

Advances in the study of the relationship between HPV infection and colorectal cancer

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Abstract. Colorectal cancer, as a malignant tumour that seriously endangers human health, has shown an increasing trend in incidence and mortality worldwide. It poses a threat to the health of the population and a heavy economic burden to both society and individuals, and is an important public health problem worldwide, especially in developing countries. Risk factors for colorectal cancer include many. A growing number of studies have shown that human papilloma virus (HPV) infection is closely associated with the development of colorectal cancer, especially high-risk HPV16 and HPV18, but much controversy still exists. Therefore, this article will briefly review the recent studies on the relationship between HPV infection and the development of colorectal cancer.

Keywords: HPV, CRC, Gene.

1. Introduction

According to the Global Cancer Database 2020 (GLOBOCAN2020), colorectal cancer is one of the most common gastrointestinal tumours in the world, with the third highest incidence and second highest mortality rate of malignant tumours respectively, and is now the third most common cancer in the world[1], and the second most common cancer in China after lung cancer. The etiology and pathogenesis of colorectal cancer have not been fully elucidated to date. In recent years, evidence from domestic and international studies has shown that the occurrence of human colorectal cancer is associated with HPV infection[2-5]. The relationship between the development of colorectal cancer and HPV infection has also received increasing attention from scholars at home and abroad.

2. HPV biological characteristics and structure

HPV was first discovered in humans in 1933[6]. HPV belongs to the papilloma virus A genus of the papilloma virus family. It contains about 8,000 base pairs and presents an envelope-free and 20-sided symmetric nucleocapsid structure. HPV has a distinct host-specific affinity and species specificity, and humans are its only hosts. HPV mainly infects human epidermal and mucosal squamous epithelium[7]. Based on its association with human tumours, HPV can be classified into high-risk types (HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, etc.) and low-risk types (HPV6, HPV11, HPV42, HPV43). Among them, infection with high-risk HPV types is closely associated with the development of cervical, bladder and colorectal cancers[8].

In the early open reading frame, the E4 protein is involved in cytoskeletal disruption and facilitates the expulsion of viral particles from the cell, while the E5, E6 and E7 proteins have transforming activity. The E5 protein binds to a variety of cell growth factor receptors and stimulates cell proliferation by activating a variety of cell growth factor receptor signalling pathways[9]. e6 and E7 proteins act as the main transforming proteins of the virus. e6 protein binds to the p53 gene and renders it functionally inactive. In addition, E6 activates telomerase expression and regulates the activity of PDZ structural domain proteins and tumour necrosis factor receptors. e7 proteins have evolved as major targets of the retinoblastoma (Rb) protein family, controlling the degradation activity of E2F transcription factors and leading to increased expression of E2F response genes[10].

The HPV genome can be divided into three regions: the early transcribed region (E region, 8 orf), the late transcribed region (L region, 2 orf) and the non-transcribed region (up stream regulatory region, URR). The early transcribed region is involved in DNA replication, transcription, translation

and transformation. The late transcribed region encodes the two capsid proteins that make up the viral capsid. The non-transcribed region is the regulatory progenitor containing the starting point for DNA replication and essential for gene expression. e6 and e7 can usually be integrated into host cells, suggesting that e6 and e7 have oncogenic potential[11]. hpv causes cancer through several mechanisms: (1) early gene expression activates cell proliferation; (2) viral gene integration disrupts the cellular genome, activating oncogenes and inactivating oncogenes; (3) Viral oncogenes (e.g. E6, E7) can bind important oncogene products for degradation (e.g. p53) or inactivation (e.g. Rb)[12].

