Review

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INSIGHTS INTO METABOLIC LOGIC AND OXIDATIVE STRESS IN CANCER USING *C. ELEGANS*

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ABSTRACT

This review examine the nematode *Caenorhabditis elegans* as a powerful model for cancer research, moving beyond its well-established utility in dissecting conserved genetic pathways. Its true strength may lie in modeling the intricate interplay between dysregulated metabolism and oxidative stress. This review first discusses how *C. elegans* provides a whole-organism system to study the causal links between metabolic overload, the production of reactive oxygen species (ROS), and the activation of conserved detoxification pathways. The discussion then shifts to the Warburg effect, presenting the worm's unique rhodoquinone-dependent anaerobic metabolism as an evolutionary control experiment that offers a non-canonical framework for understanding the functional roles of lactate in the tumor microenvironment. Finally, this review examines the cell nucleus as an active sensor of stress, discussing how oxidative stress triggers the structural reorganization, from global chromatin remodeling to the formation of stress-induced biomolecular condensates. It is concluded that *C. elegans* offers an excellent platform to progress from studying isolated cancer-related pathways toward an integrated understanding of the metabolic and environmental stress that drives tumorigenesis.

Keywords: *chromatin remodeling; oxidative stress; reactive oxygen species, Warburg effect; metabolic reprogramming; tumor model; Ras/MAPK signaling; apoptosis.*

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1. INTRODUCTION

Barely visible to the naked eye, *Caenorhabditis elegans* is a transparent nematode of remarkable complexity, possessing developed organ systems despite its small size of 1 mm. This tiny creature is found harmlessly living in soil and rotting vegetation where they feed on bacteria. *C. elegans* has emerged as a foundational organism in biology, giving us invaluable information about the fundamental processes that guide the development of a single cell into a complete animal.

The rise of *C. elegans* as a model system was catalyzed by Sydney Brenner's seminal 1974 paper. During an exciting time for molecular genetics that followed the discovery of DNA's structure, Brenner sought a simple animal model to investigate the genetic basics of organogenesis and neural function. He identified the ideal candidate in *C. elegans* [1]. Brenner's selection was strategic. The worm presented numerous advantages for genetic questions. With a three-day life cycle and the ability to produce hundreds of progeny, it could be cultivated in large quantities. Its reproductive biology, dominated by self-fertilizing hermaphrodites, streamlined genetic analysis. Critically, its transparent body permitted the direct observation of every cell dividing, migrating, and differentiating in a live animal (Figure 1) [2].

Figure 1 – The Advantage of Transparency. A micrograph of an adult hermaphrodite *C. elegans*. Scale bar 0.1 mm [5].

This unique feature enabled Sydney Brenner, John Sulston, and Robert Horvitz to map the complete lineage of all 959 somatic cells, a monumental achievement that uncovered the core genetic mechanism of programmed cell death (apoptosis) and earned them the 2002 Nobel Prize in Medicine [3].

Today, these same attributes make the worm an exceptionally relevant tool for investigating cancer [4]. Cancer research

is expanding beyond a purely genetic perspective to include metabolic reprogramming and oxidative stress as central drivers of the disease.

2. MATERIALS AND METHODS

2.1 Source Material

This review was developed based on peer-reviewed scientific literature addressing the molecular, metabolic, and oxidative mechanisms of cancer, using *C. elegans* as a model organism. The selection of materials covered a broad interdisciplinary scope, encompassing molecular genetics, biochemistry, redox biology, systems oncology, and computational modeling.

A total of 19 scientific papers were included, comprising original research articles, systematic reviews, and book chapters from leading international and regional journals. Particular attention was given to experimental studies that investigated the relationship between metabolic reprogramming, oxidative stress, and chromatin remodeling in both *C. elegans* and mammalian tumor models.

The reviewed sources also incorporated mechanistic studies on apoptosis, mitochondrial dysfunction, and antioxidant defense systems (e.g., SKN-1/Nrf2, Ras/MAPK, and mTOR signaling), providing an integrative foundation for understanding conserved oncogenic pathways.

2.2 Data Sources and Search Strategy

The inclusion criteria focused on studies that investigated the molecular mechanisms of oxidative stress, redox regulation, and chromatin remodeling in *C. elegans*, highlighting conserved signaling pathways such as SKN-1/Nrf2, Ras/MAPK, and mitochondrial stress responses that underlie tumor metabolism and adaptation. Particular attention was given to research elucidating genetic and biochemical parallels between nematode and mammalian cancer models, as well as multi-omics approaches (genomics, transcriptomics, proteomics, metabolomics) that provide integrative insights into metabolic reprogramming and oxidative damage repair mechanisms.

