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Nonhuman Primates as Models for Studies of Prostate Specific Antigen and Prostatic Diseases

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BACKGROUND. Because prostate specific antigen (PSA) is released at increased levels into the blood early in the development of prostate cancer, benign prostatic hyperplasia (BPH) and prostatitis, it is widely used as a marker for these diseases. However, PSA has clinical limitations as a screen for prostatic diseases due to its low sensitivity and specificity. There is a strong need to better understand the biology of PSA and factors affecting its serum levels.
METHODS. We evaluated cynomolgus macaques, rhesus macaques, baboons, and marmosets for their suitability as models for the study of PSA biology and prostatic diseases.
RESULTS. Prostates of several nonhuman primates are anatomically similar to the human counterpart. Anti-human PSA antibody detected PSA antigens in all the Old World monkeys (cynomolgus macaques, rhesus macaques, and baboons) but not in marmosets. Of the Old World monkeys, cynomolgus macaques have the highest serum PSA levels; baboons have the lowest. Serum PSA levels from macaques includes a number of outlier samples with unusually high values. We also report two cases of abnormal pathologies in macaques accompanied by high serum PSA levels. One case consisted of prostatic hyperplasia involving both glandular and basal cells in a cynomolgus macaque and another of glandular hyperplasia and atrophy in a rhesus macaque. The finding that pathological changes in the prostate of macaques may lead to increases in serum PSA is worthy of further exploration.
CONCLUSION. Cynomolgus macaques and rhesus macaques are promising animal models for PSA biology studies. *Prostate 68: 1546–1554, 2008.* © 2008 Wiley-Liss, Inc.

KEY WORDS: **PSA; nonhuman primates; prostate; macaque; baboon**

INTRODUCTION

A major hindrance to the study of the pathogenesis of prostate diseases such as cancer, benign prostatic hyperplasia (BPH), and prostatitis is the lack of appropriate animal models. In the case of prostate cancer, animal models for this condition are very limited due to the very few species (lions and dogs) that are known to develop prostate cancer spontaneously. However, the usefulness of these animal models is questionable due to either availability or the differences in anatomy and histology of the prostates of these animals compared to humans.

Although nonhuman primates are phylogenetically closer to humans than any other laboratory animals and therefore should be considered suitable models for human prostatic diseases, they have not been studied

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systematically as models of prostatic diseases mainly because of the widely held view that nonhuman primates do not develop prostatic diseases [1].

Presently, a number of proteins are used in the diagnosis, monitoring and management of prostatic diseases. In healthy males, prostate specific antigen (PSA) is restricted to the prostate gland and very little leaks into the bloodstream. Increased amounts are detected in the blood in cases of prostatic diseases and therefore PSA is used for screening, diagnosing and monitoring of prostate cancer. Alpha-methyl-acyl-CoA racemase (AMACR) is a mitochondrial and peroxisome enzyme that is overexpressed in prostate cancer and is presently used as an auxiliary immunohistochemical test for prostate cancer [2].

We evaluated four nonhuman primate species commonly used in research for their suitability as models of PSA biology and prostatic diseases. The study also examined AMACR, a protein that is clinically important in the diagnosis of prostate cancer. Two cases of prostatic lesions which were accompanied by elevated serum PSA are also reported.

MATERIALS AND METHODS

Animals and Tissue Collection

Cynomolgus macaques (*Macaca fascicularis*), rhesus macaques (*Macaca mulatta*), baboons (*Papio hamadryas anubis*), and common marmosets (*Callithix jacchus*) maintained at the Southwest National Primate Research Center, Southwest Foundation for Biomedical Research (SFBR) in San Antonio, Texas, were used for this study. A total of 114 baboons, 66 cynomolgus macaques, 12 rhesus macaques and 5 marmosets were examined.

We opportunistically sampled animals that presented for necropsy and an attempt was made to use animals across the whole lifespan. Male baboons reach sexual maturity between 6 and 7 years of age, male cynomolgus macaques and rhesus macaques between 4 and 5 years of age, and male marmosets reach sexual maturity at between 9 and 13 months.

Body weights were obtained either from SFBR animal records or when animals underwent necropsy. All animals were humanely euthanized. Only male animals were used in these studies. Complete necropsies were carried out for each animal. Male reproductive organs were removed and weighed. Tissue samples were either frozen at −80°C or fixed in neutral buffered formalin and processed for routine histological examination. All histopathological slides were examined by two board-certified veterinary pathologists (GBH and EJD). Two slides with microscopic lesions and elevated serum PSA were also sent to the Armed Forces Institute of Pathology (AFIP, Washington, DC) for evaluation.