3. HPV infection and colorectal cancer

HPV is common in the population and is transmitted mainly through sexual contact, but can also be transmitted through skin-to-skin contact. The majority of the population is spontaneously cleared of HPV infection in a transient form, which does not cause malignancy, and only in the case of persistent infection with high-risk HPV types does it cause cancer[13]. Studies have confirmed the potential oncogenic potential of the E6 and E7 genes, which, in concert with the E5 gene, promote cervical cancer development through a variety of cytokines, signalling pathways and interactions with host cells[14]. mechanisms by which the E6 protein promotes malignant transformation of cells include: (i) E6 specifically binds to the tumour suppressor protein p53, causing its rapid degradation and leading to uncontrolled cell cycle. (ii) Activation of telomerase can allow cells to escape proliferation limitation during senescence and achieve immortality. (iii) Combined interferon regulatory factor 3 (IRF3) reduces the functional expression of interferon B (IFNB), allowing the virus to escape the normal immune response. ④Adheres to tumour necrosis factor (TNF) and prevents cell-induced apoptosis. In addition, E6 proteins can interact with, among others, E6 target proteins, thereby affecting apoptosis[15]. E7 binds to pRb and the related proteins p107 and p130, leading to the functional inactivation of these proliferation regulators and thus the release of active E2F causing excessive cell proliferation[16]. Furthermore, E6 and E7 proteins can synergistically uncouple centrosome replication from the cell cycle, leading to altered centrosome numbers, spindle cell division and altered genomic integrity, which further promotes tumour cell development.

The main mechanism of HPV oncogenic action is the binding of E6 and E7 to the intracellular tumour suppressors p53 and PRb respectively. p53 is an important oncogene that promotes apoptosis and DNA repair. When cellular DNA is damaged, p53 induces the expression of the downstream target genes p21 and Mdm2 and Bax to exert its anti-proliferative effect. The high-risk HPV E6 protein has a high affinity for wild-type p53. The combination of the two is likely to cause rapid degradation of p53, initiate the cell cycle and inhibit apoptosis[15]. HPV E6 proteins activate telomerase, allowing normal cells to escape from proliferation-restricted cells during senescence and become immortalised[17]. HPV E6 and HPV E7 can alter the terminal differentiation of epithelial cells in vivo, allowing cells expressing E6 and E7 proto-oncoproteins to bypass the normal cell cycle detection sites, leading to genetic damage and eventual development of tumours[18].

McGregor et al[19] used PCR combined with Southernblot to find 13 positives in 38 carcinomas (32%), 8 positives in 21 adenomas (38%) and 2 positives in 24 normal biopsy specimens (8%). On statistical analysis, the difference in HPV infection rates between the adenoma and colon cancer groups was not statistically significant ($p>0.05$), but both were significantly higher than in normal mucosal tissue ($p<0.05$) These observations confirm the presence of HPV in the human colon mucosa and in this mucosal tumour. Jin Dachuan et al[20] showed that the prevalence of HPV infection was significantly higher in the colorectal cancer case group than in the control group ($OR = 17.97, P<0.05$). There was heterogeneity in the results ($I^2 = 83.90, P<0.05$). The subgroup results that eliminated heterogeneity showed that there was still a strong correlation between colorectal cancer and HPV infection ($OR = 20.00, P<0.05$). Han Ke et al[21] used the method of immunohistochemistry to detect the positive rate of HPV type 16 in two groups of people and found that the occurrence of colorectal cancer was closely related to human papillomavirus type 16 infection, and there were significant differences in the infection rate by clinical Dukes stage. Zuo Linni et al[22] selected 80 colorectal

cancer patients and took lesion tissue samples (lesion group) and paracancer tissue samples (paracancer group) from all patients respectively. HPV16 and 18 infections were detected by PCR fluorescence technique, and the expression levels of vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMP)-9 were detected by immunohistochemistry, and correlation analysis was performed. The infection rates of HPV16 and HPV18 in the lesion group were 33.8% and 37.5%, respectively, which were significantly higher than those in the paracancer group (6.3% and 7.7%) ($P<0.05$). The positive expression rates of VEGF and MMP-9 in the lesion group were 75.0% and 71.3%, respectively, which were significantly higher than those in the paracancer group (16.3% and 24.4%) ($P<0.05$). In lesion tissue specimens, the differences in infection rates of HPV16 and 18 in patients with different VEGF and MMP-9 expression profiles were statistically significant ($P<0.05$).

