Review Article

Mammalian models of chemically induced primary malignancies exploitable for imaging-based preclinical theragnostic research

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Abstract: Compared with transplanted tumor models or genetically engineered cancer models, chemically induced primary malignancies in experimental animals can mimic the clinical cancer progress from the early stage on. Cancer caused by chemical carcinogens generally develops through three phases namely initiation, promotion and progression. Based on different mechanisms, chemical carcinogens can be divided into genotoxic and non-genotoxic ones, or complete and incomplete ones, usually with an organ-specific property. Chemical carcinogens can be classified upon their origins such as environmental pollutants, cooked meat derived carcinogens, N-nitroso compounds, food additives, antineoplastic agents, naturally occurring substances and synthetic carcinogens, etc. Carcinogen-induced models of primary cancers can be used to evaluate the diagnostic/therapeutic effects of candidate drugs, investigate the biological influential factors, explore preventive measures for carcinogenicity, and better understand molecular mechanisms involved in tumor initiation, promotion and progression. Among commonly adopted cancer models, chemically induced primary malignancies in mammals have several advantages including the easy procedures, fruitful tumor generation and high analogy to clinical human primary cancers. However, in addition to the time-consuming process, the major drawback of chemical carcinogenesis for translational research is the difficulty in noninvasive tumor burden assessment in small animals. Like human cancers, tumors occur unpredictably also among animals in terms of timing, location and the number of lesions. Thanks to the availability of magnetic resonance imaging (MRI) with various advantages such as ionizing-free scanning, superb soft tissue contrast, multi-parametric information, and utility of diverse contrast agents, now a workable solution to this bottleneck problem is to apply MRI for noninvasive detection, diagnosis and therapeutic monitoring on those otherwise uncontrollable animal models with primary cancers. Moreover, it is foreseeable that the combined use of chemically induced primary cancer models and molecular imaging techniques may help to develop new anticancer diagnostics and therapeutics.

Keywords: Chemically induced primary malignancy; carcinogen; carcinogenesis; noninvasive imaging; magnetic resonance imaging (MRI)

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Introduction

Cancer is a systemic disease that initially presents local manifestations (1) and later advances in a multistep process with various hallmarks including rapid proliferation, resisting cell death, neoangiogenesis, local invasion, remote metastasis, etc. (2). Due to diverse pathologic features, genomic variations and patient outcomes in clinic oncology, no individual animal models can completely mimic this complex progress. In order to simulate different human cancer pathologies and address various research questions, there have been numerous animal cancer models including (I) transplanted tumors, (II) genetically engineered models and (III) environmentally caused cancers such as chemically induced malignancies.

Models of transplantable tumor are generated by transplantation of living cancer cell suspension or solid tumor tissue from a donor to another animal, which can be further classified as either xenograft or allograft based on whether the tumor donor and the host belong to different species or the same species of close genome (3). In the xenograft, the host animals are usually immune-compromised and tolerable to cross-species cancer cells (3). In contrast, allograft refers to the tumor transplantation strictly between the individuals from the same species. In both, the transplants can be orthotropic, subcutaneous or intravascular in order to study different stages of the tumor progression (4).

The genetically engineered model (GEM) for cancer refers to an animal strain with manipulated genomic alterations, specifically involving the overexpression of an oncogene or the loss of a tumor suppressor gene function (5). The GEMs can be simply divided into transgenic and endogenous ones (6). Such models allow the investigation of the functions of certain genes or pathways during tumor development or progression (7). Despite their sophistication in preparation, some available GEMs may accurately simulate the pathophysiology and molecular mechanism of certain human cancers (6).

Environmentally induced cancer models refer to particular cancer types developed in animals that have been exposed to certain environmental risk factor such as carcinogenic chemicals, radiation, viruses, microbial flora or even physical stimuli (8). Some GEMs are also applied in combination with the environmental exposures. Such primary cancer models can simulate the originality, evolution and consequence of clinical cancer process from the early initiation, through midterm progression and clinical onset until late exacerbation, and are ideally used to investigate the etiology, prevention, diagnosis and treatment of cancer in all stages. Furthermore, the primary tumor lesions also possess the histological complexity and heterogeneity comparable to the actual human malignancies (3).

Among the environmentally induced cancers, the chemically induced cancer model is generated by certain synthetic chemical compounds that are exposed to the body via ingestion, inhalation, injection, dermal absorption or other ways. Here, we highlight the chemically induced primary cancer models due to their diverse advantages including non- or less invasiveness, abundant tumor burden, full spectrum of cancer types, and reproducible process. Moreover, due to the very similar carcinogenesis process, chemically induced cancers mimic the human cancer occurrence from the initiating stage on.

Mechanisms of primary cancer development

Chemical carcinogenesis usually undergoes three-steps, namely initiation, promotion and progression (*Figure 1*). The plausible cellular and molecular mechanisms involve interactions or covalent binding of carcinogens with intracellular DNA, RNA and proteins, resulting in gene-mutational alterations (9).

Tumor initiation, promotion and progression

Initiation is the first step in cancer development. Initiators are the chemicals that are often not reactive with DNA, but altered by drug-metabolizing enzymes in the body and are then able to cause changes in DNA (mutations) often after a covalent binding (7). Many initiators are specific to particular species or tissue types. Initiation is irreversible, i.e., once a particular cell has been affected by an initiator it is susceptible to promotion. Since initiation causes permanent genetic change, any daughter cells from the division of the mutated cell will also carry the mutation. There is a linear relationship between the dose of initiator and the quantity of produced tumor cells, i.e., the more exposure the higher risk of carcinogenesis.

