The Role of PKHD1 Mutation in Colorectal Cancer

Ao Li

Department of Pharmacology, Yale University School of Medicine, New Haven, CT 06520, USA

*Corresponding author: Ao Li, Department of Pharmacology, Yale University School of Medicine, New Haven, CT 06520, USA; Tel: 203-432-4771; E-mail: ao.li@yale.edu

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Abstract

Colorectal cancer (CRC) is one of the most common human malignancies. Although the method of screening for colorectal cancer has been significantly improved, only 30%-40% of patients are diagnosed at the early time. Colorectal cancer is a result of both environmental and genetic factors and about 35% of colorectal cancers are associated with hereditary susceptibility. The colon cancer related genes are APC, KRAS, TP53 and ABCA1. However, most of the genes in tumors that affect cellular functions including transcription, adhesion and invasion remain unknown. Identification and characterization of new colorectal cancer-related genes will benefit us to understand the mechanism of colorectal cancer and colorectal cancer clinical diagnosis and treatment. High-throughput exome sequencing result have demonstrated that there is relationship between colorectal cancer and gene mutation. In this study, PKHD1 had a CaMP value of 3.5, which was the 7th most common gene in cell adhesion and motility. However, some researchers pointed that the relationship between PKHD1 gene and colorectal cancer may not be statistically significant under the more stringent criteria. Some groups even indicated that the mutation of PKHD1 may play a protective role in the occurrence and development of colorectal cancer. Hence, the role of PKHD1 mutation development and progression of colorectal cancer remains unclear.

Keywords: Colorectal cancer; Intestinal tumors; ARPKD; PKHD1

Introduction

Colorectal cancer (CRC), including colon and rectal cancers, is one of the most common human malignancies [1]. In the past 30 years, there is an increasing morbidity and mortality of colorectal cancer worldwide. The number of patients with colorectal cancer in the world is about 2.8 million, with more than 1 million new cases each year. The incidence ranks the third in malignant tumors with the fourth highest mortality. With the aging of the population and the evolution of lifestyle, the incidence of colorectal cancer in the world increases by 2% each year. Because colorectal cancer seriously threatens people’s healthy life, it is particularly important to study the pathogenesis of colorectal cancer and reduce the mortality of colorectal cancer.

Colorectal cancer is caused by the interaction between environmental and genetic factors. Genetic factors play a role in the pathogenesis of colorectal cancer. About 35% of colorectal carcinomas are associated with hereditary susceptibility [1]. The overall frequency of APC mutations in colorectal cancer is about 60% [2]. The loss of APC gene and the loss of APC function due to point mutations are important causes of 80% of sporadic colorectal cancers and 100% of familial adenomatous polyposis (FAP) [3]. With the completion of the human genome project, the usage of systems biology tools makes it possible to precisely analyze tumor cells genome and to seek for new tumor-associated genes. [4]. have systematically investigated the relationship between gene mutations and breast and colorectal cancer through high-throughput exome sequencing of 120839 exons of normal somatic cells and colon cancers samples [4]. The CaMP (cancer mutation prevalence) method was used to statistically assess the frequency of mutations in a given gene.

Experimental

The CaMP value reflects the ratio of the frequency of mutations observed in one gene to the frequency of background mutations. The confirmed CaMP values greater than 1.0 are candidate cancer genes (CAN genes). 90% of the genes with CaMP>1.0 were predicted to have a mutation frequency higher than the background mutation frequency. Sjöblom et al. [4] confirmed 189 CAN genes that CaMP values>1.0 through rigorous investigation. These genes involved in cell adhesion, signal transduction and transcriptional regulation. The CaMP value of the known CAN gene of colorectal cancer is: APC (>10), KRAS (>10), TP53 (>10), FBXW7 (5.1), SMAD4 (4.6) and MLL3 (3.7). Among these, the CaMP value of PKHD1 reached 3.5 ranking at the 7th position and topping the genes of cell adhesion and motility.
ARPKD and PKHD1

