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Review Article

# *Caenorhabditis elegans* as a Valuable Model for Studying Apoptosis and Autophagy in Cancer Development: Current Insights, Future Directions, and Challenges

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**ABSTRACT**

Despite significant progress in the fight against cancer, it remains a significant public health concern and a societal burden worldwide. To develop better intervention strategies to counter or prevent tumor development, understanding the molecular and cellular mechanisms underlying oncogenic diseases is crucial. *In vivo* and *in vitro* models have traditionally been utilized to understand the biological processes involved in cancer, including apoptosis, proliferation, angiogenesis, invasion, metastasis, genome instability, and metabolism. The present review explored how *Caenorhabditis elegans* (*C. elegans*) can aid in understanding cancer's cellular and molecular bases, concentrating on mechanisms like apoptosis and autophagy. In recent years, *C. elegans* has emerged as a promising model organism for studying the molecular basis of tumorigenesis. This model organism is attractive because it is genetically tractable and has a simple and well-understood anatomy. *Caenorhabditis elegans* exhibits conserved cellular pathways and mechanisms relevant to human diseases, including cancer. Studies using *C. elegans* have provided valuable insights into the regulation of apoptosis and autophagy in cancer and have identified novel regulators of these pathways. Furthermore, *C. elegans* has been used to study the roles of tumor suppressor genes and oncogenes in tumorigenesis. In conclusion, *C. elegans* is an emerging animal model that has the potential to facilitate the development of better intervention strategies to prevent or counter tumor development and to advance our understanding of cancer progression with further research.

## 1. Introduction

*Caenorhabditis elegans* (*C. elegans*) is a soil nematode that has become an important model organism in biomedical research due to its numerous advantages[1]. Its ability to feed on various bacteria and to be raised easily in the laboratory using *Escherichia coli* bacteria makes it a cost-effective and convenient organism for large-scale studies[2]. Its short generation time and lifespan make it an efficient model for aging and longitudinal studies of development and disease progression[3]. *Caenorhabditis elegans* is also unique in its anatomy and genetics. It exists mainly as a hermaphrodite, but males occasionally arise at a frequency of 0.1%[4]. It has an invariant number of somatic cells in its "female" and male mature adults, with an invariant cell lineage and precise anatomical arrangements. Its transparent body at all stages of its life cycle and small size make it ideal for non-invasive optical methodologies that enable manipulation and tracking of normal function and dysfunction at the cellular level during development and aging[5]. Despite the evolutionary distance between *C. elegans* and humans, researchers have identified homologs for 60-80% of human genes[6]. Many biological processes are conserved between *C. elegans* and mammals, including apoptosis, cell signaling, cell cycle, cell polarity, metabolism, and aging[7]. This makes *C. elegans* a valuable model organism for studying diverse pathologies, including neurodegeneration and cancer. Tumor formation and dissemination are associated with key traits such as sustained proliferation, resisting cell death, genome

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instability, induction of angiogenesis, invasiveness and metastasis, and deregulated energy metabolism[8,9]. *Caenorhabditis elegans* has been used to assess the functional impact of specific gene mutations on tumor development and outcome at the organismal level and to screen for new anticancer drugs[10].

The present review examines the potential of *C. elegans* in shedding light on the cellular and molecular mechanisms involved in tumorigenesis. The focus is on exploring various processes, including apoptosis and autophagy. Furthermore, we propose that *C. elegans* could provide valuable insights into cancer development from a less-appreciated perspective, such as cellular metabolism, stem cell reprogramming and dedifferentiation, and host-microflora interactions. With the ease of forward and reverse genetics in *C. elegans*, this model organism presents a unique opportunity to systematically study the genes and pathways involved in diverse pathologies and develop better intervention strategies to counter or prevent tumor development.

