Progress of non-human primate animal models of cancers

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Abstract: Cancer is the second leading disease causing human death. Pre-clinical in vivo studies are essential for translating in vitro laboratory research results into the clinic. Rodents, including the mouse and rat, have been widely used for pre-clinical studies due to their small size, clear genetic backgrounds, rapid propagation, and mature transgenic technologies. However, because rodents are evolutionarily distinct from humans, many pre-clinical research results using rodent models cannot be reproduced in the clinic. Non-human primates (NHPs) may be better animal models than rodents for human cancer research because NHPs and humans share greater similarity in regards to their genetic evolution, immune system, physiology and metabolism. This article reviews the latest progress of cancer research in NHPs by focusing on the carcinogenesis of different NHPs induced by chemical and biological carcinogens. Finally, future research directions for the use of NHPs in cancer research are discussed.

Key words: Non-human primate; Cancer; Tree shrew
systems. It has been shown that almost all human cancer genes are highly conserved between chimpanzees and humans (Puente et al, 2006). However, the use of NHPs in cancer research is limited because they are rare, expensive, and of a large size. In addition, cancer incidence in NHPs is very low. In this article, we summarize results on spontaneous and experimentally induced tumors in NHPs and discuss future study directions for using NHPs in cancer research.

1 Spontaneous tumors in NHPs

Spontaneous tumors have been observed in NHPs bred in zoos and research institutions all over the world. By 1989, a total of 783 spontaneous tumors in monkeys and apes had been reported (Beniashvili, 1989). From 1989 to 2000, 1,388 cases of benign and malignant tumors (582/806) in NHPs were found (Huang & Cheng, 2002). Most tumors were found in baboons (Cianciolo & Hubbard, 2005) and macaques because these two species were more commonly used for research than other NHP species (Beniashvili, 1989).

The incidence of spontaneous tumors in NHPs depends on the animal species, sex and age. Autopsy records of 373 breeders and normal controls from the National Cancer Institute (NCI), USA showed a very low incidence of spontaneous malignant tumors in cynomolgus (1.5%) and rhesus (2.8%) monkeys, but a considerably higher incidence in African green monkeys (8%) (Thorgeirsson et al, 1994). Most types of spontaneous tumors occurred equally in male and female NHPs. However, spontaneous tumors of the reproductive system were more common than those of other organ systems (Beniashvili, 1989). It is clear that while tumors of the respiratory system are rare in NHPs, they are common in humans due to air pollution and smoking (Coggins, 2007). Although the tumor epidemiology of NHPs reflects the natural carcinogenesis, there are some limitations for studying spontaneous tumors. Firstly, only individual cases were described in many studies. Secondly, most tumor cases were found accidentally during an autopsy rather than in live animals. Thus, spontaneous tumors of NHPs provide us with clues for establishing cancer animal models (Huang & Cheng, 2002).

2 Experimental tumors in NHPs

Due to the low incidence of spontaneous tumors, experimental tumor models of NHPs are necessary for human cancer research. It is well known that tumors are initiated by environmental and genetic factors. Approximately 85% of malignant neoplasms are related to chemical, biological and physical environmental factors and chemical, biological and physical carcinogens have been used to induce tumors in NHPs. Several tumor models were established by utilizing combinations of different carcinogens. NHPs can be divided into three groups: anthropoids, prosimians and tree shrews. Carcinogenesis studies have been performed on different species of NHPs from these groups including monkeys (Pfeiffer & Allen, 1948) and tree shrews (Adamson et al, 1970).

2.1 Carcinogenesis studies in anthropoids

Anthropoids, particularly monkeys, have been used to develop cancer models. Monkeys primarily consist of old world monkeys and new world monkeys. Old world monkeys, such as baboons and macaques, inhabit Asia and Africa. New world monkeys are distributed in tropical forests of southern Mexico and Central and South America. Most of them are fairly small in size and are exclusive tree dwellers.

