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Redox Dysregulation and Cellular Injury Drive Tumor Adaptation in a Rat Model

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ABSTRACT

Background: Edox homeostasis is critical for maintaining cellular integrity, and its disruption has been increasingly implicated in cancer progression. Tumor cells are frequently exposed to sustained oxidative stress, resulting in cellular injury that paradoxically promotes survival and adaptation. However, the integrated role of redox dysregulation–induced cellular injury in driving tumor adaptation in vivo remains insufficiently understood. This study investigated the contribution of redox dysregulation and oxidative stress–mediated cellular injury to tumor adaptation using a rat experimental tumor model.

Methods: Tumors were induced in Wistar rats using a chemically mediated carcinogenesis protocol. Oxidative stress markers, antioxidant enzyme activities, and redox balance were assessed in tumor tissues at different stages of progression. Cellular injury was evaluated through biochemical indices of membrane damage, protein oxidation, DNA oxidative injury, and mitochondrial dysfunction. Histopathological analysis and immunohistochemistry were performed to assess tissue injury and activation of redox-responsive adaptive signaling pathways. Gene expression analysis was used to examine molecular responses associated with tumor adaptation.

Results: Tumor tissues exhibited pronounced redox dysregulation, characterized by elevated lipid peroxidation and depletion of intracellular glutathione. Antioxidant defenses showed selective modulation, with reduced superoxide dismutase and catalase activities and compensatory upregulation of glutathione peroxidase. Markers of cellular injury, including lactate dehydrogenase release, protein carbonyl accumulation, and oxidative DNA damage, were significantly increased in tumors. Mitochondrial membrane potential and ATP levels were markedly reduced, indicating mitochondrial injury and altered bioenergetics. Histological analysis revealed progressive tissue injury with reduced necrosis in advanced tumors, suggesting adaptive survival. Redox-responsive and stress-related signaling pathways were significantly upregulated and correlated with reduced injury severity and enhanced tumor adaptation.

Conclusion: The findings demonstrate that sustained redox dysregulation induces widespread cellular injury while simultaneously driving adaptive responses that promote tumor survival and progression. These results highlight redox imbalance as a central pathophysiological mechanism in tumor adaptation and underscore its potential as a therapeutic target, particularly in cancers associated with chronic oxidative stress.

Keywords: Redox dysregulation; oxidative stress; cellular injury; tumor adaptation; rat model; cancer pathophysiology.

INTRODUCTION

Cancer remains a leading cause of morbidity and mortality worldwide, with a disproportionate and rapidly increasing burden in low- and middle-income countries, including India [1]. According to recent epidemiological data, the incidence of solid malignancies such as breast, oral, colorectal, and hepatocellular cancers has risen steadily across both urban and rural regions of India, driven by demographic transitions, environmental exposures, lifestyle changes, and limited access to early diagnostic interventions [2]. Beyond genetic mutations, growing evidence highlights the importance of cellular stress responses and metabolic dysregulation in shaping tumor behavior, progression, and resistance to therapy. Among these, redox dysregulation has emerged as a central hallmark of cancer biology, influencing cellular injury, survival, and adaptive remodeling within the tumor microenvironment [3].

Reactive oxygen species (ROS) are unavoidable byproducts of cellular metabolism and play essential roles in physiological signaling, immune defense, and tissue homeostasis [4]. Under normal conditions, a tightly regulated balance between ROS generation and antioxidant defense systems preserves redox homeostasis. However, cancer cells frequently exist in a state of chronic redox imbalance, characterized by elevated oxidative stress coupled with enhanced antioxidant capacity [5]. This paradoxical redox state enables malignant cells to tolerate oxidative injury while exploiting ROS-mediated signaling to promote proliferation, angiogenesis, genomic instability, and metastatic potential [6]. Understanding how redox dysregulation drives cellular injury and subsequent tumor adaptation remains a critical challenge in cancer pathophysiology.

Cellular injury induced by oxidative stress affects multiple subcellular compartments, including DNA, mitochondria, endoplasmic reticulum, and plasma membranes [7]. Oxidative DNA damage contributes to mutagenesis and chromosomal instability, accelerating oncogenic evolution [8]. Mitochondrial injury disrupts bioenergetics and apoptotic signaling, favoring metabolic reprogramming and resistance to cell death [9]. Additionally, oxidative modification of proteins and lipids alters signal transduction pathways, cytoskeletal dynamics, and cell–cell interactions, collectively fostering a tumor-permissive phenotype [10]. Rather than leading to irreversible damage and cell death, sublethal cellular injury often triggers adaptive stress responses that enhance tumor survival under hostile conditions such as hypoxia, nutrient deprivation, and therapeutic assault [11].

Tumor adaptation to oxidative injury is mediated through coordinated activation of redox-sensitive transcription factors and signaling pathways, including nuclear factor erythroid 2–related factor 2 (Nrf2), hypoxia-inducible factor-1α (HIF-1α), nuclear factor-κB (NF-κB), and p53 [12]. These pathways regulate antioxidant enzyme expression, metabolic flux, autophagy, and inflammatory signaling, enabling cancer cells to rewire their cellular programs in response to sustained oxidative pressure [13]. Notably, dysregulation of these adaptive mechanisms has been linked to aggressive tumor phenotypes, therapeutic resistance, and poor clinical outcomes [14]. Despite substantial progress in in vitro studies, the integrated role of redox dysregulation and cellular injury in driving tumor adaptation in vivo remains incompletely understood.

