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Potential Collaborative Markers for Nasopharyngeal Carcinoma Diagnosis and Therapy: AGR2 and AKR1B10

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KEYWORDS

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ABSTRACT

Nasopharyngeal carcinoma is a prevalent malignant tumor, which lacks specific diagnostic markers and effective therapeutic evaluation indexes. AGR2 (Pregradient protein 2) and AKR1B10 (aldoketone reductase 1B10) are oncoproteins secreted by cancer cells into peripheral blood. Prior researches have suggested that the upregulation of AGR2 and AKR1B10 occurs in both primary and metastatic NPC tissues, indicating their potential as biomarkers for NPC development. In the present study, NPC patients had considerably greater serum levels of AGR2 and AKR1B10 than did healthy persons, and these levels decreased following treatment. Furthermore, the serum concentrations of AGR2 and AKR1B10 in patients with NPC were positively correlated with the grade of TNM (tumor lymph node metastasis) and the occurrence of meta stasis. Consistently, AGR2 and AKR1B10 positive rates in NPC tissues were notably greater than those in nearby normal tissues. Additionally, there was an affirmative linear connection between AGR2 and AKR1B10 in NPC patients. In conclusion, there appears to be a close relationship between the expression of AGR2 and AKR1B10, both serving as synergistic biomarkers for early diagnosis and treatment evaluation indicators for patients with nasopharyngeal carcinoma.

INTRODUCTION

The nasopharyngeal epithelium is the source of nasopharyngeal carcinoma (NPC), a malignant tumor that is most common in East Africa and Asia[1], particularly in southern China[2, 3]. The development of NPC is associated with EBV (Epstein-Barr virus) infection[4], environmental factors, hereditary predisposition, and contact with chemical carcinogens[5, 6]. Furthermore, high-risk pathogenic genes for NPC are predominantly found in China, leading to familial inheritance and clustering of the disease[7]. Metastasis and invasion of NPC often result in poor treatment outcomes and prognosis[8]. Hence, it is imperative to discern novel indicators for NPC in order to enhance the survival rate of patients.

Previous researches have established the correlation between the expression levels of AGR2 and AKR1B10 and the metastasis and progression of nasopharyngeal carcinoma[9, 10]. AGR2, a part of the PDI (protein disulfide isomerase) group, helps regulate the production of UPR (unfolded protein response) proteins, and is involved in endoplasmic reticulum (ER) stress-related pathways[11]. The secretion of AGR2 by tumor cells serves as a valuable biomarker for the diagnosis and prognosis of tumor. It has been significantly associated with OS (overall survival) in various sorts of cancer, containing prostate cancer[11, 12], breast cancer[13], ovarian cancer[14], lung adenocarcinoma cancer[15], GC (gastric cancer)[16], CRC (colorectal cancer)[17] and NSCLC(non-small cell lung cancer)[18]. AKRs (Aldo-keto reductases) constitute a category

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The Latest Research Progress of IER3 in Clinical Significance and Mechanisms: Hepatocellular Carcinoma and Other Malignant Tumors

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KEYWORDS

Hepatocellular Carcinoma; Immediate Early Response 3; Clinical Significance; Mechanism

ABSTRACT

Malignant tumor is one of the diseases threatening human health, and liver cancer is the most common. Hepatocellular carcinoma (HCC) is the most common clinicopathological subtype. Immediate early response 3 (IER3) plays a regulatory role in a variety of malignant tumors. This article reviews the latest research progress on the clinical significance and mechanism of IER3 in HCC and a variety of malignant tumors.

INTRODUCTION

Malignant neoplasms impose a substantial disease burden on global populations, with recent epidemiological projections estimating 2.04 million new cancer cases and approximately 620,000 cancer-related deaths annually in the United States alone [1]. Hepatocellular carcinoma (HCC), the predominant histopathological subtype of liver cancer, represents a major contributor to this burden, exhibiting persistently high incidence and mortality rates worldwide [2]. Notably, HCC demonstrates elevated epidemiological prevalence in both Chinese and international cohorts, with current data underscoring its significant public health impact [3]. Contemporary analyses reveal evolving epidemiological trends in HCC, characterized by a younger age of onset, geographic homogenization of incidence, male predilection in elderly populations, narrowing urban-rural disparity in case distribution, low curative rates, and disproportionately high mortality [4]. Projections indicate a continued upward trajectory in HCC incidence and mortality, necessitating urgent advancements in understanding its pathogenesis and improving clinical management strategies.

