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Assessing the Benefits of Mouse Models for Cancer Research

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Mice have served as the preferred species to conduct experiments for the advancement of cancer research. They have been able to contribute to our understanding and have helped in the development of many treatments. There are numerous advantages as to why mouse models are utilized, such as inexpensiveness, easy maintenance, rapid development, and both biological and genetic similarity to humans. They have been able to provide information on oncogenes, tumor-suppressor genes, gene function, and tumor development. Despite the extensive knowledge this animal has been able to provide to medicine, there are still several limitations that prevent further progress. All of these will be furthered discussed in this micro review to decide whether or not mouse models are really the best instrument to utilize for cancer research.

Introduction

Mouse models allow researchers to study tumor biology in physiological systems. There were two major discoveries that set forth the use of mouse manipulation: homologous recombination in mammalian cells in the 1970s and development of methods for identifying desired genetic events in murine embryonic stem (ES) cells in the 1980s. Later in 2007, the Nobel Prize in Physiology or Medicine was awarded for "developing technology for introduction of specific mutations of mammalian genes and transferring these mutations to the mouse germline" (Zhang). This technology was composed of many steps that leads to knockout, which is when a coding sequence of a gene is deleted or knockin, when exogenous sequences are introduced to a specific region of a genome. Knockout approaches are used when studying the loss-of-function and knockin approaches are used for studying gain-of-function. All of these discoveries have contributed to our current knowledge on cancer, including the role of oncogenes and tumor-suppressor genes, biomarkers, metastasis, mutations, etc. Mice have served immensely because of their similarities to humans in the anatomical, physiological, and genetic aspects.

Using comparative medicine, a science that relates and compares biological similarities and differences within different species, we have been able to acquire insight that helps us understand cancer. This information then allows for better understanding of the complex mechanisms that are living organisms. Like the research on embryonic stem cells granted valuable information on molecule interplay, oncogene cooperation and other interactions. There are several types of mouse models like gene-targeting, conditional and inducible, RNA interference, chromosomal engineering, etc. All of these different models have served and continue to serve as a significant source of information. The current techniques available and the unique features of mouse modeling will be discussed in this micro review.

Recent Progress

Genetically engineered mouse models (GEMMs) are mice that have been genetically altered to either overexpress or lack specific genes that can induce or inhibit tumor growth. They can mimic tumor initiation, growth, and progression with a controlled genetic background, making it a very powerful tool. However, just like many of the other mouse models, it does have some drawbacks. Some of these include species-specific differences, limited recapitulation of genetic alterations, and deficiencies in effective drug testing. The RNA interference mouse model

uses short hairpin RNA (shRNA) to silence specific genes quickly. The Chromosomal Engineering approach studies chromosomal abnormalities such as deletions, inversions, and translocations that also occur in the human body. This model has been extremely helpful when performing recombination of chromosome segments and has even enabled the replication of human acute myeloid leukemia in mice. "Disadvantages of this approach include the need to generate double-targeted ES cells with two independent targeting events and the extremely low recombination frequency between distant chromosomal sites" (Cheon). Transgenic mice are a different type of mouse model that is developed by injecting foreign DNA into the pronuclei of fertilized zygotes. Unlike gene-targeting, transgenic mice are generated much faster, but it also is not able to control transgene expression as precisely. Gene-targeting has helped us comprehend tumor-suppressor genes in embryonic development and tumorigenesis. Another useful approach is the virus-mediated gene delivery, which mimics sporadic human cancers where genetic alterations happen in few initiating cells. Cross-contamination of neighboring tissues and low efficiency of *in vivo* infection are some of the main concerns to consider when performing this method.

Cancer is an intricate process that involves abnormal growth, proliferation, and metastasis. Mice have made a pivotal contribution to the study of metastasis. This is a complex process where cancer cells spread from their original location to other parts of the body. It has been the main cause of cancer mortality which is why it is essential to understand how and why it happens. Two of the most common models used to analyze metastasis are genetically engineered mice and xenograft models, which are created by subcutaneously implanting human tumor cells into immunocompromised mice. These xenograft models can also be easily manipulated *in vitro*, which lets them alter the cells to then introduce to mice for further evaluation on metastatic effects. "Cancer metastasis models driven by the introduction of oncogenic mutations in a tissue-specific manner can faithfully recapitulate important aspects of tumor metastasis." (Zhang).

Some of the reasons as to why this animal is used as the ideal experimental tool is their genetic component; "rats, mice, and humans each have approximately 30,000 genes of which approximately 95% are shared by all three species". Having access to their complete nucleotide sequences has allowed us to compare it to our own, providing critical characterization of genes. These rodents are also small in size, making them easy to maintain. However, their difference in size from humans does not accurately reflect our same biological characteristics. They also have a short life span which makes it very convenient when trying to achieve fast results. They "have a gestation period of approximately 19-21 days; can be weaned at three to four weeks of age, and reach sexual maturity by five to six weeks of age, allowing large numbers of mice to be generated for studies fairly quickly" (Bryda). Mice also differ from humans in terms of metabolism, where theirs is much faster. The activity of telomerase is also very different in mice and humans because it's almost inactive in human adults. The mosaic analysis with double markers (MADM) system has been helpful in humanizing the mouse by making genetic changes on the single-level cell. Another tool used to identify novel oncogenes, tumor-suppressor genes, and mutations is retroviral insertional mutagenesis. They insert a provirus into a host genome, inducing oncogenic mutations that lead to tumor development.

Mouse models have helped in the investigation of cancer initiation, factors that drive metastasis, and therapeutic response during cancer treatment. Cancer biologists have been the most common users of transgenic mouse models since the development of gene targeting in mice. Mouse models are a key tool that allow researchers to examine interactions between tumor cells and their environment *in vivo*, something other methods like cell culture systems which are *in* vitro would not allow.

Discussion

Laboratory mice have had a huge impact on biomedical research and continue to aid in new discoveries. "Future challenges in mouse modeling include the generation of clinically relevant mouse models that recapitulate the molecular, cellular, ang genomic events of human cancers and clinical response as well as the development of technologies that allow for efficient *in vivo* imaging and high-throughput screening in mice" (Cheon). These mouse models are critical to further our understanding of tumor development and how the immune response develops in terms of the tumor. Manipulations of mouse models are becoming more and more sophisticated as ways are being found to alter their genes, cells, and tissues so they are closer to the human ones. These variations can lead to improved models that can continue to be used as a powerful tool for research advancement in cancer.

Mice have had a big impact on the study of the origin, progress, and clinical behavior of cancer. Some of the understanding's mice have granted us are the initiating genetic alterations in cancer development, cell origin in different tumors, genetic modifiers, tumor susceptibility, impact of environmental factors on cancer, interaction of tumor cells and stromal cells, chemoresistance, tumor dormancy and recurrence. The attributes of the mouse have facilitated the development of research models in close proximity to that of the human. They have also helped prove new preventative and therapeutic strategies to study the resistance of new medicine for cancer. Utilizing mouse models for research on human cancer can lead a finding more effective manners cancer prevention and treatments.

Although the ideal mouse model that resembles human tumors at the same genetic and morphological level may not fully be achieved, they are still an easily accessible model that renders intellect that will help develop new discoveries. They will never be the best model for accurate research, but they are tremendously useful in studying gene function and tumor progression. Cancer in humans is very complex and to grasp a better understanding of it, we must use a combination of many scientific approaches.

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