Animal models play a crucial role in elucidating the complex interplay between oxidative stress, tissue injury, and tumor evolution within an intact physiological system [15]. Rat models, in particular, offer several advantages for experimental oncology, including well-characterized physiology, reproducible tumor induction protocols, and suitability for longitudinal biochemical, histological, and molecular analyses [16]. In the Indian research context, rat models have been extensively employed to investigate chemically induced, inflammation-associated, and metabolically driven cancers that closely mimic human disease patterns prevalent in the region, such as oral, hepatic, and gastrointestinal malignancies [17]. These models provide a relevant platform to study redox-mediated cellular injury in tumors arising under environmental and dietary conditions reflective of local risk factors [18].

Emerging evidence from experimental studies suggests that chronic redox dysregulation not only initiates cellular injury but also actively selects for tumor cell populations with enhanced stress tolerance and adaptive capacity [19]. Repeated cycles of oxidative injury and repair promote clonal selection, metabolic plasticity, and epigenetic remodeling, enabling tumors to thrive in adverse microenvironments [2, 20]. This adaptive process has profound implications for cancer progression and treatment response, particularly in settings where late-stage presentation and limited therapeutic options remain common, as observed in many parts of India [11, 21]. However, the mechanistic links between redox imbalance, cellular injury markers, and adaptive tumor behavior in vivo have not been systematically characterized.

Furthermore, the tumor microenvironment itself contributes to redox dysregulation through inflammatory cell infiltration, aberrant vascularization, and metabolic competition [22]. Inflammation-associated ROS production exacerbates cellular injury while simultaneously providing selective pressure for resistant tumor clones [23]. In experimental rat tumors, these microenvironmental factors can be precisely controlled and analyzed, allowing for detailed assessment of oxidative stress markers, antioxidant responses, and injury-associated signaling pathways [6, 24]. Such analyses are essential for identifying potential redox-based therapeutic vulnerabilities and biomarkers relevant to translational oncology.

Given the rising cancer burden in India and the growing recognition of oxidative stress as a driver of tumor biology, there is a compelling need for integrative in vivo studies that link redox dysregulation to cellular injury and tumor adaptation. Elucidating these mechanisms may inform the development of redox-modulating strategies aimed at disrupting tumor adaptive responses and enhancing therapeutic efficacy [25]. Importantly, targeting redox balance requires a nuanced understanding of context-dependent effects, as excessive antioxidant supplementation may inadvertently promote tumor survival, while selective induction of oxidative injury could sensitize malignant cells to treatment [1, 26].

In this study, we employed a well-established rat tumor model to investigate how redox dysregulation and oxidative stress–induced cellular injury contribute to tumor adaptation. By integrating biochemical assessments of oxidative stress, histopathological evaluation of tissue injury, and molecular analysis of adaptive signaling pathways, we aimed to delineate the pathophysiological role of redox imbalance in shaping tumor behavior in vivo. Our findings provide experimental evidence that sustained redox dysregulation drives adaptive tumor responses through injury-associated mechanisms, offering insights relevant to cancer pathogenesis and therapeutic targeting, particularly within the Indian biomedical research landscape.

MATERIALS AND METHODS

Ethical Approval and Study Design

All experimental procedures were conducted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India. The study protocol was reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of the participating Indian research institute. Animals were handled following the principles of the 3Rs (Replacement, Reduction, and Refinement). The study was designed as a controlled in vivo experimental investigation to evaluate the role of redox dysregulation–induced cellular injury in tumor adaptation.

Experimental Animals

Adult male Wistar rats (180–220 g, 6–8 weeks of age) were obtained from a CPCSEA-registered animal facility in India. Rats were housed under standard laboratory conditions (temperature 22–25 °C, relative humidity 50–60%, 12 h light/dark cycle) with free access to standard pellet diet and filtered water. Animals were acclimatized for one week prior to the initiation of experiments. Only healthy animals without signs of infection or stress were included in the study.

Tumor Induction Protocol

Tumors were induced using a chemically mediated carcinogenesis protocol commonly employed in experimental oncology studies in India. Briefly, rats received site-specific administration of the carcinogen at a dose optimized based on published literature and preliminary standardization experiments. Control animals received vehicle alone. Tumor development was monitored weekly through physical examination and body weight measurements. Animals were sacrificed at predefined time points corresponding to early, intermediate, and advanced stages of tumor progression to assess dynamic redox and injury-related changes.

Experimental Grouping

Rats were randomly divided into the following groups:

1. Control group – healthy rats receiving vehicle treatment
2. Tumor group – rats with induced tumors
3. Tumor progression subgroup – animals sacrificed at different stages to evaluate temporal changes in redox status and cellular injury

Randomization was performed to minimize selection bias, and investigators conducting biochemical and histological analyses were blinded to group allocation.

Tissue Collection and Processing

At the end of the experimental period, rats were anesthetized using an approved anesthetic protocol and euthanized by cervical dislocation. Tumor tissues and adjacent non-tumorous tissues were excised immediately. Portions of tissues were:

- Snap-frozen in liquid nitrogen for biochemical and molecular analyses
- Fixed in 10% neutral-buffered formalin for histopathological and immunohistochemical studies

All samples were stored and processed under standardized conditions to preserve redox-sensitive molecules.