Promotion is the second step that occurs on those cells already mutated by an initiator (10). The promoters refer to the compounds that promote the proliferation of the cell into a large number of daughter cells containing the mutation created by the initiator. Promoters take effect only when the organism has been previously exposed to

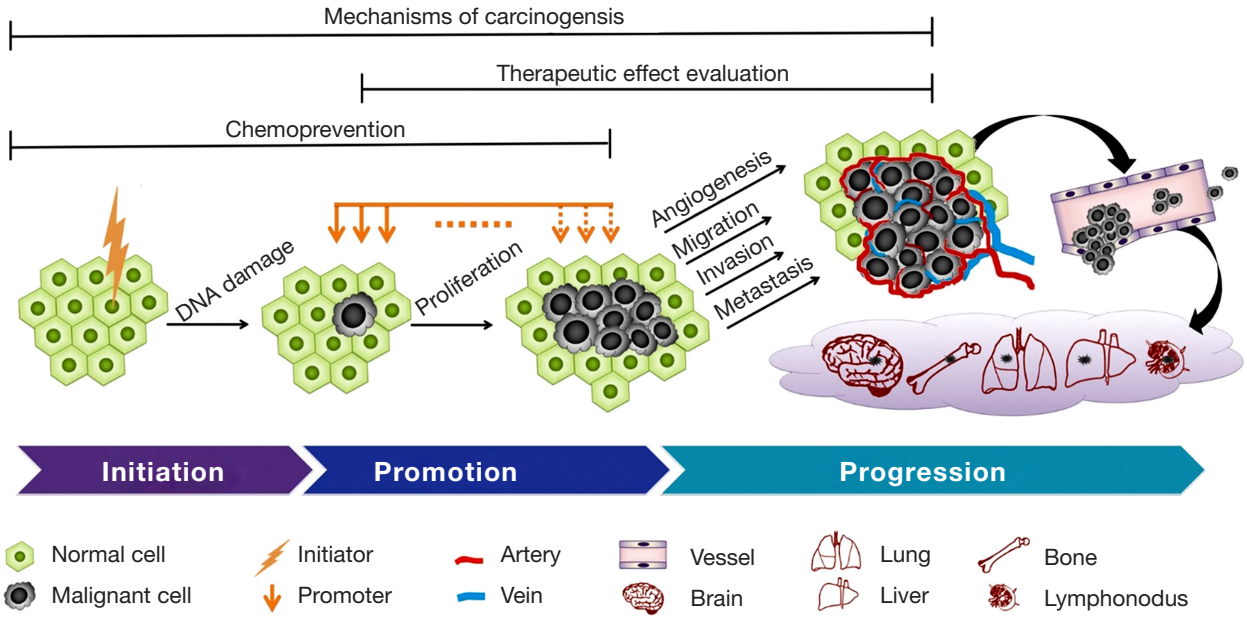

Figure 1 Three-phase process of carcinogenesis upon carcinogen administration and the various research applications based on animal models of primary cancers.

an initiator. Unlike initiators, promoters do not covalently bind to macromolecules or DNA within the cell, but many bind to receptors on the cell surface to affect intra-cellular pathways that increase cell proliferation (11). Two categories of promoters exist: specific promoters that interact with receptors on or in target cells and nonspecific promoters that alter gene expression without involving a known receptor. Tumor growth thus promoted is dose-dependent with a threshold and a maximum effect of promoters, i.e., very low doses will not promote tumor development and extremely high doses will not produce more risk. Promoters do not necessarily cause cancer on their own, but increase the clonal expansion of initiated cells, and ultimately leads to malignancy (11).

The third step progression refers to the serial transformations from a benign tumor to a neoplasm and to malignancy. Progression is associated with karyotypic changes since most advanced tumors show aneuploidy with the wrong number of chromosomes. This karyotypic change is coupled with an increased growth rate, invasiveness, metastasis and alterations in biochemistry and morphology due to the continuing mutations or genetic instability (12). Once this step is triggered, progression is irreversible.

In the practical animal models of malignancy, a two-stage carcinogenesis strategy is frequently employed to shorten the cancer development period by treating animals with an organ-specific cancer initiator followed by a promoter (13).

Genotoxic and non-genotoxic carcinogens

The mechanisms of action of carcinogens can be simply divided into genotoxic (GTX) and non-genotoxic (NGTX) ones. GTX events may damage DNA or chromosome by direct interactions (14), while in the NGTX procedure carcinogens are capable of eliciting more diverse cellular effects largely via biotransformation, which subsequently cause multiple cellular signal transduction alterations (12,15).

GTX carcinogens, acting as electrophiles, can covalently bind to and interact with DNA which induces DNA adducts and mutations (16,17). Thus, GTX carcinogens may be considered as the tumor initiators. For example, benzo(a) pyrene (BaP) is able to form bulky BaP-DNA adducts and basic sites, or alternatively cause DNA damage by the reactive oxygen species (ROS) and metabolites produced during metabolic processing (18). From carcinogen risk assessment, GTX can be further divided into three groups: initiators with clear DNA-reactive function, borderline initiators, and weak initiators genotoxic through secondary mechanisms (12).

As opposed to GTX carcinogens, NGTX carcinogens do not affect DNA directly but target a series of physiological processes modulating cell growth, division,

chronic inflammation (19), immunosuppression, ROS, steroid hormone receptor (SHR) activation and epigenetic silencing (20) by the generation of their metabolites catalyzed by cytochrome P450 (CYP) (12,21). Commonly, NGTX carcinogens, acting as promoters, function through several different modes including pro-mitogenesis by phenobarbital (PB) (22), receptor-interacting protein-mediated pathways (19) such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (23,24) and asbestos (25), gap junction intercellular communication (26) or cytotoxicity like chloroform. A classic example is 2,2,4-trimethylpentane (TMP), which is a classical promoter of renal cancer in male rat. As a representative nephrotoxic isoparaffinic component of unleaded gasoline, the metabolites of TMP can reversibly bind to alpha 2u-globulin, which decreases the catabolism of alpha 2u-globulin in the kidney and results in chronic lysosomal overload, cell death and cell compensatory proliferation leading to kidney cancer (27).

Complete and incomplete carcinogens

In terms of the participation in different carcinogenesis phases, carcinogens can be also regarded as complete or incomplete carcinogens.