Cheng et al[23] analysed HPVDNA in 70 colorectal carcinomas and 37 adenomas. HPVDNA was detected in 11 (29.7%) of the 37 adenomas and 37 (52.9%) of the 70 carcinomas. the difference in HPVDNA expression between adenoma and carcinoma tissues was statistically significant ($P<0.05$), with the HPV-positive group having the The difference in expression of HPV16 was the largest ($P<0.05$). However, there was no correlation between HPV infection and colorectal cancer location, survival, differentiation and staging. The data suggest that HPVDNA, especially HPV16, is closely related to the development of colorectal cancer. Wang Haijiang et al[24] tested the HPV L1 gene in 75 cases of surgically resected tumour tissue and normal rectal tissue adjacent to the cancer in a Xinjiang population with 55 cases showing positive HPV L1 gene in tumour tissue (73.3%) and no HPV L1 gene was detected in normal tissue.

4. Genes associated with HPV infection and colorectal cancer

4.1. K-ras genes

The ras gene family consists of three members, K-ras, H-ras and N-ras, of which the K-ras gene is most closely associated with colorectal cancer. mutations in the K-ras gene keep the ras protein active, affecting the signal transduction pathway, keeping the signal transduction pathway continuously active, stimulating cell growth and differentiation, and leading to malignant cell transformation[25].

YilmazN et al[26] found that the expression levels of miR-181d and miR-217 were associated with increased K-ras gene expression in tumor tissues and that K-ras gene expression was regulated by miR-181d and miR-217. miR-663 expression was significantly correlated with tumor differentiation, invasion, lymph node metastasis and TNM stage. miR -181d and miR-217 may function as oncogenic miRNAs in colorectal carcinogenesis and development. jiashengXu et al[27] collected 250 cases of colorectal cancer tissues from the First Affiliated Hospital of Nanchang University and randomly selected normal intestinal mucosal tissues from 20 patients as a control group. PD-L1 expression was detected by immunohistochemistry, and K-ras gene mutations in colorectal cancer tissues were detected by sequencing. Immunohistochemical detection showed that PD-L1 was highly expressed in colorectal cancer, and the 5-year survival rate was significantly lower in pd-l1 positive patients than in pd-l1 negative patients. the mutation rate of K-ras gene was 35.6%, and the main mutation site was codon 12. the positive expression rate of PD-L1 was significantly higher in patients with K-ras gene mutation than in patients with wild-type K-ras gene mutation. the expression of PD- L1 expression is closely related to mutations in the K-ras gene, and the status of the K-ras gene may affect PD-L1 expression. Furthermore, AdamT. Boutin et al [28] established a CRC mouse model in which whole-exome sequencing showed that Kras-mut alleles were heterozygous in primary tumours and homozygous in metastases, a pattern consistent with activated Kras-mut signalling being a driver of metastatic progression. Systemic level and functional analyses revealed that the TGF- β pathway is a key mediator of kras-mut-driven invasion. extinction of the Kras-mut gene led to specific elimination of the Kras-mut subpopulation in primary and metastatic tumours, resulting in the elimination of apoptosis in advanced aggressive and metastatic tumours. It is shown that oncogenic K-ras signalling is indispensable for adenoma growth and is particularly critical for the progression of aggressive and metastatic growth.