2.3 Research Tools and Keywords

The primary keywords and search terms included combinations of: “chromatin remodeling,” “oxidative stress,” “reactive oxygen species (ROS),” “Warburg effect,” “metabolic reprogramming,” “tumor model,” “Ras/MAPK signaling,” and “apoptosis (CED-3, CED-4, CED-9).” Data synthesis emphasized mechanistic insights rather than descriptive summaries, with particular attention to translational connections between nematode models and mammalian oncology.

3. A SOLID SYSTEM FOR CANCER BIOLOGY

The value of *C. elegans* arises from a potent synergy of biological simplicity and deep evolutionary conservation, which together create an ideal living system for dissecting the mechanisms of cancer. *C. elegans* was the first multicellular organism to have its entire genome sequenced, providing a clear genetic landscape. A significant portion of human genes, estimated at 60-80%, have orthologs in the worm, including many key regulators implicated in cancer [3].

The fundamental cellular processes that become dysregulated in human cancer are functionally conserved in *C. elegans* . This includes the core apoptosis machinery, where the worm proteins CED-3, CED-4, and CED-9 are orthologs that perform analogous functions to human caspases, Apaf1, and Bcl-2, respectively [3]. The Ras/MAPK signaling cascade, which is a primary driver of cell proliferation, is regulated by the worm’s Ras ortholog, *let-60* [6]. The following Table 1 provides a concise overview of the conservation between the worms and humans.

While *C. elegans* does not develop metastatic cancers, its germline serves as an excellent model for tumor-like proliferative growth [3]. As the only tissue containing immortal, pluripotent stem cells in the adult worm, the germline can be induced to over-proliferate through specific mutations. For example, mutations in the worm ortholog of the Notch receptor, *glp-1*, lead to the uncontrolled division of these stem cells, resulting in a tumorous mass of undifferentiated cells that fills the animal (Figure 2) [7].

3. OXIDATIVE STRESS IN CANCER

Oxidative stress is a critical factor in carcinogenesis. This persistent cellular damage can corrupt DNA, promote mutations, and ultimately drive malignant transformation. *C. elegans* provides a uniquely tractable system for observing this process, illuminating the direct relationships between diet, intracellular stress, and the organism’s adaptive responses.

Reactive oxygen species (ROS), such as the superoxide radical (O_2^-) and hydrogen peroxide (H_2O_2), are natural byproducts of aerobic respiration [9]. While used in cellular signaling at low concentrations, excess ROS induces a state of oxidative stress that overwhelms endogenous antioxidant sys-

Table 1 – Key Cancer-Related Pathways Conserved in *C. elegans*. This table summarizes several core signaling pathways that are dysregulated in human cancer, listing the key human proteins and their corresponding functional orthologs in the nematode.

Pathways	Key human proteins	Key *C. elegans* orthologs	Conserved functions
Apoptosis	Caspase-3, APAF-1, Bcl-2	CED-3, CED-4, CED-9	Core machinery of programmed cell death execution [3]
Ras/MAPK Signaling	Ras, Raf, MEK, ERK	LET-60, LIN-45, MEK-2, MPK-1	Pro-proliferative signaling cascade [6]
Insulin/IGF-1 Signaling	IGF-1 Receptor, PI3K, Akt, FOXO	DAF-2, AGE-1, AKT-1/2, DAF-16	Regulation of metabolism, stress resistance, and longevity [6]
DNA Damage Response	p53	CEP-1	Transcription factor activated by DNA damage to induce apoptosis [3]