The complete carcinogens have the capability to induce cancer without the participation of an additional tumor-promoting agent, which means the complete carcinogens function as both initiators and promoters simultaneously under proper dosage and exposure time (10,28), taking polycyclic aromatic hydrocarbons (PAH) as an example (23).

The incomplete carcinogens refer to the mutagenic chemicals either instigating DNA damage irreversibly or accelerating benign lesion growth, but not capable of initiating malignancy (28).

Organ-specific tumor induction by chemicals

Although there are different administrating types of carcinogens including oral, dermal, inhalation or even intraperitoneal routes, carcinogens tend to target certain particular peripheral tissues via blood circulation (29-32). More than 80% of tested chemical carcinogens were reported to be positive in at least the following 8 most frequent targeting organs mainly in different mammal species: the liver, lung, mammary gland, stomach, vascular system, kidney, hematopoietic system and urinary bladder (33). The biological basic mechanisms of underlying organ specificity are variable.

One possible explanation is that the cytochrome P450 (CYP) expression profiles in response to carcinogens in various tissue types differ markedly (34), which is critical to determine what particular tissue develops tumor (21,23). In the promotion stage, the CYP system triggers the carcinogenesis by catalyzing the activation of promoters from procarcinogen status, resulting in formation of DNA adducts (35,36). Therefore, the preference and regulation of CYP in different substrates are central to the occurrences of chemically induced malignancies in different organs (21,29,37).

For other chemical carcinogens, their sex hormone activities were also reported to contribute to the tissue specific properties. For example, in breast cancer, estrogen is a well-known risk factor. The breast carcinogen 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine (PhIP) works as the agonists of estrogen receptor alpha (ERα) and affects miRNA specifically in mammary gland during the initiation and progression of breast cancer (38).

Classifications of chemical carcinogens

A wide variety of chemical carcinogens have been proven capable of inducing cancers in experimental animals after prolonged or excessive exposures, comprising cooked meat derived carcinogens, food additives, industrial chemicals and environmental pollutants, tobacco smoke carcinogens, antineoplastic agents, naturally occurring compounds and synthetic carcinogens (*Table 1*) (16,23,49).

N-Nitroso compounds

N-nitroso compounds (NOCs) have initially been brought into attention for their carcinogenicity most likely from preserved food (143,144), drinking water contamination (145,146) and tobacco smoking (147).

Some NOCs like N-nitrosodiethylamine (DENA) and N-methyl-N-nitro-N-nitrosoguanidine (MNNG), can be endogenously converted in our stomach and bowel from nitrites that are usually added to preserve processed meats like bacon, ham, sausage (143,144).

DENA is a powerful and consistent hepatocarcinogen that is able to induce multifocal primary liver tumors such as hepatocellular carcinoma (HCC) superimposed on varying degrees of liver cirrhosis not only in rodents (39,148) but in monkey as well (49). Importantly, DENA-induced hepatocarcinogenesis can highly simulate the histopathological evolution of clinical liver cancers (149). DENA is usually administrated to male Sprague Dawley (SD) or Wistar rats (150-300 g) in the drinking water at

Table 1 Classification of some chemical carcinogens in experimental animal models

Classification	Compound	Abbreviation	Mechanism	Target organ	Susceptible species
N-nitroso compound (NOC)	N-Nitrosodiethylamine	DENA	Complete carcinogen/ initiator	Liver	Rat (35,39-46), mouse (47,48), primate (49)
			Initiator	Kidney	Rat (50), mouse (50)
			Initiator	Lung	Rat (51), mouse (52)
	N-Methyl-No-nitro-N-nitrosoguanidine	MNNG	Complete carcinogen	Stomach	Rat (53,54), primate (49)
	N-Nitrosodimethylamine	NDMA	Initiator	Liver	Rat (55), mouse (56)
			Initiator	Esophagus	Rat (56)
	Dimethylnitrosamine	DMN	Initiator	Liver	Rat (57)
	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone	NNK	Complete carcinogen/ initiator	Lung	Mouse (58-61), rat (62,63)
			Complete carcinogen	Pancreas	Hamster (64)
	N-Butyl-N-(4-hydroxybutyl) nitrosamine	BBN	Complete carcinogen	Bladder	Mouse (65-69), rat (70-72)
Heterocyclic amine (HCA)	2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine	PhIP	Compete carcinogen	Breast	Rat (73,74)
			Compete carcinogen	Colon	Rat (75,76)
			Complete carcinogen	Prostate	Rat (76,77)
	2-Amino-3,8-dimethylimidazo-[4,5-f]quinoxaline	MeIQx	Initiator	Liver	Rat (78,79)
			Complete carcinogen	Lung	Mouse (80)
	2-Amino-3-methylimidazo[4,5-f] quinoline	IQ	Initiator	Liver	Rat (81,82), primate (49)
			Initiator	Colon	Rat (81,82), mouse (83)
Polycyclic aromatic hydrocarbon (PAH)	2-Acetylamino-fluorene	2-AAF	Promoter	Liver	Rat (42,84), mouse (44,85)
	7,12-Dimethylbenzanthracene	DMBA	Complete carcinogen	Breast	Rat (86-92), mouse (93,94)
			Initiator	Skin	Mouse (87)
			Complete carcinogen	Oral cavity	Hamster (95)
	Benzo[a]pyrene	BaP	Complete carcinogen	Lung	Mouse (96,97)
			Complete carcinogen	Stomach	Mouse (98)
			Complete carcinogen	Colon	Mouse (99)
	3-Methylcholanthrene	MCA	Initiator	Lung	Mouse (100), rat (101)
Food additive	Potassium bromate	KBrO3	Complete carcinogen	Kidney	Rat (102)
Polychlorinated biphenyl (PCB)	2,3,7,8-Tetrachlorodibenzo-p-dioxin	TCDD	Promoter/initiator	Liver	Mouse (103), Rat (104)
			Promoter	Lung	Mouse (61), Rat (104)
Antineoplastic agent	N-Methyl-N-nitrosurea	MNU	Complete carcinogen	Breast	Rat (73,105-109), mouse (110)
			Initiator	Prostate	Gerbil (111), rat (112), primate (49)
			Initiator	Thyroid	Rat (113)
			Complete carcinogen	Esophagus	Primate (49)
			Complete carcinogen	Stomach	Mouse (114), primate (49)
			Complete carcinogen	Colorectum	Shrew (114)