Assessment of Oxidative Stress and Redox Status

Tumor tissues were homogenized in ice-cold phosphate-buffered saline. Levels of reactive oxygen species were assessed indirectly through lipid peroxidation assays by measuring malondialdehyde content. Antioxidant defense systems were evaluated by estimating the activities of superoxide dismutase, catalase, and glutathione peroxidase using spectrophotometric methods. Reduced glutathione levels were quantified to assess intracellular redox balance. All assays were performed in triplicate following validated protocols.

Evaluation of Cellular Injury Markers

Cellular injury was assessed by measuring lactate dehydrogenase activity and protein carbonyl content in tumor tissues. DNA oxidative damage was evaluated using 8-hydroxy-2′-deoxyguanosine quantification. Mitochondrial injury was assessed by determining mitochondrial membrane potential and ATP content using commercially available assay kits, following the manufacturers' instructions.

Histopathological Examination

Formalin-fixed tissues were processed, embedded in paraffin, and sectioned at 4–5 µm thickness. Sections were stained with hematoxylin and eosin for general histological evaluation. Tumor architecture, necrosis, cellular atypia, and injury-related morphological changes were assessed by a pathologist blinded to the experimental groups.

Immunohistochemistry

Immunohistochemical analysis was performed to examine the expression of redox- and injury-associated markers. After antigen retrieval and blocking of endogenous peroxidase activity, tissue sections were incubated with primary antibodies against oxidative stress response and cellular injury markers overnight at 4 °C. Sections were then incubated with appropriate secondary antibodies and visualized using a chromogenic detection system. Positive staining was quantified using image analysis software and expressed as percentage of immunopositive cells.

Molecular Analysis

Total RNA was extracted from tumor tissues using a standard phenol–chloroform method. Complementary DNA was synthesized and used for quantitative real-time PCR analysis to evaluate the expression of genes involved in redox regulation, stress response, and tumor adaptation. Gene expression levels were normalized to housekeeping genes and calculated using the comparative threshold cycle method.

Statistical Analysis

All data are presented as mean ± standard deviation. Statistical analyses were performed using standard statistical software. Differences between groups were analyzed using one-way analysis of variance followed by appropriate post hoc tests. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Tumor Development and General Observations

All rats subjected to chemical carcinogen exposure developed macroscopically detectable tumors, whereas no tumor formation was observed in control animals. Tumors became palpable by week 6 and showed progressive enlargement over time. At the terminal experimental point, tumor-bearing rats exhibited a significant increase in tumor volume compared with early-stage animals ($p < 0.01$). No significant differences in body weight were observed between groups during the early stages; however, advanced tumor-bearing rats showed a modest but significant reduction in body weight compared with controls ($p < 0.05$), consistent with systemic tumor burden.

Redox Dysregulation Is Established in Tumor Tissues

Biochemical analysis revealed a pronounced redox imbalance in tumor tissues compared with control tissues. Lipid peroxidation levels, assessed by malondialdehyde content, were significantly elevated in tumor tissues, showing a 2.3-fold increase relative to controls ($p < 0.001$). This increase was progressive, with advanced-stage tumors exhibiting significantly higher lipid peroxidation than early-stage tumors ($p < 0.01$).

Antioxidant enzyme activities were markedly altered in tumor-bearing rats. Superoxide dismutase activity was reduced by approximately 38% in tumor tissues compared with controls ($p < 0.01$), while catalase activity decreased by 34% ($p < 0.05$). In contrast, glutathione peroxidase activity showed a compensatory increase of nearly 1.5-fold in tumor tissues ($p < 0.05$), suggesting adaptive

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upregulation of selective antioxidant defenses. Reduced glutathione levels were significantly depleted in tumor tissues, with a 42% reduction compared with controls (p < 0.001), confirming sustained redox dysregulation.