2.1.1 Chemical carcinogens induce different types of cancers

Many different types of human cancers are caused and promoted by chemical carcinogens in food, water and air. Chemical carcinogens can be administrated to NHPs to create a model for human cancer. A long-term study of chemical-induced tumors in macaques began in 1961 by the NCI, USA (Thorgeirsson et al, 1994; Schoeffner & Thorgeirsson, 2000; Takayama et al, 2008).
Three species of NHPs, the rhesus monkey (*Macaca mulatta*), cynomolgus monkey (*Macaca fascicularis*), and African green monkey (*Cercopithecus aethiops*) were tested. A large number of substances, including a variety of food additives, food components, environmental contaminants, N-nitroso compounds, “classical” rodent carcinogens, anti-neoplastic agents, and immunosuppressive agents were evaluated for any long-term carcinogenic effects.

The fungal food contaminants, aflatoxin B1 (AFB1) (Adamson et al, 1973) and sterigmatocystin (SMT) (Thorgeirsson et al, 1994), were found to be potent hepatocarcinogens. Noticeably, AFB1 did not induce the p53 gene mutation in macaques although p53 is frequently mutated in human HCC from southern Africa and Qidong in China (Fujimoto et al, 1992). This suggests that the p53 mutation in humans may be induced by carcinogens other than AFB1. AFB1 also induced adenocarcinomas of the pancreas, osteosarcomas and other tumors (Adamson et al, 1976). Three of four nitrosamines, particularly diethylnitrosamine (DENA), induced HCC (Adamson, 1989; Lapis et al, 1995). Cycasin or its aglycone, methyazoxymethanol (MAM) acetate, induced a variety of tumors, primarily hepatocellular and renal cell carcinomas (Sieber et al, 1980).

Ohgaki et al (1986) reported that gastric carcinomas in the pyloric region were developed in five monkeys (*Macaca mulatta* and *Macaca irus*) after adding N-Ethyl-N’-nitro-N-nitrosoguanidine (ENNG) to their drinking water. Similar results were obtained with N-methyl-N-nitro-N-nitrosoguanidine (MNNG) in cynomolgus monkeys (Sharashidze et al, 1989).

In conclusion, numerous chemical agents can efficiently induce a variety of cancers in NHPs (Tab. 1).

### 2.1.2 Hormones and breast cancers

Hormone levels are well known to regulate the occurrence of breast cancer in women, making this an important focus of cancer research using animal models. The mammary epithelial cells of postmenopausal macaques are shown to express estrogen receptors (ERs) (Isaksson et al, 2002) and progesterone receptors (PRs) (Isaksson et al, 2003). Spontaneous breast tumors in macaques showed selective loss of sex steroid receptors and over-expression of the HER2 protein (Wood et al, 2006). Due to these findings, many attempts have been made to establish a breast cancer model with macaques. An early study showed that high doses of estrogen failed to induce breast neoplasm (Geschickter & Hartman, 1959). In the 1960s, a long-term study in adult monkeys sponsored by the FDA, USA assessed the risk of high doses of oral contraceptives in juvenile. A total of 213 treated and 16 control monkeys were used to evaluate the effects of a variety of synthetic oral contraceptive steroids, including synthetic estrogen mestranol, progestogens ethynerone, chloroethyl norgestrel, and anagostone acetate, on the mammary gland over a 10 year period (Drill et al, 1974; Geil & Lamar, 1977; Drill & Golway, 1978; Fitzgerald et al, 1982; Tavassoli observation period (Lillie et al, 2004). Neither cyclamate (Takayama et al, 2000) nor saccharin (Takayama et al, 1998), which had been used as food additives and induced tumors in rats, showed any evidence of carcinogenic effects. The tumorigenic potential of dichlorodiphenyltrichloroethane (DDT), which has been extensively used as a pesticide, was also negligible after dosing for 15–22 years (Takayama et al, 1999).