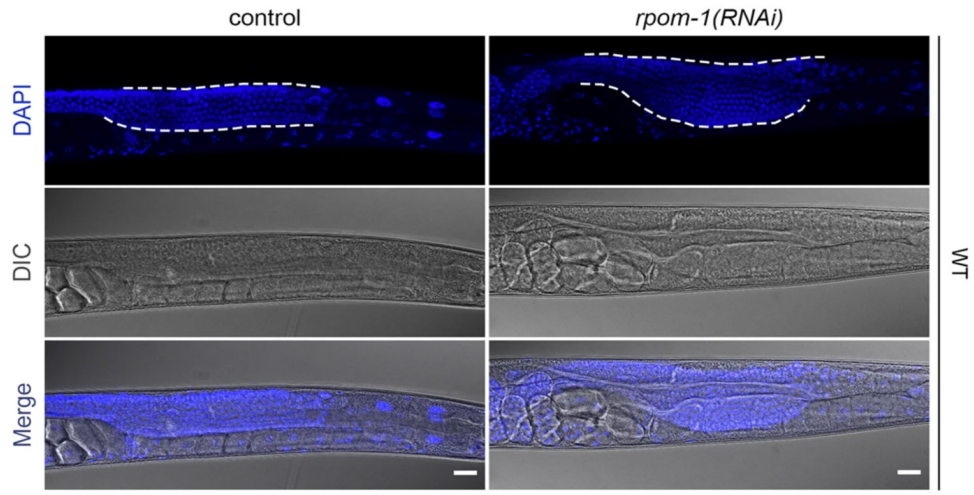

Figure 2 – A Germline Tumor in C. elegans. Micrographs comparing a healthy worm (left panels) to one with a tumor-like mass in its germline (right panels). The germline is the reproductive tissue where stem cells reside. The top panels visualize cell nuclei, which are stained blue with DAPI. The middle panels show the worm's overall structure using DIC (Differential Interference Contrast) microscopy. Scale bar 20um [8].

tems. The consequences include damage to lipid membranes, protein misfolding, and DNA lesions. This accumulation of molecular damage is a recognized contributor to both aging and the onset of cancer.

Organisms have developed a robust defense system to mitigate oxidative stress. Central to this response, in both nematodes and humans, is the master transcriptional regulator Nrf2, known as SKN-1 in *C. elegans* [10]. Under normal conditions, it stays quiet in the cytoplasm. Upon exposure to oxidative stress, it translocates into the nuclei of intestinal cells, which is the worm's primary metabolic organ, where it initiates a large-scale detoxification program. The importance of this pathway is underscored by the fact that worms lacking a functional *skn-1* gene exhibit increased sensitivity to stress and have a shortened lifespan [11].

4. EVOLUTIONARY CONTROL FOR THE WARBURG EFFECT

A central insight of modern cancer biology is that tumors actively remodel their metabolism to support their growth. With its unique metabolic adaptations, *C. elegans* offers an exceptional opportunity to study the underlying logic of cancer's energy and biomass acquisition strategies.

In the 1920s, Otto Warburg observed that cancer cells exhibit a high rate of glucose uptake but primarily metabolize it through glycolysis, producing lactate even in the presence of enough oxygen [11]. This phenomenon, known as Warburg effect, was initially thought to be a result of defective mitochondria. It is now understood as a deliberate metabolic shift directed by oncogenes. This strategy prioritizes the diversion of glycolytic intermediates into biosynthetic pathways to produce the nucleotides, lipids, and amino acids necessary for rapid cell proliferation [13].

The central question of the Warburg effect is "why cancer cells produce lactate?". The question is typically analyzed from a vertebrate perspective. However, comparative biology reveals that lactate fermentation is not the only metabolic solution for surviving hypoxia. *C. elegans* employ a distinct anaerobic strategy. Under low-oxygen conditions, the worm reconfigures its mitochondrial electron transport chain. It replaces the canonical electron carrier, ubiquinone (UQ), with a related molecule, rhodoquinone (RQ) [14]. This RQ-based system uses fumarate instead of oxygen as the terminal electron acceptor. This adaptation is vital for the worm's survival in its native hypoxic environments. Critically, this entire mode of anaerobic energy production generates no lactate.

The existence of a lactate-independent anaerobic metabolism in a complex animal like *C. elegans* provides a powerful intellectual tool [14]. It leads us to ask a deeper question about the Warburg effect "is lactate just a byproduct of rapid glycolysis, or is it a functionally active molecule in the tumor microenvironment?". A majority of evidence supports the latter hypothesis. Lactate is not metabolic waste. It is a signaling molecule and a microenvironmental modulator. Cancer cells export lactate to acidify their surroundings, which enhances invasion, promotes angiogenesis, and suppresses local immune responses. The *C. elegans* system, with its endogenous lactate-free alternative, serves as an ideal evolutionary control group to dissect these functions. It allows researchers to separate lactate's role in bioenergetics from its function as a signaling agent, thereby clarifying why human cancers may have evolved such a strong dependence on its production.

This metabolic framework can be directly tested using the worm's germline tumor models. The hyperproliferative cells in these tumors are metabolically insatiable and undergo significant reprogramming. For example, caloric restriction through fasting can double the lifespan of worms with tumors. The cellular recycling process of autophagy also has a dual role. Its inhibition exacerbates tumor growth, whereas its enhancement can restrain it [15]. These findings establish a direct, *in vivo* link between an organism's metabolic state and tumor progression.

