Experimental colon cancer

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SUMMARY

All the experimental models for the induction of colon cancer have several potential advantages, such the ability to precisely control the animals diets and other environmental factors, the opportunity to systematically investigate biochemical and molecular parameters of interest during the premalignant phase and so on. It is clear that they are only models and that the data generated may or may not be directly applicable to the colonic malignant transformation processes in humans.

Key words: Chemical compounds, Carcinogens, Tumour cell lines, Colon, Animal model

INTRODUCTION

In recent years great strides have been taken toward the development of an animal model for studying colonic cancer. Intestinal tumours, both adenomas and carcinomas, can be induced in some animals by a variety of methods[1].

Among the most effective are 1,2–dimethylhydrazine and azoxymethane. Several studies have shown that rats, which rarely develop cancer spontaneously, are good animals to use for the induction of intestinal tumours by these chemicals. Furthermore, many protocols of orthotopic implantation refer to the technique of implanting tumour cells into the organ from which those cells derived. For example, colon cancer cells may be implanted in the wall of the colon. Several lines of evidence have shown that interactions between the tumour cells and the host microenvironment are critical for tumour development and metastasis[2].

CELL LINES

Table 1 shows methods commonly used for colon carcinoma development, as well as for the metastasis of cells into other organs. Several lines of evidence have shown that interactions between the tumour cell lines and the host microenvironment are critical for tumour development and metastasis. Implantation of human colon carcinoma cells into the cecal wall produced both regional and liver metastases, but subcutaneous implantation of these cells produced no metastases[3].

Other experiments have shown that the site at which tumour cells are implanted also affects their resistance to chemotherapeutic agents[4]. A follow-up study assessed the sensitivity of CT 26 colon carcinoma cell line injected intravenously, subcutaneously, into the cecal wall and into the spleen to systemic administration of 5–fluorouracil and doxorubicin[5]. The tumours in the cecar and spleen were the most sensitive to doxorubicin, and metastatic tumours in the liver were highly resistant to both drugs.

Further justification of the use of orthotopic models in the study of colon cancer and metastasis comes from the observations that the site of injection alters gene expression by tumours cells. Each organ expresses distinct cytokines and growth factors that mediate homeostasis for that organ. These and other results underscore the importance of host microenvironment in the expression of tumour cell genes[6].

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Table 1. Commonly Used Models for Tumor Growth and Metatstasis

Cell Line	Tumor type	Site of implantation	Result	Reference
1. KM 12 L 4	Human colon carcinoma cells	cecal wall of nude mice	after 7 weeks lung metastasis	Oda H et al[9]
2. H T 29 and 25	Human colon carcinoma cells	orthotopic	liver metastasis	Fazekas K et al[10]
3. Wi Dr				
4. DLD – 1	Human colon cancer	orthotopic	colon cancer	Xu W et al[11]
5. CT26-KSA	Colon carcinoma	BALB/MICE	lung metastasis	Ruehlmann J et al[12]
6. KM12SM KM12L4A	Human colon cancer	orthotopic	liver/lung metastasis	De Lange R et al[13]
7. HCT-116	Colon carcinoma	xenograft model	metastases – variety of organs	Ozawa Y et al [14]
8. C-26	Murine colon carcinoma	orthotopic	hepatic metastases	Chiodoni C et al[15]
9. MC38-CEA--KS- Ag	Murine colon carcinoma	orthotopic	colon cancer	Xiang R et al[16]
10. LS 180	Human colon cancer	xenograft model	colon cancer	Kinuya S et al[17]
11. WB 2054M5	Tumor cells	cecal wall	95 % cecal wall tumor	Tomita H et al[18]
12. Colon 38	Colon cancer	subcutaneously	10 days → induction of tumors	Winczyk K et al[19]
13. Colon 26-L5	Murine colon cancer	orthotopic	lung metastasis	Ogasawara M et al[20]
14. CC531	Colon carcinoma	peritoneal cavity	12 tumor growth	Gahlen J et al[21]

CHEMICAL METHODS AND MOLECULAR BIOLOGY

Tables 2A and 2B show the chemical methods for the induction of colon cancer (1,2–dimethylhydrazine and azoxymethane respectively). All the methods have advantages according to the purpose of the study. For example for the study of mechanism of chemoprotective role of ursodeoxycholic acid, the model of azoxymethane is more effective that others[7].

Finally, all the models described above for the study of colon cancer have involved either implanting tumour cells or administarion of chemical compounds. More recent models have incorporated molecular biology techniques to allow investigators to target more specifically the biologic function of specific genes. One such model, the transgenic model, involves the insertion of new or

Table 2A. Chemical Compounds for the Induction of Colon Cancer. (examples of experimental protocols)

A. 1,2 - dimethylhydrazine - DMH

1. Sprague – Dawley rats - DMH for 27 weeks - 85% of the animals → adenomas/adenocarcinomas[22].
2. Rats on DMH and diatery copper - + 25 mg/Kg DMH ip after 30 days on diet - high risk of colon cancer[23].
3. Rats on DMH - 20 mg/Kg weekly for 6 weeks - colon and spleen tumor[24].
4. Rats on DMH - 20 mg/Kg ip weekly for 5 weeks - colon carcinogenesis[25].
5. Rats on DMH - colorectal cancer[26].
6. Rats on DMH, 5 and 20 mg/Kg + or – vagotomy prior DMH - Truncal vagotomy does not increase the incidence of colorectal cancer[27].
7. Rats on DMH - 15 mg/Kg weekly for 9 months - 91% colon cancer[28].

Table 2B. Chemical Compounds for the Induction of Colon Cancer. (examples of experimental protocols)

B. Azoxymethane - AZO

1. One dose of AZO - 15 mg/Kg sc - 83% of animals after 32 weeks with neoplastic histology[29].
2. One dose of AZO - 15 mg/Kg sc - after 5 weeks - aberrant crypt foci and preneoplastic lesions in the rat colorectum[30].
3. Three doses of 15 mg/Kg AZO sc - after 32 weeks > 83% of the animals colon tumors[31].
4. Two doses of 15 mg/Kg AZO sc + cholic acid - after 28 weeks > 73% animals colon cancer[7].
5. Two doses of 15 mg/Kg AZO + ursodeoxycholic acid - after 28 weeks decrease colon cancer[7].

modified genes into the host genome through the microinjection of germ-line cells[8].

In the future, a better understanding of the biology of carcinogenesis and biology of the cancer will lead to new therapeutic approaches and study systems.

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