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The development of carcinoma chemotherapy prevention agents using animal models

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ABSTRACT

Animal models are commonly used to evaluate the effectiveness of potential chemo preventive agents, including synthetic chemicals, natural products, and combinations thereof. These models help identify which agents are safe and effective for use in clinical chemoprevention trials. Organ-specific animal models are used to determine which agents are most effective for preventing specific forms of cancer without causing toxicity. These models can be induced with cancer-causing agents or created using transgenic or mutant animals. Various animal tumour models are available for chemoprevention research and are used to test combinations of agents, evaluate routes of administration, and generate pharmacokinetics and toxicology data. There is a strong correlation between outcomes of animal and human chemoprevention trials, with positive results in animal testing generally leading to positive results in humans. However, further human data is needed to validate the efficacy of animal models in predicting the success of agents in human trials. Regardless, animal efficacy data remains essential for clinical trial decision-making.

Key words: mammary cancer, chemoprevention, bladder cancer

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INTRODUCTION

Animal models are commonly used to evaluate the efficacy of synthetic and natural chemical agents for cancer prevention. Organ-specific animal models are employed to determine which agents could be useful in preventing specific forms of cancer, including colon, lung, bladder, mammary, prostate, pancreas, and skin cancer. These animal models provide a framework for evaluating agents based on defined criteria, such as a tumour endpoint, which is the primary endpoint in most Phase III clinical prevention trials. Additionally, animal data can generate valuable dose-response, toxicity, and pharmacokinetic data required prior to Phase I clinical safety testing. To be ideal for chemoprevention testing, an animal model should have relevance to human cancers, similar genetic abnormalities, genomic changes, relevant intermediate lesions, consistent tumour burden, and high predictive value for human efficacy data. Although no current animal model is ideal, research and development of better animal models is ongoing in many laboratories [1].

LITERATURE REVIEW

Mammary cancer models

The methylnitrosourea (MNU)-induced mammary gland carcinogenesis model is commonly used to screen potential mammary cancer prevention agents in rats. The model is characterized by high incidence and multiplicity of adenocarcinomas within 120-150 days of carcinogen treatment [2]. The resulting tumours are similar to well-differentiated ER+ human breast adenocarcinomas, and they are susceptible to hormonal manipulations that modulate human ER+ cancers. Another model, the Di-Methyl Benz Anthracene (DMBA) model, is used less frequently, and it requires activation by the cytochrome P450 enzyme system [3,4]. In vivo screening has shifted focus to identify agents useful against hormonally nonresponsive breast cancer, such as basal-like and Her2-amplified tumours, which have significantly different cells of origin, etiologic origins, and gene expression patterns, and different responses to therapies. Both EGFR inhibitors and farnesyl transferase inhibitors have been effective in preventing mammary cancers in these models [5,6].

Lung cancer models

The Mouse Lung Adenoma Model in A/J mice is frequently used for lung adenoma carcinogens, with 100% incidence of tumours developing in treated animals [7,8]. Chemo preventive agents

can be given in the diet, by gavage, or aerosol administration. Squamous cell carcinoma of the lung has two models, the MNU hamster tracheal model, and the NTCU-induced mouse model. These models are important as squamous cell lung cancer is being evaluated in most phase 2 clinical chemoprevention trials [9,10]. Another lung cancer chemoprevention model uses the tobacco-specific carcinogen NNK to induce lung tumours in rats. The tumour incidence is determined by dividing the number of animals with cancers by the total number of animals at risk [11].

Colon/Intestinal cancer models

The NCI's Chemopreventive Agent Development Research Group (CADRG) has conducted numerous preclinical studies on colon carcinogenesis in rats induced with the carcinogen Az-Oxy-Methane (AOM) [12]. These studies have used adenomas and adenocarcinomas or early pervasive lesions as primary efficacy endpoints and have focused on colon carcinogenesis [13]. The ACF assay is used as an initial screen, and a wide variety of agents have proven effective in preventing AOM-induced cancers. COX-2 inhibitors and NSAIDs, including NO-NSAIDs, have been the most consistently effective agents in this model [14]. Low-dose aspirin was also highly active in preventing colon tumours, and high-dose aspirin was effective in humans. Although initial studies employed early initiation of treatment, initiating treatment after ACF formation still exhibits high efficacy in reducing the development of invasive cancers. The MSH2 mismatch repair-deficient mouse is presently being employed to evaluate a series of NO-releasing NSAIDs and their parental counterparts. The CADRG has developed three genetically engineered models of intestinal cancer that mimic germline mutations predisposing subjects to colorectal cancer for prevention screening. Positive results in Min/+ mice contributed to the scientific rationale for evaluating celecoxib in FAP patients [15-18].

Bladder cancer models

The OH-BBN-induced rat and mouse model is the primary method used to assess the prevention of bladder cancer [19, 20]. The resulting tumours have invasive characteristics and are histologically similar to human bladder transitional cell carcinoma. Gene expression changes similar to those in human bladder tumours have been found in this model, including alterations in the expression of FHIT, survivin, Ki67, annexin II, cyclins and cyclin kinases, and various S100 calcium binding proteins [21]. NSAIDs, EGFR inhibitors, and tea polyphenols have shown significant efficacy in this model. Agents initiated after pervasive or even microscopically invasive lesions already exist have high efficacy, indicating that they affect later stages of carcinogenesis [22]. Two newer p53-driven models, including the Ha-ras-activated p53+/− and the uroplakin II-SV40 large T transgenic mice, are currently being evaluated for the efficacy of p53-rescue compounds.