Other chemicals have been tested in NHPs in addition to those tested in the NCI study. Rhesus macaques treated with DMBA combined with UV light, dodecylbenzene (DDB), or both applied to the skin developed dermal melanosis, papillomas, basal cell tumors and mesodermal sarcomas (Palotay et al, 1976). Ohgaki et al (1986) reported that gastric carcinomas in the pyloric region were developed in five monkeys (*Macaca mulatta* and *Macaca irus*) after adding N-Ethyl-N’-nitro-N-nitrosoguanidine (ENNG) to their drinking water. Similar results were obtained with N-methyl-N-nitro-N-nitrosoguanidine (MNNG) in cynomolgus monkeys (Sharashidze et al, 1989). In conclusion, numerous chemical agents can efficiently induce a variety of cancers in NHPs (Tab. 1).
### Tab. 1 Summary of experimental cancer models in NHPs

<table>
<thead>
<tr>
<th>Species</th>
<th>Carcinogens</th>
<th>Cancer types</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>AFB1</td>
<td>HCC, osteosarcomas.</td>
<td>Adamson, 1973; Adamson, 1976</td>
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<tr>
<td>Macaca spp.</td>
<td>DENA</td>
<td>HCC</td>
<td>Adamson, 1989; Lapis, 1995</td>
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<td></td>
<td>Cycasin or MAM</td>
<td>HCC, renal cell carcinomas</td>
<td>Sieber, 1980</td>
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<td></td>
<td>IQ</td>
<td>Malignant liver tumors</td>
<td>Adamson, 1990; Thorgerisson, 1994</td>
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<td></td>
<td>MNU</td>
<td>Esophageal squamous cell carcinomas</td>
<td>Adamson, 1977</td>
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<td></td>
<td>Procarbazine</td>
<td>Nonlymphocytic leukemias</td>
<td>Sieber, 1978</td>
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<td></td>
<td>ENNG</td>
<td>Gastric carcinomas</td>
<td>Ohgaki, 1986</td>
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<td></td>
<td>HVS C488</td>
<td>Pleomorphic peripheral T-cell lymphomas</td>
<td>Knappe, 2000</td>
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<tr>
<td>Macaca mulatta</td>
<td>DMBA &amp; UV, (or DDB)</td>
<td>Dermal melanosis, papillomas, basal cell tumors, and mesodermal sarcomas</td>
<td>Palotay, 1976</td>
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<tr>
<td></td>
<td>Ethynerone, Mestranol, Anagostone acetate, Chloroethynyl norgestrel</td>
<td>Mammary carcinomas</td>
<td>Drill, 1974; Geil, 1977; Drill, 1978; Fitzgerald, 1982; Tavassoli, 1988</td>
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<td></td>
<td>H. pylori &amp; ENNG</td>
<td>Gastric carcinomas</td>
<td>Liu, 2009</td>
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<td></td>
<td>SIV</td>
<td>AIDS-associated lymphomas</td>
<td>Murphey-Corb, 1986</td>
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<td></td>
<td>Radiation</td>
<td>Brain tumors</td>
<td>Wakisaka, 1982</td>
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<td>Macaca fascicularis</td>
<td>SIVsm</td>
<td>AIDS-associated lymphomas</td>
<td>Feichtinger, 1990; Putkonen, 1992</td>
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<td></td>
<td>MNG</td>
<td>Stomach cancers</td>
<td>Shashidzue, 1989</td>
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<tr>
<td>Saguinus oedipus</td>
<td>HVS C488</td>
<td>Acute peripheral T-cell lymphomas</td>
<td>Knappe, 1998;</td>
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<tr>
<td></td>
<td>HVA</td>
<td>Acute T-cell lymphomas</td>
<td>Hunt, 1972</td>
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<td></td>
<td>EBV</td>
<td>Malignant lymphomas</td>
<td>Shope, 1973a; Cleary, 1985; Epstein, 1985</td>
</tr>
<tr>
<td>Calithrix jacchus</td>
<td>HVS C488</td>
<td>Multicentric lymphomas</td>
<td>Dubois, 1998</td>
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<td>Galagos spp.</td>
<td>DENA</td>
<td>Nasal mucoepidermoid carcinoma</td>
<td>Thorgerisson, 1994</td>
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<td>DMBA &amp; DDB</td>
<td>Papillomas, basosquamous cell epithelioma</td>
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<td>Perodicticus potto</td>
<td>DMBA &amp; DDB</td>
<td>Dermal neoplasm</td>
<td>Palotay, 1976</td>
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<td>Tupaia belangeri chinensis</td>
<td>HBV, AFB1</td>
<td>HCC</td>
<td>Yan, 1996; Li, 2004; Li, 2008</td>
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<tr>
<td>Tupaia glis</td>
<td>AFB1</td>
<td>HCC</td>
<td>Reddy, 1976;</td>
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<tr>
<td></td>
<td>DHPN</td>
<td>Pulmonary adenomas, squamous cell epithelioma</td>
<td>Rao, 1980</td>
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et al, 1988). Seventeen mammary carcinomas were identified primarily in the groups treated with high-dose estrogen-progestogen combinations (mestranol+ethynerone, mestranol+anagostone acetate, and mestranol+chloroethynyl norgestrel) and three were observed in the group treated with ethynerone alone (Tavassoli et al, 1988). Consistently, estradiol and synthetic progestin medroxyprogesterone acetate (MPA) resulted in significantly greater breast epithelial proliferation in ovariectomized adult female cynomolgus macaques (Wood et al, 2007). However, Valerio (1989) summarized data from 17 contraceptive steroid studies in macaques and found that in situ ductal carcinomas and invasive breast carcinomas were identified in only 4/264 controls (1.5%) and 13/733 treated animals (1.7%). These results imply that hormones alone are not strong carcinogens in macaques.

