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TERT Promoter Mutation: A Molecular Link Between HCV and Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) ranks sixth among cancers globally and is the third leading cause of cancer-related mortality. Hepatitis C virus (HCV) infection accounts for approximately 25–30% of HCC cases worldwide. Although direct-acting antiviral agents (DAAs) now achieve viral eradication in over 95% of patients, HCC risk persists even after viral clearance, making it essential to understand the molecular mechanisms linking HCV to tumor development. Among the most significant molecular alterations in HCC are TERT promoter mutations, occurring in 54–60% of all cases. The two predominant mutations, C228T and C250T, create novel ETS transcription factor binding sites including GABPα driving persistent TERT activation and conferring replicative immortality upon cancer cells. HCV promotes these mutations through interconnected mechanisms: virus-induced oxidative stress damages the TERT promoter region; HCV proteins NS3/4A and NS5A enhance telomerase stability; the core protein remodels chromatin architecture; and chronic inflammation elevates IL-6 and TNF-α, activating STAT3 and NF-κB pathways that further upregulate TERT expression. Clinically, TERT promoter mutations correlate with tumor aggressiveness, elevated AFP levels, microvascular invasion, and poor prognosis. Importantly, these mutations are detectable in patient plasma, offering a promising avenue for non-invasive HCC diagnosis.

Introduction

Liver cancer is one of the most significant public health challenges globally. Hepatocellular carcinoma (HCC) accounts for approximately 75–85% of all primary hepatic malignancies. Based on GLOBOCAN 2022 data, liver cancer ranks among the sixth most common cancers and the third leading cause of cancer-related death globally, with an estimated 905,677 new cases and 830,180 deaths in 2022 (Bray et al., 2024). The five-year overall survival rate for all-stage HCC remains below 20%, highlighting an urgent need for earlier detection and more effective treatments (Llovet et al., 2021).

The molecular profile of HCC is characterized by remarkable complexity and heterogeneity arising from multiple etiologic forces including viral hepatitis (HBV and HCV), aflatoxin exposure, alcoholic liver disease, and metabolic dysfunction-associated steatotic liver disease (MASLD) each leaving a distinct molecular imprint on a background of chronic hepatic inflammation and regenerative stress (Forner et al., 2022). Among these, HCV infection is particularly significant. An estimated 58 million people are chronically infected with HCV worldwide, many of whom will develop progressive hepatic fibrosis, cirrhosis, and ultimately HCC over two to three decades (WHO, 2024). A critical scientific challenge is that HCC risk persists even after sustained virologic response (SVR) following DAA therapy a paradox that underscores the need to understand the molecular changes embedded in hepatocytes during chronic infection (Ioannou et al., 2019).

Among the broader somatic mutational landscape of HCC, TERT promoter mutations are the most frequently identified somatic genetic changes across multiple large-scale genomic studies. The predominant mutations, C228T and C250T, create new ETS family transcription factor binding sites, resulting in constitutive TERT

overexpression and replicative immortality in transformed hepatocytes (Bell et al., 2020; Heidenreich & Kumar, 2017). These mutations are significantly more frequent in HCV-associated HCC than in tumors of other etiological backgrounds, indicating a specific mechanistic relationship between HCV and TERT promoter mutagenesis (Nault et al., 2020; Schulze et al., 2019).

HCV accounts for approximately 25–30% of all HCC worldwide, though regional variation is substantial. In Southern Europe and the Middle East, HCV accounts for 60–80% of HCC cases. Countries such as Pakistan and Egypt face compounded burdens of high HCV seroprevalence (3–10% of adults) and limited access to curative antivirals (Hajarizadeh et al., 2019; Polaris Observatory HCV Collaborators, 2022). The long latency between HCV acquisition and HCC diagnosis (20–30 years) allows for the accumulation of somatic mutations, including TERT promoter mutations that persist even after viral clearance (Kanwal et al., 2020). Risk cofactors including male sex, advanced age, diabetes, obesity, and HCV genotype 3 further stratify individual risk.

Over the past decade, research has advanced significantly in characterizing HCV protein-TERT interactions, developing liquid biopsy platforms for early HCC detection, and initiating clinical trials of TERT-targeted therapies (Huang et al., 2022; Bell et al., 2020). This review comprehensively examines the molecular relationship between HCV infection and TERT promoter mutations in HCC, with focus on mechanisms of mutagenesis, epigenetic regulation, comparative molecular analysis, and clinical applications.