Serum PSA Assay and Cloning

Serum was obtained from animals prior to euthanasia or from the archived serum bank maintained at SFBR. A radioimmunoassay with the lowest standard curve point of 0.01 ng/ml was used to assay PSA in serum (AniLytics, Inc., Gaithersburg, MD).

For cloning of the baboon PSA cDNA, total RNA was extracted using Trizol reagent (Invitrogen, Carlsbad, CA) and reverse-transcribed at 42°C with Moloney murine leukemia virus (MMLV) reverse transcriptase and random decamers following the suppliers protocol (RETROscript kit, Ambion, Austin, TX). The resulting cDNA was then used as a template for PCR reaction using nested primers and touchdown conditions [3]. The primer sequences were based on the published rhesus macaque sequence. The primer sequences used were, PSA outer forward: 5′-CTG GAC AGC TGT GTC ACC AT-3′; PSA inner forward: 5′-CTG TGT CAC CAT GTG GGT TC-3′; PSA outer reverse primer: 5′-TGA GAT GTC TCC AGG CAT GA-3′; PSA inner reverse primer: 5′-AGG ACA CGG AGA GGA CAA AA-3′. The PCR products were then cloned into the pCR2.1-TOPO vector (Invitrogen). Positive clones were identified by restriction enzyme analysis and nucleotide sequencing was carried out by the Advanced Nucleic Acid Core Facility at University of Texas Health Science Center at San Antonio. The PSA cDNA of both the rhesus macaque and the cynomolgus macaque were not cloned as they were already reported in the literature [4,5].

PSA Immunoblotting

Prostate tissue samples were homogenized in sample buffer, separated by 12% SDS–PAGE, transferred to nitrocellulose membranes, and probed using standard conditions. Membranes were probed at room temperature for 1 hr with either a monoclonal mouse anti-human PSA, clone ER-PR8 (Dakocytomation), or a rabbit monoclonal alpha-methyl-acyl-CoA racemase (AMACR, P504S Zeta Corporation, Sierra Madre, CA). Goat anti-mouse secondary antibody linked to horseradish peroxidase (Pierce Biotechnology, Rockford, IL) were added to the blots at a dilution of 1:5,000 and incubated for 1 hr at room temperature. Bound antibodies were detected by chemiluminescence (Supersignal West Pico, Pierce Biotechnology).

RESULTS

Prostate Anatomy and Body Weight

The prostate of the adult cynomolgus macaque, rhesus macaque, baboon, and marmoset is located at the distal end of the urinary bladder. On gross

observation the prostate of cynomolgus macaques, rhesus macaques, and baboons is divided into two parts which are labeled cranial and caudal according to their proximity to the bladder and seminal vesicles. For the marmoset, although the prostate can be seen on gross examination, it cannot be divided into two lobes with a naked eye. However, histologically differences in acinar size and hematoxylin-eosin staining characteristics can be seen. On the basis of these differences the marmoset prostate can also be divided into two lobes which correspond with the other three species. In all these monkey species, the glandular prostate does not completely surround the urethra (Fig. 1) and in this regard differs from what has been reported in humans [6,7].

There is a major difference in the size of the two lobes of the prostate between the baboon and the two macaque species (rhesus macaque and cynomolgus macaque). In the macaque species the two lobes of the prostate are of almost equal sizes. The cranial lobe constitutes 59% of weight of the prostate in the cynomolgus while it constitutes 47% in the rhesus macaque. In the case of the baboon the two lobes are quite different in size; the cranial lobe is much smaller, contributing only 36% of the total weight of the prostate (Fig. 1). Since the marmoset prostate is quite small and the two lobes are not visible on gross examination, their relative proportions were not quantified.

The average adult body weight of the animals studied were 5.82, 10.06, 27.14, and 0.29 kg for cynomolgus macaques, rhesus macaques, baboons, and marmosets, respectively (Table I).

When the weight of the prostate is compared to body weight (g/kg), the macaque species have a higher ratio than the baboon. The prostate-to-body-weight ratios are 0.51, 0.68, and 0.31 for cynomolgus, rhesus, and baboon, respectively (Table I).

Testis and Epididymis

The rhesus and cynomolgus macaques had similar testis-to-body-weight ratios, which were in turn higher than that of the baboon. The testis-to-body-weight ratios were 2.17 and 2.36 (g/kg), respectively, in the cynomolgus and rhesus macaque. Baboons, on the other hand, had a testis-to-body-weight ratio of only 1.2. Similar trends were observed for the epididymis for which the epididymis weight-to-body-weight ratios were 0.33, 0.42, and 0.22 (g/kg) for cynomolgus, rhesus, and baboons, respectively (Table I).