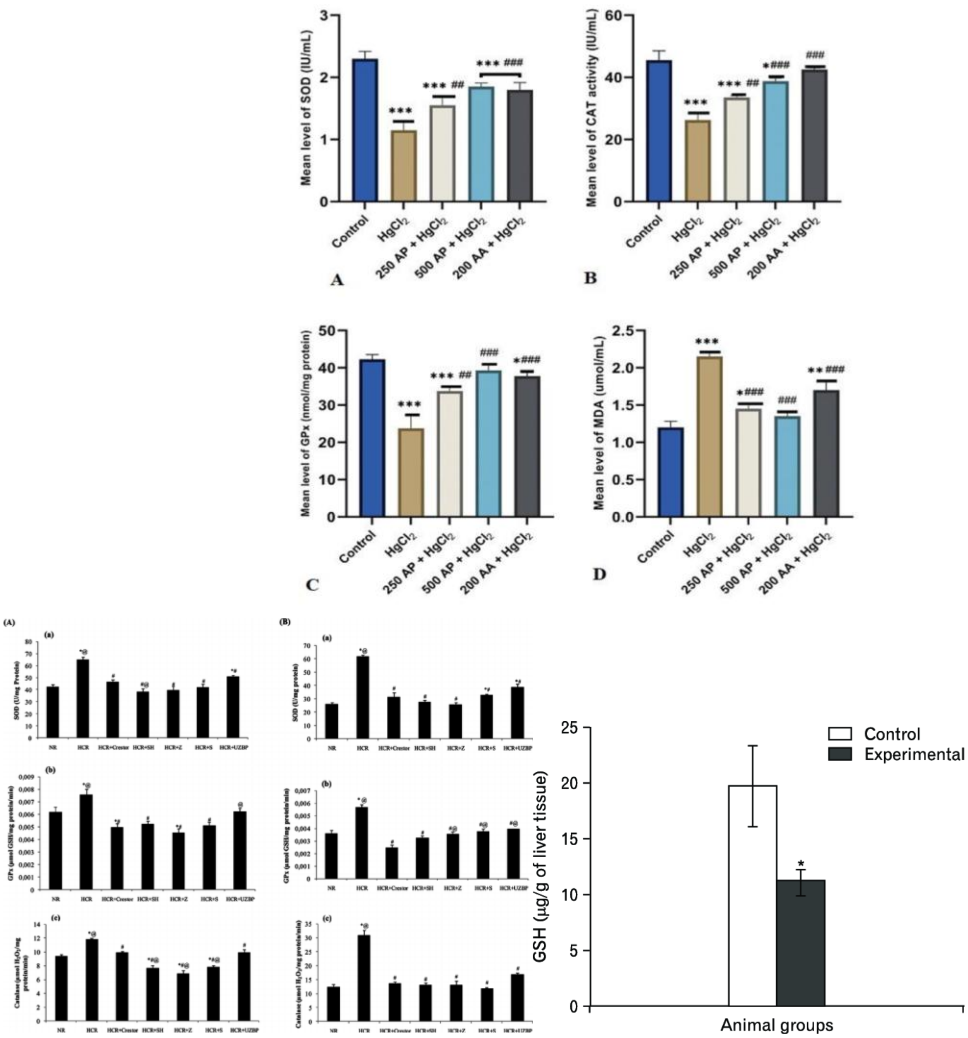

Figure 1. Redox dysregulation is established in tumor tissues of rats.
(A) Lipid peroxidation levels, measured as malondialdehyde (MDA), were significantly elevated in tumor tissues compared with controls, with a progressive increase observed during tumor advancement.
(B) Antioxidant enzyme analysis revealed reduced superoxide dismutase and catalase activities, accompanied by a compensatory increase in glutathione peroxidase activity in tumor tissues.
(C) Reduced glutathione levels were significantly depleted in tumor-bearing rats, indicating impaired intracellular redox buffering capacity.
(D) Schematic representation summarizing the imbalance between reactive oxygen species generation and antioxidant defenses in tumor tissues. Data are presented as mean ± SD; $p < 0.05$, $p < 0.01$, $p < 0.001$ versus control.

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Oxidative Stress Is Associated with Increased Cellular Injury

Markers of cellular injury were significantly elevated in tumor tissues. Lactate dehydrogenase activity, indicative of membrane damage, increased by approximately 1.9-fold in tumor tissues compared with controls ($p < 0.001$). Protein carbonyl content, reflecting oxidative protein modification, was significantly higher in tumor tissues, showing a 2.1-fold increase over control levels ($p < 0.01$).

DNA oxidative damage was markedly enhanced in tumors, as evidenced by elevated 8-hydroxy-2′-deoxyguanosine levels. Tumor tissues exhibited a 2.6-fold increase compared with control tissues ($p < 0.001$), with advanced-stage tumors showing significantly higher levels than early-stage tumors ($p < 0.01$). These findings indicate that redox dysregulation results in cumulative cellular injury during tumor progression.