Immediate early response 3 (IER3), alternatively termed p22/PRG1 or DIF-2, was initially identified by Charles et al. as a stress-inducible gene in X-ray-exposed tumor cells, with subsequent studies demonstrating its activation by diverse stimuli including ionizing radiation, ultraviolet exposure, and growth factors [5]. Functionally, IER3 regulates cell cycle progression and confers resistance to Fas- or tumor necrosis factor-alpha (TNF-α)-mediated apoptosis. Emerging evidence implicates IER3 in the pathogenesis of multiple malignancies, including colorectal cancer and neural tumors [6-8]. Preliminary single-center investigations have further elucidated its clinical relevance in HCC. This comprehensive review synthesizes current evidence on IER3 expression profiles, prognostic significance, and mechanistic contributions across common malignancies, with particular emphasis on HCC. By systematically examining the multifaceted roles of IER3 in tumor cell cycle dynamics and apoptotic regulation, this work aims to establish a theoretical framework for identifying novel therapeutic targets in oncology.

IER3 AND HCC

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Expression Levels and Prognostic Significance of IER3 in HCC

The expression levels of proto-oncogenes and tumor suppressor genes hold critical clinical implications for diagnostic and therapeutic decision-making in oncology. Current research has increasingly focused on the expression profile of IER3 in HCC. A comprehensive analysis of 2,746 clinical specimens demonstrated significant upregulation of IER3 in HCC tissues compared to normal hepatic parenchyma, with this differential expression pattern exhibiting potential diagnostic discriminative value [9] Zhou et al. identified IER3 as a component of a 17-gene glycolytic signature that was consistently overexpressed in HCC tissues, suggesting its potential role as a risk factor in hepatocarcinogenesis [10]. Experimental evidence further indicates that elevated IER3 expression promotes HCC progression in the absence of tumor suppressor activity [11]. In a clinicopathological study of 62 HCC specimens, Liu et al. established significant correlations between IER3 overexpression and key molecular markers (p53, Ki-67, EGFR), as well as with tumor size and differentiation grade, collectively supporting its pro-tumorigenic function in HCC development [12]. While studies investigating IER3 expression in HCC remain relatively limited, the existing body of evidence consistently demonstrates IER3 upregulation in HCC, strongly suggesting its potential role as an oncogenic driver in this malignancy. Historically, IER3 has been associated with prognostic outcomes in hepatic fibrosis. In glycolytic pathway-based prognostic models for HCC, the IER3-GALK1 interaction has been identified as a critical risk determinant, with high IER3 expression correlating with increased mortality rates and poorer quality of life indicators [10]. Notably, emerging evidence suggests that IER3 hypomethylation status may serve as an adverse prognostic marker, particularly in high-grade malignancies such as glioblastoma [6]. However, comprehensive studies examining the prognostic value of IER3 in HCC specifically remain scarce. Future investigations employing larger, multi-center cohorts will be essential to further elucidate the expression dynamics of IER3 in HCC and its precise impact on clinical outcomes, thereby facilitating its potential translation into clinical practice as both a diagnostic biomarker and therapeutic target.

Mechanistic Roles of IER3 in HCC Pathogenesis

Metabolic Reprogramming

IER3 has been demonstrated to play a pivotal role in modulating key metabolic pathways, including glycolysis and lipid metabolism, during HCC progression. Mechanistic studies reveal that IER3 interacts with galactokinase 1 (GALK1) to form a glycolysis-associated gene pair in HCC cells, facilitating aerobic glycolysis (the Warburg effect) that enables tumor cells to evade apoptosis and promote oncogenesis [10]. Furthermore, macrophages exhibiting elevated IER3 expression regulate lipid metabolic pathways through the SNHG25 biomarker, thereby contributing to the development of fibrotic microenvironments that indirectly foster hepatocarcinogenesis [13]. This metabolic reprogramming represents a critical mechanism by which IER3-expressing immune cells create a tumor-permissive niche in hepatic tissues.