Objectives:

(1) To understand the molecular role of TERT promoter mutations in HCV-associated HCC.

(2) To explore the mechanisms linking HCV infection with telomerase activation and liver cancer development.

LITERATURE REVIEW

Hepatitis C Virus: Molecular Virology and Pathogenesis

Genomic Organization and Replication Cycle

HCV is a positive-sense single-stranded RNA virus (genus Hepacivirus, family Flaviviridae) with a genome of approximately 9,600 nucleotides encoding one open reading frame (ORF) flanked by 5' and 3' non-coding regions essential for replication and translation (Moradpour & Penin, 2020). The ORF is translated into a single polyprotein of ~3,011 amino acids, processed into three structural proteins (Core, E1, E2) and seven non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B). NS3/4A is a serine protease that processes downstream polyprotein, while NS5B has RNA-dependent RNA polymerase (RdRp) activity directing genome replication in modified ER membranes (Stoeck et al., 2022). HCV lacks proofreading capability in its RNA polymerase, generating eight major genotypes with distinct geographical distributions. Hepatocyte entry is mediated sequentially through LDLR, SR-BI, CD81, CLDN1, OCLN, and NPC1L1 receptors, followed by IRES-dependent translation (Moradpour & Penin, 2020).

HCV Proteins and Oncogenic Potential

Each HCV protein contributes distinctly to carcinogenesis. The core protein activates c-Myc and TERT via MAPK/ERK pathways, impairs p53 tumor suppressor function, promotes hepatic steatosis through lipid metabolism disruption, and activates Wnt/β-catenin signaling—oncogenic properties confirmed in transgenic mice that spontaneously develop HCC (Moriya et al., 1998). The NS3/4A protease cleaves innate immune adaptors MAVS, TRIF, and STING, enabling immune evasion and disrupting DNA damage response via ATM pathway interactions (Machida et al.,

2020). NS5A—a membrane-anchored phosphoprotein—directly activates PI3K/AKT/mTOR, JAK/STAT, and Ras/ERK pathways, and critically binds TERT directly, increasing telomerase activity 2–3-fold through AKT-mediated phosphorylation of TERT at serine 824 (Andrisani et al., 2022; Li et al., 2021).

Table 2.1.2: HCV Proteins and Their Oncogenic Mechanisms.

HCV Protein	Molecular Function	Oncogenic Mechanism
Core	Nucleocapsid, lipid metabolism	Activates c-Myc, TERT, Wnt/β-catenin; inhibits p53; promotes steatosis
NS3/4A	Serine protease, helicase	Cleaves MAVS/TRIF; disrupts DDR; activates NF-κB; promotes genomic instability
NS4B	ER membrane remodeling	Activates Ras/MAPK; promotes ER stress and UPR; inhibits apoptosis
NS5A	Replication complex scaffold	Activates PI3K/AKT/mTOR, JAK/STAT3; directly upregulates TERT via Akt
NS5B	RNA-dependent RNA polymerase	Interacts with p53; promotes genomic instability; modulates cell cycle
E1/E2	Envelope glycoproteins	Promotes oxidative stress via receptor signaling; modulates TGF-β pathway

Hepatocellular Carcinoma: Molecular Pathogenesis

Stepwise Progression from Chronic Hepatitis to HCC

HCC typically develops over decades through discrete histological stages: Chronic Hepatitis → Hepatic Fibrosis → Cirrhosis → Dysplastic Nodules → Early HCC → Advanced HCC. Cumulative somatic and epigenetic alterations in hepatocytes, driven by repeated injury-death-repopulation cycles, characterize this progression (Forner et al., 2022). Driver mutations have been characterized at each stage: TERT promoter mutations and CTNNB1 mutations emerge early, while TP53 mutations, CDKN2A deletions, and widespread chromosomal instability predominate at later stages. Large-scale genomic studies—including TCGA (Cancer Genome Atlas Research Network, 2017), the French cohort (Schulze et al., 2019), and the HEPTROMIC project (Totoki et al., 2022)—have established mutation frequencies: TERT promoter (54–60%), TP53 (25–31%), CTNNB1 (26–32%), ARID1A (10–16%), CDKN2A (12–19%), and others. Crucially, TERT promoter and TP53 mutations occur largely independently, reflecting distinct telomere maintenance pathways dependent on tumor etiology (Nault et al., 202(

