Prostate Cancer

Chapter 1

Human and Animal Prostate Cancer Similarities and Differences: Models to Study This Disease

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Abstract

Prostate cancer is the second most common cancer in men, is associated with high morbidity and mortality rates. The study of prostate cancer biopathology and the discovery of new therapies is very important to reduce these numbers and increase patients' quality of life. Animal models performed with laboratory animals or studying spontaneous tumours in company animals, allow us to study the mechanisms underlying the onset and development of cancer and to explore different therapeutic approaches. For a better extrapolation of the results of animals studies to the human clinical practise, it is very important understand the differences and similarities between them.

Keywords: Models; Prostate; Cancer

1. Introduction

Worldwide, prostate cancer is the second most common cancer and the fifth leading cause of oncological death among men [1]. There were approximately 1.3 million new cases and 358 989 deaths estimated in 2018 [2]. Although the causes of the prostate cancer are not fully understood, many risk factors have been considered, such as age, race, family history, diet, hormone exposure and inflammation [3,4]. Steroid hormones, particularly androgens play an important role in human prostate cancer. Prostate cancer is dependent on androgen receptor activation for growth and survival, but the precise mechanism underlying this process is not clear [4–6]. Adenocarcinomas represent more than 95% of prostate cancers and arises from the prostate gland epithelial cells. Other type of prostate cancer includes sarcomas, small cell carcinomas, neuroendocrine tumours and transitional cell carcinomas [7]. Intraepithelial neoplasia (PIN), that is characterized as an intra-luminal proliferation of epithelium exhibiting varying degrees of malignant criteria, is considered a precursor of prostate cancer [8]. Prostate glands with extensive PIN also have more multifocal carcinomas and these developed preferentially in the peripheral zone of the gland [9]. Proliferative inflammatory atrophy (PIA) is also a pre-neoplastic disorder, that is caused by tissue damage, by an initiating inflammatory insult [8] and are often found in close proximity to foci of PIN and carcinoma, and commonly contain somatic mutations that are present in PIN lesions and carcinoma [10]. Prostate cancer metastasizes manly to bone [11], but also to lymph nodes, lungs, liver and brain [12].

Over the years, animal models have been used to study several diseases, including cancer, and contribute to understand many aspects involved in disease progression and for the discovery and development of new pharmacology and non-pharmacology therapies and preventive strategies [13,14]. An ideal animal model should be simple, not expensive and could mimic the Human disease as much as possible.

In the present book chapter, we summarized the features of animal's models, namely non-human primates, dogs, cats, mice and rats to study prostate cancer, in relation to the prostate anatomy, epidemiology and etiology of prostate cancer, and compared the similarities and differences with Human prostate cancer.

2. Human Prostate

The man prostate is a walnut-size gland located behind the inferior border of the pubic symphysis and pubic arch and anterior to the rectal ampulla and it is just one tubule-alveolar gland [7,15]. It is composed of a base, attached to the neck of the bladder, an apex, on the superior surface of the urogenital diaphragm that makes contact between the medial surface of the levator any muscles, anterior, posterior and inferior-lateral surfaces [16].

The prostate contains distinct regions with different functions which are differentiated by their histology pattern and anatomic landmarks. Peripheral zone (PZ) represents approximately 70% of the glandular prostate and most of the adenocarcinomas arise in PZ as well chronic prostatitis, inflammation and post inflammatory atrophy [7]. Central zone (CZ) represents approximately 25% of prostate volume and is located at the base of the prostate between the peripheral and transition zones. The transitional zone (TZ) represents only 5% of the glandular prostate volume and is the most common site for benign hyperplasia lesions and less commonly adenocarcinoma [7,17]. The periurethral gland or anterior fibromuscular stroma (AFMS) represents less than 1% of the glandular prostate and fills the space between PZ and pre-prostatic urethra [18].