Immune Microenvironment Crosstalk

IER3 plays a significant role in the regulation of the tumor immune microenvironment. Single-cell analyses have revealed that IER3-positive macrophages exhibit anti-inflammatory and pro-lipid metabolic functions, which may contribute to the promotion of HCC progression by modulating an immunosuppressive tumor microenvironment [13]. Elevated IER3 expression has been shown to suppress the expression of tumor immune checkpoint molecules, such as PD-L1, thereby indirectly influencing the sensitivity to immunotherapy [6]. Additionally, IER3 has been implicated in the depletion of T cells, enhancing the immune evasion capabilities of tumors and further promoting HCC development [14]. The immunomodulatory effects of IER3 on the HCC microenvironment not only facilitate tumor cell survival and proliferation but also pose significant barriers to the host immune system's ability to clear the tumor. Although the initial mechanisms by which IER3 regulates HCC initiation and progression have been elucidated, the complete molecular mechanisms and signaling pathways remain incompletely understood. Further research is required to fully delineate the complex interactions and regulatory roles of IER3 in oncogenesis and immune evasion.

Therapeutic Targeting of IER3 in HCC

In recent research, the expression of IER3 in HCC has been extensively studied, with a focus on its potential as a therapeutic target. Pharmacological studies have demonstrated that dasatinib may directly target IER3, suppressing its expression to reduce immune evasion in HCC cells, thereby promoting tumor apoptosis and enhancing the efficacy of targeted therapy [6, 15]. Additionally, alternative approaches using CRISPR activation systems or combination therapies with immune checkpoint inhibitors, such as nivolumab, have shown promise in specifically downregulating IER3 expression, improving the tumor immune microenvironment in HCC, and potentially improving patient prognosis [16]. Functional studies involving genetic manipulations, such as partial gene truncation or knockout of IER3 and related oncogenes, have revealed that IER3 inhibition suppresses various cellular processes, including cell survival, lipid metabolism, growth, proliferation, molecular transport, and cell motility, suggesting its potential as a therapeutic target in HCC [17, 18]. However, contradictory findings from Kwon et al. indicate that IER3 knockdown in Hep3B and HuH-7 cells does not affect cell viability, possibly due to their stem-like characteristics [18]. These results highlight the complexity of IER3's role in HCC and emphasize the need for further mechanistic studies and large-scale drug trials to support its clinical application in HCC treatment.

IER3 AND COMMON MALIGNANT TUMORS

IER3 and Gastric Cancer

A DNA microarray-based expression profiling study demonstrated that Toll-like receptor 2 (TLR2)-induced growth responses in human gastric cancer cells corresponded with upregulation of IER3 [19]. In a study conducted by Sasada et al., cell line cultures and immunohistochemical analyses revealed elevated IER3 protein expression in gastric tumor tissues, while no detectable IER3 protein expression was observed in normal tissues. The study identified IER3 as a stress-inducible gene involved in regulating cell cycle progression and apoptosis. Furthermore, the research suggested that IER3 might encode cytotoxic T lymphocyte (CTL) epitopes capable of inducing restricted human leukocyte antigen A33 and tumor-reactive CTLs in gastric cancer patients, with high IER3 expression potentially contributing to apoptosis resistance and enhanced proliferation of tumor cells. The authors proposed that since IER3 is expressed at the mRNA level in normal tissues - particularly in the heart, kidneys, lungs, and peripheral blood lymphocytes - these organs might represent potential targets for IER3-mediated adverse outcomes [20]. Another study indicated that IER3-mediated alterations in the immunosuppressive tumor microenvironment could also facilitate gastric cancer progression [21]. Current research on IER3 in gastric cancer remains limited, and its underlying mechanisms have not been fully elucidated.

IER3 and Pancreatic Cancer

Research on IER3 expression levels in pancreatic cancer was initially reported over a decade ago, but subsequent investigations have revealed contradictory findings, underscoring the need for larger clinical cohorts to validate its role in pancreatic carcinogenesis. Sasada et al. employed immunohistochemical methods to analyze IER3 protein expression in 78 paraffin-embedded pancreatic cancer specimens, correlating results with clinicopathological parameters and patient survival. Their study demonstrated a significant association between elevated IER3 expression and reduced survival duration, as well as tumor serosal invasion and arterial infiltration, marking the first evidence linking IER3 to pancreatic cancer progression [22]. Conversely, other studies have proposed that IER3 positivity correlates with favorable prognosis in pancreatic cancer [23]. Intriguingly, Garcia et al. reported opposing outcomes in their analysis of 34 pancreatic cancer tissues and animal models, associating IER3-positive expression with poor prognosis. To reconcile these discrepancies, the authors hypothesized that while IER3 acts as a critical regulator in pancreatic cancer development, its dynamic expression profile—higher in early disease stages and diminished in advanced phases—precludes its utility as a reliable prognostic biomarker. Mechanistically, Garcia et al. revealed that IER3 sustains p-ERK1/2 phosphorylation by inhibiting phosphatase PP2A, thereby potentiating Kras-driven oncogenesis in the pancreas [24]. This molecular framework aligns with findings from Molejon and Iovanna, whose pancreatic cancer models demonstrated that IER3 inactivation suppresses tumorigenesis. Their work further elucidated IER3's direct interaction with the PP2A-B56 regulatory subunit, driving sustained ERK1/2 phosphorylation to facilitate Kras-mediated cellular transformation [25]. Notably, the authors attributed the discrepant results between Sasada's and Garcia's studies to temporal variations in IER3 detectability, proposing that IER3 expression is predominantly detectable during early tumorigenic stages and essential for initiating malignant transformation. The ongoing controversies regarding IER3's expression patterns and its precise mechanistic contributions to pancreatic cancer pathogenesis highlight the imperative for future studies with larger cohorts and more robust methodologies to resolve these ambiguities.

