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Review article

From mice to men: Murine models of colorectal cancer for use in translational research

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ABSTRACT

Colorectal cancer (CRC) is the third most common carcinoma worldwide and despite advances in treatment, survival for patients with metastatic disease remains poor. With nearly 50% of patients developing metastases, in vivo investigation is essential to improve outcomes for these patients and numerous murine models of CRC have been developed to allow the study of chemoprevention and chemotherapy, in addition to improving our understanding of the pathogenesis of CRC. Selecting the most appropriate murine model for a specific application will maximize the conversion of potential therapies from the laboratory to clinical practice and requires an understanding of the various models available. This review will provide an overview of the murine models currently used in CRC research, discussing the limitations and merits of each and their most relevant application. It is aimed at the developing researcher, acting as a guide to prompt further reading in planning a specific study.

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1. Introduction

Colorectal cancer (CRC) is the third most common carcinoma worldwide with approximately 1.2 million cases annually and over 600,000 deaths (Ferlay et al., 2010). Although survival across all stages of CRC continues to improve, with 56% of patients surviving five years, outcomes for those presenting with metastatic disease remain poor with five year survival reportedly as low as 6%. Approximately 20–25% of patients present with metastases and an additional 20–25% will develop them during the course of their disease (van der Pool et al., 2012; Mantke et al., 2012).

Surgical resection is the mainstay of curative treatment but chemotherapy and/or radiotherapy are of benefit in selected patients, either in the adjuvant or neoadjuvant setting, or to prolong survival in un-resectable disease. Advances in chemotherapy have reduced recurrence rates and prolonged survival, but further developments can only be achieved through greater understanding of the pathogenesis of CRC and the pharmacology of chemotherapeutic and biological treatments. In vivo investigation is essential to achieving these aims.

Only 5% of anticancer candidate therapies that enter clinical testing are approved by the Food and Drug Administration for clinical practice, suggesting that current murine models do not faithfully reflect the human disease (Sharpless and Depinho, 2006; Roper and Hung, 2012). Maximising the conversion of therapies from bench to bedside by selection and optimisation of the most appropriate murine model requires an understanding of the options available. This review will provide an overview of the carcinogen-induced, genetically engineered and tumour implantation murine models currently used in CRC research and the imaging modalities utilised for assessment of tumour growth. The relative merits and limitations of each will be discussed for studies of CRC pathogenesis, chemoprevention and chemotherapy.

2. Spontaneous and chemically induced CRC in rodents

The incidence of spontaneous CRC in rodents is less than 1% (Anisimov et al., 2001). Higher incidences (30–40%) have been reported in in-bred WF-Osaka rats but none of these developed metastases and many of the tumours showed signs of spontaneous regression (Miyamoto and Tani, 1989; Miyamoto et al., 1989). Although these rats may develop carcinoma at an early age, the unpredictability of this model makes it inadequate for routine experimental use. This has resulted in the use of CRC-inducing carcinogens in rodents, the effectiveness of which varies between species and dose used as well as the duration of exposure.

2.1. Dimethylhydrazine (DMH) and azoxymethane (AOM)

1,2-Dimethylhydrazine (DMH) and the metabolite azoxymethane (AOM) are methylazoxymethanol (MAM) precursors and the two most commonly used CRC inducing carcinogens. MAM, the carcinogen in cycad flour, yields a methyl diazonium ion that can alkylate macromolecules such as guanine in the liver and colon leading to tumour development (Laqueur, 1964; Fiala, 1977). The majority of these tumours contain mutations in the β-catenin gene (*Ctnnb1*) which stabilise β-catenin and increases WNT signalling, driving tumourigenesis (Yamada et al., 2000). AOM is used more frequently due to increased potency and greater stability, inducing colonic malignancy in rodents when administered repeatedly over 6–8 weeks via subcutaneous (sc) or intra-peritoneal (ip) injection; assessment of disease burden is undertaken from approximately 30 weeks (Neufert et al., 2007).

AOM administered with oral dextran sodium sulfate (DSS) can provide a useful model of colitis induced CRC; 100% of Crj:CD-1 mice given a single ip injection of AOM followed by a week of oral DSS developed CRC within 20 weeks (Rosenberg et al., 2009). This AOM combined with DSS model has proved useful in studying dietary chemoprevention of CRC by targeting factors that drive inflammation (Long et al., 2015).

2.2. Heterocyclic amines (HCAs)

The heterocyclic amines 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and 2-amino-33-methylimidazo[4,5-f]quinoline (IQ) are genotoxic compounds in cooked meat and fish. HCAs are activated by cytochrome P450s in the liver with conversion of an amino group to a hydroxyamino group. These are further activated by forming esters which induce carcinogenic DNA adducts (Kato, 1986; Nakagama et al., 2005). PhIP is the most abundant HCA in cooked meat and although it only induces aberrant crypt foci in mice it can cause colonic carcinomas in rats with prolonged administration; 50% of F344 rats fed continuously with high doses of PhIP for 52 weeks developed CRC (Ito et al., 1991). In a recent study only 35% of the same animals developed carcinomas after 20 weeks of PhIP ingestion (Canene-Adams et al., 2013).

Interestingly many of the genetic mutations associated with colon cancer in humans are not noted in PhiP induced tumours, notably K-Ras and P53, an important consideration when undertaking studies on gene targeting therapies or interactions (Toyota et al., 1996).

2.3. N-*Methyl*-N-*nitro*-N-*nitrosoguanidine (MNNG) and* N-*methyl*-N-*nitrosourea (MNU)*

N-Methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG) and *N*-methyl-*N*-nitrosourea (MNU) are DNA alkylating agents that can induce malignancy in any organ through direct action. By transferring a methyl group to nucleobases these direct carcinogens lead to the accumulation of genetic mutations that can result in the development of carcinomas. Originally reported to cause gastric carcinoma following oral administration (Sugimura and Fujimura, 1967) it was later found that intra-rectal instillation caused carcinoma in the distal colon and rectum of rodents (Narisawa et al., 1971; So et al., 1973) with 43% of F344 rats developing rectal cancers after 20 weeks of weekly administration (Narisawa et al., 1971). Increasing the dosing frequency to three time a week in the same rat strain increased tumour incidence to 78% (Nakayama et al., 2009).

2.4. Advantages, limitations and applications

Many of the cellular and biochemical defects found in human carcinomas are present in chemically induced rodent models making them advantageous in the study of gene—environment interactions and chemoprevention (Perse and Cerar, 2011). For example, the administration of the cyclooxygenase (COX)-2 inhibitor NS-398 to AOM treated rats significantly reduced the formation of preneoplastic lesions (Kishimoto et al., 2002). More recently diet induced obesity was found to promote CRC development in an AOM induced murine model (Tuominen et al., 2013).

The use of chemically induced CRC for therapeutic testing is limited. Assessment of disease burden is often only possible at necropsy with advanced imaging techniques required for longitudinal disease monitoring. Long latency periods of up to 52 weeks mean prolonged follow up periods are required and the formation of metastases is rare making this model unsuitable for studies on advanced disease (Kobaek-Larsen et al., 2000; Derry et al., 2014). Significant variation in tumour development has been noted between murine strains and standardised dosing regimens are required to allow comparisons between studies (Rosenberg et al.,

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