Prostate cancer is an age-related disease, with the majority of the cases diagnosed in men between 60 and 70 years [2,3,19]. Early prostate cancer detected by screening usually has asymptomatic. In advanced stage, the symptoms included weak or interrupted urine flow, the inability to urinate or difficulty to start and stop urine flow, the need to urinate frequently, blood in urine and pain during urination [19,20]. These symptoms may also be due to the benign prostatic hyperplasia, so it's is important confirm prostate cancer through other methods, like biopsy [21]. Prostate-specific antigen (PSA) is and androgen-regulated serine protein and is produced by the secretory epithelial cells in the ducts and acini of the prostate [18] and is the most widely used serum marker for prostate cancer [3,22,23]. However, it is not specific for prostate cancer and levels can be elevated in other prostate disorders like benign prostatic hyperplasia (BHP) [22]. To categorize prostate biopsy the pathologists use a grading system known as the Gleason Scoring system [15] based upon the architecture differentiation of the carcinomas cells in hematoxylin-eosin stained tissue section. These system helps in the determination of the aggressiveness of prostate cancer and in choosing the most appropriate treatment options and the most suitable animal models to study this disease[8].

3. Animal Models of Prostate Carcinogenesis

There are several animal models to study prostate cancer. In this section we focused in non-human primates, dogs, cats, mice and rats' models. There are significant anatomical differences between the prostate of the different animal models (see **Table 1**), but also similarities. It is important to understand them when choosing the most suitable animal model.

Table 1: Overview of the human, non-human primates, dogs, cats and rat and mice's prostate anatomy

	Localization	Lobulation	Shape	Relation to the urethra
Human	Behind the inferior border of the pubic symphysis and pubic arch and anterior to the rectal ampulla	Alobular structure	conical	Completely surrounds the proximal urethra
Non-human primates	Distal end of the urinary bladder	Bilobed (cranial and caudal lobes)	ovoid	Does not complete surround the urethra
Dogs	Dorsal to the pubic symphysis, ventral to the rectum and caudal to the urinary bladder	Bilobed	ovoid	Surrounds the proximal urethra
Cats	Dorsal to the pubis, near the neck of the urinary bladder	Bilobed	ovoid	Does not surround the ventral portion of the urethra
Rats and mice	Caudal to the urinary bladder	Four lobes (dorsal, lateral, ventral and anterior)	Not a compact unit	Incompletely surrounding the urethra

3.1. Non-human primates

Non-human primates can be used as models to study several diseases such as Alzheimer, Parkinson, diabetes and cancer [24]. Non-human primates are similar to humans in regard to genetic evolution, anatomy, physiology, biochemistry and organ systems [25]. Non-human primates could be good models for prostatic diseases, namely to study PSA however the very low incidence and the costs to maintenance these animals make them not advantageous as animal models [26].

Indeed, prostate carcinoma and benign prostatic hyperplasia (BPH) are rare diseases in non-human primates and are age-related disease [26,27]. The few reports of prostate lesions included hyperplasia involving acinar or basal cell epithelium, inflammation and adenomas and carcinomas [28–30]. PSA was detected in cynomolgus macaques, rhesus macaques, orangutans, chimpanzees, gorillas and baboons but not in marmosets [30,31].These differences in incidence and severity of prostate diseases compared to men may be related to anatomical features. The prostate of these animals is located at the distal end of the urinary bladder and it is divided into two lobes: cranial and caudal lobes according to their proximity to the bladder and seminal vesicles [26,29]. In contrasts to humans, the prostate does not completely surround the urethra [26,30]. In the macaque species the two lobes of the prostate have equal sizes but in baboon the two lobes are different in size and in histology. The cranial lobe much smaller than caudal lobe and is composed of larger irregularly shaped tortuous acini and high columnar cells. The caudal lobe is composed by small regularly shaped acini and cuboidal cells with basal oval shaped nuclei and more widely separated by stroma [30,32]. Also, baboons and rhesus monkey prostate showed histologically and anatomically similarities to human prostate: the cranial and caudal lobes corresponding to central and peripheral zones of human prostate, respectively. [32–34].