#### 2.1.3 Infection-associated cancers

Cancer is not an infectious disease, but some infectious agents can induce cancer. The World Health Organization (WHO) International Agency for Research on Cancer estimated that the total number of infection-associated cancers was approximately 1.9 million in 2002, accounting for 17.8% of human cancers. The principle causes included hepatitis B and C viruses, human papilloma viruses (HPVs), human immunodeficiency virus (HIV), T-lymphotropic viruses, Epstein-Barr virus (EBV), human herpes virus 8, and *Helicobacter pylori* (*H. pylori*) (Parkin, 2006).

#### 2.1.3.1 *Helicobacter pylori* and gastric cancer

Gastric cancer is the fourth most common cancer worldwide (almost 10% of new cancers) and the second leading cause of cancer mortality. *H. pylori* is well known to cause chronic infection in the human gastric
mucosa, to be a major cause of peptic ulcer disease, and a principal risk factor for gastric cancer (Parsonnet et al., 1991). Several rodent models such as the mouse, rat and Mongolian gerbil, have been used extensively to study H. pylori-induced diseases. The Mongolian gerbil was found to be the only species in which gastric cancer could be induced by H. pylori infection (Ogura et al., 2000). H. pylori has been shown to infect several NHPs including chimpanzees (Pan troglodytes) (Hazell et al., 1992), rhesus monkeys (Euler et al., 1990), cynomolgus monkeys (Euler et al., 1990) and Japanese monkeys (Macaca fuscata) (Shuto et al., 1993). The infection of H. pylori caused atrophic gastritis and p53 mutations in the Japanese monkey model (Oda et al., 2002); however, the Japanese monkey model did not develop gastric carcinoma after five years after the first infection. Liu et al reported that gastric intraglandular neoplasia were carcinomas after five years after the first infection. Liu et al (1992), rhesus monkeys (Euler et al., 1990), cynomolgus monkeys (Euler et al., 1990) and Japanese monkeys (Oda et al., 2002); however, the monkey species did not develop gastric carcinomas caused by H. pylori infection (Ogura et al., 2000).

2.1.3.2 Virus-associated cancers

The vast majority of human and animal viruses do not cause cancer after infection. However, some viruses do initiate cancer in a small percentage of cases and are appropriately named tumor viruses. Tumor viruses induce tumors potentially by causing genetic changes in host cells. A number of these viruses have been associated with specific cancers in humans such as HPV and cervical cancer, HBV and liver cancer, EBV and nasopharyngeal cancer and lymphoma, and HIV and lymphoma (Ma & Chan, 2009).

