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C. elegans in cancer research

Disease Modeling, View from the Bench / By Yoanne Clovis, Ph.D.

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. To facilitate the development of better intervention strategies to counter or prevent tumor development, it is crucial to accelerate the elucidation of the key molecular and cellular mechanisms of oncogenic diseases. As emerging findings highlight the importance of the tumor microenvironment, exploring its contribution to tumor growth and metastasis has become crucial for a better understanding of the molecular and physiological requirements of tumorigenesis.

In recent years, the nematode *C. elegans* has emerged as a model for systematic dissection of the molecular basis of tumorigenesis. Many cancer genes and pathways are highly conserved and often easier to parse in *C. elegans* as the gene families involved contain fewer members, reducing genetic redundancy. Several worm models have pioneered the field by helping decipher underlying mechanisms relevant to human tumors such as apoptosis and autophagy. Over the last decade, *C. elegans* has also been used to advance our understanding of cancer progression, such as deregulation of energy metabolism, stem cell reprogramming, and host-microflora interactions (1).

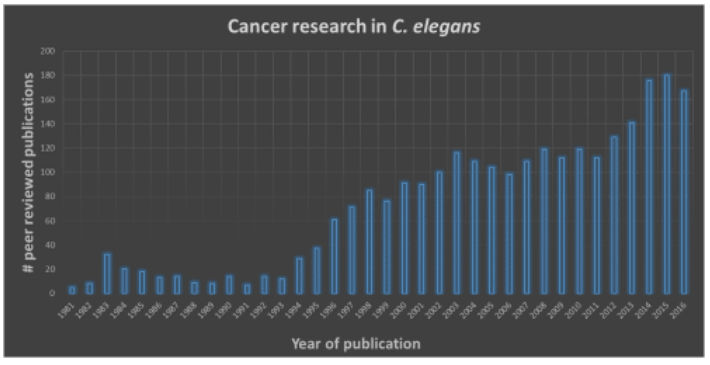

Figure 1: Number of publications using C. elegans a model organism to study cancer mechanisms. Over the last 2 decades, C. elegans has gained recognition as a suitable model to study the genetic,

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Several aspects of the *C. elegans* germ line make it a valuable genetic system for analyzing the cellular and molecular underpinnings of cancer:

- the worm germ line is pluripotent and immortal;
- it is the only *C. elegans* tissue in which the pattern of apoptosis is not invariant;
- it is the only tissue that undergoes apoptosis in adults.

When the cell cycle and the apoptotic machinery are compromised, the stem cell niche expands, filling the gonad with mitotic nuclei in a way that is similar to tumor development (2, 3). Additionally, many of the genes that modulate tumor growth are orthologs to known human tumor suppressors or oncogenes. Taken together, these traits validate the use of *C. elegans* as a cancer model.

Researchers have been successfully using *C. elegans* to:

- **Rapidly assess the functional impact of specific gene mutations on tumor development.** *C. elegans* was used to uncover a novel link between hypoxia and apoptosis in tumor progression (4). In addition to apoptosis, *C. elegans* has contributed significant insights into the role of autophagy in cancer. For example, the pathway in which the tumor suppressor FLCN functions was first delineated in nematodes (5). This study showed that loss of flcn-1, the *C. elegans* homolog of FLCN, confers resistance to oxidative stress. Autophagy induction, in turn, protects against apoptotic cell death and promotes survival under stress. This pathway was shown to be conserved in mammalian cells, suggesting that FCLN prevents tumor formation by negatively regulating the activity of AMPK (5).
- **Assess the outcome of these genes at the organismal level.** Pathways that are implicated in mitochondrial repair during mitochondrial dysfunction have been identified in *C. elegans*. Specifically, a genome-wide RNAi screen revealed 45 genes that are required for mitochondrial repair, detoxification, and pathogen response during compromised mitochondrial function (6). These genes were involved in ceramide and mevalonate metabolism. The mevalonate pathway has been involved in mitochondria-

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- **Screen for new anticancer drugs.** The epidermal growth factor receptor (EGFR) is a well-established target for cancer treatment. EGFR is over-expressed or aberrantly activated in various types of human cancer, such as breast, ovarian, and non-small-cell lung carcinoma and is involved in various steps of cancer development. A number of chemical compounds that target the EGFR pathway have been tested using *C. elegans* vulval development as a model (9,10,11). Using constructed transgenic *C. elegans* containing several different EGFR constructs, Bae et al. conducted a pilot screen of 8,960 chemicals, isolating an EGFR inhibitor and a MEK inhibitor as suppressors. This study suggest that this *C. elegans*-based system can be used efficiently to screen for new anti-cancer drugs (12).

***C. elegans* Genes**	***C. elegans* Phenotypes**	**Human Genes**	**Human Phenotypes**
him gene family[a]	high incidence of males	p53, BRCA1	cancer (various)
ksr[b]	aberrant cell specification (multivulva)	RAS family (proto-oncogenes)	improper signal transduction, proliferation and malignant transformation
Let-60/LIN-45/MEK-, MPK-1[c]	vulva development impairment	RAS/RAF/MEK/ERK	cell proliferation defect during development
Sep 1	embryos fail to develop and die at a certain temperature	ESPL1	tumorigenesis
fos-1a	Anchor cell invasion into the vulval epithelium	FOS	metastasis
mlh-1	spontaneous mutation rate	MLH1	hereditary non-polyposis colon

- (*a*) Cancer and the Him phenotype are both the result of chromosome segregation defects.
- (*b*) Discovery of the ksr gene in D. melanogaster and *C. elegans* in the mid-1990s has great implications for cancer research.
- (*c*) The genetic pathways were practically identical: the tyrosine kinase growth factor receptor-Ras-Raf-MEK-MAPK pathway. The same set of orthologs is required for these three biological

mlh-2	spontaneous mutation rate increased	MSH2	hereditary non-polyposis colorectal cancer

Conclusion:

C. elegans is widely accepted as a simple model system for elucidating key aspects of stem cell biology (3). The hermaphrodite germ line is the only tissue in *C. elegans* that can lead to bona fide tumors caused by germline hyper-proliferation and the only tissue capable of undergoing apoptosis throughout adulthood. These characteristics make the worm a straightforward, easily tractable system for studying biological phenomena pertinent to cancer and stem cells.

See C. *elegans* genes used as experimental models for investigating other human diseases.

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