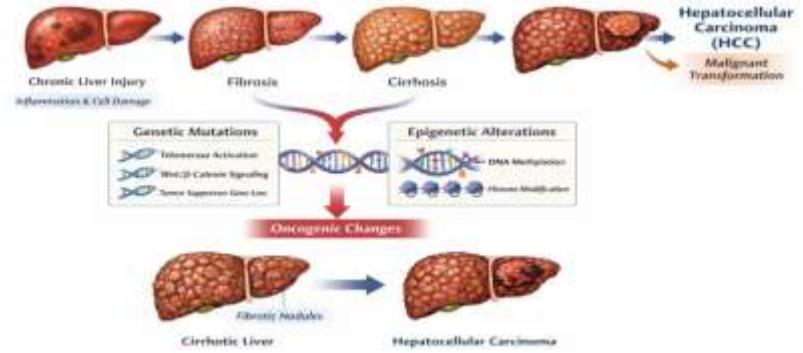

Figure 2.2.1: Molecular Pathogenesis of HCV-Induced Hepatocarcinogenesis

Key Signaling Pathway Alterations in HCC

Multiple dysregulated signaling pathways collectively drive HCC hallmarks. The Wnt/β-catenin pathway is activated in 26–32% of cases through CTNNB1 gain-of-function mutations, or in 8–11% through AXIN1/AXIN2 loss-of-function mutations, leading to nuclear accumulation of β-catenin and upregulation of cyclin D1, c-Myc, survivin, and TERT itself—establishing a synergistic link between CTNNB1 and TERT mutations (Nault et al., 2020). The RAS/MAPK/ERK pathway activates ELK-1, ETS-1, and GABP transcription factors that bind mutant TERT promoter sequences to drive TERT expression (Bell et al., 2020). The PI3K/AKT/mTOR pathway, activated in 40–51% of cases, directly phosphorylates TERT through AKT, promoting nuclear localization and telomerase activity (Llovet et al., 2021).

TERT and Telomerase Biology

Structure and Function of Telomerase

Telomerase is a ribonucleoprotein complex that synthesizes telomeric repeats (5'-TTAGGG-3') to counteract the end-replication problem, preventing progressive telomere shortening with each cell division. The human telomerase holoenzyme comprises the catalytic subunit hTERT (encoded at chromosome 5p15.33) and the template RNA hTR/TERC (~451 nucleotides), along with accessory proteins DKC1, NHP2, NOP10, GAR1, TCAB1, and TPP1 required for assembly, stability, nuclear import, and activity (Blackburn et al., 2015). The TERT protein (127 kDa) contains the TEN domain, RNA-binding domain (TRBD), reverse transcriptase domain (with conserved YADD motif), and C-terminal extension. In normal differentiated somatic tissues, TERT transcription is repressed through CpG methylation, repressive histone modifications (H3K27me3), and transcriptional repressors including CTCF, MZF-2, and Mad/Max heterodimers (Hanahan & Weinberg, 2011).

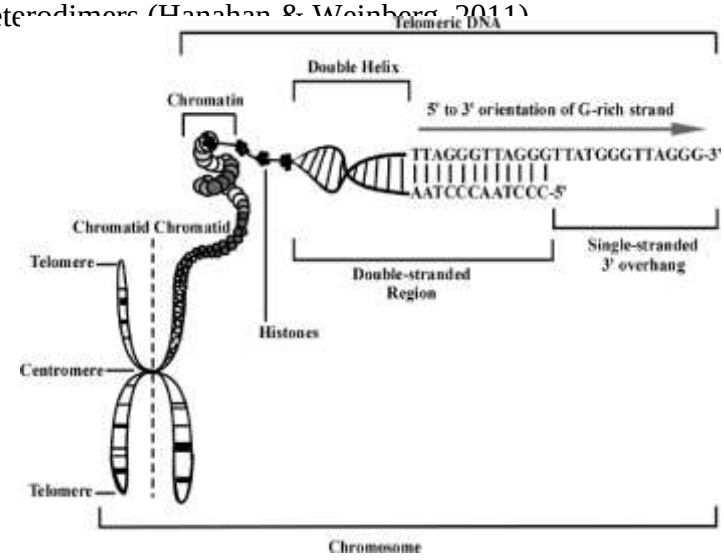

Figure2.3.1: Structure of Telomerase.