Growth and Development of the Prostate and Testis Across the Lifespan

Changes in body, prostate, and testes weights of the Old World monkeys across the lifespan are shown in Figure 2. The weights increased with age up to around 6 years in cynomolgus macaque, rhesus macaques, and

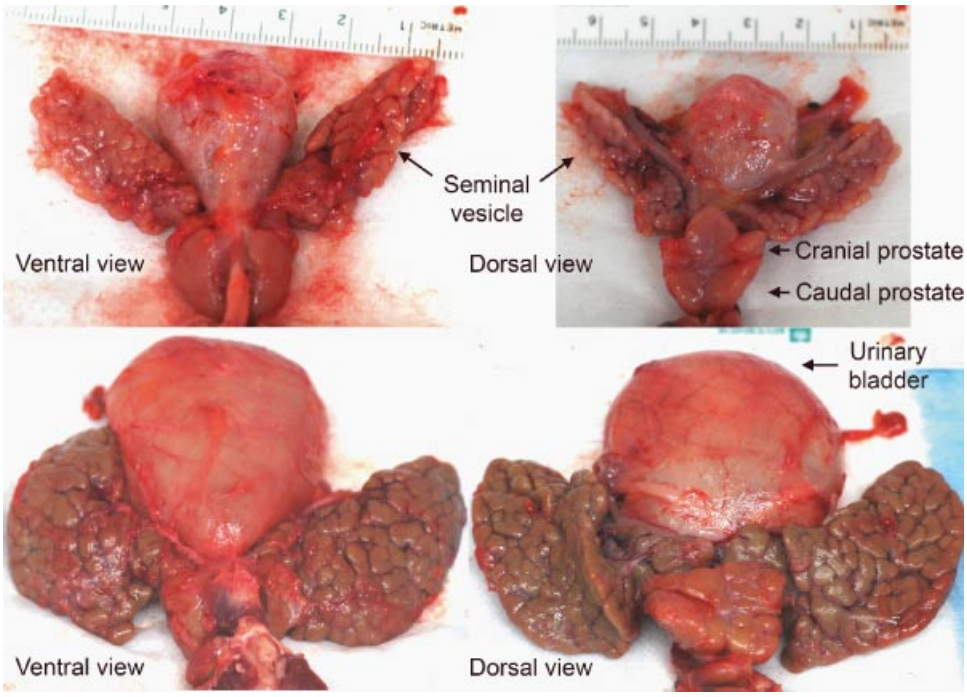

Fig. 1. Ventral and dorsal views of the prostates of the cynomolgus macaque (**top**) and baboon (**bottom**) showing the relationship of the prostate to the other urinogenital organs. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE I. Comparison of Reproductive Organ Weights (Mean ± SD) of Adult Cynomolgus Macaques, Rhesus Macaques, and Baboons

	Cynomolgus macaque (≥4 years old) N = 42	Rhesus macaque (≥6 years old) N = 11	Baboons (≥6 years) N = 67	Marmoset (≥3 years) N = 5
Anatomical measurements				
Body weight (kg)	5.815 ± 3.16	10.06 ± 2.04	27.14 ± 4.49	0.29 ± 0.045
Prostate parameters				
Cranial prostate weight (g)	1.73 ± 1.56	3.22 ± 0.63	2.95 ± 1.22	ND
Caudal prostate weight (g)	1.38 ± 1.09	3.58 ± 1.19	5.33 ± 1.93	ND
Total prostate weight (g)	2.94 ± 2.37	6.80 ± 1.54	8.28 ± 3.06	0.25 ± 0.09
Total prostate to body weight ratio (g/kg)	0.51	0.68	0.31	0.86
Testis parameters				
Left testis weight	12.61 ± 11.42	23.76 ± 5.45	33.87 ± 9.88	0.43 ± 0.054
Right prostate weight	13.23 ± 11.60	24.18 ± 5.66	33.90 ± 10.05	0.40 ± 0.13
Left testis weight to body weight ratio (g/kg)	2.17	2.36	1.25	1.48
Epididymis parameters				
Left epididymis weight (g)	1.94 ± 1.38	4.27 ± 0.93	5.93 ± 3.02	0.10 ± 0.03
Right epididymis weight (g)	2.21 ± 1.40	4.36 ± 0.55	6.04 ± 3.27	0.11 ± 0.04
Left epididymis to body weight ratio	0.33	0.42	0.22	0.34
Seminal vesicle parameters				
Left seminal vesicle weight (g)	3.27 ± 2.76	14.76 ± 7.99	18.82 ± 10.20	ND
Right seminar vesicle weight (g)	3.48 ± 2.91	16.35 ± 8.69	19.05 ± 10.23	ND
Seminal vesicle to body weight ratio (g/kg)	0.56	1.47	0.69	ND