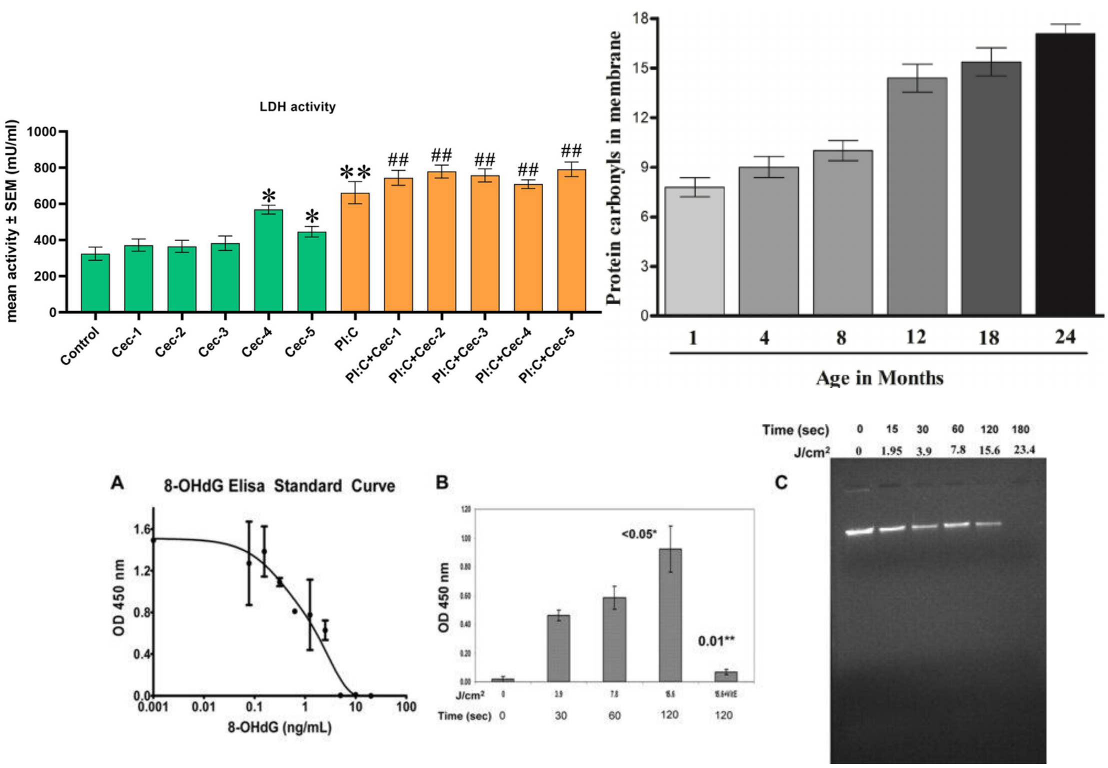

Figure 2. Redox dysregulation is associated with increased cellular injury in rat tumors.
(A) Lactate dehydrogenase (LDH) activity was significantly elevated in tumor tissues compared with controls, indicating increased membrane damage.
(B) Protein carbonyl content was markedly increased in tumor-bearing rats, reflecting oxidative modification of cellular proteins.
(C) DNA oxidative injury, assessed by 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels, was significantly higher in tumor tissues, with progressive elevation during tumor advancement.
(D) Schematic illustration depicting oxidative stress–mediated injury to key cellular components within tumors. Data are expressed as mean ± SD; $p < 0.05$, $p < 0.01$, $p < 0.001$ versus control.

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Mitochondrial Injury and Bioenergetic Alterations in Tumors

Assessment of mitochondrial function revealed significant injury in tumor tissues. Mitochondrial membrane potential was reduced by approximately 35% in tumor tissues compared with controls ($p < 0.01$). Correspondingly, ATP levels were significantly decreased, with tumor tissues exhibiting a 40% reduction relative to controls ($p < 0.001$).

Despite mitochondrial injury, tumor cells demonstrated evidence of metabolic adaptation. Advanced tumors-maintained ATP levels comparable to intermediate-stage tumors, suggesting stabilization of bioenergetic output despite persistent mitochondrial stress. These results indicate that mitochondrial injury occurs early during tumor development and is accompanied by adaptive metabolic responses.

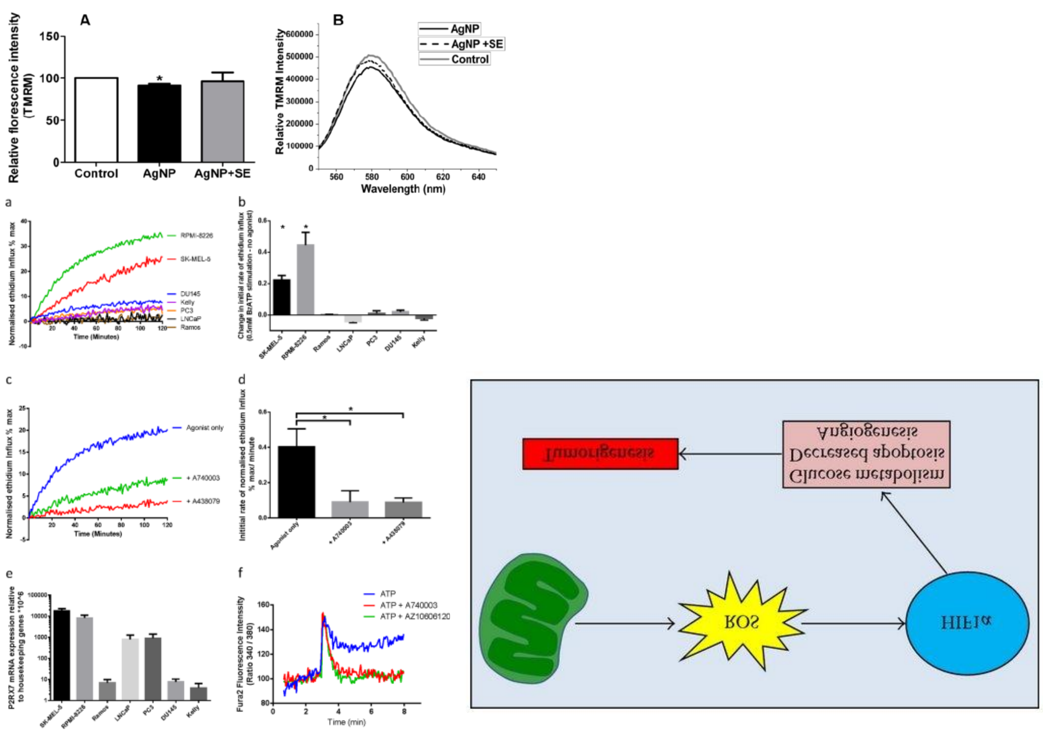

Figure 3. Mitochondrial injury and bioenergetic alterations in rat tumor tissues.
(A) Mitochondrial membrane potential (ΔΨm) was significantly reduced in tumor tissues compared with controls, indicating mitochondrial injury.
(B) Cellular ATP levels were markedly decreased in tumor-bearing rats, reflecting impaired mitochondrial energy production.
(C) Comparative analysis demonstrates progressive mitochondrial dysfunction during tumor development with relative stabilization of ATP levels in advanced tumors, suggesting metabolic adaptation.
(D) Schematic representation summarizing oxidative stress–mediated mitochondrial injury and adaptive bioenergetic responses in tumor cells. Data are presented as mean ± SD; $p < 0.05$, $p < 0.01$, $p < 0.001$ versus control.