2.3.2 The TERT Promoter: Structure and Regulatory Elements

The human TERT gene regulatory region spans approximately 4 kb upstream from the transcription start site (TSS) into the first intron. The core promoter region (~300 bp upstream) contains binding sites for Sp1, AP-2, E-boxes (c-Myc/Max), STAT3 cis-elements, NF-κB sites, multiple ETS family motifs, and hormone response elements—reflecting the context-dependent, multi-signal integration controlling TERT expression. The critical C228T and C250T gain-of-function mutations occur at -124 bp and -146 bp relative to the ATG start codon (chr5p15.33, GRCh38 positions 1,295,228 and 1,295,250), creating novel ETS binding motifs absent in the wild-type promoter (Heidenreich & Kumar, 2017).

Table 2.3.2: Key Characteristics of TERT Promoter Mutations in HCC.

Feature	C228T Mutation	C250T Mutation
Genomic Position (GRCh38)	Chr5:1,295,228	Chr5:1,295,250
Distance from TSS	-124 bp	-146 bp
Nucleotide Change	Cytosine → Thymine	Cytosine → Thymine
Frequency in HCV-HCC	~70–80% of TERT mut. cases	~15–20% of TERT mut. cases
New Binding Site	GABPα/β ETS motif	GABPα/β ETS motif
Promoter Activity Increase	2.5–4 fold	2–3 fold

TERT Promoter Mutations in HCC: Epidemiology and Clinical Associations

A comprehensive meta-analysis of 21 independent HCC cohorts (3,408 patients) demonstrated an overall TERT promoter mutation prevalence of 54.2%, with significant etiology-based variation. The HCV cohort had the highest prevalence at 61.3%, followed by alcohol (54.7%), NASH (41.2%), non-cirrhotic (47.8%), and HBV (36.9%). In HBV-associated HCC, TERT activation frequently occurs via viral DNA integration into the TERT locus in ~10–15% of cases—an alternative pathway that reduces dependence on promoter mutation as a mechanism of TERT reactivation (Totoki et al., 2022; Schulze et al., 2019). The higher prevalence of TERT promoter mutations in HCV-HCC thus reflects distinct, promoter mutation-dependent mechanisms of TERT reactivation driven by chronic HCV infection.

HCV-Mediated Mechanisms of TERT Promoter Mutagenesis and Activation

Oxidative Stress-Induced Mutagenesis

Chronic HCV infection generates substantial reactive oxygen species (ROS) through four interconnected mechanisms: (1) NS3/4A-mediated disruption of mitochondrial membrane potential leading to superoxide formation; (2) NS5A interactions with glutaredoxin and thioredoxin systems impairing cellular redox homeostasis; (3) HCV core protein-induced upregulation of NADPH oxidase isoforms; and (4) HCV-induced ER stress activating ERO1 and PRDX4 oxidases (Machida et al., 2020). The resulting oxidative microenvironment accumulates 8-oxo-2'-deoxyguanosine (8-oxodG) within genomic DNA—a pre-mutagenic lesion promoting G-C to T-A transversions—and facilitates cytosine deamination by activation-induced cytidine deaminase (AID/AICDA) at CG dinucleotides within the TERT promoter, driving C→T transitions at C228 and C250 positions.

The TERT promoter is structurally predisposed to oxidative damage. G-quadruplex (G4) structures in the TERT promoter and telomeric DNA are particularly susceptible to oxidative attack due to guanine concentration and altered stacking geometry, while inefficient base excision repair (BER) at G4-structured DNA within actively replicating hepatocytes provides the mechanistic basis for preferential mutation accumulation at these hotspot positions during chronic HCV infection (Machida et al., 2020).

