Genetics of Colorectal Cancer: Role of p53

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Abstract

The tumor suppressor TP53 gene is one of the most frequently mutated in different types of human cancer. Particularly in colorectal cancer (CRC), it is believed that TP53 mutations play a role in the adenoma-carcinoma transition of tumors during pathological process. The TP53 mutation is the key step driving the transition from adenoma to adenocarcina. The functional roles of TP53 mutation in tumor development have been comprehensively investigated. In this mini review, we comprehensively summarize the p53 mutants in CRC progression and discuss the current strategies for p53 mutants in malignancies.

Keywords: p53 mutants, colorectal cancer, Tp53 mutation

Introduction

Colorectal cancer is a major cause of cancer death and, in most cases, develops from a pre-existing adenoma and then adenoma-carcinoma sequence. This sequence is characterized by an accumulation of molecular genetic alterations causing disorders in cell growth, differentiation and apoptosis. It is generally believed that the balance between the rates of cell growth and apoptosis maintains intestinal epithelial cell homeostasis and that during cancer development this balance gets progressively disturbed. Amongst others, an important function of apoptosis lies in the elimination of damaged cells. There is increasing evidence to support the hypothesis that failure of apoptosis may be an important factor in the evolution of colorectal cancer and its poor response to chemotherapy and radiation. It has been firmly established that colorectal carcinogenesis is characterized by a stepwise accumulation of genetic alterations. Most studies have focused on the possible roles of the tumour suppressor genes adenomatous polyposis coli (APC) and p53 and the oncogene K-RAS, which will be briefly discussed below.

1.1 Role of APC in CRC:

The APC gene product is a 312 kD protein consisting of 2843 amino acids. Mutations in the APC gene have been implicated in both sporadic and familial colorectal Neoplasia.

The frequency of APC mutations is similar in colonic adenomas and carcinomas (approximately 60%), suggesting that APC mutations may be an early or even the initiating event in the process of colorectal carcinogenesis. The functional significance of the APC gene probably lies not only in the regulation of apoptosis, but also in control of cell cycle progression, migration and differentiation. APC is a key player in the regulation of the Wnt signaling pathway. It has been shown that in normal cells, the APC protein resides in a large complex with axin, glycogen synthase kinase 3β (GSK3β) and β-catenin. Loss of tumour suppressor APC gene and APC protein function leads to β-catenin accumulation in the nucleus which leads to cell proliferation and cancer.

1.2 Role of p53 in CRC:

p53, also known as TP53 or tumour protein is a gene that codes for a p53 protein which regulates the cell cycle and hence functions as tumour suppressor. The human p53 plasmid is located on the seventeenth chromosome (17p13.1). It plays an important role in cell cycle control and apoptosis. Defective p53 could allow abnormal cells to proliferate, resulting in cancer. DNA damage and other stress signals may trigger the increase of p53 proteins, which have three major functions: growth arrest, DNA repair and apoptosis. It is very important for cells in multicellular organisms to suppress cancer. p53 has been described as "the guardian of the genome", referring to its role in conserving stability by preventing genome mutation. Its product, the p53 protein, may respond to DNA damage by
triggering either growth arrest during G1 or G2 phase of the cell cycle or programmed cell death. In this manner, p53 may protect the normal cell from proceeding to replicate damaged DNA Figure 1. The wild-type p53 protein, but not the mutant, can initiate apoptosis.\textsuperscript{1,11,27,28} Mutations of the p53 gene occur in various human tumours, including colorectal cancer. Deletions and mutations of the p53 gene can be detected in up to 85\% of colorectal tumours and usually occur during the transition from adenoma to adenocarcinoma. Vogelstein et al. reported that a loss of a large portion of chromosome 17p was seen in 75\% of colorectal carcinomas. The loss of the p53 gene is probably the key event in the conversion of a severely dysplastic adenoma into a carcinoma.\textsuperscript{29,30} Thus, mutations of the p53 gene occur late in the adenoma-carcinoma sequence and are more common in carcinomas that have invaded past the mucosa. It has also been found that p53 has profound effects on responses to chemotherapeutic drugs used in colorectal cancer, and that these effects vary considerably depending on the drug. It has been postulated that tumours with mutations of the p53 gene may be more resistant to chemotherapeutic agents and have a higher mutation rate which allows for earlier metastasis as compared to tumours with intact p53 gene.\textsuperscript{31,32}

1.3 Other genes important in CRC:

1) KRAS in CRC: Activation of KRAS occurs when it binds GTP at the expense of GDP, mutation of KRAS commonly maintains the protein in its GTP bound state and therefore renders it constitutively active. Up to 50\% of sporadic colorectal tumours are found to contain mutations of the KRAS oncogene.\textsuperscript{33,34}

2) PI3-Kinase pathway in CRC: Like the MAPK pathway the PI3-Kinase pathway is downstream of RAS and activation of the pathway can promote a wide range of cellular functions, including cell growth, survival and motility.\textsuperscript{35,36}

**Conclusion**

There is no doubt that reactivation and restoration of p53 function have great potential as a novel therapeutic strategy in CRC. However, the majority of molecules that lead to cell cycle arrest and apoptosis in CRC cells, has only been tested in cell lines and animal models, and has yet to enter in clinical trials. In addition, it is clear that mutant p53 promotes various oncogenic events. Nevertheless, the critical mechanisms are still not completely understood. Riding on the last 30 years of intensive research in p53 area, this is now the time to harvest the fruits from this body of work and translate our knowledge of p53 into clinical practice for CRC patients.

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