Table 1 (*continued*)

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Classification	Compound	Abbreviation	Mechanism	Target organ	Susceptible species
Naturally occurring compound	Aflatoxin B1	AFB1	Complete carcinogen	Liver	Rat (115), mouse (116,117), fish (118), primate (49)
	Asbestos	/	Complete carcinogen	Lung, pleura	Rat (119), mouse (120), hamster (120)
			Complete carcinogen	Peritoneaum	Mouse (121), rat (122)
	Aristolochic acid	AA	Complete carcinogen	Forestomach	Rat (123), mouse (124)
			Complete carcinogen	Kidney	Rat (123), mouse (124)
Synthetic carcinogen	1,2-Dimethylhydrazine dihydrochloride	DMH	Complete carcinogen	Colorectrum	Rat (125-128), mouse (129)
	Azoxymethane	AOM	Complete carcinogen	Colorectrum	Rat (130), mouse (130)
	Methylazoxymethanol	MAM	Complete carcinogen	Colorectrum	Mouse (131)
	4-Nitroquinoline 1-oxide	4NQO	Complete carcinogen	Oral cavity, esophagus	Rat (132,133), mouse (133,134)
	Ethylnitrosourea	ENU	Complete carcinogen	Central nervous system	Rat (135,136), mouse (137,138)
	N-Nitrosobis(2-hydroxypropyl) amine	BHP	Complete carcinogen	Lung	Rat (139,140)
			Complete carcinogen	Pancreas	Hamster (139,141)
	Phenobarbital	PB	Promoter	Liver	Rat (45,142)

100 ppm (40), or by frequent gavage feeding at 10 mg/kg body weight (41,150). However, this classical liver cancer model has been proven time consuming, as the appearance of recognizable tumor lesions in most cases occurs after a quite long latent period, normally 16-32 weeks after the first DENA exposure. In addition, DENA also acts as initiator for renal and pulmonary cancers in rodents (50-53).

MNNG is a well-known gastric carcinogen in rodents and primates (49,54,151).

N-nitrosodimethylamine (NDMA) acts as a initiator of hepatocarcinogenesis (56) and esophageal carcinogenesis (57) in rodents, while dimethylnitrosamine (DMN), the NDMA's precursor, is used as a mutagen for liver cancer in rats (152).

4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and its major metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) are powerful determinants of pulmonary cancer incidence, and biomarkers indicating the exposure of tobacco smoke (147). For the experimental model, female A/J mouse is a more sensitive strain to study lung cancer (58-60,62,63,153-155). Practically, mice treated with a single intraperitoneal injection of NNK (100 mg/kg body weight) developed lung cancer by 30 weeks at a 100% tumor incidence (61,156). Furthermore, exposure of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) combined with NNK could significantly increase lung cancer development (61). Besides, hamsters developed pancreatic cancer as well upon NNK exposure, but with a lower organ-specificity (64).

Exposure of rodents to N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN) reproducibly induces high-grade and invasive squamous cell urinary bladder cancers (65-67,70-72), which resembles the development of the most human bladder cancer based on histopathology (157). For mice, after 2-6 weeks treatment of BBN at 500 ppm in the drinking water, mutagenesis in urothelial cells was greater than the spontaneous mutation background and that in the smooth muscle cells of the urinary bladder (68); after 20 weeks of BBN treatment at the same concentration, bladder cancer developed in all treated mice (66). For models in both F334 and Wistar rats, bladder cancers were highly induced during 6-8 months after 8- to 14-week single exposure of BBN at 500 ppm in the drinking water (70). In a two-stage model, phenylethyl isothiocyanate (PEITC) was reported to promote the development of transitional cell carcinomas at 1,000 ppm in diet from the 4th to 8th week

combined with BBN administration (13).

Heterocyclic amines

Red meats, cooked at high temperature and for long periods of time, tend to promote several carcinogenic compounds such as heterocyclic amines (HCAs) (143,158,159).

HCAs represent a group of mutagenic compounds which are able to increases the risk of cancer in various organs in rodents (16,23,49). Three HCAs are frequently used in animal cancer models, i.e., 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine (PhIP), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), and 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) (49).

PhIP is the most abundant HCA subtype, which has complete carcinogenicity of DNA damaging and mutagenic activities as an initiator, and estrogenic activity as a promoter as well. Exposure of rats to PhIP can cause cancers in breast (73), colorectum (75,76) and prostate (76,77).

MeIQx exposure leads to increased liver and lung cancer risks in rodents mainly as a genotoxic carcinogen during the initiation phase (78-80).

Similarly, IQ is a genotoxic carcinogen in rodents to induce liver and colon tumors (81-83), and in primate as well to induce liver cancer (49).

Polycyclic aromatic hydrocarbons

Similarly, polycyclic aromatic hydrocarbons (PAHs) are also generated during meat grilling and roasting (143,158). They include 2-acetylamino-fluorene (2-AAF), 7,12-dimethylbenzanthracene (DMBA), benz[a]anthracene (BaA), benzo[a]pyrene (BaP), and 3-methylcholanthrene (MCA), all with high carcinogenic properties (160-162).

2-AAF has been largely used as a promoter in the 8-week Solt-Farber protocol for multistep experimental hepatocarcinogenesis in rats. Briefly, initiation is triggered by a single intraperitoneal injection of DENA, normally at a dose of 200 mg/kg body weight; the initiated hepatocytes are then promoted by either feeding rats a daily diet containing 2-AAF or by gavage of 4-6 single doses (normally 20 mg/kg body weight/day) of 2-AAF on consecutive days at 1-2 weeks after DENA initiation; afterwards rats are subjected to a 2/3 partial hepatectomy to stimulate mitosis of selected initiated hepatocytes (42-44,84,163,164). Immunohistochemical staining of the placental glutathione s-transferase (GST-P) is frequently used as an accurate marker enzyme to detect liver preneoplastic focal lesions in liver cancer and indicates the endpoint of evaluation of certain chemopreventive agents (42,43,164). In mice models, 2-AAF was also found to induce liver mutations (85,165).