## 2. Advantages

*Caenorhabditis elegans*, a non-parasitic soil nematode, has several advantageous features that make it a valuable model organism in biomedical research[11]. One such advantage is its invariant cell lineage and precise anatomical arrangements[12]. This means that researchers can study the development and function of individual cells and tissues with great accuracy and reproducibility, which is important for understanding disease processes and developing new treatments. Additionally, *C. elegans* has a transparent body at all life cycle stages, enabling non-invasive optical methodologies for manipulating and tracking normal function and dysfunction at the cellular level[13]. This transparency also allows researchers to observe the internal workings of the organism without the need for invasive procedures. The *C. elegans* is also unique in its hermaphroditic reproductive system, with males occasionally arising at a frequency of 0.1%[14]. This allows researchers to study the genetics and physiology of male and female individuals and their interactions. This is important for understanding how sex-specific differences contribute to disease risk and progression. Moreover, the short generation time and lifespan of *C. elegans* make it an efficient model for longitudinal studies of aging, development, and disease progression[15]. This allows researchers to track changes in the organism over time and to observe the effects of different interventions on disease outcomes. The genetics of *C. elegans* are also advantageous for biomedical research. Despite the vast evolutionary distance between *C. elegans* and humans, researchers have identified homologs for 60-80% of human genes in *C. elegans*[16]. Many biological processes, including apoptosis, cell signaling, cell cycle, cell polarity, metabolism, and aging, are conserved between *C. elegans* and mammals[17]. Researchers can use *C. elegans* to study the molecular mechanisms underlying diverse pathologies, including neurodegeneration and cancer[18,19]. In particular, *C. elegans* has been used to assess the functional impact of specific gene mutations on tumor development and outcome at the organismal level and to screen for new anticancer drugs[20,21].

In conclusion, the unique anatomy and genetics of *C. elegans* make it a valuable model organism for biomedical research. Its precise cell lineage, transparent body, hermaphroditic reproductive system, short generation time, and conservation of many biological processes with mammals make it an efficient and cost-effective model for studying aging, development, and disease progression. Moreover, the genetics of *C. elegans* allows researchers to study the molecular underpinnings of diverse pathologies, including cancer, and to screen for new drugs and interventions to counter or prevent tumor development.

## 3. *Caenorhabditis elegans* in cancer development and progression

Cancer development is a complex and multifactorial process involving numerous genetic and environmental factors. One aspect that has gained increasing attention in recent years is the role of cellular metabolism in tumorigenesis[22]. Cancer cells have altered metabolic pathways that allow them to maintain high levels of proliferation and survival even under conditions of nutrient limitation or hypoxia[23]. These metabolic alterations are thought to be an adaptation to the harsh microenvironment of solid tumors and provide a selective advantage to cancer cells.

*Caenorhabditis elegans* provides a unique platform to study the role of cellular metabolism in tumorigenesis[24]. The worm has a simple and well-defined metabolism amenable to genetic manipulation. Many genes and pathways involved in *C. elegan's* metabolism are conserved in humans, making this organism a valuable model for investigating the metabolic basis of cancer [25]. Researchers have already used *C. elegans* to study the role of specific metabolic pathways, such as the glyoxylate cycle and the pentose phosphate pathway, in tumorigenesis[26].

In addition to its intrinsic metabolic pathways, *C. elegans* has a symbiotic relationship with its intestinal bacteria, which play important roles in host metabolism and immune function[27]. Alterations in the gut microbiome have been implicated in various human diseases, including cancer. *Caenorhabditis elegans* provides a unique opportunity to study the interactions between the host and its microbiome in the context of cancer development. Researchers have used *C. elegans* to identify specific bacterial strains that can either promote or inhibit tumor growth, highlighting the potential of this model organism for investigating the role of host-microbiome interactions in cancer[28].

Another aspect of cancer development that has gained increasing attention in recent years is the role of stem cells in tumor initiation and progression. Cancer stem cells are thought to be a subpopulation of cells within a tumor that can self-renew and differentiate into multiple cell types and is responsible for tumor initiation and recurrence[29].