3.2. Cats and dogs

Dogs' prostate is bilobed and ovoid-shaped and surrounding the neck of the urinary bladder and the proximal urethra [35]. The dorsal surface of the prostate is separated from the ventral surface of the rectum by the two layers of the fold of peritoneum bounding the rectogenital fold [36]. The ventral surface is covered by a layer of retroperitoneal fat. The prostate has a prominent median septum which separate the right and left lobes, and each lobe is divided into lobules by capsular trabeculae. The prostate gland is recovered by a fibromuscular capsule (36,37).It is located dorsal to the pubic symphysis, ventral to the rectum and caudal to the bladder, and is the unique accessory gland in the dog [37].

In cats, prostate located near the neck of the urinary bladder and in contrast to dogs, prostate does not encircle the urethra, just covers only the top and sides [38–41]. As in the dogs, cat prostate is bilobed [38].

Dogs, like humans, develop spontaneous prostate carcinomas more frequently in older animals, with an average age at diagnosis of 10 years [26,36]. Besides, also benign prostatic hyperplasia (BHP) and high-grade prostatic intraepithelial neoplasia (HGPIN) spontaneously developed in intact adult male dogs [42]. In dogs, BHP affects the prostate gland in a diffuse pattern [35], it can be severe and cause others clinical disease, including dorsal compression of the colon and dyschezia, but in contrast to men, does not appear to be a preneoplastic condition [42]. Histologically, there are two patterns depending on dogs' age [43]. In dogs up to 4 years age, BHP is referred to as diffuse glandular with an intra-alveolar increase in papillary proliferation of prostatic secretory epithelium. Dogs with 6 years of age and older display diffuse glandular BHP along with an increased stromal component [35]. HGPIN had cytological similarities with man, including cell crowding, loss of polarity and nuclear and nucleolar enlargement, basal cell disruption, proliferative index and micro vessel density [44,45]. The prevalence seems to be influenced by aging and testicular androgens [45], however the presence of HGPIN and the risk of development prostate cancer remains unknown [35,42]. The precise location of origin of the carcinomas is not yet know, but may originate from prostatic ductular epithelium adjacent to the periurethral zone, prostatic acinar epithelium or urothelium lining the prostatic urethra, e.g. transitional cell carcinoma [35,36,42].

Another difference between men and dog's prostate cancer pathogenesis is the role of androgens. As previously mentioned, men prostate cancer is androgen dependent for growth and survival, but in dogs it's different. In dogs, normal prostatic tissue express androgen receptor and they are important for normal function. Dogs with prostate cancer have no expression of the androgen receptor[35]. Also, the castration does not decrease the risk cancer development, on the contrary, several studies showed that castration may be associated with an increased risk of cancer [46-48]. On the one hand castration alters the prostate stromal component

from primarily actin-positive smooth muscle cells to vimentin-positive mesenchymal cells which could promote the development of prostate cancer in castrated dogs [49]. On the other hand, castrated dogs have a higher average life expectancy than intact dogs and have higher predisposition to develop carcinomas [35]. So, the tumor growth is not androgen dependent [26] and the androgen receptor does not seem to play a central role in the pathogenesis of canine prostate cancer development [42].The common type of canine prostate cancer are adenocarcinomas, but the majority of the tumors showed several morphologic changes that included two or more types of differentiation in the same tissue section, like glandular, urothelial, squamoid or sarcomatoid [36]. Histologically, carcinomas show an intra-alveolar pattern, but also contain similar patterns to transitional cell carcinoma [35]. Like humans, prostate cancer in dogs metastasizes to bone, with osteoblastic and osteolytic lesions and formation of new woven bone [35,50-53].

Beyond the ethical issues, the long latency period, the high cost to maintain into laboratory, long gestation period and difficulty of genetic manipulation make the dog an unusual animal model to study prostate cancer [54,55].

The prostate cancer in cats is very rare disease and in the few cases reported the tumors were classified as high-grade carcinomas and adenocarcinomas. The sites of metastasis included lymph node, lungs and pancreas [56]. The development of carcinomas is more frequently in older cat, with average age of eight years [56], and castrated animals [41] and the survival after diagnosis is lower, beyond 3 months [41]. There is no much information about the characteristics of feline prostate cancer, namely risk factors, the role of androgens and the mechanisms of tumor development.

