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Review Article

Model Organisms in Cancer Research-Powers and Limitations

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ABSTRACT

Background: Cancer is a term that is used to describe a wide range of diseases, but they all have some characteristics in common. The goal of this review is to highlight the most commonly used cancer models as well as their role in tumor biology. Although each model has inherent powers and limitations in faithfully mirroring the complexity of tumorigenesis, there is no perfect single model for cancer. **Main body:** Oncologists can learn about the tumor microenvironment, gene mutations, and complex physiological systems using model organisms for cancer research. The widespread use of model organisms in cancer research has greatly improved understanding of how mutations in humans lead to cancer. Human cancer cell lines, drosophila, yeast, and mice are among the model organisms used to study cancer. However, these model organisms have flaws that can cause the tumor microenvironment to be falsified and restrict the defined targets in translational studies. **Conclusion:** The overwhelming message from various animal models allows us to better understand the state of the disease and develop new cancer treatments. Mice are a good substitute and surrogate for patients in the evaluation of diagnosis and prognosis among the various model organisms used in cancer research.

BACKGROUND

The global health and wealth crisis is being exacerbated by the rising incidence of various cancers. Oncologists and research scientists have spent a lot of time and effort trying to figure out how to control or eliminate the threat. Cancer kills a huge number of people every year all over the world. It has the appearance of a weed and induces irregular cell growth in the wrong areas, resulting in a series of genetic changes in the cell (DNA). This mechanism, known as mutations, accumulates over time by taking advantage of unscheduled, rapid cell growth and division on a regular basis [1, 2]. The ultimate effect of this process is the formation of tumours, which then spreads to other organs and tissues through invasion and metastasis. [3]. Animal models are being used to learn more about how these mutations cause cancer in humans and how the cell-cycle machinery operates in normal circumstances [2].

THE USE OF MODEL ORGANISMS FOR STUDYING CANCER RESEARCH-POWERS AND LIMITATIONS

All living beings are identical in terms of the fundamental life process, especially at the cellular level. This means that scientists will research the basic aspects of cell growth and development in a number of organisms, including *Drosophila*, Zebrafish, C. *elegans*, yeast, and mice, and adapt what they discover to humans. Furthermore, these organisms share genes with humans, making them ideal for use as “model organisms” in research studies of human diseases and genes [1, 2, 4]. As we learn more about a similar process in humans at the cellular and molecular levels, the importance of model organisms becomes clear. However, over time, some model organisms have lost favor. The best example is the rat, which was once one of the most common laboratory animals two decades ago, but is now less due to its genome’s failure to handle foreign DNA injection to the same degree as the mouse genome [5].

According to Rathore K et al., cancer has been broadly characterized based on several hallmarks during its multistep developmental process such as "sustaining proliferative signalling, evading growth suppressors, enabling replicative immortality, resisting cell death, tumour-promoting inflammation, induction of angiogenesis, activation of invasion and metastasis, genome instability and mutations, avoidance of immune destruction, and deregulation of cellular energetics’’[6]. According to the American cancer society (ACS), cancer is the second most common cause of death in the United States of America. A change in the structure of the tissue or organ detects cancer in normal circumstances. Early detection of tumors in patients, as well as precise, intensive monitoring of tumor response to treatment, are critical

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components for survival [6]. New molecular activities, such as tumor-specific molecular targets, are still required to enhance tumor diagnosis and early cancer care. As a result, there is a requirement for the proper use and production of animal models in cancer research [3, 6].

The use of the ideal animal for cancer research necessitates a few key components. A model should be applicable to human cancer, which means it should be capable of not only site-specific organ localization, but also of developing cancerous lesions with pathology and genetic anomalies similar to those observed in humans. In terms of histology and molecular processes, a model should have intermediate lesions that promote cancer development and are similar to the progression of human cancer. An ideal model should be capable of producing a consistent tumor (80%) in a short period of time, i.e. a few months [5]. For the induction of carcinogen or genetic defect used to induce cancer in the animal models should resemble with what we encounter in humans which means efficiency should be in the similar way either positive in animal tests and clinical trials or negative effect in animal tests and clinical trials. While it is generally understood that there are several types of cancers and different types of models but no current animal cancer model is an ideal one [1, 3, 5, 6].