Autosomal recessive polycystic kidney disease (ARPKD) is one of the most common hereditary renal cystic diseases in infants and children, with an estimated incidence of ~1 in 20,000 live births and a prevalence of heterozygous carriers of ~1 in 70 [5,6]. The disease is caused by mutations in PKHD1, which encodes a 16 kb transcript, contains at least 86 exons and spans 470 kb on chromosome 6p12 [7]. The longest ORF is predicted to be 66 exons and yields a 4074-amino acid of renal epithelia to regulate cell behaviors [30]. Recently, a colorectal cancer carcinogenesis, PKHD1 and its protein FPC and spans 470 kb on chromosome 6p12 [7]. The longest ORF is predicted to be 66 exons and yields a 4074-amino acid [TMEM] homology domains [24], are located in the COOH-terminal half of the protein [25,26]. At the proximal region, the FPC extracellular domain bears a proprotein convertase site and a minimum of 7 or 8 IPT/TIG and 5 TIG-like repeats[23], which assemble into two transmembrane protein (TMEM) homology domains [24], are located in the COOH-terminal half of the protein [25,26]. At the proximal region, the FPC extracellular domain bears a proprotein convertase site which may be cleaved to release the extracellular domain into the tubular lumen through the apical domain/primary cilium of renal epithelial cells [27,28]. Only one putative transmembrane domain is predicted in the COOH-terminal portion. The last 192 amino acids of FPC are predicted to reside in the intracellular cytoplasm which can be proteolytically cleaved [29,10] and transported into the nuclei of renal epithelia to regulate cell behaviors [30]. Recently, a ciliary targeting sequence (CTS) was also identified in the intracellular portion of FPC. It is believed to associate with a regulatory protein Rab8 and mediate FPC trafficking through the ER onto the primary cilium of epithelial cells [31].

Results and Discussion

PKHD1 and colorectal cancer carcinogenesis

At present, a great number of studies focus on PKHD1 gene and its encoded protein FPC. If PKHD1 is associated with colorectal cancer carcinogenesis, PKHD1 and its protein FPC will become new targets for the diagnosis and treatment of colorectal cancer. However, some studies have showed that it is still controversial that PKHD1 is considered as colorectal cancer CAN gene (CaMP value is 3.5). There may not be statistical significance between PKHD1 gene and colorectal cancer under the more restrict standard [32,33,34,35].

Another group compared the frequency of T36M mutations in colorectal cancer patients with normal population and assessed whether mutations in the PKHD1 gene increase the risk of colorectal cancer. This group first screened 1842 patients with a history of sporadic colorectal cancer (European Americans) and found no mutations in the T36M locus in colorectal cancer (0.0% probability). In the control group, there were 1601 people without a history of colorectal cancer (with the matched age, sex and nationality as the cancer group), of which 6 were heterozygous for T36M. The probability of occurrence was (0.37%) and the difference was significant [36].

The second time samples of this group came from patients with colorectal cancer in Europe and these samples did not overlap with the original samples. Only 1 of the 1925 colorectal cancer patients in the cancer group was T36M heterozygote (0.05%), while 9 of the 2002 control group had T36M heterozygote (0.45%) The difference was significant. According to their results, they believed that the T36M mutation does not increase the risk of colon cancer. On the contrary, the T36M mutation has a protective effect on human colorectal cancer.

In order to reveal the relationship between PKHD1 gene and the colorectal cancer carcinogenesis, our group studied the role of PKHD1 mutation in the intestinal tumor of ApcMin/+ mice using our established PKHD1-/-mice [37]. We crossmated PKHD1-/-and ApcMin/+ mice in the same genetic background and compared differences in the number, size of intestinal tumors and the degree of malignancy of intestinal tumors between ApcMin/+ and PKHD1-/-; ApcMin/+ mice at the age of 1-, 3- and 6-month-old. The resulting ApcMin/+ mice with and without PKHD1-/-alleles were randomly sorted into two experimental groups (i.e. PKHD1-/-; ApcMin/+ n=36; ApcMin/+ n=23). Our result showed that the number and size of the intestinal tumors in 3 and 6-month-old PKHD1-/-; ApcMin/+ mice are significantly increased than that of ApcMin/+ mice alone (P=0.017, P=0.022). In addition, at 3-month-old, PKHD1-/-; ApcMin/+ mice exhibited severer atypical hyperplasia in the intestinal tumor than ApcMin/+ mice do; while at 6-month-old, focal necrosis can be often seen in intestinal tumors of PKHD1-/-; ApcMin/+ mice, but not of ApcMin/+ mice. Strikingly, tumor infiltration into the muscular mucosa was also seen in a 6-month-old PKHD1-/-; ApcMin/+ mice. Survival rate was also investigated between the two group mice. There was no statistically survival difference between ApcMin/+ and PKHD1-/-; ApcMin/+ mice. Our data suggested that loss of PKHD1 promotes the intestinal tumorigenesis and induces tumor malignant transformation in ApcMin/+ mice [38].

Therefore, this study demonstrated that PKHD1 deficiency promote the intestinal tumorigenesis in mice. This result can
enhance the understanding of whether PKHD1 mutations are involved in the colorectal carcinogenesis.

**Conclusion**

Colorectal cancer is caused by the interaction between environmental and genetic factors. Progression of colorectal cancer includes the accumulation of genetic mutations and epigenetic changes. Further exploring the relationship between PKHD1 mutation and colorectal cancer will help to understand the mechanism of colorectal cancer, to provide more possibilities for the study of tumor biology and to improve the clinical diagnosis and treatment of colorectal cancer.

**Reference**