3.3. Rats and mice

The prostate gland of the rats and mice are significantly different from men. The rodents´ prostate consists of four distinct lobes with different histological characteristics and different physiological functions. It is located circumferentially around the urethra, immediately caudal to the urinary bladder. The lobes are classified as ventral, dorsal, lateral and anterior (or coagulating gland) and are named according to their relative position to the urinary bladder [9,17,57]. Spontaneous prostate cancer in wild-type mice are rare [54,57] and in rats also, but the incidence varies with the rats' strain, are reported 70% of spontaneous rat cancer for ACI/Seg and 8% for Lobund-Wistar [57].

In 1963, was reported the first spontaneous prostate tumor in a 22-month-old Copenhagen male rat [58]. This tumor was classified as a papillary adenocarcinoma that involved the dorsal prostate lobe and were not identified metastases [58]. Pollard, in 1973, reported the development of spontaneous carcinoma in dorso-lateral and anterior prostate in Wistar rats with 26 months of age[59]. Metastatic lesions in lungs, spleen, liver, pancreas and intestine were also identified

[59]. Lobund-Wistar rats developed adenocarcinomas in the anterior prostate and also in seminal vesicles that expand to the dorsolateral lobes [60,61]. Prostatic intraepithelial neoplasia (PIN) is present in most cases as a tumor precursor [62]. In early stages of tumorigenesis the tumors are androgen dependent and in advanced stages became testosterone independent [60,62]. The long latency period, low tumor incidence and no bone metastases are disadvantages of these spontaneous models [62]. ACI/Seg rats, aging on average 24 months, demonstrated high susceptibility to develop spontaneous ventral prostate adenocarcinomas. These tumours classified as adenocarcinomas of cribriform pattern without metastases [57,63,64]. Atypical hyperplasia and dysplasia in the ventral prostate are considered pre-malignant lesions [62].

Table 2: Comparative aspects of human, non-human primates, dogs, cats and rat's spontaneous prostate cancer

	Pre-malignant lesions	Risk factors	Incidence	Average age at diagnosis	Role of androgens	Metastases	Aggressivity	Histological classification
Human	PIN	Age, race, family history, hormone exposure, inflammation	Variable	>65 years	Significant	Bone (Lumbar spine, pelvis), pelvic lymph nodes, lungs, liver, brain	Variable	Adenocarcinomas
Non-human primates	NR	Age	Low	Variable	Significant	NR	NR	Hyperplasia, inflammation, adenomas, carcinomas
Dogs	NR	Castration, Age	High	10 years	Independent	Bone (Sub-lumbar lymph nodes, lumbar spine, pelvis) lung	High	Ductal carcinomas
Cats	NR	Age (?)	Low	8 years	NR	Lymph node, lungs and pancreas	High	High-grade carcinomas and adenocarcinomas
Rats								
ACI/Seg	Atypical hyperplasia/ dysplasia in ventral prostate	Age	High	24-33 months	Independent	NR	Variable	Cribriform adenocarcinomas
Lob und-Wistar	PIN	Age	Low	26 months	Androgen-dependent in early stages, then independent	Lungs, peritoneal cavity	Variable	Adenocarcinomas

NR: not reported

In contrast to rats, mice are resistant to induction of prostate cancer by chemical carcinogens [57]. Mice are most commonly used as xenograft models and genetically-engineered models [54]. Over the years, many experimental works were performed to discovered chemical compounds to induce tumors and understand how they induce these changes. Carcinogenic agents have the ability to induce tumors in several tissues depending on application site (i.e., prostate, urinary bladder, mammary tissue), absorption site (i.e., subcutaneous injection, oral administration), organ of metabolism (i.e., liver) and excretory organs (i.e., urethra, urinary bladder) [65]. The metabolic activation of the carcinogenic compound has a specific route. The first step is carcinogenic exposure that can be absorbed in several ways (i.e., cutaneous, injection, oral or inhalator) and depends on the physicochemical properties of the substance. Then, the compound is distributed and suffered biotransformation on liver, kidneys or lungs, occurring its activation. Then may occurred genotoxic mechanisms, such as DNA adducts and chromosome breakages, or non-genotoxic mechanisms, such as inflammation, reactive oxygen species or immunosupression. These mechanisms cause a genomic damage and altered signal transduction which leads to cancer development [66].

4. Chemically-Induced Rat Prostate Cancer Models

Chemically-induced rat models allows the development of tumors in short period of latency, high reproducibility and allow monitoring all carcinogenesis process in a target organ and are also important to evaluate the chemopreventive effects of different agents [66]. However, they have some limitations namely high costs to obtain and maintain the animals, time-consuming and labor-intensive, application of the carcinogen in high doses and during a long-time period, toxicity of the carcinogen compounds to animal and people that handle the animals and the environment and lack of organ specific of the carcinogen compounds [56,67].

Four chemical compounds have described to induce prostate cancer in laboratory rats: N-nitrosobis (2-oxopropyl) amine (BOP), N-Methyl-N-nitrosourea (MNU), 3,2-dimethyl-4-aminobiphenyl (DMAB) and the 2-amino-1-methyl-6-phenylimidazol[4,5-b]pyridine (PhiP) [68]. The main characteristics of each can be found in **Table 3**.

Table 3: Features of chemically-induced rat prostate cancer models

	BOP	MNU	DMAB	PhiP
Chemical origin	Nitrosamine	Nitroso	Polycyclic aromatic hydrocarbon	Heterocyclic amine
Metabolic activation	yes	no	yes	yes
Rat's strain(s) with more affinity	MRC	Lobound-Wistar Wistar-Unilever	F344 a	F344
Administration route	Subcutaneous injection, Intragastric intubation	Intravenous injection Subcutaneous injection	Subcutaneous injection	In diet, gavage
Average dose	5-20 mg/kg/body weight	30-50 mg/ mg/kg/ body weight	25-50 mg/kg/body weight	100-400 ppm into diet or 70-200 mg/ kg/body weight
Average latent period (weeks)	60-70	50-60	40-60	40-50
Type of tumor	Squamous cell carcinomas	Adenocarcinomas	Adenocarcinomas	Carcinoma
Prostate lobe preferential	Ventral	Dorsolateral and anterior	Ventral, dorso-lateral and anterior	Ventral
Metastasis sites	Bladder, colorectum, urethra	Lymph nodes, lungs, liver	Liver, lymph nodes, zymbal gland, small intestine	Lungs, colon

The N-nitrosobis (2-oxopropyl) amine (BOP) belongs to the family of nitrosamines. It is represented by the molecular formula $C_6H_{10}N_2O_3$ and has a molecular weight of 158.16 g/mol [69]. It is reported to induce pancreatic and liver tumors in Syrian golden hamsters [70,71], biliary and hepatic neoplasms in guinea pigs [72] and in rats induce tumors in prostate [73], nasal cavities, colorectal and urothelium [74,75]. After exposition BOP is converted, in the liver, to CO_2 and N-nitrosobis (2-hydroxypropyl)amine (BHP) and N-nitroso (2-hydroxypropyl) (2-oxopropyl) amine (HPOP), both compounds are nitrosamine metabolites [75,76]. Thus BOP cause DNA methylation, and methylation induces cancer [74]. Prostate cancer in rats induced by BOP, was reported for the first time in 1981 by Pour [77]. MCR rats developed tumors in the dorsal lobe after an intragastric intubation at a dose of 10 mg/kg weekly. The same author performed a study for 74 weeks, in which BOP was administered at different doses (10, 5 or 2.5 mg/kg) by the same route of administration in MRC rats. The tumor, more specific squamous cell carcinomas, developed mainly in the ventral prostate and were dose-related [73]. Testosterone treatment can be used in combination with BOP to yield high incidence of carcinomas. This combination induce the development of adenocarcinomas and