1) Simian herpesvirus and T-cell lymphomas

Both herpesvirus saimiri (HVS) and herpesvirus atelis (HVA) belong to the simian herpesvirus group, and are known to cause no disease or only minor disease in their natural new world monkey hosts squirrel monkeys (Saimiri sciureus) and spider monkeys (Ateles paniscus) respectively. However, HVS and HVA can induce lymphomas or lymphoblastic leukemias in other monkey species. HVS caused acute peripheral T-cell lymphomas in other new world primates such as tamarins (Saguinus spp.), common marmosets (Callithrix jacchus), and owl monkeys (Aotus trivirgatus) (Meléndez et al., 1969; Fleckenstein et al., 1978). These monkey species are presumably not infected by HVS in the wild. Tamarins are observed to be susceptible to all subgroups (A, B, and C) of HVS. Wild type HVS (type C) caused acute peripheral T-cell lymphomas within only a few weeks in common marmosets and in cotton-top tamarins (Saguinus oedipus) (Duboise et al., 1998; Knappe et al., 1998). HVS C488 (a mutant species) even induced pleomorphic peripheral T-cell lymphomas in old world monkeys (Knappe et al., 2000). Similar to HVS, HVA also induced acute T-cell lymphomas in cotton-top tamarins (Hunt et al., 1972).

2) Epstein-Barr virus and lymphomas

EBV is one of the five human herpesviruses, human herpesvirus 4 (HHV-4). EBV is known to cause several lymphoproliferative disorders and cancers, particularly Burkitt’s lymphoma, nasopharyngeal carcinoma, and central nervous system lymphomas associated with HIV (Long et al., 2010). The cotton-top tamarin is the only species in which experimental EBV infection is observed to regularly cause malignant lymphomas. Shope et al (1973a) inoculated cotton-top tamarins with EBV and found that one of the four monkeys that received autologous cells transformed in vitro by EBV developed lymphoma in mesenteric lymph nodes and three of the four monkeys inoculated with cell-free EBV developed lymphoma. Cleary et al (1985) inoculated cotton-top tamarins with EBV and observed multiple tumors within 14 to 21 days. Additionally, each lymphoma from the same animal induced by EBV arose from different B-cell clones. This resembles EBV-associated human lymphomas that occur with organ transplants. Importantly, tamarins vaccinated with virus-determined membrane antigen gp340 were effectively protected from tumor induction by a massive challenge dose of EBV (Epstein et al., 1985). However, EBV cannot induce tumors in adult squirrel monkeys (Shope et al., 1973b) and gibbons (Hylobates lar) (Werner et al., 1972).

3) Simian AIDS-associated lymphomas

The frequency of lymphomas in AIDS patients is approximately 60 to 100 times that of the general population (Spittle, 1998). Despite the fact that Highly Active Anti-Retroviral Therapy (HAART) reduces the incidence of opportunistic infections and prolongs the survival time for HIV-infected patients, the incidence of AIDS-associated lymphomas (AAL) is not reduced. It has been reported that macaques infected with Simian immunodeficiency virus (SIV) developed malignant lymphomas and an AIDS-like syndrome (Feichtinger et al., 1990). Since 1984, complete necropsy examinations...
have been performed on more than 1,000 SIV-infected rhesus macaques at the Tulane Regional Primate Research Center and lymphomas have been detected in 38 animals (Murphey-Corb et al, 1986). The low incidence of AAL in SIV-infected rhesus macaques (~4%) is similar to that in AIDS patients. Several approaches, such as using cynomolgus macaques, administering cytokines, using less pathogenic SIV strains, or combining SIV with various herpesviruses have been proposed to increase the incidence of lymphomas in macaques to establish models using less animals (Baskin et al, 2001). The incidence of simian AAL in cynomolgus macaques is eight-fold higher than that in rhesus macaques. Malignant lymphomas were observed in nine of 24 (38%) SIVsm-infected cynomolgus monkeys and all tumors were high-grade B-cell lymphoblastic or pleomorphic lymphomas with extranodal and disseminated growth (Feichtinger et al, 1990). Similar results were observed in another independent study (Putkonen et al, 1992). Thus, SIV-infected macaques (both rhesus and cynomolgus) demonstrated similar features of AAL, including B-cell origin, extranodal anatomic distribution, the absence of SIV in tumor cells and the presence of rhesus lymphocryptovirus (Habis et al, 1999). Interestingly, SIV-infected macaques that had lymphomas with large nuclei survived longer than those that had lymphomas with small nuclei (Habis et al, 1999). This phenomenon was also observed in patients with Burkitt’s-like lymphomas. Taken together, SIV-infected monkeys are appropriate animal models to study human AAL.