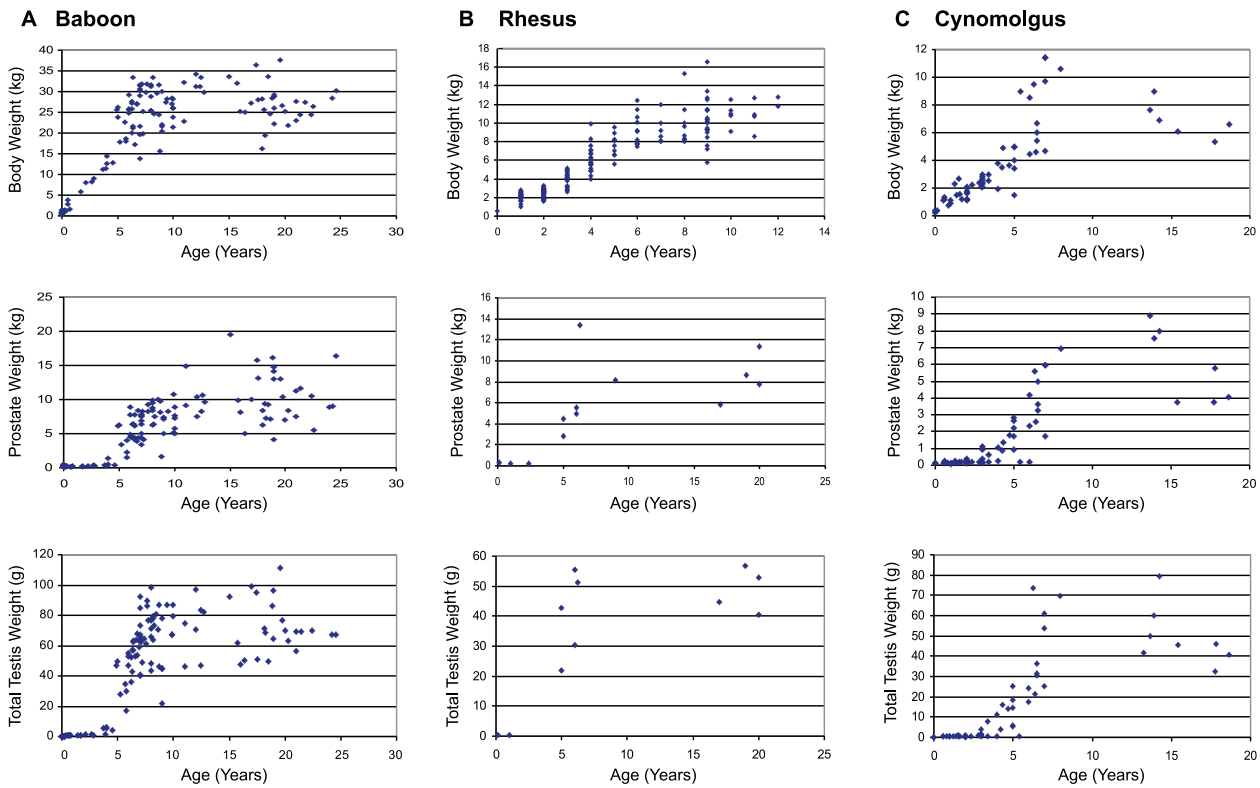

Fig. 2. **A**: Body, prostate, and total testis weights across the baboon lifespan; (**B**) body, prostate and total testis weight across the rhesus macaque lifespan; (**C**) body, prostate and left testis weights across the cynomolgus macaque lifespan. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

baboons and thereafter there was minimal change in the weights. The changes in growth of the prostate and testis were initially slow or undetectable, but at around 5 years in baboons and rhesus macaques, and at around 4 years of age for cynomolgus macaques, rapid changes occurred (Fig. 2).

Serum Prostate Specific Antigen Assay

Serum PSA was detected in all the three Catarrhine (Old World) monkeys (cynomolgus macaques, rhesus macaques, and baboons) studied but not in marmosets, which are members of the Platyrrhine (New World) monkeys. Serum PSA concentration in cynomolgus macaques ranged from 0.04 to 6.2 ng/ml, with a median value of 1.2 ng/ml. Serum PSA values of the rhesus macaques ranged from 0.07 to 2.35 ng/ml with a median value of 0.31, while those of baboons ranged from 0.05 to 0.78 ng/ml with a median value of 0.32 ng/ml. Serum PSA could not be detected in marmosets.

Serum levels of PSA correlated positively with age. The coefficient of correlation (R^2) was 0.30 for cynomolgus macaques, 0.183 for rhesus macaques, and 0.059 for baboons. This correlation was statistically significant for both cynomolgus macaques and rhesus macaques but not for baboons (Fig. 3). For both the cynomolgus macaques and rhesus macaques, the serum PSA data include a subset of animals whose values are higher than the rest and are therefore outliers (see Supplementary Table II). When the serum PSA values for the three Old World monkey species are plotted together on the same graph, the cynomolgus macaques and rhesus macaques values are higher and follow a different trend from those of baboons (Fig. 3).

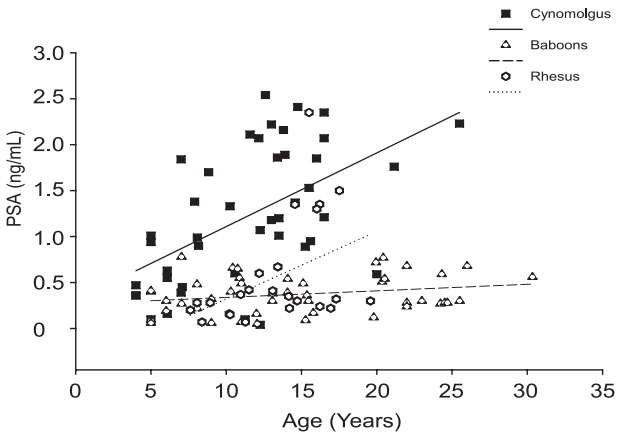

Fig. 3. Changes of serum PSA values with age of cynomolgus macaques, rhesus macaques, and baboons. The coefficient of correlation (R^2) was 0.30, 0.183, and 0.059 for cynomolgus macaques, rhesus macaques, and baboons, respectively. The correlations were statically significant for both cynomolgus macaques and rhesus macaques but not for baboons. Outliers are excluded in this figure (see Supplementary Table II for all the data).

Histopathology Lesions

The most common pathological change in the animals studied was inflammation. The inflammatory response was either lymphocytic, suppurative, or a combination of both. Most of the inflammatory changes occurred in the caudal prostate.

A case of prostate hyperplasia in a 17-year-old cynomolgus macaque was studied further and it was found that the hyperplasia involved both the glandular and basal cells (Fig. 4). The prostate in this animal contained a single nodular, minimally expansive area composed of closely packed solid nests and glands of cells supported by a thin fibrovascular stroma. The cells had indistinct cell borders, clear to slightly basophilic cytoplasm, round to oval nuclei with lightly stippled chromatin and prominent nucleoli. The cells lining the glandular structures frequently formed papillary structures that extended into the lumen. There was occasional eosinophilic fluid within the lumen of these glands. Mitoses were not observed (Fig. 4). An independent examination of this case by the Armed Forces Institute of Pathology (AFIP, Washington, DC) confirmed our earlier diagnosis of hyperplasia involving both the glandular and basal cells. Immunohistochemical staining done by the AFIP showed basal cells that were immunopositive for p63 but not K903. Immunostaining for prostatic acid phosphatase was negative. The serum PSA values at the time of sacrifice for this animal that had prostate hyperplasia was 2.07 ng/ml. Serum PSA in this animal rose 1.12 units in a period of 10 months. A case of focal glandular atrophy, acute prostatitis with subsequent reactive change of mild prostatic hyperplasia in a 20-year-old rhesus macaque was also further studied. This case had a serum PSA level of 2.35 ng/ml. Most prostatic glands in this animal were distended by clear space and lined by attenuated epithelium. Others contained luminal cellular debris and were lined by plump cuboidal cells with increased amounts of basophilic cytoplasm and prominent nuclei with lightly stippled chromatin (Fig. 4).

Baboon PSA Cloned and Compared With Other Primate PSA Sequences

Using cloning primers which were based on the published rhesus macaque sequence, the baboon PSA cDNA was cloned. The cloned baboon cDNA sequence has been deposited in the GenBank under accession number EF676031. This sequence was compared to the already published cynomolgus macaque, rhesus macaque, and human PSA sequences. The PSA protein

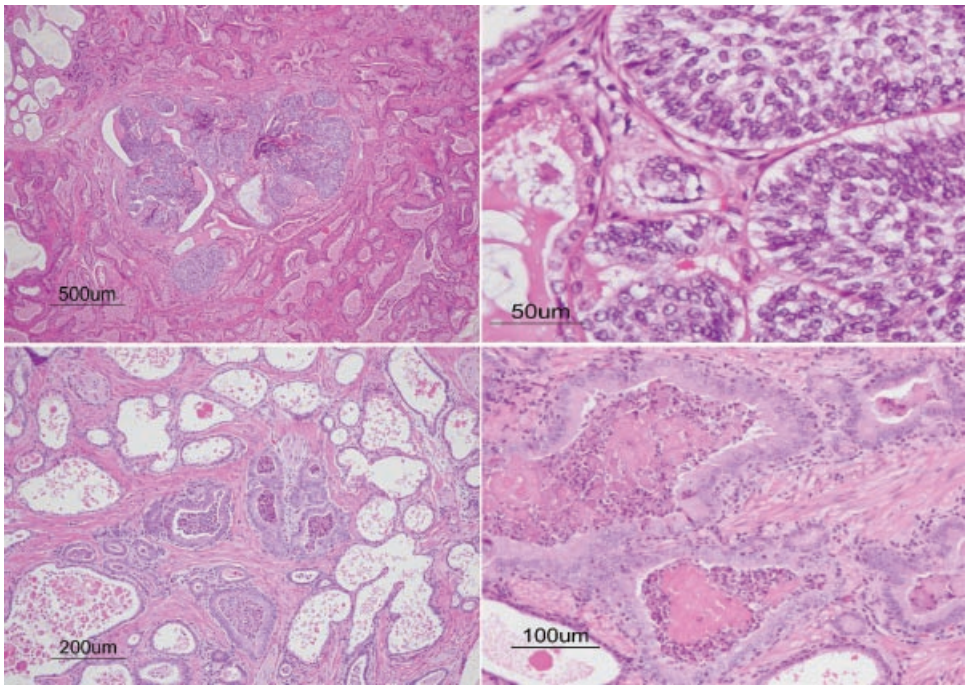

Fig. 4. Top, Prostatic hyperplasia involving both glandular epithelium and several foci comprised exclusively of hyperplastic basal cells in the cynomolgus macaque prostate (PSA = 2.07 ng/ml); Bottom, Glandular atrophy and acute prostatitis with subsequent reactive change of mild glandular hyperplasia in the rhesus macaque prostate (PSA = 2.25 ng/ml).

sequences of the rhesus, cynomolgus macaque, and baboon were 89.65%, 89.65%, and 90.42% similar to human PSA, respectively. The rhesus and cynomolgus protein sequences were 99.23% similar to each other and 98.45% similar to their baboon counterpart (Fig. 5).

PSA and AMACR Expression in the Prostate of the Three Species

Western blots done on prostate tissue showed that PSA and AMACR were both expressed in cynomolgus macaques, rhesus macaques, and baboons. The macaque species seemed to express more PSA and AMACR per tissue than baboons (Fig. 6).

DISCUSSION

The aims of this project were to study the male reproductive systems of nonhuman primates that are commonly used in research in order to evaluate their suitability as models for PSA biology studies in particular and for prostatic diseases in general. Preliminary data reported in this study suggest the macaque species are more suitable for these studies.

New World monkeys like the marmoset are not useful models for studies of PSA biology and prostatic diseases because they do not have the PSA gene. A previous study had reported the presence of the PSA gene in a number of nonhuman primates including orangutans, chimpanzees, gorillas, and macaques but not in dogs, mice, rats, or cows [8]. However, the nonhuman primate species examined in these studies did not include New World monkeys. More recent studies have reported the absence of the PSA gene in both the marmoset and cotton-top tamarin [9–11]. Our failure to detect PSA in marmoset serum in this study confirms the absence of the PSA gene. However, the possibility that the human antibodies used in our studies cannot detect marmoset PSA cannot be ruled out. Probably the PSA gene arose in the Catarrhine primates (Old World monkeys, anthropoid apes and humans) after their phylogenetic lineage separated from the Platyrrhines (New World primates) approximately 35–45 million years ago [12,13].

PSA, also called human kallikrein 3 (hK3), is one of the 15 members of the tissue kallikrein family that are located in a 300-kb region on chromosome 19q13.3-19q13.4 in humans. The sequences of two members of this group, KLK1 and KLK2, are 62% and 80% similar to PSA, respectively [14–16] and it is highly likely that the PSA gene could be a result of a duplication and further mutation of one of these two genes.

Serum PSA was detected in all the Old World monkeys we studied (cynomolgus macaques, rhesus macaques, and baboons). However, there were significant differences in quantity and correlation to age.