squamous cell carcinomas in dorsolateral and ventral prostate in MRC rats [78]. BOP can be administered by intragastric intubation or subcutaneously and the experimental protocol after carcinogenic administration takes, on average, 60 weeks. However, as BOP mostly induced squamous cell carcinomas and tumors in the ventral lobe prostate, the only lobe that does not have a human homologue, it is not a very adequate animal model to mimic human prostate cancer [63]. The N-methyl-N-nitrosourea (MNU) is a nitroso-compound does not require metabolic activation; it is a direct-acting alkylating agent by methylation of the guanine nucleosides. MNU is represented by molecular formula $C_2H_5N_3O_2$ and has a molecular weight of 103.08 g/mol [65]. This compound is a carcinogenic agent in various animals' species (rats, hamsters, gerbils, fishes and shrews) and may induce tumors in breast, ovary, uterus, hematopoietic organs, kidney, urinary bladder, liver, intestine, spleen, retina and prostate [65]. Pollard and colleagues developed a method to induced prostate cancer in Lobund-Wistar rats through the administration of MNU associated with hormonal treatment [79,80]. They used 30-40 mg of MNU injected intravenously, followed by a long-term administration of 10-40 mg testosterone propionate via silastic implants. This protocol induced adenocarcinomas and atypical hyperplasia lesions in ventral, dorsolateral and anterior prostate. Metastases can be found in lungs and peritoneal cavity but not in bone [62]. However, others experimental works demonstrated that the majority of the carcinomas originated from the seminal vesicles [81,82]. Bosland developed an animal model that involves stimulation of prostatic cell proliferation by sequential treatment with cyproterone acetate, that inhibit androgen secretion causing atrophy of prostatic epithelial cells, and testosterone propionate [83]. Wistar-Unilever rats are treated with 50 mg of cyproterone acetate, and then receive daily injections of 100 mg/kg body weight testosterone propionate for three consecutive days. One day after the last testosterone injection, rats received a single intravenous injection of MNU (50 mg/kg). The rats were sacrificed 79 weeks after MNU treatment. The tumors developed were classified as adenocarcinomas in the dorsolateral prostate, were invasively growing and metastasize to the lymph nodes and lungs [57,84].

Over the years, this Bosland protocol was improved and now the sequential treatment with an antiandrogen (cyproterone acetate or flutamide), testosterone propionate, MNU and chronic treatment with testosterone is frequently used for prostate cancer induction [63,81]. With more details: the cyproterone acetate or flutamide is given once daily for 2-3 weeks by gavage or by subcutaneous injection, followed by the administration of testosterone propionate (10-100 mg/kg) by subcutaneous injection during three consecutive days after last cyproterone acetate treatment or a single subcutaneous injection of 100 mg/kg on that day. Forty-eight hours later, a single intravenous or intraperitoneal injection of MNU, in doses between 30 and 50 mg/kg, and finally to achieve a high carcinoma incidence, testosterone propionate in silastic implants are placed subcutaneously in interscapular region by surgical approach under general anesthesia. The experimental work should be conducted until 50-60 weeks after MNU

injection, to achieve maximal tumor incidence [63,81,85]. The vast majority of the prostate tumors induced were adenorcarcinomas in dorsolateral and anterior prostate, that share some important characteristics with human prostate carcinomas, being this model a suitable model for prostate cancer studies, and nowadays, the most used [82].