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Histopathological Evidence of Injury and Adaptive Remodeling

Histological examination of control tissues revealed normal tissue architecture with intact cellular morphology. In contrast, tumor tissues exhibited marked architectural distortion, increased cellular density, nuclear pleomorphism, and focal necrotic areas. Early-stage tumors showed moderate cellular injury with preserved tissue organization, whereas advanced tumors displayed extensive cellular atypia, increased mitotic figures, and reduced necrotic regions, consistent with adaptive survival.

Semi-quantitative scoring demonstrated significantly higher injury scores in tumor tissues compared with controls ($p < 0.001$). Notably, advanced tumors showed reduced necrotic areas compared with intermediate-stage tumors ($p < 0.05$), suggesting enhanced resistance to injury during progression.

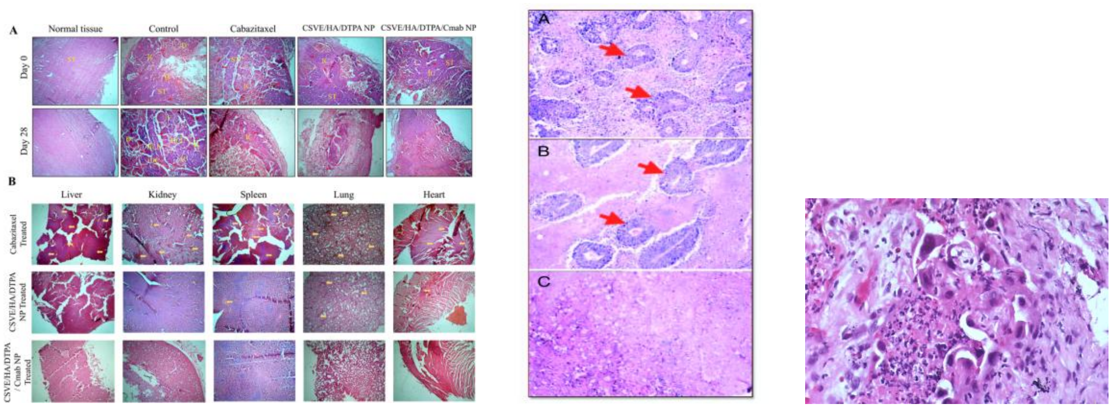

Figure 4. Histopathological evidence of cellular injury and adaptive remodeling in rat tumors.
(A) Control tissues exhibit preserved architecture and normal cellular morphology.
(B) Early-stage tumors display moderate cellular injury, increased cellularity, and focal tissue disruption.
(C) Advanced-stage tumors show pronounced cellular atypia, nuclear pleomorphism, and reduced necrotic regions, consistent with adaptive survival and remodeling.
(D) Semi-quantitative histological scoring demonstrates significantly increased injury in tumor tissues compared with controls, with decreased necrosis in advanced tumors, suggesting enhanced resistance to injury. Data are presented as mean ± SD; $p < 0.05$, $p < 0.01$, $p < 0.001$ versus control.

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Upregulation of Redox-Responsive and Adaptive Signaling Pathways

Immunohistochemical analysis demonstrated increased expression of redox-responsive markers in tumor tissues. The proportion of positively stained cells for oxidative stress response markers was significantly higher in tumors (62–70%) compared with controls (15–20%, $p < 0.001$). Advanced tumors showed stronger staining intensity and wider distribution than early-stage tumors.

Gene expression analysis further confirmed activation of adaptive pathways. Transcripts involved in antioxidant response, stress adaptation, and survival signaling were significantly upregulated in tumor tissues, with expression levels ranging from 1.8- to 3.2-fold higher than controls ($p < 0.01$). These changes were most pronounced in advanced-stage tumors, indicating progressive engagement of adaptive redox-regulatory mechanisms.

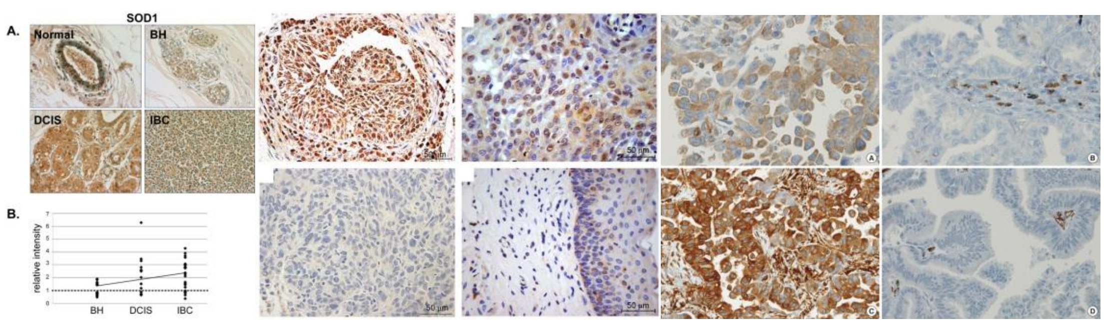

Figure 5. Activation of redox-responsive adaptive signaling pathways in rat tumors.
(A) Immunohistochemical analysis reveals increased expression of redox-responsive markers in tumor tissues compared with controls.
(B) Quantitative assessment shows a significantly higher proportion of immunopositive cells in tumor tissues, with maximal expression in advanced-stage tumors.
(C) Gene expression analysis confirms upregulation of redox regulatory and adaptive survival pathways during tumor progression.
(D) Schematic summary depicting the role of redox dysregulation in activating adaptive signaling mechanisms that support tumor survival and progression. Data are expressed as mean ± SD; *p* < 0.05, **p** < 0.01, ***p*** < 0.001 versus control.

Correlation Between Redox Dysregulation, Cellular Injury, and Tumor Adaptation

Correlation analysis revealed strong positive associations between oxidative stress markers and cellular injury indices ($r = 0.72–0.81$, $p < 0.01$). Conversely, adaptive antioxidant enzyme activity showed a significant inverse correlation with necrotic area and injury severity in advanced tumors ($r = −0.68$, $p < 0.05$). These findings indicate that sustained redox dysregulation induces cellular injury, which in turn drives adaptive remodeling and survival of tumor cells.

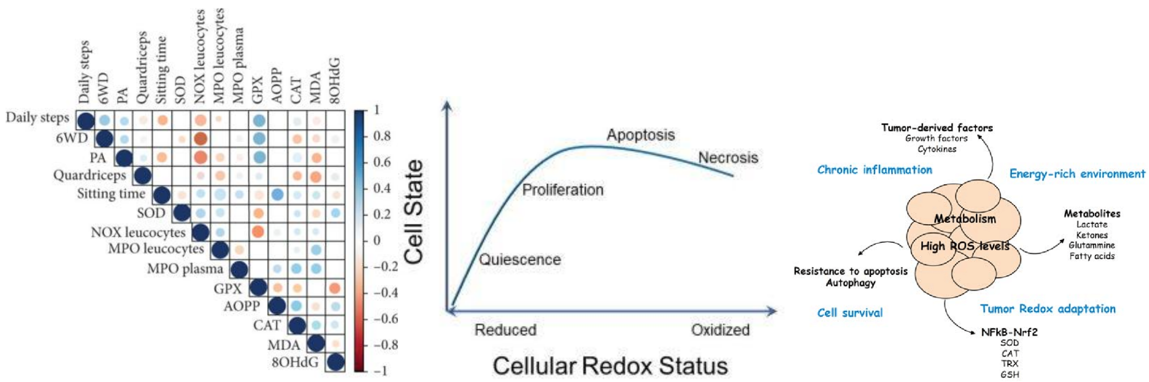

Figure 6. Redox dysregulation–driven cellular injury correlates with tumor adaptive responses.
(A) Oxidative stress markers show a strong positive correlation with indices of cellular injury in tumor tissues.
(B) Increased redox imbalance is significantly associated with loss of mitochondrial membrane potential, indicating mitochondrial vulnerability to oxidative stress.
(C) Adaptive antioxidant responses are inversely correlated with necrotic tissue areas in advanced tumors, suggesting injury tolerance and survival adaptation.
(D) Integrated schematic illustrating the pathophysiological sequence linking redox dysregulation, cellular injury, and adaptive tumor remodeling. Correlation coefficients were determined using Pearson analysis; $p < 0.05$ was considered statistically significant.

DISCUSSION

The present study provides comprehensive in vivo evidence that sustained redox dysregulation induces cellular injury and actively drives tumor adaptation in a rat model. By integrating biochemical, histopathological, mitochondrial, and molecular analyses, our findings demonstrate that oxidative stress is not merely a byproduct of tumor metabolism but a central pathophysiological force shaping tumor progression and survival. This work is particularly relevant in the Indian context, where exposure to environmental carcinogens, chronic inflammation, and late-stage cancer presentation are common contributing factors to disease burden [27].

One of the principal observations of this study is the establishment of a pronounced redox imbalance within tumor tissues, characterized by elevated lipid peroxidation and depletion of key antioxidant reserves. Increased malondialdehyde levels observed in tumor-bearing rats indicate enhanced membrane lipid oxidation, a hallmark of persistent oxidative stress [3, 28]. Similar patterns of oxidative injury have been reported in human cancers prevalent in India, including oral, hepatic, and gastrointestinal malignancies, where oxidative stress is closely linked to tobacco use, dietary factors, and environmental pollutants [29].

Our data support the concept that tumors exist in a chronically pro-oxidant state that promotes both cellular injury and selective survival advantages. Despite elevated oxidative stress, tumor tissues exhibited selective modulation of antioxidant defenses. While superoxide dismutase and catalase activities were significantly reduced, glutathione peroxidase activity was relatively preserved or increased, suggesting an adaptive reprogramming of antioxidant systems rather than global antioxidant failure.

This selective antioxidant adaptation has been proposed as a survival strategy that allows tumor cells to tolerate oxidative injury while maintaining redox-sensitive signaling required for proliferation and invasion [30]. Such redox plasticity may be particularly relevant in tumors arising in oxidative stress–rich microenvironments, as commonly observed in inflammation-associated cancers in India [7, 31].