*Caenorhabditis elegans* has a simple and well-defined lineage that includes stem cell populations in the germline and the somatic gonad. Researchers have used *C. elegans* to study the genetic and environmental factors that regulate stem cell proliferation and differentiation, providing important insights into the basic biology of stem cells that can be applied to the study of cancer stem cells[30,31].

Overall, the unique features of *C. elegans*, including its simple and well-defined anatomy and genetics, its transparent body, its symbiotic relationship with its intestinal bacteria, and its conserved metabolic pathways and stem cell populations, make it an ideal model organism for investigating the cellular and molecular underpinnings of tumorigenesis from a less-appreciated perspective. With the ease of forward and reverse genetics in *C. elegans*, this model organism presents a unique opportunity to study the genes and pathways involved in diverse pathologies systematically and to pave the way for developing better intervention strategies to counter or prevent tumor development.

## 4. Role of apoptosis and autophagy in tumorigenesis

*Caenorhabditis elegans* has proven to be an invaluable model organism for studying the cellular processes of apoptosis and autophagy in cancer development[32,33]. Apoptosis, or programmed cell death, is a critical process in maintaining cellular homeostasis and preventing tumorigenesis[34]. On the other hand, autophagy is a process by which cells degrade and recycle their components and has been implicated in both tumor suppression and promotion[35].

Researchers have used *C. elegans* to identify and characterize genes and pathways involved in apoptosis and autophagy and understand their roles in cancer development. For instance, studies have shown that mutations in key apoptosis regulators, such as the tumor suppressor gene p53, can lead to the development of tumors in *C. elegans*[36]. Additionally, researchers have used *C. elegans* to investigate the mechanisms by which autophagy promotes tumorigenesis, such as by facilitating the survival of cancer cells under nutrient-deprived conditions[37].

The transparency of *C. elegans* has also allowed researchers to visualize and track the development of tumors *in vivo*, providing a unique opportunity to study the effects of specific mutations on tumor growth and progression[38]. Moreover, the genetic similarity between *C. elegans* and humans, with homologs of 60-80% of human genes, makes it an ideal model for studying the conserved molecular and cellular mechanisms underlying cancer development[39].

Furthermore, the ease of forward and reverse genetics in *C. elegans* allows for systematic screening of genes and pathways involved in apoptosis and autophagy and for identifying new anti-cancer drugs[40]. For example, researchers have used RNA interference (RNAi) to silence specific genes and study their effects on tumor growth in *C. elegans*, leading to the identification of potential drug targets[41,42].

Overall, using *C. elegans* as a model organism for studying apoptosis and autophagy in cancer development has provided valuable insights into the molecular and cellular mechanisms underlying tumorigenesis. By further leveraging the advantages of *C. elegans*, such as its ease of culture and manipulation, researchers can continue to uncover new insights and potential therapeutic targets for cancer treatment.

## 5. Tumor suppressor gens

*Caenorhabditis elegans* has proven to be a valuable tool for investigating the molecular mechanisms underlying cancer development and progression. The simplicity of its anatomy and genetic tractability has allowed researchers to study several tumor suppressor genes and oncogenes in the nematode, shedding light on their roles in regulating cell growth and division, apoptosis, and autophagy[43]. One of the most extensively studied tumor suppressor genes in *C. elegans* is the homolog of the human p53 gene[44]. The *C. elegans* p53 homolog has been shown to regulate cell cycle progression, DNA damage response, and apoptosis, making it an important player in preventing tumorigenesis [45]. Mutations in the human p53 gene are found in most human cancers, and the study of its homolog in *C. elegans* has provided important insights into its function and regulation[46,47]. Another tumor suppressor gene studied in *C. elegans* is PTEN, which regulates the PI3K/Akt signaling pathway[48,49]. Dysregulation of this pathway is frequently observed in cancer, and the *C. elegans* homolog of PTEN has been shown to play a critical role in germline development and lifespan regulation[50]. Loss of PTEN in *C. elegans* leads to increased Akt signaling and germline hyperplasia, providing insight into its potential role in tumorigenesis[51]. Similarly, the study of the *C. elegans* homolog of the human APC gene has provided important insights into its role in regulating cell division and asymmetric cell fate decisions[52]. Mutations in the human APC gene are associated with colon cancer. Studying its homolog in *C. elegans* has helped elucidate its regulation of Wnt signaling and asymmetric cell division[53]. *C. elegans* has also been used to study oncogenes, including the RAS family of genes frequently mutated in human cancers.