Animal models became important tools for conducting cancer research because of its practical and ethical concerns associated with human clinical trials which were codified as the Nurenberg Code soon after the Second World War [4]. Ascitic murine leukemia models were initially used in invivo tumor models which were implemented in the year 1960 [5]. Later progression in animal research, scientists were focused towards modelling solid tumors into mice to enable us important tools for screening anticancer drugs in medicine. This concept has been adopted by law in respective drug agencies such as the FDA (Food and Drug Administration, USA) and the European Medicines Agency (EMA, Europe) for medical evaluation to allow conducting animal studies prior to human tests for approval in various disciplines in biomedicine [4, 6]. Several animal models are used in cancer research, but only a few are widely used, such as human cancer cell lines, drosophila, yeast, and mice [1, 2].

Human Cancer Cell lines

One of the best in vitro cancer models to study biochemical processes of cancerous cells is the human cancer cell line (Figure 1a). These are extracted from cancers with a high grade and level. Using viral vectors to manipulate the regular cell line to make it immortal. The immortalized cancer cell line HeLa was the first to be used in biomedical science. The use of patient-derived cancer cell lines became an insightful resource for doing research and development for cancer treatment regimens [8]. There are several advantages by using in vitro cancer models: those are highly controlled conditions, quick results, homogeneity, the discovery of molecular mechanisms, consistency and reproducibility, easy to manipulate the culture conditions, the possibility to obtain single-cell information, minimal genetic drift and phenotype change if the cells were handled in a right manner, the endless supply of cells, easy to grow and cheap. On the other hand, there are some drawbacks: cell-to-cell communication is lost, cross-contamination occurs in two-dimensional in vitro cell culture, and cancer cells accumulate mutations over time in culture. Selecting phenotype and genotype during adaptation to in vitro conditions, a homogeneous cell population, and isolating desired population from the entire tumor microenvironment is difficult. Well-defined 3-D and co-culture systems allowed for a wide range of diagnostics and therapeutic applications in the case of three-dimensional in vitro model-cells in cultures mimicking the interaction between tumor cells and cellular matrix. Despite its limitations when it comes to using in vitro model systems, it allows scientists to conduct basic research on human cancer cell lines, making it an ideal model organism [8, 9].

Yeast

Fungi have been used to make beer for centuries, and now this fungus is being used as a model organism for advanced cancer research. *Schizosaccharomyces pombe,* (Figure 1c) commonly known as yeast, is a single-celled , non-pathogenic and widely studied model organism because it provides insightful information on how normal and cancer cells grow and divide. *S. pombe* is also known as fission yeast, which consists about 5000 genes. Unfortunately, because the human genome contains over 20,000 genes and each gene has multiple functions, human cells are not an ideal system for cell-cycle research. There is a difficulty in the manipulation of human cells in lab conditions that lead to a tricky situation to unpick a particular desired gene function in this manner. Yeast became more popular model in the year 1950 and scientists were more focused on genetics and cell cycle. It is having great powers due to a fewer number of chromosomes and it easier to manipulate the genome which means the desired genes can be removed or added to DNA, cells are quick, cheap and easy to grow, division time is less, many genes have human orthologs, the cell cycle is simplest and easier to find the stage of the cells under a microscope. However, it is unable to explain the complexity of the human system,