Furthermore, these metabolic programs are governed by the same oncogenic pathways found in humans. The conserved Ras/MAPK pathway is a key driver of cell proliferation in the worm's germline [6]. Recent studies have demonstrated that the activity of this oncogenic pathway is modulated by nutritional inputs, such as dietary vitamin B12 [16]. This pro-

vides a tractable system to figure out how oncogenes hijacks the body's metabolism to fuel malignant growth.

5. CHROMATIN REMODELING AS A STRESS RESPONSE

While metabolic conflicts occur in the cytoplasm and mitochondria, the nucleus is where the ultimate consequences of oxidative stress are often manifested. The nucleus is not a static library of genetic information. It functions as a dynamic center that physically reorganizes in response to cellular stress. Leveraging its unique advantages for in vivo imaging, *C. elegans* has been instrumental in exploring this edge, revealing the structural changes nucleus undergoes to ensure cell survival.

The packaging of DNA into chromatin determines the gene expression patterns. It is now evident that this packaging undergoes rapid and extensive remodeling upon cellular stress. In *C. elegans* , stress originating from mitochondrial dysfunction induces widespread alterations to chromatin structure. This process involves the extensive deposition of specific histone modifications, that are typically associated with transcriptional repression [17].

Paradoxically, this global chromatin condensation appears to be a prerequisite for a successful defense. By compacting the majority of the genome, the cell may enhance the relative accessibility of specific stress-response loci, facilitating their activation [18]. This balance is critical. Other studies have demonstrated that if chromatin becomes decondensed, the worm cannot launch an effective response to oxidative stress, leading to a shortened lifespan. This indicates that the nucleus must maintain a precise physical organization.

Beyond epigenetic modifications, severe oxidative stress can trigger the de novo formation of distinct structures within the nucleus. One such structure, identified in the *C. elegans* germline, is the Stress-Induced Nuclear Granule (SING) [19]. These are membraneless biomolecular condensates that assemble quickly when cells are exposed to stressors like hydrogen peroxide and nutrient deprivation. The composition of SINGs points to their function. They are enriched with ubiquitin, the molecular tag for protein degradation, as well as components of the proteasome. This composition strongly suggests that SINGs function as transient quality-control centers, sequestering and processing damaged proteins that accumulate in the nucleus during the stress. The appearance of SINGs is a marker of severe cellular damage and is correlated with cell cycle failure and death.

6. DISCUSSION

C. elegans offers a compact yet highly integrative system for exploring how oxidative stress and metabolic remodeling converge in carcinogenesis. Beyond its classical role in developmental genetics, its conserved redox pathways, particularly SKN-1/Nrf2, mirror mammalian mechanisms linking ROS exposure to antioxidant defense and detoxification. Through this axis, *C. elegans* connects metabolic overload to oxidative damage, genomic instability, and altered lifespan, reflecting fundamental tumor biology principles.

The organism's rhodoquinone-dependent anaerobic metabolism provides an evolutionary parallel to the Warburg effect, allowing hypoxic survival without lactate production. This contrast helps distinguish lactate's signaling functions from its energetic roles in mammalian tumors. Furthermore, oxidative stress in *C. elegans* triggers chromatin condensation, histone modification, and stress-induced nuclear granules, underscoring the nucleus as a redox-sensitive hub coordinating metabolic and structural adaptation.

The worm's germline tumors further illuminate the interplay between oncogenic signaling and metabolism. The conserved Ras/MAPK cascade, modulated by vitamin B_{12}–dependent one-carbon metabolism, exemplifies how nutrient status fine-tunes proliferation and stress tolerance. Collectively, these mechanisms establish *C. elegans* as an efficient organismal model for dissecting redox regulation and metabolic control in tumorigenesis.

7. CONCLUSION AND FUTURE PERSPECTIVES

C. elegans bridges genetic simplicity with physiological complexity, conserving key oncogenic and metabolic pathways such as insulin/IGF-1, mTOR, MAPK, and redox signaling. Its transparency, mapped cell lineage, and short lifespan enable real-time visualization of tumor-like processes and rapid validation of metabolic or oxidative hypotheses.

The model's suitability for in vivo high-throughput screening allows simultaneous evaluation of drug efficacy, systemic toxicity, and redox balance. Integrating *C. elegans* assays with single-cell transcriptomics, metabolomics, and mitochondrial imaging can reveal how metabolic flexibility shapes tumor adaptation.

Future research should focus on cross-species integration and AI-assisted modeling to map conserved metabolic nodes linking oxidative imbalance, chromatin remodeling, and apoptosis regulation. Special attention should be given to antioxidant defense systems – glutathione, thioredoxin, and ascorbate derivatives – that stabilize the redox state and epigenetic landscape in tumor cells.