As a complete carcinogen, DMBA is more efficient than the other PAHs in inducing breast cancer, which is routinely used in female SD rats at the age of around 50 days (86,87). Previous studies have proved that a single dose of 50-100 mg/kg of DMBA by gavage is able to cause mammary tumors at the incidence of 100% (87). Furthermore, the developed cancerous lumps are morphologically heterogeneous and hormone dependent (86). However, in the mouse skin squamous carcinogenetic model, DMBA is used as an initiator combined with the promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) (166).

BaP is a main suggested indicator of PAH, which causes cancers usually in the lung, stomach, colon and other organs and tissues (98,99). Meanwhile, their chlorinated compounds, e.g., Cl-BaA, have also been reported showing the organ-specific distribution and even greater accumulation compared with their parents, and presenting carcinogenic impacts in various organs like the liver (167).

MCA serves as an initiator of lung cancer in rodents, usually followed by the promoter butylated hydroxytoluene (BHT) (100,168).

Potassium bromate

Potassium bromate ($KBrO_3$) used to be a flour improver widely used as a food additive in the bread-making process, while bromate is also a disinfection byproduct formed in drinking water (169). $KBrO_3$ acts as a complete carcinogen in renal cancer development in rat models (102).

Polychlorinated biphenyls

Polychlorinated biphenyls (PCBs) are a class of dioxin-like carcinogens, which are formed as the industrial by-products and known as the widespread environmental contaminants. The best studied member is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (104).

TCDD has no direct genotoxicity but acts as a multi-site, multi-species tumor promoter, which might be mediated either by the agonist-specific activation of hydrocarbon receptor (AhR) that leads to the transcription of cytochrome P450 enzymes and induces oxidative stress, or by the alterations of Akt and ERK apoptosis signaling pathways which causes attenuation of apoptosis (61,103,104,170).

N-Methyl-N-nitrosourea

N-Methyl-N-nitrosourea (MNU) was originally designed as a chemotherapeutic alkylating compound, but later proven to exert direct mammary carcinogenic effects (171), a single dose of which has been shown to induce breast cancer in SD rats (105,106). Notably, although both MUN and DMBA-induced mammary cancers are generally hormone-dependent (4), MUN-induced mammary cancers tend to be locally aggressive and spontaneously metastasized, which are quite different from DMBA-induced breast tumors, and thus suitable for study of malignant progression or the advanced stage of mammary cancers (172). Besides, MNU is also able to enhance various cancers in experimental animals such as esophageal, gastric and colorectal malignancies (49,111,114), and initiate prostate and thyroid cancers (49,112,113,173).

Naturally occurring compounds

(I) Aflatoxins are a group of mycotoxins naturally produced from Aspergillus flavus or Aspergillus parasiticus as secondary fungal metabolites. They frequently contaminate foods and impose a global problem (174). Aflatoxin B1 (AFB1) is a well-known hepatocarcinogen acting with potent mutagenicity and cytotoxicity in experimental models (49,115-118,175-177);

(II) Asbestos fibers consist of several distinct types occurring in soils and rocks, which used to be heavily used in the industry. Asbestos has been identified to produce oxygen derivatives in cytotoxicity and DNA double strand breaks extensively (178,179). In the experimental murine models, asbestos has been used to develop pleural and peritoneal malignant mesotheliomas by intratracheal instillation and intraperitoneal injection receptively (119-122,125);

(III) Aristolochic acids (AAs) are major components extracted from Aristolochia plants, which used to be an ancient herbal medicine, but have been identified as a strong nephrotoxin for the first time by Belgian scientists in 1991 (180-182). In rodents, AA is a potent carcinogen. Long term oral administration of AA both in rats and mice leads to multiple tumors largely in forestomach and kidney (123,124).

Synthetic carcinogens

(I) 1,2-Dimethylhydrazine dihydrochloride (DMH) and its inter-metabolites azoxymethane (AOM) and methylazoxymethanol (MAM) are a group of synthetic compounds with the general structure of cycasin, which are highly specific complete carcinogens for rodent colorectal tumor models (126-132,183);

(II) 4-Nitroquinoline 1-oxide (4NQO) is a manufactured derivative of quinolone for research purposes, possessing a heterocyclic aromatic structure. As a complete carcinogen, 4NQO is able to induce all the stages of oral squamous cell carcinoma, which has been identified to highly mimic the histological and molecular features in human oral cancers (133,184);

(III) Ethylnitrosourea (ENU) is a highly potent mutagen first reported by Bill Russell *et al.* in 1979, which is largely used as neurotropic carcinogen to generate glioma rat models (135,136). Additionally, infant Big Blue transgenic mice are susceptive to ENU-induced hepatic mutation (185); and exposure to ENU markedly increases mammary tumor multiplicity and incidence in mice defective in Apc tumor suppressor gene (137);

(IV) N-Nitrosobis(2-hydroxypropyl)amine (BHP) is a hydroxylated dipropylnitrosamine first synthesized by Krüger *et al.* in 1974 (139). The complete carcinogenetic effects of BHP alter due to the routes of treatment and the host species as well. For instance, BHP is known as a pancreatic carcinogen by subcutaneous injection in Syrian golden hamsters (140,141), but a pulmonary carcinogen by oral administration in Wistar rats (139,142);

(V) As a synthetic non-genotoxic carcinogen or promoter, phenobarbital (PB) compound is extensively used in rodents to enhance hepatic and renal carcinogenesis (35,45,186).