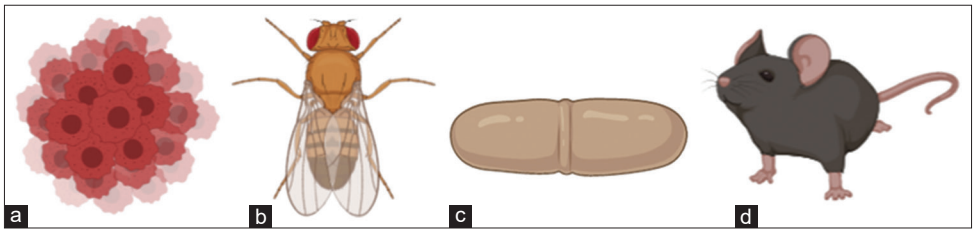

Figure 1. The common most prevailing model organisms that are used in cancer research a) human cancer cell lines, b) *Drosophila melanogaster*, c) *Schizosaccharomyces pombe* d) mouse. The image has been modified and adapted from [7]

which is thought to have global control over cell growth and differs from human physiology [2].

Drosophila

Research on flies over the last decade has given fruitful resource for the better understanding of the molecular mechanisms involved in cancer initiation and progression and which reveals unknown mechanisms and concepts in signalling pathways involved in various cancer diseases. This has shown light for researchers who use animal models to study cancer. *Drosophila melanogaster* (Figure 1b) genome has shown reduced redundancy when compared to humans, coupled with the ability to perform a large- scale genetics screens in this model and this enabled its use to determine the various process in the molecular levels likely, signalling cascade events, developmental process and growth control. For example, Notch, JAK-STAT, Hippo and Dpp are the important signalling pathways but are also involved in tumour initiation and progression as revealed by research in *Drosophila* [10]. *Drosophila* genetics has revealed a number of genes that, when mutated or dysregulated, contribute to tumorigenesis, making *Drosophila* an ideal animal model for cancer research. In *Drosophila* possesses many advantages, which have a coupled with powerful genetic tools, more simplicity than the vertebrate model, greater complexity than yeast model, a streamlined genome for providing us to have a better understating of the unique system which mainly explores molecular signalling pathways involved in tumorigenesis and its regulation of metastatic growth of tumours. it has certain limitations as it is not possible to study secondary tumours by using *Drosophila* because it is having rudimentary haematopoietic systems and lymphatic system which is quite different from humans [1, 10, 11].

Mouse

Mouse research has laid a strong foundation for understanding the major advancements in our ability to treat life-threatening diseases in various conditions. They look entirely different from us and also species as diverse as yeast, *Drosophila*, worms, zebrafish, dog, cat and mice but it shares a lot of genes and molecular pathways with humans [4]. Among those, mice (Figure 1d) have provided 95% identical genes when compared to humans thus it makes so special among the other animal models for researching studying the function of human genes involved in health prospects and as well as diseases such as cancer, heart diseases and obesity [4]. Several mice models have been developed and each model has its advantages and limitations. For examples, most widely used mouse models in cancer research, such as syngeneic models (mice bear tumours originates from their species), xenogeneic models (mice bear tumours originates from different species either its human cell lines or explants) and genetically engineered mice models (mice bear tumours originated from alterations in the genes or spontaneous carcinogenesis) [4]. Mice models have proven to be useful with several advantages in various aspects such as small in size, inexpensive to maintain, rapid reproduction and have large litters, enables genetic manipulation, genome similarity to humans. These characters help us to validate gene functional studies, identification novel targets for cancer genes and biomarkers, the in-depth mechanism involved in cancer initiation and progression in tumorigenesis and providing better models for pre-clinical studies for testing therapeutic drugs against cancer. Although there are significant limitations in mice models for human cancer research which includes variation in species-specific difference, cancer treatment differs in mice from humans and inaccurate recapitulation in case of *de novo* human tumour development process and also difficult to study early acting mutant phenotypes [6, 12, 13].

DISCUSSION

Decades of focused cancer research has revealed that tumorigenesis is a frustratingly complex process, with scientists still grappling with an incomplete understanding of the disease's genetic basis. Surprisingly, animal models are used heavily in human cancer genetics. Selection of the best cancer model is always challenge to the scientists because there is no unique system which relies on basic features like genome stability, heterogeneity of transplanted cell lines, immunogenicity within the host and accuracy in biological endpoints. As a result, there is no better model that explains the complexities of cancer disease; therefore, research is ongoing to develop a better model that provides an insightful resource for understanding the cellular and molecular processes in order to improve prognosis.