A

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Baboon          MWVLVVFLTLSVTWIGAAPLILSRIVGGWECEKHSQPWQVLVASRGRAICGGVLVHPQWV
Cynomolgus      MWVLVVFLTLSVTWIGAAPLILSRIVGGWECEKHSQPWQVLVASHGRAVCGGVLVHPQWV
Rhesus          MWVLVVFLTLSVTWIGAAPLILSRIVGGWECEKHSQPWQVLVASRGRAVCGGVLVHPQWV
                ******************************************:***:***********

Baboon          LTAAHCIRSNSVILLGRHNPFYPEDTGQVFQVSHSFPHPLYNMSLLKNRYLGPGDDSSHD
Cynomolgus      LTAAHCIRSHSVILLGRHNPYYPEDTGQVFQVSHSFPHPLYNMSLLKNRYLGPGDDSSHD
Rhesus          LTAAHCIRSNSVILLGRHNPYYPEDTGQVFQVSHSFPHPLYNMSLLKNRYLGPGDDSSHD
                *********:**********:************************************

Baboon          LMLLRLSEPAEITDAVQVLDLPTWEPALGTTCYASGWGSIEPEEHLTPKKLQCVDLHIIS
Cynomolgus      LMLLRLSEPAEITDAVQVLDLPTWEPELGTTCYASGWGSIEPEEHLTPKKLQCVDLHIIS
Rhesus          LMLLRLSEPAEITDAVQVLDLPTWEPELGTTCYASGWGSIEPEEHLTPKKLQCVDLHIIS
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Baboon          NDVCAQVHFQKVTKFMLCAGSWMGGKSTCSGDSGGPLVCDGVLQGITSWGSQPCALPRRP
Cynomolgus      NDVCAQVHSQKVTKFMLCAGSWMGGKSTCSGDSGGPLVCDGVLQGITSWGSQPCALPRRP
Rhesus          NDVCAQVHSQKVTKFMLCAGSWMGGKSTCSGDSGGPLVCDGVLQGITSWGSQPCALPRRP
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Baboon          SLYTKVVRYRKWIQDTIMANP
Cynomolgus      SLYTKVVRYRKWIQDTIMANP
Rhesus          SLYTKVVRYRKWIQDTIMANP
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B

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Baboon      MWVLVVFLTLSVTWIGAAPLILSRIVGGWECEKHSQPWQVLVASRGRAICGGVLVHPQWV
Human       MWVPVVFLTLSVTWIGAAPLILSRIVGGWECEKHSQPWQVLVASRGRAVCGGVLVHPQWV
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Baboon      LTAAHCIRSNSVILLGRHNPFYPEDTGQVFQVSHSFPHPLYNMSLLKNRYLGPGDDSSHD
Human       LTAAHCIRNKSVILLGRHSLFHPEDTGQVFQVSHSFPHPLYDMSLLKNRFLRPGDDSSHD
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Baboon      LMLLRLSEPAEITDAVQVLDLPTWEPALGTTCYASGWGSIEPEEHLTPKKLQCVDLHIIS
Human       LMLLRLSEPAELTDAVKVMDLPTQEPALGTTCYASGWGSIEPEEFLTPKKLQCVDLHVIS
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Baboon      NDVCAQVHFQKVTKFMLCAGSWMGGKSTCSGDSGGPLVCDGVLQGITSWGSQPCALPRRP
Human       NDVCAQVHPQKVTKFMLCAGRWTGGKSTCSGDSGGPLVCNGVLQGITSWGSEPCALPERP
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Baboon      SLYTKVVRYRKWIQDTIMANP
Human       SLYTKVVHYRKWIKDTIVANP
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Fig. 5. **A**: Comparison of baboon, cynomolgus and rhesus macaque PSA amino acid sequence; (**B**) comparison of baboon with human PSA amino acid sequence. The comparisons were made by the CLUSTAL W (1.82) software program (www.ch.embnet.org/software/clustalw.html).

Both macaque species exhibited greater abundance and stronger correlation with age than the baboons. Both macaque species also had more PSA in prostate tissue than the baboon. The significance of having higher PSA per unit of tissue is not clearly understood, but PSA's main function is to liquefy coagulated semen. Although this study did not investigate the differences in mating behavior of these four species, we speculate that the higher concentration of proteins related to reproduction, and larger size of the testis, epididymis and prostate in macaques compared to baboons might be related to breeding patterns, seasonality of breeding, and dominance structure. We speculate that large testis able to produce enough sperm, large seminal vesicles and epididymis able to store and nourish the sperm, and large prostate for the production of PSA that maintains semen fluidity are advantageous or necessary for reproductive success.