Experimental applications

The above-specified chemicals only exemplify a little bit of the immense known and unknown carcinogens, of which the experimental applications are still preliminary and empirical, leaving rooms for further exploitations. Nevertheless, primary cancer models are useful tools for performing various fundamental and translational investigations including (I) understanding biological and molecular mechanisms involved in tumor initiation, promotion and progression; (II) looking into influential and preventive factors of carcinogenesis; and (III) evaluating the diagnostic/therapeutic potentials of candidate drugs on induced models of primary tumors (*Figure 1*).

Related genes and pathways in carcinogenetic process

Cancer development and progression may involve multiple abnormal aspects such as sustained proliferation, resisting cell death, migration and metastasis, angiogenesis, interaction with immune system, reprogramming energy metabolism, etc. (2). By using many multistage carcinogens, the molecular changes associated with the initiation and promotion of cancer development are possible to be analyzed.

A range of genomic alterations and somatic mutations of different oncogenes and tumor suppressors have been recently found in various human malignancies, while the mutation-inducing factors remain not fully elucidated. For instance, in human lung adenomas and adenocarcinomas, the epidermal growth factor receptor (*EGFR*) gene alterations have been frequently reported; from the representative rodent lung cancer models generated by NNK, BHP, MeIQx, urethane, as well as X-ray, the mutation patterns of *Egfr* and *K-ras* were able to be detected and compared with equivalent human lesions to better understand the upstream regulation (156). Moreover, using a cross-species analysis of global gene expression profiles, differentially expressed genes and relative altered molecular pathways allow mining of the promising target genes for anti-cancer strategies (67).

In addition, when combined with carcinogen treatments, GEM such as *p16*, *p19*, *p53*, *Apc*, *c-Ha-ras*, *myr-Akt*, *TGF-α* and *Kfl6* models show their unique advantages, which not only enable the assessment on effects of these genes on the tumor progression, but provide abundant information about the regulation of intracellular signaling networks (47,73,138,187-192).

Cancer preventive and influential factors for tumorigenesis

Research innovations have contributed to cancer therapeutic strategies by developing new technologies or drugs. However, according to the overview of global cancer burden issued from WHO, overall cancer incidence and mortality rates worldwide have been rising (193). Therefore, more attentions and efforts are required for research in the field of cancer prevention. Especially, as one of the most promising approaches to reduce cancer risks, chemoprevention is a method to suppress, delay or even reverse carcinogenesis during the early stage by means of specific chemical substances (84,98). In the experimental animal models, the evaluation of preventive effects of various drugs on tumor formation and progression can be achieved simply by early administration of the drug together with the carcinogen treatment (66,194) or even in advance of the carcinogen exposure (35,195).

Recently, many natural compounds extracted from medicinal plants such as resveratrol, curcumin, capsaicin, allicin, etc. have been reported to demonstrate chemopreventive activities (43,196), largely because of their potent activities against oxidative stress and toxic injuries that continuously occur during the entire carcinogenetic process including initiation, promotion and progression. For example, in the case of the chemically induced rat hepatocarcinogenesis, lutein, a kind of carotenoid existing in green leafy vegetables, inhibited hepatic preneoplastic lesions when administrated during promotion and DNA damage stage (44). Some other natural substances, e.g., aqueous extract of the dried leaf of *A. compressa*, a component of herbal tea in Mexico, astragalus membranaceus, a natural herbal medicine in traditional Chinese medicine for liver diseases (164), and betaine, particularly found in wheat, spinach and sugar beets (40) are also promising to delay rat hepatocarcinogenesis (195).

Preclinical evaluations of new specific contrast agents

Diagnostic imaging provides essential information for early diagnosis, precise staging, timely clinical treatment, and appropriated palliative therapies of various cancers in clinical patients. However, the main challenge lies in the relatively insufficient soft-tissue contrast between malignant lesion and surrounding tissues. In this context, different new specific contrast agents in preclinical settings have been explored, which extend the applications of different imaging modalities from anatomical structure to functional assessment or even to molecular imaging, particularly in the field of MRI, which offers superior life tissue contrast (3). In previous preclinical evaluations of MRI diagnosis in DENA-induced rat liver cancers, multifocal liver tumors were better detected and characterized by using liver specific contrast agents such as Mn-DPDP and Gd-EOB-DTPA relative to nonspecific contrast agents Gd-DTPA and Gd-DOTA (3,148).

Therapeutic strategies for primary malignancies

Chemically induced cancer models are also widely used to explore the therapeutic potencies of various treatments (39,66,86,87,166,194,197,198), owning to the ability to

better mimic the complexity of clinical multistep malignant process, and to be more predictive in preclinical studies as well as basic research. For instance, in the study on the Rapamycin treatment upon the two-stage mouse skin tumor model, the cancer development was first initiated by DMBA and subsequently promoted by phorbol esters, which allowed to test the therapeutic effects of Rapamycin during the entire process of carcinogenesis, including both the early lesions around 9-10 weeks after the initiation and the advanced lesions after approximately 16-18 weeks of initiation (166).

Advantages and disadvantages

Among commonly adopted cancer models, chemically induced primary malignancies in mammal have multiple advantages including the eased procedures, abundant tumor generation and high analogy to human primary cancers seen in the clinic.

First of all, chemically induced primary cancer models are simple and economical due to the fact that carcinogens can be easily administrated via single intraperitoneal injection, continuous gavage feeding, repeated subcutaneous injection, daily drinking water or routine dietary supplement, requiring neither experienced manipulators nor complicated facilities or devices.

Secondly, carcinogen induced tumor models are productive owning to high success rate and multifocal lesions simultaneously induced in the targeted organs. Moreover, animal primary cancer models can produce a full spectrum of primary cancers, frequently with various sizes, differentiation degrees, and even tumor origins. Take DENA-initiated rodent hepatocarcinogenesis as an example, multifocal primary liver tumors on general liver cirrhosis can be successfully induced in SD rats after months of DENA gavage feeding (199). This enables the comparison between benign and malignant neoplasia, tumor lesions and paratumor tissues in the same carrier, thus contributing to reliable evaluation of therapeutic effects of newly discovered drugs, and exploratory study of diagnostic potentials of different imaging technologies (148,200).