2.1.4 Radiation-induced cancers

It is well established that radiation can induce cancer in humans. An early study in NHPs showed that radiation induced brain tumors in rhesus monkeys (Wakisaka et al, 1982). Consistently, rhesus monkeys exposed to 55-MeV protons displayed a high incidence of malignant brain tumors with latent periods ranging from 13 months to 20 years (Wood, 1991).

2.2 Carcinogenesis studies in prosimians

Prosimians have few similarities with humans. They are small in size, nocturnal and only found in the old world. To date, only two prosimian species (Galagos and Pottos) have been used in cancer research. When Galagos were administered DENA, a potent hepatocarcinogen in cynomolgus, rhesus, and African green monkeys intraperitoneally the animals developed primarily mucoepidermoid carcinomas of the nasal cavity (Thorgerisson et al, 1994). In another study, galagos (Galago crossicaudatus) were treated with DMBA and DDB biweekly for four years and papillomas, basal cell tumors and basosquamous cell epidermal tumors with satellite lipomas were observed within eight years (Palotay et al, 1976). When DMBA and DDB were applied to the skin of pottos (Perodicticus potto) neoplasms were observed in 17 of the 19 primates that lived longer than nine weeks (Palotay et al, 1976).

2.3 Carcinogenesis studies in tree shrews

Tree shrews (Tupaia spp.) are non-rodent and primate-like animals native to the tropical forests of Southeast Asia. Previously, tree shrews were grouped with prosimians because of certain internal similarities (brain anatomy for example) but now they have been assigned a separate order, scandentia, based on recent molecular phylogenetic studies. There are 20 species in five genera. All tree shrews share some common characteristics such as a relatively small body mass, generally omnivorous diet, and non-prehensile hands and feet (Martin, 1990). Since 1966 when the first spontaneous case of breast cancer was observed in tree shrews (Elliott et al, 1966) further cases of other spontaneous cancers have been described such as HCC (Hofmann et al, 1981), epidermoid carcinoma, and lymphoma (Brack, 1998). Hence, tree shrews may also be useful experimental animal models for carcinogenesis studies.

2.3.1 Hepatocellular carcinomas

HCC is a major cause of cancer deaths worldwide and accounts for ~6% of all human cancers. The development of HCC is considered to be caused by the HBV infection and chemical carcinogens such as AFB1. During the 1970s, Reddy et al (1976) successfully induced HCC in tree shrews (Tupaia glis) by administering AFB1. Yan et al (1996) found that tree shrews (Tupaia belangeri chinensis) could be infected with human HBV. Further investigation revealed that HBV in combination with AFB1 significantly increased the incidence of HCC (52.9%) compared to HBV alone (11.11%) or AFB1 alone (12.50%). Oltipraz treatment protected tree shrews from AFB1-induced liver cancer in a manner similar to that observed in rodents and humans (Li et al, 2000). The tree shrew p53 sequence shares 91.7% (nucleotide) and 93.4% (amino acid) homology with the human p53 sequence (Park et al, 2000). Park et al (2000) detected mutations in the p53 gene in tree shrews exposed to AFB1 and/or HBV (Park et al, 2000).
In addition to the mutation of p53, AFB1 and HBV upregulated the expression of the Ras gene in tree shrews before HCC development (Su et al, 2004). To understand the mechanism by which AFB1 induced HCC, Li et al (2004) examined gene expression profiles during AFB1-induced hepatocarcinogenesis in tree shrews and identified a set of genes that were up- or down-regulated in HCC. Following that, a group of candidate proteins that were differentially expressed in tree shrew HCC were obtained by proteome analysis (Li et al, 2008). The peroxiredoxin (Prx) II protein was found to be overexpressed in both tree shrew and human HCC. When Prx II expression was inhibited by siRNAs in human Hep3B cells, cell proliferation and survival decreased significantly (Li et al, 2008). These findings suggest that the tree shrew is a suitable animal model for studying the mechanisms of human HCC.