## 6. Future

As with any model organism, there are still challenges and limitations to using *C. elegans* to study tumorigenesis. One major challenge is that *C. elegans* does not naturally develop tumors; its somatic cells are postmitotic and do not divide[52]. This limits the ability to study certain aspects of cancer development, such as metastasis and invasion. Another challenge is that C. elegans lacks certain molecular pathways and components that are present in humans and involved in cancer development[54,55]. For example, *C.*

*elegans* does not have a homolog of the human KRAS gene, which is frequently mutated in human cancers. Furthermore, while *C. elegans* provides a powerful tool for studying the basic mechanisms of apoptosis and autophagy; these processes may not be identical in humans[56,57]. Therefore, while *C. elegans* can provide valuable insight into these processes; confirming findings in mammalian systems is important. Despite these challenges, *C. elegans* remains a valuable model organism for studying tumorigenesis. Future studies may focus on developing *C. elegans* models that more closely mimic human tumors, such as through the expression of oncogenes or the deletion of tumor suppressor genes [58]. Additionally, advances in genome editing technologies such as CRISPR/Cas9 may allow for the creation of more sophisticated *C. elegans* models of cancer[59,60]. In conclusion, using *C. elegans* as a model organism has provided valuable insight into the molecular basis of tumorigenesis, particularly regarding apoptosis and autophagy, as well as the function of tumor suppressor genes and oncogenes. While challenges remain, continued research using *C. elegans* will likely provide further insight into the fundamental mechanisms of cancer development and potential avenues for therapeutic intervention.

## 7. Conclusion

In conclusion, using the nematode *C. elegans* as a model organism has provided valuable insights into the molecular basis of tumorigenesis, specifically the regulation of apoptosis and autophagy and the function of tumor suppressor genes and oncogenes. The genetic tractability and well-understood anatomy of *C. elegans* have allowed for identifying and studying numerous genes and pathways relevant to human diseases, including cancer. Despite the progress made in using *C. elegans* as a cancer model, challenges still need to be addressed. For instance, the fact that *C. elegans* does not naturally develop cancer limits its relevance to certain aspects of cancer research, such as the study of metastasis. Additionally, the use of *C. elegans* as a model for studying drug development and testing may be limited due to differences in drug metabolism between C. elegans and humans. Nonetheless, the future of *C. elegans* as a cancer model organism remains promising. The continuing development of genetic and imaging tools will allow for even more precise manipulation and visualization of cellular processes and pathways in *C. elegans*. Additionally, using CRISPR-Cas9 technology in *C. elegans* has expanded the potential for targeted genome editing, further enhancing its value as a model organism. Overall, *C. elegans* serves as an important model organism for studying the molecular basis of tumorigenesis and has the potential to further our understanding of cancer and lead to the development of new therapies.

## Declarations

### *Competing interests*

The authors have declared no conflicts of interest.

### *Authors' contributions*

Ashkan Hajjafari, Pouria Ahmadi Simab, Narges Lotfalizadeh, and Hassan Borji wrote the draft of the manuscript. Soheil Sadr revised the draft of the manuscript and check the final version of the article. All authors have read and approved the final version of the manuscript for publication in the present journal.

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### *Ethical considerations*

The authors declare that this manuscript is original and has not been submitted elsewhere for possible publication. The authors also declare that the data used/presented in this manuscript has not been fabricated.

### *Availability of data and materials*

The authors will provide the data from the present study in case of request.

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