4.2. P53 genes

The p53 gene, one of the most important oncogenes, is located on the short arm of chromosome 17 and is involved in the processes of tissue apoptosis, life cycle arrest and DNA damage repair [29]. p53 mutations are an important cause of tumour progression and are found in approximately 50% of cancer patients [30]. HPV infection has been found to be associated with mutations in the P53 gene, and patients with mutant p53CRC are more chemoresistant than patients with wild-type p53 [31]. The wild-type P53 gene monitors the extent of damage during DNA replication. the less damaged P53 is, the more it promotes cellular self-repair, while the more damaged it is, the more it directly induces apoptosis, reflecting the important role that p53 mutation status plays in CRC progression and poor prognosis. p53 mutations cause cells to lose the ability to undergo DNA repair and apoptosis. Mutant P53 can act as an oncogene to promote malignant transformation of cells. Its protein product, P53, prevents the negative regulation of wild-type P53. P53 mutations lead to DNA damage in cells. To a large extent, it has the ability to initiate the cell cycle, enabling cells to proliferate rapidly and in large numbers, leading to malignant transformation [32, 33]. magdalenaCLiebl et al [34] showed that the transcription factor p53 plays an important role by coordinating cellular responses (e.g. DNA repair, cellular senescence, cell death, cell cycle arrest, cell differentiation, and metabolism) exerting an important tumour suppressive role. In CRC, the TP53 gene is mutated in 43% of tumours, with the remaining tumours typically compromising p53 function due to alterations in genes encoding proteins involved in p53 regulation. In addition, the findings show that TP53 mutations in CRC are usually missense mutations that impair wild-type p53 function (loss of function) and may even provide neoform (gain of function) activities such as cell proliferation, invasion, metastasis and promotion of cancer cell stemness for cancer development.

4.3. MSH2 genes

The MSH2 gene, an important member of the DNAmismatchrepairsystem (MMR), encodes a protein capable of participating in the DNA mismatch repair response. dMMR defects (dMMR) result in microsatellite instability (MSI), a strongly mutated phenotype. MSI is considered to be a major oncogenic pathway in colorectal cancer (CRC) pathway:it represents a molecular marker for hereditary non-polyposis colorectal cancer (HNPCC)[35]. Xu Jinheng et al[36] studied 120 colorectal cancer patients with lymph node metastasis as cases and 120 colorectal cancer patients without lymph node metastasis were selected as controls during the same period. The MLH1 and MSH2 protein positive expression deletion rate, MLH1 and MSH2 mRNA and protein expression levels in normal paracancer tissues and focal tissues of the two groups were detected by immunohistochemistry, quantitative real-time fluorescence PCR (qRT-PCR) and Westernblot, respectively. The results showed that the rate of positive expression of MLH1 and MSH2 was higher in the focal tissues than in the paraneoplastic tissues of both groups, while the relative expression levels of MLH1 and MSH2 mRNA and protein were lower than those of the paraneoplastic tissues, and the differences were statistically significant. None of the differences were statistically significant, which indicated that the expression levels of MLH1 and MSH2 were significantly lower in lymph node metastatic colorectal cancer, and it was speculated that they played an important role in the progression of colorectal cancer from lymph node-free metastasis to lymph node metastasis.

It has been pointed out that the main causes of colorectal cancer differed between sites, and the probability of MSI phenotype in sporadic colorectal cancer was 10-fold higher in right-sided colon cancer than in left-sided colon cancer [37]. the rate of loss of MLH1 and MSH2 expression in patients with colorectal cancer was related to tumor location and differentiation, and was higher in right-sided colon cancer than in left-sided colon cancer. Patients with loss of MLH1 and MSH2 expression in right colon cancer had relatively early age of onset, were less differentiated and less prone to neural invasion; while cases with loss of MLH1 and MSH2 expression in left colon cancer showed no significant correlation[38]. During DNA repair, mismatch repair genes encode corresponding enzymes that also recognise base pairs, and if MMR defects or mutations impair cellular DNA

capacity, cell death or genomic instability may occur. Therefore, MLH1, MSH2, PMS2 and MSH6 are important in the development of colorectal cancer.

5. Conclusions

HPV infection may play a role in the development of colorectal cancer at all stages. The relationship between HPV infection and colorectal cancer and its oncogenic mechanism provides new avenues for the prevention, early diagnosis, treatment and prognosis of colorectal cancer. However, the findings of the relationship between HPV infection and the development of colorectal cancer at home and abroad still need to be further explored, and the role of HPV infection in the pathogenesis of colorectal cancer has not yet been clearly elucidated.

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