2.3.2 Pulmonary adenomas

Lung cancer is the leading cause of human cancer deaths worldwide. Therefore, the task of finding an effective NHP model to study lung cancer is an important objective in cancer research. In one study with NHPs, the carcinogenic effects of 2, 2'-dihydroxy-di-n-propylnitrosamine (DHPN) on tree shrews (Tupaia glis) was examined. DHPN was subcutaneously administered to tree shrews at a dose of 250 mg/kg of body weight once a week for 80 weeks. Eight of the nine males (89%) and 11 of the 14 females (78%) that received DHPN developed pulmonary adenomas between weeks 65 and 102 (Rao & Reddy, 1980). Additionally, 9% of the DHPN-treated tree shrews developed squamous cell carcinomas of the skin and HCC. Taken together, tree shrew may be a suitable animal model for lung cancer research.

3 NHPs for cancer genetics studies, therapies and prevention

NHPs have been used in cancer genetics studies in the past. For instance, the evolution of tumor suppressor genes such as BRCA1 (Pavlicek et al, 2004; Puente et al, 2006) and p53 (Contente et al, 2003) in NHPs has been previously reported. To identify potential human cancer-related genes, comparative genomic hybridization (CGH) has been used to generate cytogenetic profiles of malignant gliomas in four monkey tumors (Jaikumar et al, 2007). In 2005, the chimpanzee genome was sequenced (Chimpanzee Genome Sequencing and Analysis Consortium et al, 2005) and two years later, the rhesus macaque genome was sequenced (Rhesus Macaque Genome Sequencing and Analysis Consortium et al, 2007). The sequencing of more NHP genomes will further accelerate comparative cancer genetic studies in NHPs and humans.

In addition to the study of cancer-related genes, NHP models are ideal for studying drugs for cancer therapies and chemoprevention because of their genetic similarity with humans. NHPs have been widely used to evaluate the safety and pharmacokinetics of anti-tumor drugs and vaccines (Parker et al, 1995; Kim et al, 2001; Hassan et al, 2007; Kapetanovic et al 2010; Morera et al, 2010). The rhesus monkey in particular is suggested to be an excellent candidate for a NHP model for ovarian cancer chemoprevention (Brewer et al, 2001a, b). Using cultured rhesus ovarian surface epithelium cells, Wright et al (2005) demonstrated that high-dose estrogen and clinical selective ER modulators induced growth arrest in vitro. Rodriguez et al (1998) showed that oral contraceptive progestin induced apoptosis in the ovarian epithelium. Additionally, an agonist of toll-like receptor 5 has been reported to protect rhesus monkeys from lethal irradiation routinely used to treat cancer patients (Burdelya et al, 2008). More recently, caloric restriction has been demonstrated to delay the onset of age-associated diseases, including cancer, in rhesus monkeys (Colman et al, 2009).

4 Conclusions and perspectives

NHPs share numerous similarities with humans and have been widely used to study human diseases such as AIDS, hepatitis and neurodegenerative diseases. However, NHPs have not been widely used for cancer research because of the low incidence of spontaneous tumors, long latency, slow propagation and high costs. Different chemical, biological (including hormones, bacteria, and viruses), and physical carcinogens have been used to induce a variety of tumors in different NHPs, including macaques and tree shrews. These NHP cancer models provide valuable knowledge for human cancer prevention and treatment due to their similarity to human cancers.

More NHP cancer models are required to better understand mechanisms of human carcinogenesis and to design more effective prevention and treatment options for cancer patients. An ideal animal model for cancer research should faithfully reflect various aspects of the human disease such as the etiology, pathology, genetics.
and therapy. Additionally, tumors should be expected to develop with a high incidence and a relatively short latency. NHPs have the potential to grow as tools for human cancer research with the development of technology. For example, NHP transgenic techniques have recently been established (Niu et al, 2010). Finally, as primate-like animals, tree shrews which are smaller in size, propagate rapidly and cost comparatively less than larger NHPs and may be a superior model for cancer research and help overcome the disadvantages of using rodents and other NHPs. We are currently trying to establish tree shrew cancer models by using chemical and biological carcinogens. It is our belief that NHPs will play a more significant role in future cancer research.

References:


