Journal of Coloproctology

www.jcol.org.br

Review Article

A review of experimental models in colorectal carcinogenesis☆

Vanessa Foresto Machado, Marley Ribeiro Feitosa, Jose Joaquim Ribeiro da Rocha, Omar Féres*

Division of Coloproctology, Department of Surgery and Anatomy, Faculdade de Medicina de Ribeirão Preto (FMRP), Universidade de São Paulo (USP), Ribeirão Preto, SP, Brazil

ARTICLE INFO

Article history:
Received 28 April 2015
Accepted 4 September 2015
Available online 20 December 2015

Keywords:
Animal models
Colorectal neoplasms
Diagnosis

ABSTRACT

Colorectal cancer is the leading cause of malignancy of the gastrointestinal tract. A better understanding of the molecular and cellular changes that lead to the disease is necessary to develop early diagnosis and optimal treatment modalities. Rodent models are rapid, reproducible and exhibit an adenoma-carcinoma sequence similar to that found in humans. The objective of this manuscript is to review the most common chemical carcinogens used to induce experimental tumors and the usual methods of evaluation.

Modelos experimentais de carcinogênese colorretal

Palavras-chave:
Modelos animais
Neoplasias colorretais
Diagnóstico

RESUMO

O câncer colorretal é a principal neoplasia maligna do trato gastrointestinal. Um melhor entendimento dos processos moleculares e celulares é necessário para o desenvolvimento de estratégias que permitam um diagnóstico precoce e um tratamento mais eficaz. Modelos que utilizam roedores são rápidos, reprodutíveis e permitem o estudo da sequencia adenoma-carcinoma de forma similar a encontrada em humanos. O objetivo desse manuscrito é revisar os principais modelos de carcinogênese química e os métodos mais usuais para avaliação dos resultados.

☆ Study performed at the Department of Surgery and Anatomy, Faculdade de Medicina de Ribeirão Preto (FMRP), Universidade de São Paulo (USP), Ribeirão Preto, SP, Brazil.

* *Corresponding author.*
E-mail: marleyfeitosa@yahoo.com.br (M.R. Feitosa).

http://dx.doi.org/10.1016/j.jcol.2015.09.001

Introduction

Colorectal cancer (CRC) is the most common gastrointestinal malignancy. Worldwide, CRC is the third most common cancer in men and the second in women. In Brazil, a total of 32,000 new cases of CRC are expected in 2015.[1,2]

Colorectal malignant neoplasms are characterized by an excessive and uncontrolled growth of abnormal cells originating from any part of the colon. Unlike benign lesions, cancer is morphologically different from the normal tissue of origin, have the ability to invade and destroy surrounding tissues, metastasis to distant organs and, if left untreated, will lead to death.

The factors involved in the origin and progression of colon tumors have been an area of increasing interest. Since the first experiment of colon tumors induction, more accurate models and various substances with carcinogenic activity have been studied. Carcinogen-induced colon cancer, have proved to share many similarities with human tumors and significantly contributed to our actual understanding regarding cancer pathogenesis.[3]

The ideal experimental carcinogen should induce neoplasms in the colon, however, most agents lack specificity (e.g. 1,2-dimethylhydrazine, that may induce liver tumors). Reproducibility is another important feature that may be hampered by the heterogeneous species and lineages of animals, each with different patterns of drug response. Moreover, there is no standardization of dose and time of tumor development, to the various studied drugs.

Rodents are widely accepted models of colorectal carcinogenesis because of their similarity with humans. Advantages include rapid, reproducible tumor induction and the possibility to study the adenoma-carcinoma sequence.[4]

Natural colorectal carcinogenesis factors may be divided into two main categories: those related to genetic or environmental factors.

Genetic factors

The importance of oncogenes and suppressive genes are widely recognized. Early genetic changes include chromosome 5 (*APC*) and *ras* mutations while allelic losses in chromosomes 17 (*p53*) and 18 (*DCC*) happen late in the adenoma-carcinoma sequence.[5] A schematic genetic model of the adenoma-carcinoma sequence is shown in Fig. 1.

Environmental factors

Diet plays an important role on carcinogenesis and, in some countries with higher CRC prevalence, an attributed risk of 50% is estimated.[6] Geographic variations in CRC incidences and studies with immigrant populations suggest that lifestyle factors including poor diet, physical inactivity and alcohol consumption are associated to an increased risk of CRC. While increased read meat consumption may be harmful, omega-3, vitamin D, phenolic compounds and a fiber-rich diet may lower the risk of CRC. Regular physical activity may lower the risk in 24%; on the other hand, obesity may increase it in 19%. Although moderate to high doses of alcohol have proven to be deleterious, some studies have observed a protective effect when light doses are consumed.[7,8]

Methods of chemical carcinogenesis

There are two types of chemical agents: (1) direct agents, that do not need metabolization by the organism to have the deleterious effect and (2) indirect agents, which are not active unless enzymatic reactions convert them to an active form.[9]

1,2-Dimetilhidrazine (DMH)

DMH is the metabolic precursor of methylazoxymethanol (MAM). It is the oldest and the most used carcinogen to induce tumors in rats. Uptake of DMH is three times greater in the colon cells compared to the enterocytes. The carcinogenic effect may be obtained after a single injection or via a series of weekly injections.[10,11] The malignant lesion originates from the non-dysplastic mucosa and becomes evident after 4–30 weeks after administration of the drug. Even after the administration of small doses of the drug, up to 80% of the treated mice can develop adenocarcinoma.[12]

Azoxymethane (AOM)

AOM is a metabolite of DMH. Its carcinogenesis mechanism is attributed to c-fos overexpression, reduced expression of c-myc and k-ras mutation. These changes are similar to those observed in spontaneous carcinogenesis in humans.[13] Compared to DMH, AOM is more potent and requires fewer reactions to its activation, which makes a better option. It is activated in the liver by N-oxidation, and produces essential reactive compounds for chemical carcinogenesis (methylazoxymethanol and methyl-diazoxide), which are brought to the colon through the bloodstream or bile as conjugated glucuronide.

Heterocyclic amines (HAs)

Among the HAs, 2-amino-3-methylimidazo [4,5-f] quinolone (IQ) and 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine (PhIP) have gained attention after proved to be highly mutagenic and tumorigenic in rodents. They appear to have target-organ specificity and can induce malignancies of the colon, prostate and mammary glands. Creatinine, sugars and amino acids from red meat and fish are the precursors of IQ. The final active compound is formed hepatic metabolization. Incidence of induced colon cancer may reach 28% after administering a diet rich in IQ and PhIP, for 52 weeks. They became not only an interesting model of carcinogenesis but can also help investigation of chemoprotection effect against cancer, of some substances.[14]

Aromatic amines

In 1941, *Lorenz et al.* observed the induction of intestinal tumors in mice fed with 1,2,5,6-dibenzanthracene and 20-methyleholanthrene. This effect was also studied by *Walpole*