In summary, *C. elegans* remains a uniquely powerful platform for decoding how redox regulation, nutrient signaling, and chromatin dynamics shape the transition from adaptive survival to malignant transformation – linking molecular mechanisms to translational cancer therapy.

AUTHOR CONTRIBUTIONS

Conceptualization, A.F., D.D.S.; formal analysis, A.K, D.A., G.A.; resources, A.K.; writing-original draft preparation, A.F, D.D.S., D. B.; and writing-review and editing, A.F, D. B.; funding acquisition, D.B. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ПОНИМАНИЕ МЕТАБОЛИЧЕСКИХ ЗАКОНОМЕРНОСТЕЙ И ОКИСЛИТЕЛЬНОГО СТРЕССА В ОНКОЛОГИИ С ИСПОЛЬЗОВАНИЕМ МОДЕЛИ *C. ELEGANS*

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АННОТАЦИЯ

В обзоре рассматривается использование нематоды *C.elegans* в качестве мощной модели для исследований в области онкологии, выходящей за рамки традиционного анализа консервативных генетических путей. Основная ценность этой модели заключается в возможности изучения сложного взаимодействия между нарушенным метаболизмом и окислительным стрессом. В первой части обзора обсуждается, как *C. elegans* позволяет исследовать причинно-следственные связи между метаболической перегрузкой, образованием активных форм кислорода (*ROS*) и активацией консервативных детоксикационных путей на уровне целого организма. Далее рассматривается феномен эффекта Варбурга: уникальный ронокинон-зависимый анаэробный метаболизм нематоды представлен как эволюционный «контрольный эксперимент», предлагающий нетрадиционный подход к пониманию функциональной роли лактата в микроокружении опухоли. В заключительной части анализируется ядро клетки как активный сенсор стресса, участвующий в структурной перестройке хроматина и формировании стресс-индуцированных биомолекулярных конденсатов под действием окислительного стресса. Таким образом, *C. elegans* представляет собой эффективную модель для перехода от изучения отдельных сигнальных путей, связанных с опухолевым ростом, к интегрированному пониманию метаболических и средовых факторов, определяющих процессы опухолеобразования.

Ключевые слова: *ремоделирование хроматина; окислительный стресс; активные формы кислорода, эффект Варбурга; метаболическое перепрограммирование; модель опухоли; сигнализация Ras/MAPK; апоптоз.*

C. ELEGANS ҮЛГІСІН ҚОЛДАНУ АРҚЫЛЫ ОНКОЛОГИЯДАҒЫ МЕТАБОЛИКАЛЫҚ ЗАҢДЫЛЫҚТАР МЕН ТОТЫҒУ СТРЕССІН ТҮСІНУ

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АҢДАТПА

Бұл шолуда *C. elegans* нематодасы онкологиялық зерттеулерде қолданылатын қуатты модель ретінде қарастырылады. Ол дәстүрлі консервативті генетикалық жолдарды зерттеуден тыс, бұзылған метаболизм мен тотығу стрессінің (oxidative stress) өзара күрделі байланысын зерттеуге мүмкіндік береді. Шолудың алғашқы бөлімінде *C. elegans* организм деңгейінде метаболикалық шамадан тыс жүктеме, реактивті оттек түрлерінің (ROS) түзілуі және консервативті детоксикация жолдарының белсенуі арасындағы себеп-салдарлық байланыстарды зерттеуге мүмкіндік беретіні талданады. Келесі бөлімде Варбург әсері (Warburg effect) қарастырылады. *C. elegans* организміндегі ронокинонға тәуелді анаэробты метаболизм эволюциялық «бақылау тәжірибесі» ретінде сипатталып, ісік микроортасындағы лактаттың функционалдық рөлін түсінудің дәстүрден тыс үлгісін ұсынады. Соңғы бөлімде жасуша ядросы стресс сенсоры ретінде қарастырылып, тотығу стрессінің әсерінен хроматин құрылымының қайта ұйымдасуы және стресс-индукцияланған биомолекулалық конденсаттардың түзілуі сипатталады. Жалпы алғанда, *C. elegans* үлгісі жеке сигналдық жолдарды зерттеуден метаболикалық және қоршаған орта факторларының өзара байланысын түсінуге бағытталған кешенді онтогенетикалық тәсілге өтуге мүмкіндік береді.

Түйінді сөздер: *хроматин ремоделдеуі; тотығу стрессі; реактивті оттек түрлері; Варбург әсері; метаболикалық қайта бағдарлау; ісік моделі; Ras/MAPK сигнал жолы; апоптоз.*