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Abstract

Economic and social development has essential repercussions on the health of populations, as it alters the morbidity and mortality profile and favors the increase in exposures and risks to human health, especially the risk of cancer. Cancer is considered a significant public health problem worldwide, and remains with high incidence rates, being considered a complex disease, with multifactorial causes. The permanent incidence rates of prostate cancer prove to be one of the most prevalent, considered the second most common cancer in men worldwide, and a leading cause of deaths from chronic noncommunicable diseases. Among the different types of cancer, prostate cancer has been the subject of great scientific interest. In this context, animal models are valuable for studying cancer-related aspects, the use of animal models has the potential to increase our understanding of carcinogenesis, tumor biology, and the impact of specific molecular events on tumor biology. Animal models with specific human cancer characteristics can be used to test cancer prevention and treatment strategies. In this review, we aim to show how the use of animal models as an essential tool in the study of the molecular mechanisms of carcinogenesis.

Keyword: Neoplasms, Immunology, Neoplasm Transplantation, Oncogenesis

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Abstract

Economic and social development has essential repercussions on the health of populations, as it alters the morbidity and mortality profile and favors the increase in exposures and risks to human health, especially the risk of cancer. Cancer is considered a significant public health problem worldwide, and remains with high incidence rates, being considered a complex disease, with multifactorial causes. The permanent incidence rates of prostate cancer prove to be one of the most prevalent, considered the second most common cancer in men worldwide, and a leading cause of deaths from chronic noncommunicable diseases. Among the different types of cancer, prostate cancer has been the subject of great scientific interest. In this context, animal models are valuable for studying cancer-related aspects, the use of animal models has the potential to increase our understanding of carcinogenesis, tumor biology, and the impact of specific molecular events on tumor biology. Animal models with specific human cancer characteristics can be used to test cancer prevention and treatment strategies. In this review, we aim to show how the use of animal models as an essential tool in the study of the molecular mechanisms of carcinogenesis.

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1. Introduction

Cancer is considered a public health problem in the world, and a significant cause of mortality, presenting a significant psychosocial and economic burden[1].

It is noteworthy that cancer is responsible for one-third of deaths worldwide, and this impact is felt mainly by countries with miserable subsistence and underdeveloped conditions, such as Brazil. For example, when addressing early mortality, it is estimated that in 2008, 36 million deaths (63%) occurred as a result of chronic noncommunicable diseases, in this case, câncer[2,3]. Therefore, the current relations between society, physical environment, and health are complex and dynamic. For, the economic and social development brings direct repercussions on the environment and the health of the populations, being one of the main consequences of the alteration of the morbidity and mortality profile[4].

As an example of chronic aggravation, we can mention the risks to human health associated with the use and exposure to pesticides, specifically the risk of cancer, which has been the object of great scientific interest[5,6].

According to WHO (2019), "Cancer is a generic term for a large group of diseases characterized by abnormal cell growth beyond their usual limits that can then invade adjacent parts of the body and/or spread to other organs"[7].

The term cancer, is a common term used for all malignant neoplasms, being considered to be a multifactorial disease, in which its development depends on genetic (hereditary or sporadic mutations) and environmental (carcinogenic agents) factors. On the other hand, the term neoplasia means “new growth”, defined as “an abnormal tissue mass that grows uncoordinated and over normal tissue and persists to grow in the same way after the stimulus that caused its change has ceased”[8].

In this review, we provide an overview of prostate cancer, the purpose of which was to describe the use of animal models as an essential tool in the study of the molecular mechanisms of carcinogenesis in an attempt to test preventive and therapeutic potential strategies for cancers.

2. Literature selection and analysis procedure

The narrative study aims to broaden the understanding of the studies considered, in this case, the use of mice in experimental models in studies of carcinogenesis. We used the electronic libraries “Scientific electronic Library Online (SCIELO-BRAZIL) and PubMed to perform this narrative review. We chose those databases because they are considered the two most significant free platforms in the scientific literature in Brazil.

3. Results and analysis

3.1 Thematic analysis

The selected articles were thoroughly analyzed and then divided into thematic categories, with the following topics: Prostate Cancer, Experimental Cancer Models, and Prostate Cancer Experimental Models.

3.2 Prostate cancer

According to Quijada et al. (2017), prostate cancer has high frequency worldwide, is present in all countries of America, Europe, Australia, and Africa, being considered the second most common cancer in men worldwide. And in 2012, around 1 million new cases were estimated; in Brazil, it is the most common type of cancer in all regions, disregarding non-melanomic skin tumors, and in 2016 around 61,200 cases per 100,000 inhabitants were estimated. According to the same authors: "Most prostate cancer diagnoses are associated with men over 65 years and less than 1% to men under 50 years. Is expected to increase by 60% of the number of new cases due to the increase in world life expectancy "[9].

Data from the American Cancer Society (2015) show that prostate cancer strikes men of all races, "being a silent threat to men's health," ranking third as the cause of deaths from chronic noncommunicable diseases. American statistics show that one in six men in the world will develop prostate cancer (CP) throughout their lifetime[10].

The incidence of prostate cancer (PC) proves to be one of the most prevalent in the world, being one of the most intensely studied diseases. According to the American Cancer Society, in 2016, over 180,000 new cases of PC diagnosed in the US were estimated, resulting in about 26,000 deaths[10].

In Brazil, the National Cancer Institute (INCA) estimated for 2018 and 2019 the risk of 66,120 new cases per 100,000 Brazilian men, which is much higher than in developed countries such as the United States, Canada, and England.[2].

According to Araújo, Conceição, and Zago (2019), "the cure for PC is a phenomenon investigated by multiple scientific perspectives, and each year discoveries are evidenced". Where having the disease and living with it is still challenging, especially in the care given to patients and the implementation of public policies in the health system directed to the treatment of the disease[11]. In Brazil, for example, available treatments have side effects such as sexual dysfunction, changes in body image, and social stigma, which often make the patient even more vulnerable, especially concerning aspects that involve his masculinity[12,13].

3.3 Experimental cancer models

Several animal models are valuable for researchers to study aspects related to cancer biology. In this context, the use of animal models has the potential to increase our understanding of carcinogenesis, tumor biology, and the impact of specific molecular events on tumor biology. However, it is crucial for the researcher to bear in mind that no animal model can faithfully reproduce all aspects of human disease[14,15,16].

With the advent of knockout technologies, the studies were based directly on the concept of immunological surveillance. Becoming evident that spontaneous or chemically induced murine tumor models are useful in demonstrating that the immune system continually watches for the appearance of aberrant cells and plays a crucial role in preventing tumor formation. Through the use of murine T lymphoma, the authors were able to unravel the functions of some immune system cells in immunological surveillance against tumors[17,18,19].

The *Mus musculus* is considered one of the best model systems for cancer investigations due to several factors including its small size and propensity to breed in captivity, its three-year shelf life, extensive physiological similarities and molecular with humans and a fully sequenced genome[14,15,20,21].

According to Shen (2010), transplantable models (xenographic and syngeneic) are the most used because they allow a better study of metastases and more easily reproduce the tumor microenvironment. They can favor the modeling of experiments and enabling various approaches, and these models are designed in immunodeficient mice such as NUDs[22].

In any case, mouse transplant models present the essential conditions such as high graft rates, association between malignant and adjacent benign tissue, reproduce tumor heterogeneity and genetic profiles and reproduce the hormonal state of the human tumor, in addition to enabling use of human cancer cell lines or human primary cancer tissues, xenographic transplantable models[21,23].

According to Lin et al., (2014), among the specific characteristics, and according to the site of inoculation, there are advantages and disadvantages for murine cancer models. In subcutaneous cancer cell inoculation, the advantages are easy implantation and easy monitoring of the tumor, and the disadvantages: less nutrient supply and low development rate, being difficult in these conditions to have advanced cancer. In orthotopic models, the advantages are a microenvironment similar to that of primary cancer and the possibility of spontaneous metastases. The disadvantages are difficult implantation, the low rate of tumor development, and limited cancer development[23]. On the other hand, subrenal capsule (CRS) inoculations have the advantage of having good blood supply and a higher rate of tumor development, as well as more significant heterogeneity, being the hard implantation a disadvantage[24].

3.4 Experimental models of prostate cancer

A significant limitation in the study of prostate cancer in the recent past has been the lack of adequate animal models that faithfully recapitulate all stages of disease progression[25].

The NCI Mouse Models of Human Cancers Consortium has convened a group of human and veterinary pathologists to analyze current animal models of human prostate cancer (PCa) and make recommendations on the pathological analysis. They reviewed more than 40 different models with 439 samples, including xenograft models, genetically modified rat, and canine models. They are reporting that were developed numerous relevant models in the last 15 years, and each approach has strengths and weaknesses[21].

According to Ittmann et al. (2013), for over 15 years, the first generation of genetically modified prostate cancer (GEM) models has been introduced. These transgenic models used prostate-specific promoters to express SV40 oncogenesis in the prostate epithelium. Animal models, particularly rat models, played a central role in the study of the etiology, prevention, and treatment of PCa. While tissue culture models are useful in understanding PCa biology, they cannot recap the complex cellular interactions within the tumor microenvironment, which play a crucial role in cancer initiation and progression[21].

The development of optimized PCa models has already accelerated our understanding of the biological complexity of PCa and in the future will improve the development of new approaches to prevention, detection, and treatment of this malignancy[15,21,23].

Pavese et al. (2013) demonstrated an orthotopic implantation model of PCa. In this model, cells are implanted directly into the ventral prostate lobe in Balb / c mice and may progress for 4-6 weeks. This

model provides an image of the ability of cells to invade and escape the primary organ, enter and survive the circulatory system, and implant and grow at a secondary site[26].

Since death by PCa is not due to the primary tumor, but instead to the formation of distinct metastases, the ability to effectively a model of this preclinical progression is of high value. Thus models such as that used by Pavese et al. (2013) have been used effectively to measure the metastatic response to both changes in protein expression, as well as the response to small molecule therapy in a short response period[26].

Due to the molecular complexity of cancer and the cost of therapy, the researchers still looked for functional in vivo genomic characteristics to support patient care. Cancer models often faithfully recap basic biology, tumor microenvironment, and their interactions, drug responses, and therapeutic resistance similar to human disease, and effectively favor the search for responses to PCa[18,27].

The xenographic or xenotransplantable transplant models, allow the use of human cancer cell lines as well as the use of primary human cancer tissues. Accordingly, the classical models for human prostate cancer consist of immunodeficient mice carrying subcutaneous prostate cancer cell line xenograft generated by injection of cultured prostate cancer cells (e.g., LNCaP, PC3 or DU145) or co-injection of cultured prostate cancer cells and stromal cells[23,27] (LIN et al., 2014; HUANG et al., 2016).

4. Conclusion

The use of cancer animal models has provided an alternative means for disease-related research. They represent immense potential in understanding cancer in its many aspects of cell proliferation and development, as researchers can observe and manipulate murine models with cancer, increasing the sophistication of modeling, providing new knowledge and advances in research.

We conclude that murine models characterize efficient methods to elucidate the mechanisms involved in tumor progression and metastasis development, and thus allow the development of specific drugs for the treatment of cancer patients.

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