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Review article

Experimental mammary carcinogenesis - Rat models

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ABSTRACT

Mammary cancer is one of the most common cancers, victimizing more than half a million of women worldwide every year. Despite all the studies in this field, the current therapeutic approaches are not effective and have several devastating effects for patients. In this way, the need to better understand the mammary cancer biopathology and find effective therapies led to the development of several rodent models over years. With this review, the authors intended to provide the readers with an overview of the rat models used to study mammary carcinogenesis, with a special emphasis on chemically-induced models.

Contents

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1. Introduction

Breast cancer remains as one of the most frequent cancers among women, affecting approximately one out of ten women worldwide [1]. According to the World Health Organization, in 2012 breast cancer was responsible for the death of more than half a million of women around the world [2]. In this way, a better knowledge about the cancer biopathology is important to the development of new preventive and therapeutic strategies to fight this disease.

Since early times, animal models have been used by researchers in order to better know the anatomy and physiology of the human body. Aristotle (384–322 BCE), who is considered one of the most important thinkers, used animals to study intern differences among species. His studies were well documented and spread to other countries, contributing to the use of animal models as a research tool in several European and Arabian countries [3]. Since then, animal models have been frequently used and they have had a great importance in biomedical research. Proofing this is the fact that over the last century, all Nobel prizes in the field of physiology and medicine used animals as models of diseases [4]. Nowadays, animal models still represent an important tool to study several diseases, including cancer. They allow the researchers to better understand many aspects of this disease, such as the etiology, the pathogenesis, the progression, the genetic and molecular basis, and the development and evaluation of several therapeutic approaches that may improve the quality of life and lifespan of oncologic patients [5–8].

2. How to select an animal model?

Several animal species, such as fishes, rabbits, rats, mice, dogs, non-human primates and large animals may be used as models, and the researchers should be able to choose the most adequate model to answer to their questions/hypotheses [9]. An ideal animal model of human diseases should be simple, not expensive and similar to Human as much as possible [10]. When confronted with the need to choose an animal model, the researchers should take into consideration the following aspects: the aim of the study, available species, advantages and disadvantages of each specie, accommodation expenses, manipulation, required equipment and ethical considerations [10,11]. Mice (*Mus musculus*) and rats (*Rattus norvegicus*) are among the species more frequently used in research protocols performed in the European Union [12]. Indeed, when compared with other species, they have some advantages, namely their physiology and genetic are well known, they are small animals, easy to accommodate and manipulate, they are relatively cheap, their use is easily approved by legislation on the protection of animals used for scientific purposes, and the most important one, they are mammals and have many similarities with humans, like anatomy, physiology, genetic and biochemistry [6,13].

3. Rat as a model of mammary cancer

The occurrence of mammary tumors (mammary fibroadenoma) in female rats was described by the first time by Mceuen in 1938 after the daily vaginal application of a solution of estrone in corn oil for two years and an half [14]. Since then, the female rat has been continuously used as a model of mammary cancer and nowadays it constitutes one of the most frequently used animal models to study mammary carcinogenesis [13]. Indeed, the mammary cancer in female rats resembles that of women in several features, namely in its hormone responsiveness, histology, biochemical properties, molecular and genetic characteristics. Additionally to this, when compared with mice, the rats provide a higher quantity of blood and tissue samples for posterior studies [15,16].

3.1. Rat mammary gland anatomy and histology

The female rat has two mammary chains (right and left) with six mammary glands with a nipple each one: three pairs in thoracic region (extended to the cervical region) and three pairs in abdominal-inguinal region [17]. The mammary glands of each mammary chain are usually numbered by the nipple from one to six in the cranio-caudal direction and the gland tissue of the thoracic region are smaller when compared with those of the abdominal-inguinal region [18]. Inversely to that happens in women, the rat mammary glands are poorly developed and they can be identified externally only by the presence of the nipple. Rat mammary glands are greatly vascularized by the branches of several arteries, namely superficial cervical, thoracic internal and external, external pudendal and axillary [17] (Fig. 1).

Microscopically, the rat mammary gland has a tubuloalveolar conformation, being composed by a group of branched tubular ducts and alveolar buds [19]. It consists of two main tissues: the parenchymal and the stromal tissue (connective, adipose and vascular network tissues) [20]. When compared with mice mammary gland, the rat mammary gland tissues have a higher stromal and parenchymal component [15,16]. Like in women, the rat mammary gland tissue is hormone dependent and grows during estrous cycle and pregnancy [21].

The development of rats' mammary gland occurs through different phases. An extensive development occurs during puberty by the day 21, being this phase characterized by the differentiation of the epithelium into terminal end bud units that correspond to the bulbous end of the branch lactiferous duct [19,22]. The duct is composed by a layer of luminal epithelial cells (ductal epithelial cells) fated to form the walls of the ductal lumen with outer of myoepithelial cells and the basement membrane. Terminal end bud is composed by multi-layered of preluminal epithelial cells (also called body cells) surrounded by a layer of pluripotent stem cells (also called cap cells) that are progenitors of mioephitelial cells. Both body cells and cap cells are very proliferative (Fig. 2A) [13,23,24]. Terminal end bud proliferates dichotomously into alveolar buds and terminal ductules with continuous branching ducts and ductules that drain into the duct of the nipple (Fig. 2B) [21]. Each alveolar buds and duct have one layer of simple epithelial cells surrounded by a layer of myoepithelial cells and the basement membrane, supported by the stroma. Near to 50–55 days of age, the alveolar lobules are formed from the alveolar buds in both non-pregnant and pregnant rats [19,21].

As mentioned above, the rat mammary gland tissue is hormone dependent and consequently the secretory structure is influenced by the sexual maturity (reached at about 6 weeks of age), estrous cycle and pregnancy [25]. Estrogen and growth hormone are considered the main hormones responsible for the ductal elongation. Despite these, the proliferation, branching and differentiation of mammary gland may be influenced by other hormones, such as progesterone and thyroid hormones. When the pregnancy occurs, the progesterone is the

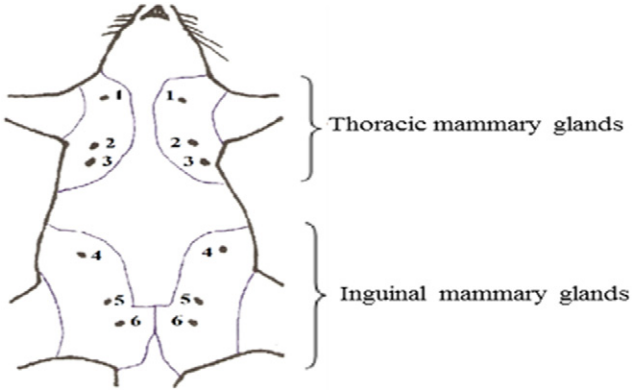

Fig. 1. Schematic representation of anatomic location of mammary glands in female rat.