Additionally, primary cancer models such as DENA-induced hepatocarcinogenesis (149), BBN-induced bladder cancer (157), NNK-induced lung cancer (62) and 4NQO-induced oral carcinogenesis (133) can ideally resemble the clinical course and evolution of multiple human cancers with respect to the similar morphology, histopathology characteristics and molecular changes. Furthermore, different carcinogens are able to cause different cancer subtypes with variant cancer biologic features. For instance, DMBA and MNU are two classical carcinogens frequently used to induce mammary tumors. The majority of DMBA- induced tumors are hormone dependent, while MUN-induced tumors tend to be hormone independent and aggressive (107,172). Therefore, primary cancer models also provide us with a tool with great value for better understanding of the mechanisms of cancer pathogenesis.

However, there are also some disadvantages of such models. In addition to the time-consuming progress of carcinogenesis, the major drawback is the difficulty in noninvasive tumor burden assessment in small living animals, because, like cancer patients in reality, tumors occur unpredictably and heterogeneously in terms of timing, location, number, size, differentiation and blood supply of lesions (3). Especially for the visceral tumors in the liver, lung, kidney or pancreas, it is quite difficult in detection of newly generated tumor lesions and monitor of their growth in individual organs. Consequently, this brings challenges in grouping and defining the endpoints of model building-up. In fact, for some experimental studies aiming at investigating cancer development, chemoprevention or cancer therapy of primary cancers in animals, tumor formation and therapeutic effects can only be assessed by histopathology via sacrificing the animals and removing the target organs (35,66), or via biopsy during the process as a supplemental method (200).

Workable solution: noninvasive MR imaging

Compared with the other clinical imaging techniques like computed tomography (CT) or ultrasonography (US), and nuclear imaging such as single photon emission computed tomography (SPECT) or positron emission tomography (PET), MRI and US are noninvasive and harmless modalities for the diagnosis and therapeutic evaluation of visceral tumors. However, the application of US for animals, especially rodents, is limited mainly due to the small size of animals and relative low sensitivity as a result of the low frequency of the usual echography probes. On the other hand, multiparametric MRI (MP-MRI) has been increasingly used for detection, localization, stage and even characterization of experimental models with primary cancers. Importantly, all these imaging results in small animals like rats can be simply achieved by clinical MR scanners (3).

Detection and diagnosis

Early diagnosis of multifocal visceral tumors has been a big challenge in both clinical and experimental situations. MRI can be ideally used for the morphological evaluation of primary cancers owing to the high sensitivity, resolution and, consequently, the excellent soft tissue contrasts.

For morphological imaging, tumor lesions tend to appear hyperintense on T2 weighted imaging (T2WI), but iso- to slight hypointense on T1 weighted imaging (T1WI), which can become hyperintense by contrast-enhanced T1WI after using conventional extracellular contrast agents (CAs) like gadoterate meglumine (Gd-DOTA). According to the earlier report about the application of MRI performed in a 1.0T Magnetom SP (Siemens, Erlangen, Germany) on primary liver cancer induced by DENA, tumor lesions can be detected with a minimum diameter of 2 mm, and in numbers varying from 1 to ≥10 (199). Recently, by using a clinical 3.0T whole body MR magnet (Trio; Siemens, Erlangen, Germany) for monitoring hepatic tumor growth we also managed to observe the original small tumor lesions continuously, which enabled us to differentiate between the static benign lesion and fast-growing malignant HCC (*Figure 2*). Moreover, during the real progress of cancer generation in rat models, MRI could reveal complex intratumoral changes along with tumor growth, for instance tumoral hemorrhage (*Figure 3*), which helped us to intensively follow up the dynamic changes of local lesions, evaluate the systemic condition of tumor-bearing animals, make proper decision on the following treatment, and secure the designed experiments being successfully performed in animals with other simultaneously occurring tumor lesions.

By using organ-specific CAs, MRI can provide various functional information of tumor lesions. For instance, the hepatobiliary CAs, such as mangafodipir trisodium (Mn-DPDP), gadoxetic acid disodium (Gd-EOB-DTPA) and gadobenate dimeglumine (Gd-BOPTA), can be specifically taken up by hepatocytes through corresponding transmembrane proteins and excreted into bile canaliculi through conjugated export pumps. Therefore, these organ-specific CAs may help distinguish tumor and tumor-bearing organ, relatively well differentiated and poorly differentiated lesions with or without normal biological functions (3,199).

Treatment and therapeutic monitoring

In addition to the *in vivo* monitoring of tumor growth before treatment, MRI, as a harmless imaging technique without ionizing radiation, is also strong at providing real-time follow-up imaging serially at different time points as frequently as every several minutes, hours or days, which enables comparing the therapeutic effects.

For evaluation of therapeutic effects, MRI also provides multi-parametric functional information (201). For instance, dynamic contrast enhanced (DCE)-MRI can help evaluate tumor vascular properties including blood flow, blood volume, vascular permeability and extravascular extracellular space, while apparent diffusion coefficient (ADC) derived from diffusion-weighted imaging (DWI) can help distinguish the lytic necrosis of less restricted diffusion caused by therapy from the non-reacted viable tumor (202-206).

Developing new diagnostics and therapeutics or theragnostics

Generally, effective anticancer therapy may cause tumor growth inhibition or even tumor necrosis. Necrosis avid contrast agents (NACAs) have been largely explored in the past decade, which is used to image physiological and biochemical processes under *in vivo* conditions. Hypericin is a nonporphyrin NACA, extracted from the plant Hypericum perforatum or semi-synthesized from emodin anthraquinone (207,208). In necrosis, aminophospholipids of phosphatidylethanolamine (PE) and phosphatidylserine (PS), primarily located in the intracellular membrane, are externalized from the inner leaflet to the outer leaflet of the cell membrane (209,210). Radiolabelled hypericin has been designed to target exposed PE and PS with the breakdown of cell membrane asymmetry. Using *in vivo* MRI and scintigraphy, the previous studies have investigated the promising therapeutic effect of the combined treatment strategy of CA4P (combretastatin A4 phosphate)/^{131}I-Hyp (hypericin) or briefly OncoCiDia (211,212). To further expand the utility of hypericin to radionuclide imaging, the radiotracers such as ^{123}I-Hyp and ^{64}Cu-Bis-DOTA-Hyp have recently been synthesized, which allow detection and quantification with microSPECT and microPET/CT (60,207,208) with possibility to be studied in chemically induced tumor models.

