ISSN: 2755-015X

Journal of Surgery & Anesthesia Research

SCIENTIFIC Research and Community

Research Article

Open Access

RNA Adenosine Deaminases Modulate Oxidative Stress-Mediated Hepatocellular Carcinoma Cell Damage via KEAP1/Nrf2 Axis

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ABSTRACT

This study investigates the role of RNA adenosine deaminases (ADAR1/2) in oxidative stress-induced Hepatocellular Carcinoma (HCC) cell damage. We demonstrate that hydrogen peroxide (H_2O_2)-mediated oxidative stress downregulates ADAR1/2 expression, impairing A-to-I RNA editing of antioxidant genes. Mechanistically, ADAR2 deficiency reduces KEAP1 editing, activating Nrf2 signaling and promoting HCC cell survival. These findings establish ADARs as critical regulators of redox homeostasis in HCC, providing novel therapeutic targets.

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Received: November 07, 2024; **Accepted:** December 01, 2024; **Published:** June 19, 2025

Keywords: ADAR, Oxidative Stress, Hepatocellular Carcinoma, RNA Editing, KEAP1, Nrf2

Introduction

Hepatocellular Carcinoma (HCC) is characterized by chronic inflammation and oxidative stress, which drive oncogenic transformation through Reactive Oxygen Species (ROS) accumulation [1]. RNA adenosine deaminases (ADARs) catalyze A-to-I RNA editing, a post-transcriptional modification influencing gene expression [2]. Recent studies link ADAR dysfunction to HCC progression, but their role in redox regulation remains unclear [3-5]. Here, we explore the ADAR-ROS regulatory axis in HCC cells.

Materials and Methods

Cell Culture and Treatments

HepG2 and Huh7 HCC cells were treated with H_2O_2 (0–500 μM) for 24 h. ADAR1/2 were knocked down using siRNA (Dharmacon).

RNA Editing Analysis

RNA-seq libraries were prepared and sequenced on an Illumina NovaSeq platform. Editing sites were identified using REDIportal.

Oxidative Stress Assays

ROS levels (DCFH-DA), MDA content, and SOD activity were measured using commercial kits.

Western Blotting

Antibodies against ADAR1 (ab188797), ADAR2 (#86106), Nrf2 (#12721), and β-actin (A5441) were used.

Statistical Analysis

Data are presented as mean ± SD. Student's t-test and ANOVA were used for comparisons (GraphPad Prism 9).

Results

ADAR1/2 Downregulation Correlates with Oxidative Stress

Western blot analysis revealed dose-dependent ADAR1/2 reduction in H_2O_2-treated HCC cells (Table 1).

Table 1: ADAR1/2 Expression in HCC Cells

Treatment	HepG2 ADAR1	HepG2 ADAR2	Huh7 ADAR1	Huh7 ADAR2
Control	1.00 ± 0.12	1.00 ± 0.08	1.00 ± 0.10	1.00 ± 0.09
H_2O_2 (200 μM)	0.58 ± 0.06	0.62 ± 0.05	0.65 ± 0.07	0.68 ± 0.06
H_2O_2 (500 μM)	0.32 ± 0.04	0.35 ± 0.03	0.38 ± 0.05	0.40 ± 0.04

$p < 0.05$ vs. control (n=3).

Oxidative Stress Impairs RNA Editing Landscape

RNA-seq identified 1,245 A-to-I editing sites in control cells, with 40% fewer sites after H_2O_2 treatment (Table 2).

Table 2: RNA Editing Changes in HCC Cells

Parameter	Control	H_2O_2 Treated
Total Editing Sites	1,245	748
Editing Efficiency	28.6%	16.5%*

$p < 0.01$ vs. control (n=2).

ADARs Regulate Antioxidant Defense

ADAR1/2 knockdown increased ROS levels by 1.8-fold and MDA content by 2.9-fold (Table 3).

Table 3: Oxidative Stress Biomarkers

Parameter	Control	ADAR1 KD	ADAR2 KD
ROS (DCFH-DA)	1.00	1.82	1.65
MDA (nmol/mg)	1.2	3.5	3.2
SOD Activity (U/mg)	85	52	55

$p < 0.05$ vs. control (n=4).

ADAR2 Modulates KEAP1/Nrf2 Signaling

ADAR2 knockdown reduced KEAP1 editing efficiency from 35.2% to 12.1%, increasing Nrf2 nuclear translocation (Table 4).

Table 4: KEAP1/Nrf2 Axis Regulation

Treatment	KEAP1 Editing (%)	Nuclear Nrf2
Control	35.2 ± 4.1	1.00
ADAR2 KD + H_2O_2	12.1 ± 1.8	1.45 ± 0.12

$p < 0.05$ vs. control (n=3).

Discussion

Our study identifies ADAR1/2 as critical regulators of redox homeostasis in HCC. Oxidative stress downregulates ADARs, impairing editing of antioxidant genes like SOD2 and KEAP1 [6-8]. This leads to ROS accumulation and mitochondrial dysfunction [9].

Notably, ADAR2-mediated KEAP1 editing disrupts its interaction with Nrf2, activating antioxidant defenses [10]. However, ADAR2 loss in HCC enhances Nrf2 signaling, paradoxically promoting cell survival under stress [11]. This suggests a dual role for ADARs in HCC progression, depending on cellular context [12].

Clinically, ADAR expression may predict HCC response to oxidative therapies. Restoring ADAR activity could sensitize tumors to ROS-inducing agents, while targeting ADAR2 might overcome Nrf2-mediated drug resistance [13]. Future studies should validate these findings in patient-derived models and explore ADAR editing of non-coding RNAs [14].

Conclusion

ADAR1/2 maintain redox balance in HCC by editing antioxidant genes. Targeting this pathway offers a novel strategy to combat oxidative stress-driven HCC progression [15].

Conflict of Interest Statement

The authors declare no competing interests.

Author Contributions

Changquan Li designed the study performed the experiments, Houhong Wang analyzed data and supervised the project.

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