Despite the fact that cancer cell lines have had a positive impact in the biomedical field, there is a large debate in the scientific community about whether they are a representative of the original tumors due to differences in genomic variation compared to the original tumors and the fact that after the second passage, they are widely transformed and may not be similar to the original tumors. According to Raquel Chaves et al, they conducted comparative studies between cancer cell lines derived from early-stage tumors and the original tumor tissues and discovered several similar parameters, including P53 (100%) and ERBB2 (93% [14]. This indicates that these cells are more representative of the original tumour and also reflects cancer progression events in a similar manner in vivo. In vitro cancer model is not ideal all the time except for drug testing which enables us to understand basic biochemical pathways and difficult to control mutations. Therefore, this eventual process differs from patient to patient [6, 8].

Yeast has given a break-through for cancer research and sorted out orderly sequential events that may occur in cell cycle and duplication of a cell to become two daughter cells. Many researchers have been enlightened by this information, which has allowed them to better understand cell cycle regulation, whether a gene is turned on or off, oncogenes, and tumour suppressor genes, as well as to investigate many cancer drugs that alter the normal process. But this model system is far limited to explain the complexity of cancer disease because of different genes in different cancer patients [15].

Researchers made the unanticipated breakthrough in fruit flies and discovered that genetically controlled cancer death plays

a vital role in cancer progression and other diseases. By using *Drosophila*, performing a genetic screen makes it easier for researchers to better understand the different important key aspects of signalling pathways, and how these are involved in tumorigenesis [10]. The immune system appears to play an important role in *Drosophila* tumour models, just as it does in mammalian tumors, according to research. The haemocyte, which is part of the fly immune system, has been found to have a strong relationship with the Ras signaling pathway in *Drosophila*. However, this model is not accurate in explaining metastasis tumours because of lacking advanced circulation system and immune system like humans. Although, it greatly helps us to understand the tumour progression in complex organisms [11].

A powerful platform for the study of various complex associated cancer genes and their function in the tumor microenvironment has emerged in the form of a mouse model for cancer research. It is a challenge for researchers to design a mice model for cancer research because of the diversity in genome and limitations of research in humans. For example, many drugs work well in clinical trials but it turned out ineffective in case of humans because of different physiological and metabolic variance in both mouse and humans [4, 5]. Therefore, a combinatorial approach has to be implemented in various mice models to better understand the complexity of human cancers. Knowledge of the normal development of tissue is essential to understand the aberrant development of cancer because cancer genes also play vital roles in normal physiology and development. For example, disruption of oncogenes and tumour suppressor genes in mice leads to embryonic lethality and severe tissue phenotype and also showed an aberrant expression in various important developmental signalling pathways like Wnt / beta-catenin and sonic hedgehog [3, 6, 12, 13, 16].

Human cell lines, yeast, *Drosophila*, and mice are among the various model organisms for cancer research that will help us understand cancer progression at various levels of complexity. However, none of the models will execute as a similar clone to the human system. A model is just to understand the basic fundamental concepts involved in tumour initiation, progression, and different key factors involved in signalling mechanisms to help us to find out drug targets for various cancer types.

CONCLUSION

Although each of the model systems can help researchers had better understand disease or human cancer, we must remember that models are just that: models. So the only perfect model for studying human cancer or disease would be humans themselves but performing numerous kinds of research on humans is not allowed ethically and practically to execute. We are grateful to the researchers and animal models, particularly the mice model, for enabling cancer survival rates to gradually increase and they continued to rise as clinical trials progressed.

ABBREVIATIONS

FDA: Food and drug administration; EMA: European medicines agency; ACS: American cancer society; ERBB2: Erb-b2 receptor tyrosine kinase 2.

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