Direct HCV Protein–TERT Interactions

HCV NS5A protein interacts with TERT through domains II and III, stabilizing TERT from proteasomal degradation and directing it to the nucleus. This stabilization is dependent on AKT phosphorylation of TERT at serine 824, resulting in a 2–3-fold increase in telomerase activity measured by the TRAP assay (Li et al., 2021; Andrisani et al., 2022). The HCV core protein promotes TERT transcription through

two mechanisms: (i) activation of the c-Myc/Max complex at E-boxes in the TERT promoter; and (ii) activation of NF-κB via TRADD interaction, promoting IKK-mediated IκBα phosphorylation and nuclear transport of NF-κB subunits that bind κB sites in the TERT promoter. Additionally, NS3 helicase activity may facilitate TERT transcription by unwinding G-quadruplex structures in the TERT locus, enabling transcription elongation through the first exon (Machida et al., 2020).

Epigenetic Mechanisms

In normal hepatocytes, the TERT promoter is maintained in a silenced state through dense CpG methylation at eight sites within 300 bp of the TSS, combined with repressive histone modifications including H3K27me3 by PRC2 (Heidenreich & Kumar, 2017). Chronic HCV infection induces selective CpG hypomethylation of the TERT proximal promoter through three intersecting mechanisms: (1) HCV core protein downregulates DNMT3a and DNMT3b via miR-152 inhibition; (2) NS5A directly inhibits DNMT1 activity through protein-protein interactions; and (3) HCV-induced mitochondrial ROS activates TET dioxygenases, oxidizing 5-mC to 5-hmC and facilitating active demethylation (Li et al., 2021). Additionally, HCV-induced IL-6/STAT3 and TGF-β/SMAD signaling pathways modulate PRC2 activity and EZH2 expression, altering the histone methylation landscape at the TERT promoter to create the chromatin permissiveness needed for TERT transcriptional activation. This epigenetic reprogramming establishes an epigenomic "field defect" that predisposes hepatocytes to malignant transformation.

Comparative Molecular Analysis: HCV-HCC vs. Other Etiologies

HCV-HCC vs. HBV-HCC: Divergent Molecular Pathways

Although both HCV and HBV are primary HCC causes, their mechanisms of TERT reactivation differ fundamentally. HBV can integrate randomly into the host genome—frequently at the TERT locus on chromosome 5p15.33—driving TERT transcriptional upregulation through insertion of a viral promoter, enhancer, or gene truncation (Totoki et al., 2022; Schulze et al., 2019). This integration-dependent pathway is mechanistically distinct from, and partially substitutes for, TERT promoter mutation in HBV-HCC. Consequently, HBV-HCC has substantially higher TP53 mutation rates (35–38% vs. 25–28% in HCV-HCC), while CTNNB1 mutations are more prevalent in HCV-HCC (30–34% vs. 16–18%). HBV-HCC also shows higher chromosomal instability due to insertional mutagenesis at integration sites. The immune microenvironment differs as well: HCV-HCC features highly exhausted CTLs with elevated PD-1, TIM-3, LAG-3, and TIGIT expression, while HBV-HCC shows more dysfunctional NK cell populations and variable tumor mutational burden—differences that may explain differential immunotherapy responses (Llovet et al., 2021).

Table 2.6.1: Comparative Molecular Landscape of HCV-HCC vs. HBV-HCC.

Molecular Feature	HCV-HCC	HBV-HCC
TERT promoter mutation (%)	61–68	28–40
Viral integration at TERT locus	Not applicable	10–15% of cases
TP53 mutation (%)	25–28	35–38
CTNNB1 mutation (%)	30–34	16–18
ARID1A mutation (%)	12–16	8–12
Chromosomal instability	Moderate	High

Molecular Feature	HCV-HCC	HBV-HCC
Immune checkpoint expression	High PD-1/TIM-3/LAG-3	High PD-L1/TIM-3
Tumor mutational burden	Low-Moderate	Low-High

Diagnostic and Prognostic Significance of TERT Promoter Mutations

Tissue-Based Diagnostics

TERT promoter mutations—virtually absent in normal liver tissue and benign hepatic lesions—provide high specificity as a molecular marker for HCC in liver biopsies (Nault et al., 2020). In the clinically challenging differential diagnosis between well-differentiated HCC and hepatocellular adenoma (HCA), TERT mutations are detected in 40–50% of HCA cases undergoing malignant transformation and >60% of well-differentiated HCC, but are virtually absent in benign non-transformed HCA subtypes—providing a molecular criterion for distinguishing malignant from non-malignant lesions.