The 3,2'-diemthy-4-aminobiphenyl (DMAB is a classical polycyclic aromatic hydrocarbon represented by the molecular formula $C_{14}H_{15}N$ and has a molecular weight of 233.74 g/mol [69]. DMAB have multi-organ tropism, inducing tumors in the colon, urinary bladder, pancreas, prostate, mammary glands, preputial glands, seminal vesicles and Zymbal glands [57,86]. This compound needs to be active in the liver. Then, the metabolites interact with DNA causing transversions in nucleotides, inducing irreversible changes and adducts [86]. Katayama, in 1982, was the first to induce microscopic carcinomas in the ventral prostate of F344 rats by DMAB [87]. The prostate carcinogenicity of DMAB was confirmed, a couple years later, by Shirai and colleagues [88]. They induced prostatic carcinomas in F344 rats by repeated treatment with ethinyl estradiol (75 ppm) added to the basal powdered diet and DMAB (50 mg/kg by subcutaneous injection) for 60 weeks. The treatment with ethinyl estradiol induced a high incidence (up to 85%) of adenocarcinomas in the ventral lobe of the prostate [88]. The carcinogenic potential of DMAB is dose-dependent; a low-dosage of DMAB given over a long period (around 48 weeks) was more effective to induce prostate cancer than a high dosage over a short period of time (10-25 weeks) [89]. There are different susceptibilities between rat strains (F344 and ACI rats being the most susceptible and Wistar and Sprague-Dawley rats resistant) to DMAB carcinogenesis [90]. Chronic administration of high doses of testosterone incorporated into silastic tubes and implanted into subcutaneous tissue in combination with DMAB can be used to promote tumor development [78]. This combination produced a high incidence of invasively adenocarcinomas in dorsolateral and anterior prostate but not in ventral prostate in F344 rats [91]. The induction of tumours in dorsolateral and anterior prostate and seminal vesicles and the degree of invasiveness depends on the duration and doses of testosterone [91,92]. The tumors are histologically and biologically indistinguishable from those induced by MNU in combination with testosterone [57]. The co-administration of ethinyl estradiol with testosterone propionate increased the yield of carcinomas in the lateral and anterior lobes of the prostate in a dose-related fashion with lobe specificity [93]. In a general way, the induction protocol consists of a subcutaneous injection of 25-50 mg/kg, 10 times at 2-week intervals. Implants of testosterone propionate can be used and should be replaced at 6-week intervals. On average, the studies using DMAB last 60 weeks.

The 2-amino-1-methyl-6-phenylimidazol[4,5-b]pyridine (PhIP) is a heterocyclic amine represented by the molecular formula $C_{13}H_{12}N_4$ and has a molecular weight of 224.27 g/mol [69]. It is present in a variety of meats cooked and fish and induces cancer development in mammary gland, colon and prostate in laboratory rodents [57]. PhIP may be metabolized to

biologically active metabolites (N-hydroxy-PhIP and N-acetoxy-PhIP) that form DNA adducts [94]. The metabolic activation involves cytochrome P450-mediated N-hydroxylation [95]. In 1997, Shirai and colleagues, were the first to use PhiP to induce prostate cancer tumors [96]. They subjected F344 rats to PhIP, at a dose of 400 ppm mixed in the diet, for 52 weeks [96]. The adenocarcinomas developed in ventral lobe and were histopathologically equivalent to those caused by DMAB [97]. A long-term pharmacological with testosterone propionate can induce invasive carcinomas in the anterior prostate and seminal vesicles [98]. Overall, the experimental protocols using PhIP consist in administration of this compound mixed into the diet or administered by gavage (70-200 mg/kg).

5. Conclusion

There are many similarities between human and animal prostate cancer, like histology, metastatic process and spontaneous cancer incidence.

Non-human primates are closer phylogenetically to humans than the other animals, and mechanisms underlying the cancer development are expected to be similar. However, in the literature there are few reports of prostate cancer in non-human primates, which can be explained by the difficult access to these animals in their natural habitat, the high cost of captivity for long periods of time, absence of symptoms in captive animals and failure to complete detailed autopsies. Dogs are considered by many researchers the best model to study prostate cancer, due to the development of spontaneous cancer with a higher incidence when compared with other animals and the development of bone metastases. However, they were not very used in experimental studies since they are considered companion animals and for ethical reasons its use is reduced. Mice are mainly used as xenograft models and genetically-engineered models. The reports of spontaneous prostate tumors are rare and mice are resistant to induction of prostate cancer by chemical compounds. Rats also developed spontaneous prostate tumors, although with low incidence and share some similarities with humans, namely the influence of androgens in cancer development. Chemically induced protocols are designed to induce tumors in rat lobes analogues to man counterpart, mainly dorsolateral prostate lobe. However, the occurrence of bone metastases is reduced. Besides this and the anatomical differences, studies found similarities in the molecular mechanisms underlying prostate cancer development in rats and men, making the rat a valid animal model to study prostate cancer development and to evaluate the efficacy of several treatments and preventive measures. Above all, when it is necessary to choose an animal model we must always keep in mind what are the objectives of the work, the amount of samples we need to collect and the type of sample to collect.

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