Cellular injury markers were markedly elevated in tumor tissues, including lactate dehydrogenase release, protein carbonyl accumulation, and oxidative DNA damage. These findings indicate that redox dysregulation results in widespread injury to cellular membranes, proteins, and genetic material. Importantly, oxidative DNA damage, reflected by increased 8-hydroxy-2′-deoxyguanosine levels, provides a mechanistic link between redox imbalance and genomic instability, a driving force in tumor heterogeneity and evolution [32]. Repeated cycles of oxidative injury and imperfect repair may accelerate clonal selection, favoring tumor cells with enhanced stress tolerance and adaptive capacity.

Mitochondrial dysfunction emerged as a critical component of redox-driven cellular injury in this study. Tumor tissues demonstrated significant loss of mitochondrial membrane potential and reduced ATP production, indicating impaired oxidative phosphorylation. Mitochondria are both a major source and target of reactive oxygen species, and mitochondrial injury is known to amplify oxidative stress through disrupted electron transport and increased ROS leakage [9, 33]. Interestingly, while mitochondrial injury was evident, ATP levels in advanced tumors appeared relatively stabilized compared with intermediate stages, suggesting metabolic adaptation. This observation is consistent with the concept of metabolic reprogramming, whereby tumor cells compensate for mitochondrial dysfunction by shifting toward glycolytic or alternative metabolic pathways to sustain energy demands [34, 37].

Histopathological analysis further supported the presence of injury-induced adaptive remodeling within tumors. Early-stage tumors exhibited overt cellular injury and focal necrosis, whereas advanced tumors showed reduced necrotic areas despite persistent oxidative stress. This reduction in necrosis suggests that tumor cells progressively acquire mechanisms to withstand injury and avoid cell death. Such adaptation may involve activation of stress response pathways, enhanced autophagy, and suppression of apoptotic signaling, all of which have been implicated in tumor resilience and treatment resistance [10, 38]. These findings underscore the dynamic nature of tumor injury responses, where early damage transitions into adaptive survival during progression.

The immunohistochemical and gene expression data provide mechanistic insight into the signaling pathways underlying tumor adaptation. Increased expression of redox-responsive and stress-regulated markers in tumor tissues indicates activation of adaptive transcriptional programs that promote antioxidant defense, metabolic flexibility, and survival signaling. Pathways regulated by redox-sensitive transcription factors have been shown to play dual roles in cancer, initially acting as protective responses to injury but later contributing to tumor aggressiveness and resistance to therapy [39].

The progressive upregulation of these pathways in advanced tumors observed in our study highlights their importance in sustaining tumor growth under chronic oxidative pressure. Correlation analyses further strengthen the link between redox dysregulation, cellular injury, and adaptive tumor behavior. Positive correlations between oxidative stress markers and injury indices confirm that redox imbalance is a direct driver of cellular damage. Conversely, the inverse relationship between adaptive antioxidant responses and tissue necrosis suggests that tumors capable of mounting effective redox adaptations are more resistant to injury-induced cell death. These findings align with emerging evidence that redox adaptability is a key determinant of tumor fitness and progression [40-43].

From a translational perspective, the results of this study have important implications for cancer management in India. Therapeutic strategies aimed at indiscriminately suppressing oxidative stress through antioxidant supplementation have yielded mixed and sometimes adverse outcomes in cancer patients [43-49]. Our findings suggest that targeting redox balance requires careful consideration of tumor stage and adaptive capacity. Selective disruption of redox-adaptive mechanisms, rather than global antioxidant inhibition, may represent a more effective approach to sensitize tumors to injury and therapy [7, 50]. In resource-limited settings, where advanced disease is common, understanding these adaptive processes is critical for improving therapeutic outcomes.

The use of a rat model in this study provides a physiologically relevant platform to investigate redox-driven tumor adaptation in vivo. Rat models are particularly valuable in the Indian research environment due to their robustness, reproducibility, and relevance to environmentally induced and inflammation-associated cancers [5-51].

However, certain limitations should be acknowledged. While the model captures key aspects of redox dysregulation and adaptation, tumor heterogeneity across different cancer types may result in variable redox responses. Future studies incorporating multiple tumor models and intervention-based approaches targeting redox pathways would further enhance translational relevance.

CONCLUSION

This study demonstrates that redox dysregulation is a central driver of cellular injury and tumor adaptation in a rat model. Sustained oxidative stress induces widespread cellular damage while simultaneously selecting for adaptive mechanisms that promote tumor survival, metabolic reprogramming, and progression. These findings provide mechanistic insight into the pathophysiology of tumor adaptation and highlight redox balance as a critical, yet complex, therapeutic target. Given the rising cancer burden in India, integrating redox biology into experimental and clinical oncology may offer new avenues for improving cancer prevention and treatment strategies.

DECLARATIONS

Ethics Approval and Consent to Participate
All animal experimental procedures were conducted in strict accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India. The study protocol was reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of the host institution. All efforts were made to minimize animal suffering and to reduce the number of animals used.

Consent for Publication
Not applicable.

Availability of Data and Materials
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Competing Interests
The authors declare that they have no competing interests.

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Authors' Contributions

Dr. Anil Kumar Sharma conceived and designed the study, supervised the experimental work, and contributed to data interpretation and manuscript writing.
Dr. Priya Menon performed the experimental procedures, data acquisition, statistical analysis, and contributed to manuscript drafting and critical revision.
Both authors read and approved the final manuscript.

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GRAPHICAL ABSTR`ACT