Prognostically, TERT promoter mutations are significantly associated with shortened overall survival (OS), reduced disease-free survival (DFS), increased early tumor recurrence, and greater tumor aggressiveness (microvascular invasion, poor differentiation). Meta-analysis of 10 studies demonstrated a hazard ratio of 1.62 for overall mortality in TERT promoter-mutated HCC versus wild-type after adjusting for tumor size, vascular invasion, AFP levels, and BCLC stage (Rhee et al., 2021). In HCV-positive patients specifically, the hazard ratio for OS increases to 1.78, underscoring the compounded prognostic impact of TERT mutations in the viral hepatitis context.

Liquid Biopsy Applications: Circulating Tumor DNA

Plasma ctDNA-based detection of TERT promoter mutations offers significant clinical potential for non-invasive HCC surveillance. Droplet digital PCR (ddPCR) assays achieve sensitivity of 72–85% and specificity of 93–97% for detecting TERT mutations in plasma ctDNA from HCV-associated HCC patients. In prospective surveillance studies of HCV-cirrhosis patients, TERT mutations were consistently detected in plasma ctDNA an average of 4–8 months before radiologic diagnosis, establishing their utility as early diagnostic biomarkers (Huang et al., 2022).

Serial ctDNA monitoring enables treatment response assessment and minimal residual disease (MRD) detection. In patients receiving surgical resection, radiofrequency ablation, or systemic therapy, ctDNA TERT mutation levels predicted clinical recurrence 2–6 months before radiologic confirmation (Takai et al., 2021). Additionally, dynamic changes in ctDNA TERT mutation variant allele frequency (VAF) during systemic therapy with sorafenib, lenvatinib, or immune checkpoint inhibitors correlate with radiographic treatment response, suggesting utility as a pharmacodynamic biomarker.

Therapeutic Targeting of TERT in HCV-Associated HCC

Telomerase Inhibition Strategies

The near-universal overexpression of telomerase in HCC provides strong rationale for telomerase-targeted therapy. Current strategies under investigation include: (1) Oligonucleotide-based inhibitors—imetelstat (GRN163L), a 13-mer thiophosphoramidate that competitively inhibits hTR template function, has shown acceptable safety, demonstrable telomerase inhibition in PBMCs and tumor tissue, and disease stabilization in Phase I/II trials for HCC, though objective tumor volume reduction has been limited (Jafri et al., 2020); (2) Small molecule catalytic inhibitors targeting the TERT reverse transcriptase domain (BIBR1532, MST312); (3) G-quadruplex stabilizers (telomestatin, PDS, BRACO-19) that sequester telomeric G4

from telomerase action; and (4) TERT-derived peptide immunotherapy. Resistance through upregulation of the alternative lengthening of telomeres (ALT) mechanism may limit single-agent efficacy, necessitating combination approaches.

Targeting Mutant TERT Promoter: Selective Vulnerability

The novel ETS binding sites created by C228T and C250T mutations represent tumor-selective therapeutic targets absent in normal hepatocytes. Approaches under preclinical investigation include: (1) Small-molecule inhibitors of GABPα/GABPβ heterodimerization to prevent high-affinity binding at mutant ETS sites; (2) CRISPR-Cas9-mediated editing of the mutant TERT promoter to restore transcriptional repression; (3) Transcriptional repressor fusion proteins (GABPα DNA-binding domain fused to KRAB or DNMT3) to silence mutant TERT-driven expression; and (4) dCas9-EZH2 epigenetic silencing of the mutant TERT promoter using mutation-specific sgRNAs (Bell et al., 2020; Jafri et al., 2020). Clinical translation of these approaches will require hepatic-targeted delivery systems such as lipid nanoparticles (LNPs) analogous to those developed for mRNA vaccines, or tumor-targeted polymeric nanocarriers.

