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Hidden Gems in the Genome: Pseudogenes Unleashing Revolution in Hepatocellular Carcinoma Detection and Therapy

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INTRODUCTION & AIM

Hepatocellular carcinoma (HCC) causes over 800,000 deaths yearly. Major risk factors are hepatitis B/C, alcohol, obesity, and diabetes. Most HCC arises after hepatitis virus-driven liver damage. Males predominately affected. Late diagnosis is common, severely limiting treatments.

Once dismissed as inconsequential, pseudogenes have emerged as key HCC regulators. Through multifaceted genetic and molecular mechanisms, they influence cancer signaling pathways. Some pseudogenes exhibit deep conservation and immense control of cancer-linked genes.

The review article highlight seminal discoveries of liver cancer pseudogene biomarkers for early detection, monitoring, and prognosis prediction. Targeting pseudogenes could profoundly impact HCC management. These overlooked genes may enable better diagnosis, outcomes forecasting, and therapeutic advancements against this deadly disease.

PSEUDOGENES FROM JUNK DNA TO KEY PLAYERS

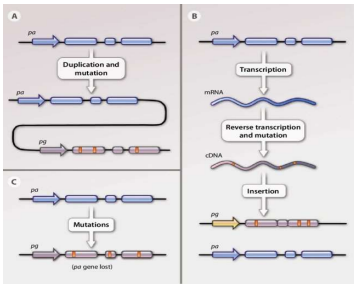

Figure 1. Types of pseudogenes:
(A) Non-processed pseudogenes
(B) Processed pseudogenes (C) Unitary pseudogenes.

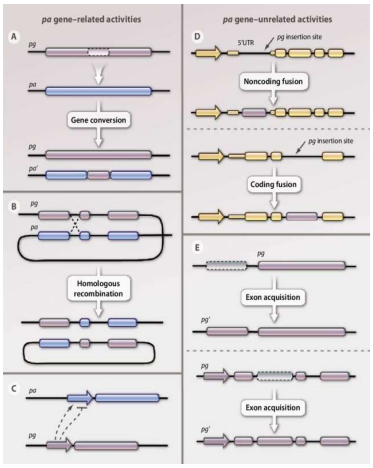

Figure 2. Mechanisms of action of pseudogenes at the DNA level. (A) Gene conversion
(B) Homologous recombination (C) Regulatory sequences (D) Insertion of a processed pseudogene
(E) Acquisition of new exons

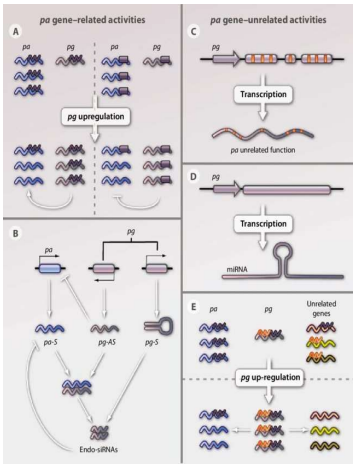

Figure 3. Mechanisms of action of pseudogenes at the RNA level. (A) Competition with parental gene mRNAs (B) Attraction of chromatin remodeling complexes (C) Acting as long non-coding RNAs
(D) Serving as precursors for microRNAs
E) Competing for microRNA binding

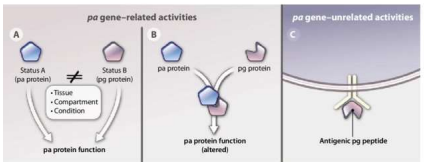

Figure 4. Mechanisms of action of pseudogenes at the protein level. (A) Pseudogenic proteins have the same activity as the parental proteins (B) Partially functional pseudogenic proteins or pseudogenic proteins with altered function (C) Short pseudogenic open reading frames

References
1. Roberts LR et al. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol 16(10): 589-604, 2019.
2 Pandey Ak et al. Hepatocellular carcinoma:causes, mechanism of progression and biomarkers. Curr Chem Genom Transl Med 12: 9-26, 2018.