IER3 and Colorectal Cancer

Building upon the foundational work of Lee et al., who first detected elevated IER3 expression in tumor tissues from two colorectal cancer (CRC) patients [26]. Muerkoster et al. utilized cell line models to demonstrate that IER3 expression mediates gastrin (G17)-induced suppression of NF-κB activity, which enhances cancer cell susceptibility to apoptosis. Their study further revealed that IER3 knockdown abolishes G17-triggered apoptotic effects, suggesting an inverse correlation between IER3 expression and cancer progression [27]. It is worth to note that Nambiar et al. identified IER3 as a potential tumor-suppressive gene in colorectal carcinogenesis, showing that its downregulation in early precancerous lesions contributes to colon cancer development [28]. While these studies have substantially clarified IER3's role and mechanisms in CRC, the validation of its expression patterns and the elucidation of its molecular underpinnings require larger-scale clinical cohorts to strengthen translational relevance.

IER3 and Bladder Cancer

Current research on IER3 expression in bladder cancer remains limited, and its mechanistic contributions are entirely unexplored. In a study by Ye et al. analyzing 88 bladder cancer specimens, IER3 protein was predominantly localized to the cytosol of bladder cancer cells, with high expression levels showing significant correlations with advanced pathological stages. Survival analysis further revealed that patients with elevated IER3 expression exhibited markedly shorter survival times compared to those with low expression [29]. Although this study provides the first evidence linking increased IER3 protein expression to aggressive progression and potential adverse prognosis in bladder cancer (BCA), the regulatory mechanisms through which IER3 influences bladder cancer cells remain to be comprehensively investigated.

IER3 and Gynecological Malignancies

Research on IER3 in gynecological malignancies has been relatively well-characterized, with a primary focus on ovarian and cervical cancers.

Persistent controversies exist regarding IER3 expression levels in ovarian cancer, and mechanistic investigations into its regulatory roles in tumorigenesis remain incomplete. Han et al. first reported IER3's role in human ovarian cancer through analysis of 56 malignant and 21 benign tumor sam-

ples, demonstrating significantly reduced IER3 expression in malignancies. Their study revealed a positive correlation between IER3 expression in tumor tissues and apoptotic index (AI), with IER3-positive patients exhibiting markedly higher survival rates than IER3-negative counterparts. These findings suggest IER3 may suppress epithelial ovarian carcinogenesis by promoting apoptosis [30]. Similarly, Lee et al. identified IER3 as a diagnostic biomarker through comparative analysis of ovarian epithelial tissues from 21 ovarian cancer patients and 35 healthy women [31]. However, these studies were restricted to tissue-level analyses. Expanding this scope, Li et al. evaluated IER3 expression in blood and saliva from 26 ovarian cancer patients, 37 benign cases, and 55 healthy controls, revealing significantly lower IER3 levels in cancer patients. ROC curve analyses demonstrated high diagnostic accuracy (AUC = 0.947 vs. benign; AUC = 0.929 vs. healthy controls), highlighting IER3's potential as a sensitive and specific liquid biopsy biomarker [32]. This work complements Han et al.'s tissue-based findings. Contrary to earlier findings, Jordan et al. identified IL6/IER3 pathway activation in tumor tissues from six patients, proposing that IER3 upregulation may correlate with poor prognosis [33]. Recent studies further position IER3 as a predictive factor distinguishing ovarian cancer patients from healthy individuals, suggesting its role as a risk factor in ovarian carcinogenesis [34]. Despite these advances, no studies have mechanistically dissected IER3's functional contributions in ovarian cancer, representing a notable gap in current research.