METHODOLOGY

This study employs a systematic narrative literature review to investigate the molecular relationship between HCV infection and HCC development, with focus on TERT promoter mutations. Literature searches were conducted across major biomedical databases (PubMed/MEDLINE, Scopus, Web of Science, Google Scholar) using keywords including "TERT promoter mutations," "hepatocellular carcinoma," "hepatitis C virus," "telomerase activation," "HCV-induced carcinogenesis," and mutation-specific terms "C228T" and "C250T."

Inclusion criteria required English-language, peer-reviewed publications focused on HCC biology, HCV-related liver cancer, telomere/telomerase function, TERT promoter mutations, or clinical applications of these topics. Study types included laboratory experiments, animal studies, clinical investigations, reviews, and meta-analyses. Studies lacking relevant molecular data, covering unrelated topics, or not fully accessible were excluded. Data extraction focused on thematic domains: HCV molecular biology, HCC pathogenesis, telomerase structure and regulation, TERT promoter mutation mechanisms, comparative etiology analysis, diagnostic/prognostic applications, and therapeutic strategies. Findings were synthesized thematically and cross-referenced for accuracy and consistency.

RESULTS AND DISCUSSION

Results

The comprehensive literature review confirms that TERT promoter mutations are among the most frequent and earliest genetic alterations in HCC, occurring in approximately 40–60% of HCC cases globally and in up to 70% of HCV-related HCC specifically. Among hotspot mutations, C228T is predominant (~90% of TERT mutation cases) while C250T plays a similar functional role. Importantly, TERT promoter mutations are detectable in pre-neoplastic lesions, indicating contribution to tumor initiation rather than late-stage progression.

Chronic HCV infection drives these mutations through persistent inflammation, oxidative DNA damage, direct viral protein–TERT interactions, and epigenetic reprogramming of the TERT locus. Once established, TERT promoter mutations increase TERT expression through novel GABPα/β binding sites, resulting in telomere maintenance, unlimited cell division, and resistance to senescence. Co-occurrence with TP53 and CTNNB1 mutations suggests cooperative oncogenic effects across multiple regulatory axes.

Discussion

The findings firmly support TERT promoter mutations as a molecular bridge between chronic HCV infection and HCC. While HCV does not integrate into the host genome (unlike HBV), it creates a pro-carcinogenic hepatic environment through continuous liver injury and regeneration cycles, ROS production, and induction of genomic instability—all converging to create preferential mutagenesis at the TERT promoter's G-quadruplex structures.

Under normal conditions, telomerase is inactive in somatic cells. TERT promoter mutations overcome this repression by creating de novo ETS transcription factor binding sites, enabling GABPα/β binding and constitutive TERT activation—conferring the hallmark of replicative immortality. This represents a key initiating step in hepatocarcinogenesis, preceding histological transformation and persisting through tumor evolution.

The clinical implications are substantial. As diagnostic biomarkers, TERT mutations enable early detection via liquid biopsy with high specificity. As prognostic markers, their association with microvascular invasion, poor survival, and early recurrence guides clinical decision-making. As therapeutic targets, the mutation-selective GABPα/β binding sites represent a rational basis for tumor-specific interventions. More broadly, these findings reinforce that cancer is driven not only by coding gene mutations but by alterations in regulatory regions, with TERT promoter mutations serving as central initiating events rather than secondary alterations in HCV-associated hepatocarcinogenesis.

CONCLUSION

This review demonstrates that TERT promoter mutations play a critical and early role in HCC development in the context of chronic HCV infection. These mutations reactivate telomerase, enable cellular immortalization, and facilitate the accumulation of further oncogenic changes. Chronic HCV infection promotes TERT promoter mutations through convergent mechanisms: oxidative mutagenesis at structurally predisposed genomic hotspots, direct viral protein interactions with the TERT enzyme, and epigenetic reprogramming of the TERT locus—establishing a multi-layered mechanistic link between viral infection and cancer development.

Their high frequency and early appearance position TERT promoter mutations as valuable diagnostic biomarkers, particularly in the liquid biopsy context. Their association with disease aggressiveness and poor prognosis confirms their prognostic value. The tumor-selective ETS binding sites created by C228T and C250T mutations offer promising targets for future therapeutic strategies. Collectively, TERT promoter mutations provide key mechanistic insight into hepatocarcinogenesis and hold significant potential for improving early detection, personalized risk stratification, and treatment outcomes in HCV-associated HCC.

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