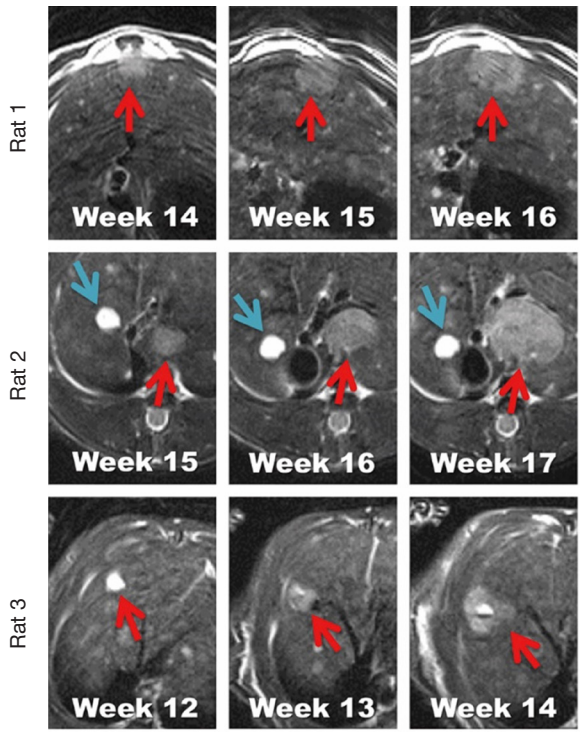

Figure 2 Magnetic resonance imaging (MRI) monitoring of dynamic tumor growth patterns of primary liver cancer model in Sprague Dawley rat (SD rats) generated by carcinogen N-nitrosodiethylamine (DENA) administration. To monitor the individual tumor growth of DENA-induced primary cancer in individual rats, noninvasive MRI was used weekly after DENA treatment. Tumor lesions appeared hyperintense on T2 weighted imaging (T2WI) (arrow). Weekly T2WIs demonstrated the gradually increased tumor sizes of 4 different lesions in 3 rats. In rat 1 (first line), tumor size rapidly increased in 3 consecutive weeks, with the diameters rising from 3 mm in week 14, to 6 mm in week 15 and to 10 mm in week 16. In rats 2 (second line), 2 lesions appeared in the same slice with the comparable sizes. Initially, lesion 1 (blue arrow) and lesion 2 (red arrow) were of similar sizes in week 15. However, the size of lesion 2 rapidly increased in the following 2 weeks, while the size of lesion 1 remained almost unchanged. By histopathology, lesion 1 proved to be a cystic benign liver tumor, but lesion 2 a hepatocellular carcinoma. At rat 3 (third line), there was a "lesion in lesion" phenomenon; different intratumoral components in the same lesion were found. At week 12, the lesion appeared a cystic feature; but from week 13 on, it evolved into a mixed lesion of solid tumor with a cystic core. T2WI (repetition time =4,320 ms; echo time =69 ms; flip angle 150°; field of view =75×56.25 mm^2; imaging acquisition matrix 512×384; in plane resolution =0.15×0.15 mm^2; slice thickness =2.0 mm; gap =0.4 mm) were obtained on a clinical 3.0T whole body MR magnet (Trio; Siemens, Erlangen, Germany) with a human wrist coil to focus on liver tumors.

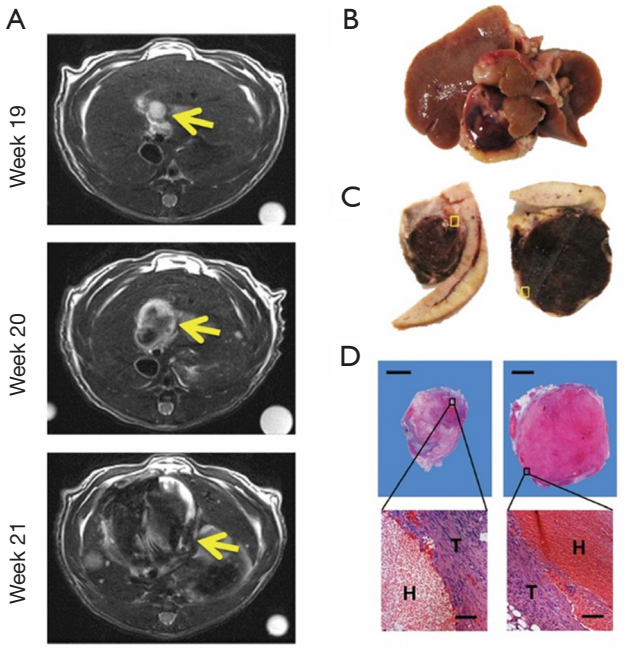

Figure 3 A case of tumor hemorrhage in a primary liver cancer model by magnetic resonance imaging (MRI) monitoring. T2 weighted imaging (T2WI) identified massive bleeding occurred rapidly in this primary liver tumor lesion from week 19 till week 21 after N-nitrosodiethylamine (DENA) administration (A). MR images were validated by macrophotography of entire liver (B). Macroscopic photograph of tumor tissue blocks (C, thickness =3 mm) and frame-focused photomicrograph of tumor tissue sections (D, H&E staining, thickness =10 μm; ×12.5 original magnification in the upper panels, scale bar =0.5 cm; ×100 original magnification in the lower panels, scale bar =50 μm.) showed massive intratumoral hemorrhage (H) surrounded by viable tumor tissue (T).

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