Limited literature exists on IER3 expression in cervical cancer, with only a few cell line-based studies providing insights. Jin et al. demonstrated that TAp73β overexpression specifically activates IER3 in cervical cancer cells, while TAp73β knockdown reduces IER3 mRNA levels by >50%. Mechanistically, TAp73β binds to the p53 consensus sequence within the IER3 promoter to drive transcription [35], marking the first elucidation of IER3 activation in cervical cancer. In a subsequent study, Jin et al. identified an FHL2-MDM2-IER3 multimeric complex regulating IER3 degradation. Here, FHL2 serves as a scaffold for signal transduction, while MDM2 acts as the E3 ligase facilitating IER3 ubiquitination. This degradation pathway was linked to enhanced cervical cancer cell proliferation, establishing the first mechanistic connection between IER3 turnover and carcinogenesis [36]. Despite these breakthroughs, the precise mechanistic contributions of IER3 in cervical cancer progression, particularly its context-dependent oncogenic or tumor-suppressive roles, remain to be fully elucidated.

IER3 and Other Malignant Tumors

Emerging studies continue to explore the role of IER3 across diverse malignancies. Ito et al. analyzed tumor and adjacent normal tissues from 16 lung adenocarcinoma patients, utilizing immunohistochemistry and sequencing to demonstrate nuclear localization of IER3-a finding discordant with Ye et al.'s cytoplasmic observations [37]. The study further revealed IER3 upregulation in lung adenocarcinoma tissues and its participation in a nuclear ERK/IER3/PP2A-B56γ1 positive feedback loop, which likely contributes to pulmonary carcinogenesis [37].Investigations into IER3's clinical implications in other tumors have also progressed. Yamashita et al. first demonstrated that IER3 overexpression enhances γ-radiation sensitivity in glioma cell lines, implicating it in radiation-induced apoptosis [38]. However, the molecular mechanisms underlying IER3-mediated radiation sensitivity modulation remain undefined. Locatelli et al. identified that PI3K/ERK inhibition triggers necroptosis in Hodgkin's lymphoma cells via IER3 downregulation, highlighting IER3 as a potential therapeutic target [39]. Xiao et al., through integrated analysis of TCGA and GEO datasets, identified IER3 as a hub gene associated with prognosis and lymph node metastasis in tongue carcinoma. Co-expression network and survival analyses corroborated its tumor-promoting role. The study further revealed that IER3 facilitates lymphangiogenesis and lymphatic metastasis by augmenting VEGF-C secretion [40].These findings collectively underscore IER3's multifaceted roles across malignancies, with researchers gradually uncovering its context-dependent molecular mechanisms and clinical relevance. Continued investment in IER3-focused research will accelerate the translation of its diagnostic, therapeutic, and prognostic potential into clinical applications.

CONCLUSIONS AND PERSPECTIVES

Over recent decades, advancements in molecular biology and the application of high-throughput sequencing technologies have expanded opportunities for identifying novel cancer biomarkers, with an increasing number utilized in cancer diagnosis, treatment, and prognosis. Accumulated evidence demonstrates differential expression of IER3 between tumor and normal tissues across multiple cancer types, with expression levels varying not only among malignancies but also across developmental stages within the same tumor. Studies report IER3 upregulation in cervical, bladder, hepatocellular, and colorectal cancers, potentially linked to its involvement in apoptosis resistance and proliferation via distinct signaling pathways. The stage-specific expression dynamics of IER3 in early tumorigenesis suggest its potential as a biomarker for early cancer detection. Notably, elevated IER3 expression has been associated with enhanced chemotherapeutic responses in bladder cancer and improved radiotherapeutic outcomes in glioma, though conflicting findings persist, necessitating validation through larger clinical cohorts. The rapid inducibility of IER3 in response to microenvironmental changes positions it as a dynamic biomarker for monitoring tumor progression. Its context-dependent expression patterns and regulatory roles hold promise for clinical applications in cancer diagnosis, therapeutic stratification, and prognostic evaluation. This review synthesizes the clinical significance and mechanistic underpinnings of IER3 in HCC and other common malignancies, providing critical insights into its tumorigenic roles. By elucidating IER3's multifaceted contributions to malignant progression across cancer types, this work establishes a theoretical foundation for identifying novel therapeutic targets in oncology.

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