PPARα [37-38]. Aflatoxin B1 also shows species differences, being metabolized to a DNA-reactive epoxide by CYP enzymes in humans but not rats. Chronic hepatitis B and C viral infection is another major risk factor for hepatocellular carcinoma in humans with no rodent equivalent. The viruses themselves

are not direct carcinogens but promote cancer by causing chronic inflammation and fibrosis [39-44]. To help bridge these species gaps, humanized animal models are being developed. An example is the PXB mouse model containing human PPARα, CYP enzymes, and a functional hepatitis B virus pathway. The PXB mice better predict human-specific PPARα and aflatoxin responses. Humanized models help incorporate key aspects of human physiology and better extrapolate rodent data to potential human risk [45-46] (Table 2).

Factor	Rodent Response	Human Response	Implications for Risk Assessment
PPARα activation	Tumor promoter through cell proliferation genes	No activation of rodent tumor genes	Not relevant to human; MOA not operative
Aflatoxin B1	Bioactivated to less carcinogenic metabolites	CYP conversion to DNA-reactive epoxide	Human more sensitive than rodents
Hepatitis virus	No equivalent infection models	Major risk factor for HCC	Significant species difference in tumor susceptibility

Table 2: Comparative analysis of key rodent-human differences impacting hepatocarcinogen risk assessment.

Non-Genotoxic Hepatocarcinogenesis

Some compounds induce liver tumors in rodents through non-genotoxic mechanisms not involving direct DNA damage. One example is activation of the nuclear receptor PPARα. PPARα regulates cell proliferation and inflammation genes in rodent liver. Chemical activation of PPARα results in increased cell replication that can progress to liver tumors. However, human PPARα does not regulate the same target genes, so this mode of action is not relevant for human risk. Another non-genotoxic mechanism involves activation of constitutive androstane receptor (CAR) and pregnane X receptor (PXR). Phenobarbital activates CAR/PXR leading to liver tumors in rodents through increased cell proliferation and decreased apoptosis. While CAR/PXR activation is an early key event, the downstream key events leading to tumors may differ between rodents and humans [47]. For non-genotoxic compounds like PPARα and CAR/PXR activators, the relevance of rodent liver tumors to human risk is determined through mode of action analysis. This involves determining the key events in tumor formation and if they occur in humans. If the mode of action is plausible in humans, the rodent findings indicate potential human carcinogenicity [48].

Regulatory Perspectives Regarding Hepatocarcinogens

The ICH S1 guidance provides recommendations for detecting potential carcinogenic activity in pharmaceuticals. It advises using two rodent species, typically rat and mouse, for lifetime 2-year carcinogenicity studies. This allows comprehensive assessment of tumor findings and potential risk to humans [49-52]. A key regulatory consideration is determining if a carcinogen acts through a genotoxic or non-genotoxic mode of action. Genotoxicity studies like Ames tests, chromosome aberration, and micronucleus assays are used to assess if DNA damage is the initiating key event. This informs whether a threshold or linear non-threshold model should be used for human cancer risk assessment [53-55].

Future Directions

Further research is critically needed to elucidate conserved versus divergent molecular mechanisms of hepatic carcinogenesis between rodents and humans. A key priority should be investigating species-specific differences in pivotal signaling pathways like MAPK/ERK, WNT/β-catenin, and nuclear receptors that modulate downstream events affecting cell proliferation, apoptosis, inflammation, and other cancer hallmarks. Incorporating complex human risk factors into experimental rodent models is also essential, particularly development of humanized mouse models containing both human drug metabolizing enzymes and functional hepatitis virus pathways to better model susceptibility [56]. Additionally, emerging omics profiling approaches including transcriptomics, proteomics, and metabolomics provide tremendous promise for elucidating biomarker signatures that are predictive of liver tumor development, progression, and human translation. Applying machine learning to develop computational tools from these multidimensional datasets can further aid mechanistic analysis and human risk assessment [57]. Further investigation into the role of the tumor microenvironment in modulating hepatocarcinogenesis and therapeutic response is also imperative. Examining bidirectional signaling between malignant hepatic cells and non-malignant stromal cell types such as fibroblasts, immune cells, and vascular endothelium may unveil new targets. Finally, development of additional alternative rodent models including patient-derived xenografts and 3D organoid culture systems can complement traditional 2-year bioassays and assess improved recapitulation of human physiology [58].

Conclusions

Both genotoxic and non-genotoxic mechanisms can promote hepatocarcinogenesis in rodent models through pathways modulating DNA damage, oxidative stress, chronic inflammation, and disrupted signaling cascades affecting cell proliferation and death. However, critical species differences exist, particularly in key events such as PPARα and CAR/PXR activation that may not be operative or lead to the same downstream signaling in human liver. Therefore, careful mode of action analysis is imperative for determining rodent liver tumor relevance and human risk, requiring evaluation of the pivotal key events from tumor initiation to progression and their conservation across species. Elucidating areas of convergence versus divergence through emerging omics techniques and humanized animal models is essential to inform science-based public health decisions around potential chemical hazards.

Recommendations

- Investigating species-specific differences in pivotal signaling pathways like MAPK/ERK, WNT/β-catenin, and nuclear receptors that modulate downstream cellular events affecting malignant transformation
- Incorporating complex human risk factors like hepatitis B/C infection into experimental rodent models through humanized mice or other systems
- Applying emerging omics techniques and machine learning to uncover biomarker signatures predictive of carcinogenic potential and human translation
- Examining the role of the hepatic tumor microenvironment and interactions between malignant and non-malignant cells
- Expanding the utility of alternative rodent models such as patient-derived xenografts and 3D organoid culture to complement traditional 2-year bioassays
- Focusing greater efforts on epidemiology and surveillance of human exposures to suspected hepatocarcinogens to enable more accurate risk assessment
- Developing defined frameworks and recommendations to standardize mode of action analysis and determination of rodent liver tumor human relevance

Ethics Approval and Consent to Participate

Not Applicable

Consent for Publication

Not Applicable

Availability of Data and Materials

All data are available and sharing is available as well as publication.

Competing Interests

The authors hereby that they have no competing interests.

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Authors' Contributions

The authors completed the study protocol and were the primary organizers of data collection and the manuscript's draft and revision process. Tamer A. Addissouky wrote the article and ensured its accuracy. All authors contributed to the discussion, assisted in designing the study and protocol and engaged in critical discussions of the draft manuscript. Lastly, the authors reviewed and confirmed the final version of the manuscript.

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