Prostate cancer models

The development of prostate cancer models has been challenging compared to breast, colon, skin, and lung cancer models [23]. The driving mutations in prostate cancer are not clearly defined, and most human prostate cancers do not progress to a lethal stage. The Boland model uses MNU/testosterone-treated rats to develop primarily microscopic cancers in the dorsolateral prostate [24]. While this model is useful for detecting chemopreventive agents, it has a long latency period, requires substantial amounts of test agents, and is expensive. Two mouse prostate models, the TRAMP model and C3(1)/T-antigen model, have been explored for identifying prostate chemopreventive agents, but they grow tumours rapidly, unlike most human prostate tumours [25,26]. Nevertheless, they have been useful in evaluating agents that show cancer preventive activity in human prostate, such as tea polyphenols and toremifene. PTEN tumour suppressor gene loss is observed early in human prostate cancer, and mouse models with PTEN alterations are being evaluated. A knockout of PTEN, combined with an androgen-responsive promoter translocation of the transcriptional activator ETS-related gene, ERG, may be a promising prostate model to pursue [27].

Skin cancer models

The DMBA-TPA mouse skin cancer model is a well-established method for testing compounds that prevent skin carcinogenesis [28, 29]. UV-induced mouse skin cancer model, using SkH-1 hairless mice, is also used to test chemopreventive agents. Both models are relevant to the etiology of human skin disease, and several compounds have been found effective in preventing skin tumours, including NSAIDs, DFMO, and green tea polyphenols. A clinical trial in humans has shown promising results [30,31]. In another skin cancer model, *PTCH* gene knockout mice have been shown to respond to various specialists, including retinoid receptor agonists and COX-2 inhibitors, which are currently in clinical trials [32].

Ovary cancer models

There is currently no established model for studying ovarian cancer prevention. One potential model involves surgically inserting a DMBA-soaked thread into a rat's ovary. This is done using Wistar-Furth rats at 7-8 weeks of age [33]. Approximately 200 ugs of DMBA can be absorbed per thread when sterile silk thread is submerged in melted DMBA. In this model, around half of the cancers are epithelial and the other half is granulose-theca cancers. Ovarian tumours occur in almost 80% of DMBA-exposed mice about 300 days after exposure to the carcinogen. Piroxicam is partially effective in this model, but bexarotene and celecoxib are not [34]. A recently reported BRCA1 model will also be investigated since BRCA1 mutation carriers are at high risk for ovarian cancer. The domestic hen is the only species, besides humans, that develop ovarian cancer on its own. This is a promising new expansion to ovarian disease models. Inhibitors of ovarian cancer, such as progestin's, have been successful in this model. Additionally, specific p53 rescue compounds' inhibitory effects are currently being investigated [35].

Esophagus cancer models

Repeated exposure to N-Nitroso-N-Methyl Benzylamine (NMBA) can lead to esophageal cancer in rats, specifically squamous cell cancer [36]. This model is also being used to identify early changes in the cancer process using computerized spectral analysis [38]. Another model that mimics acid reflux disease and leads to esophageal adenocarcinomas has been developed. COX-2 inhibitors, lipoxygenase inhibitors, and NSAIDs are effective in targeting esophagus models, and are currently being tested in this model [37]. NSAIDs have also been found to

significantly reduce the progression of premalignant esophageal tissue to adenocarcinoma in individuals at high risk of developing esophageal cancer. The NSAID sulfidic has also been found to be effective in a transgenic oesophageal cancer model [39,40].

Head and neck cancer models

Epithelial tumours of the head and neck are common in humans and are often linked to exposure to tobacco smoke. Researchers have used a model involving rats and 4-NQO induction of cancer in their tongue to study chemoprevention of head and neck cancer. [41] Rats are exposed to 4-NQO in their drinking water and given chemo preventive medication in their diet. Celecoxib and piroxicam have been shown to prevent these cancers, while zileuton has not. EGFR inhibitors have a strong inhibitory effect, and rosiglitazone and Suberoyl Anilide Hydroxamic Acid (SAHA) have moderate efficacy. Pioglitazone and Tarceva have made it to human trials. The rats' oral tissues are examined for histological evidence of hyperplasia, dysplasia, and cancer [42,43].

Pancreatic cancer model

Pancreatic cancer, like human colon cancer, is caused by a mutation in the KRAS gene. The N-nitrosobis (2-oxopropyl) amine (BOP) hamster model has been used for many years to test potential cancer-preventing agents in the pancreas. This model involves treating the pancreas with BOP and chemopreventive agents and examining it for histological lesions such as hyperplasia's, dysplasia's, and tumours. Recent studies have shown that NO-delivering anti-inflammatory medicine has demonstrated preventive activity in this model. A new transgenic mouse model has also been developed, where mice carrying the LSL-KRAS transgene develop ductal pancreatic cancer by five months of age. Atorvastatin and NO-releasing aspirin have shown significant chemopreventive properties in this model [44-46].

CONCLUSIONS

Potential chemopreventive agents have been extensively tested using animal models. Breast cancer, colon cancer, and skin cancer models are among the many animal models that have demonstrated a significant correlation with human efficacy. However, there have also been negative correlations between clinical studies and animal studies, highlighting the significance of animal models' ongoing development and improvement. Animal studies have also demonstrated that starting treatment long after cancer has started can still have a preventative effect and that using different combinations of agents or different routes of administration can keep efficacy while lowering toxicities. Additional human data on positive and negative outcomes with chemopreventive agents will be needed to validate animal models for predicting the efficacy of agents in human clinical trials.

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