Serum PSA values reported in both rhesus macaques and cynomolgus macaques are similar to those reported in a recent study by Williams et al. [17] and are comparable to those in humans [18] despite the fact that these animals are smaller in size compared to humans. The upper limit of normal for PSA in humans is currently set at 4.0 ng/ml. This is the threshold above which a patient is referred for further diagnostic

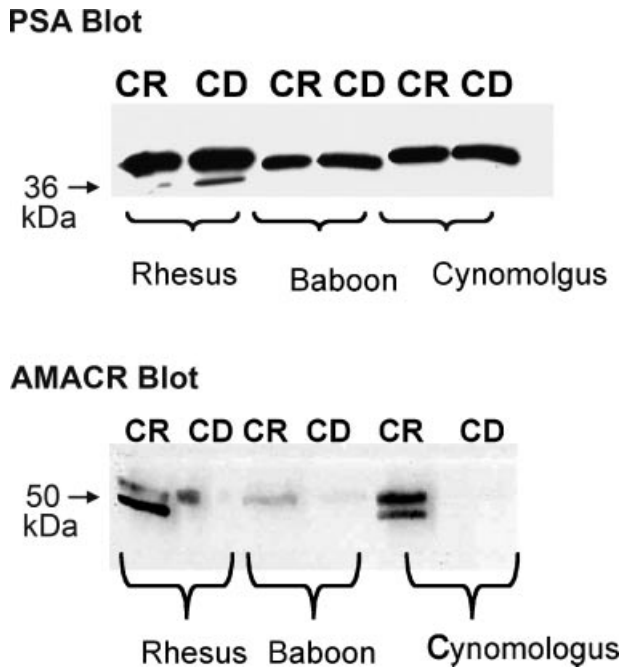

Fig. 6. The prostate of rhesus macaque, baboon and cynomolgus macaque were separated into cranial (CR) and caudal (CD) parts. Thirty micrograms of the prostate homogenate was loaded in each well and SDS–PAGE run. After transfer to a nitrocellulose membrane the blots were probed with either anti-human PSA antibody (Dakocytomation) or anti-human AMACR (P504S) antibody (Zeta Corporation, Sierra Madre, CA). The bands were visualized with chemiluminescent detection system (Pierce Biotechnology).

workup. It is interesting to note that two cynomolgus macaques in our study had serum PSA values of 5.23 and 6.2 ng/ml, which are higher than the human upper limit of normal (see Supplementary Table II). One cynomolgus macaque with a PSA value of 2.07 ng/ml was found to have prostatic hyperplasia and one rhesus macaque with a PSA value of 2.35 ng/ml had pathological lesions in its prostate. The trend of increasing PSA with age is significant in both rhesus macaques and cynomolgus macaques studied. In fact the linear regression lines for the two species are generally parallel, indicating a similar trend through life. Serum PSA distributions from both these two species also includes clear outliers with unusually high values.

The finding that pathological changes in the prostate may be accompanied by increases in serum PSA is significant, and further lends credence to exploring nonhuman primate (especially the macaque species) as models of PSA biology and prostate diseases in humans.

Significant changes in body weight, and the weights of the testis, prostate, and other reproductive organs occurred as the animals reached sexual maturity at 4–5 years in rhesus macaques and cynomolgus macaques and at 6–7 years in baboons. These findings are similar to those reported previously [19,20].

In light of the data presented here and our previously published research on the baboon [21], it is appropriate to revisit the notion that nonhuman primates do not naturally develop prostatic diseases, especially prostate cancer. A closer look at the literature shows that pathological lesions in the prostate have been reported in nonhuman primates (both Old and New World species). BPH has been reported in tamarins [22], baboons [23], and chimpanzees [24]. Prostate cancer and prostatic basal cell hyperplasia has also been reported in rhesus macaques [25–27].

We are of the view that the macaque species, especially the cynomolgus macaques can be used as animal models for studies of PSA biology. Cynomolgus macaques are native to Southeast Asia but are now readily available in breeding colonies in the USA. They can also be easily imported from their natural habitats and are of reasonably large size.

Further studies are needed to characterize fully the pathology of the male genitourinary system of macaque species, especially the cynomolgus macaque. Based on our preliminary studies, we envision both cynomolgus macaques and rhesus macaques to be a potential models not only for studies of PSA biology, as shown in this article but also in studies concerning the role of diet and individual genetic variation in determining serum PSA levels. Another potential area of research in which nonhuman primate can be used involves their use in developing PSA based targeted therapies for prostatic diseases. PSA is an androgen-regulated serine protease which is secreted by prostate cancer cells and normal prostate cells. Intensive efforts are on going to utilize the enzyme activity and specificity of PSA production by prostate cancer cells for therapeutic purposes [28–30]. PSA is inactive when it is in circulation because it is bound to protease inhibitors. It is only active enzymatically when it is in prostate tissue or in tumor microenvironments. One of the many approaches for the use of PSA for therapeutic purposes is the construction of PSA cleavable prodrugs. The prodrugs circulate in the body but only exhibit their anticancer effects at the tumor sites. The tumor cells secrete PSA that cleaves the prodrugs and therefore activates them. Nonhuman primates are ideal models in which to develop, test and study these PSA-based therapeutic agents.

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