PSEUDOGENES IN HCC PATHOGENESIS

Pseudogenes	Implications in HCC
ANXA2P2	Modulates cell proliferation, motility, and cytoskeletal regulation
DUXAP10	Involved in cell proliferation and cell-cycle modulation
PDIA3P1	Influences proliferation, migration, and invasiveness
RACGAP1P	Promotes cell growth and migration
DUXAP8	Impacts cell proliferation and cell-cycle regulation
OCT4-pg4	Enhances cell proliferation and colony formation
INTS6P1	Affects cell growth, migration, and viability
AURKAPS1	Involved in cell motility, migration, and invasion
PPIAP22	Contributes to metastasis and immune cell infiltration
E2F3P1	Roles in cell proliferation, cell-cycle modulation
MSTO2P	Multifaceted role in cell proliferation, apoptosis, and metastasis
HSPB1P1	Influences cell proliferation, apoptosis, and cell-cycle modulation
POU5F1B	Linked to increased cell proliferation
UPAT	Involved in migration, invasion, EMT, and CSC-like properties

Pseudogene Expression Studies for HCC

Table 1. Pseudogenes expression levels in primary tissues, serum, and plasma for HCC **diagnosis.**

PSEUDOGENES	REGULATION	SOURCE	DIAGNOSTIC PROFICIENCY
ANXA2P2	Up	Tissue, Serum	Differentiate HCC patients from healthy control
DUXAP10	Up	Tissues	Differentiate HCC patients from healthy control
PDIA3P1	Up	Tissues	Differentiate HCC patients from healthy control
RACGAP1P	Up	Tissues	Differentiate HCC and control
DUXAP8	Up	Tissues	Differentiate HCC patients from healthy control
OCT4-pg4	Up	Tissues	Differentiate HCC patients from healthy control
INTS6P1	Down	Tissues, Plasma	Differentiate HCC from healthy tissues in a primary tissue sample and plasma samples, Differentiate chronic HBV infection patients from normal controls
AURKAPS1	Up	Tissues	Differentiate HCC and control
PPIAP22	Up	Tissues	Differentiate HCC patients from healthy control
MSTO2P	Up	Tissues	Differentiate HCC patients from healthy control
HSPB1P1	Up	Tissues	Differentiate HCC patients from healthy control
POU5F1B	Up	Tissues	Differentiate HCC and healthy patients
UPAT	Down	Tissues	Differentiate HBV-related HCC from healthy controls

Table 2. Pseudogenes as **Prognostic Indicators** in HCC.

PSEUDOGENES	REGULATION	SOURCE	PROGNOSTIC BIOMARKERS
ANXA2P2	Up	Tissue, Serum	Poor prognosis and TNM stage
DUXAP10	Up	Tissues	Reduced overall survival, higher pathologic stage, vascular invasion
PDIA3P1	Up	Tissues	Worse overall survival, larger tumor size, metastasis, advanced TNM stage
RACGAP1P	Up	Tissues	Shortened survival time, larger tumor size, elevated AFP levels, advanced clinical stage
DUXAP8	Up	Tissues	Diminished overall survival time, increased mutation burden, higher tumor grade and stage
OCT4-pg4	Up	Tissues	Poor prognosis, associated with HCC stage
INTS6P1	Up	Tissues, Plasma	Indicates an alarming state
AURKAPS1	Up	Tissues	Poor prognosis, linked to TNM stage, tumor size
PPIAP22	Up	Tissues	Reduced overall and disease-free survival, associated with clinical-stage and tumor size
E2F3P1 (rs9909601)	Up	Tissues	Improved prognosis and extended survival
MSTO2P	Up	Tissues	Lower survival rates and unfavorable prognosis
HSPB1P1	Up	Tissues	Adverse overall survival outcomes
POU5F1B	Up	Tissues	Poor prognosis
UPAT	Down	Tissues	Decreased recurrence-free survival and unfavorable prognosis

CHALLENGES AND FUTURE DIRECTIONS

- Need to standardize Quantitative Real-Time PCR and other assays across labs and clinical settings for reliable results.
- Focusing on determining the most precise specimen type for pseudogene-based HCC biomarker data
- Addressing the high costs of whole-genome sequencing is essential to bring pseudogene diagnostics to routine clinical practice.
- Extensive studies involving diverse pseudogene panels and clinical stages of HCC are vital to validate pseudogenes role as clinical biomarkers.