Human Cytomegalovirus and Colorectal Adenocarcinoma: Any Association?

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Abstract

Background: Human cytomegalovirus (HCMV) has been implicated to transform many mammalian cells, so we tried to investigate whether HCMV participates in human colorectal carcinogenesis.

Methods: Immunohistochemistry analysis using monoclonal antibody of HCMV early protein was conducted on tissues of 32 colorectal adenocarcinomas and eight colorectal hyperplastic polyps, tissues of normal tumor margin were considered as control.

Results: HCMV early protein was detected in five out of 32 (15.6%) colorectal adenocarcinomas, while none of the eight colorectal hyperplastic polyps and tissues of normal tumor margins was positive for the virus early protein.

Conclusion: the data of this study suggests that HCMV may participate in the process of colorectal carcinogenesis as it is evidenced that HCMV was detected in colorectal cancer tissues only.

Key wards: HCMV, CRC.

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Introduction

Human cytomegalovirus (HCMV) is a member of the herpesvirus family that is a ubiquitous human pathogen worldwide. In the United States, 40% to 90% of adults are seropositive owing to exposure to the virus at some time during life [1, 2]. CMV infection is lifelong, and the latent virus can reactivate to cause serious illnesses when the host is immunocompromised [3, 4]. Various in vitro studies have demonstrated that the gene products of CMV are capable of modulating cell cycle progression and apoptosis by regulating the expression of a number of important host genes [4-7]. For example, CMV infection has been shown to transcriptionally activate the expression of the proto-oncogenes c-*fos*, c-*jun*, and c-*myc* [8, 9].

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The immediate early viral proteins also can block the induction of apoptosis by tumor necrosis factor α or the adenovirus E1A proteins [10]. In addition, CMV has been shown to transform a variety of mammalian cells that are tumorigenic in nude mice [5].

Detection of an infectious agent in human cancers might have important implications in cancer treatment and prevention. To further study whether CMV participates in human colorectal carcinogenesis, we examined colorectal hyperplastic polyps, adenocarcinomas, and normal-appearing colonic mucosa for the presence of one of the HCMV early proteins.

Material and Methods

The specimens included in the study were paraffin embedded blocks of 32 colorectal adenocarcinomas with their normal tumor margin tissues and 8 colorectal hyperplastic polyps. 5µm tissue sections on positive charged slides were subjected for immunohistochemistry analysis to detect HCMV early protein using

monoclonal antibody for HCMV early non-structural protein of 68 KDa (BioGenex, USA) in a dilution of 1:100, refer to the immunohistochemistry procedure in reference [11].

Results

HCMV early protein was detected in colorectal tumor cells in five out of 32 cases (15.6%) (Table 1), with negative normal tumor margin in all of these cases, and none of the 8 colorectal hyperplastic polyps showed positivity for the viral early protein. HCMV positive cells showed dark brown nuclear staining pattern (Figure 1).

Table 1: HCMV early protein positive colorectal cancer cases

Case no.	Tumor Grade	Tumor Stage	Tumor Type	Location	Lymph nodes involvement
1	II	C	Well differentiated	Recto-sigmoid	Positive
2	III	C	Poorly differentiated	Recto-sigmoid	Positive
3	II	B	Moderately differentiated	Colon	Negative
4	II	D	Moderately differentiated	Rectum	Negative
5	II	C	Moderately differentiated	Rectum	positive

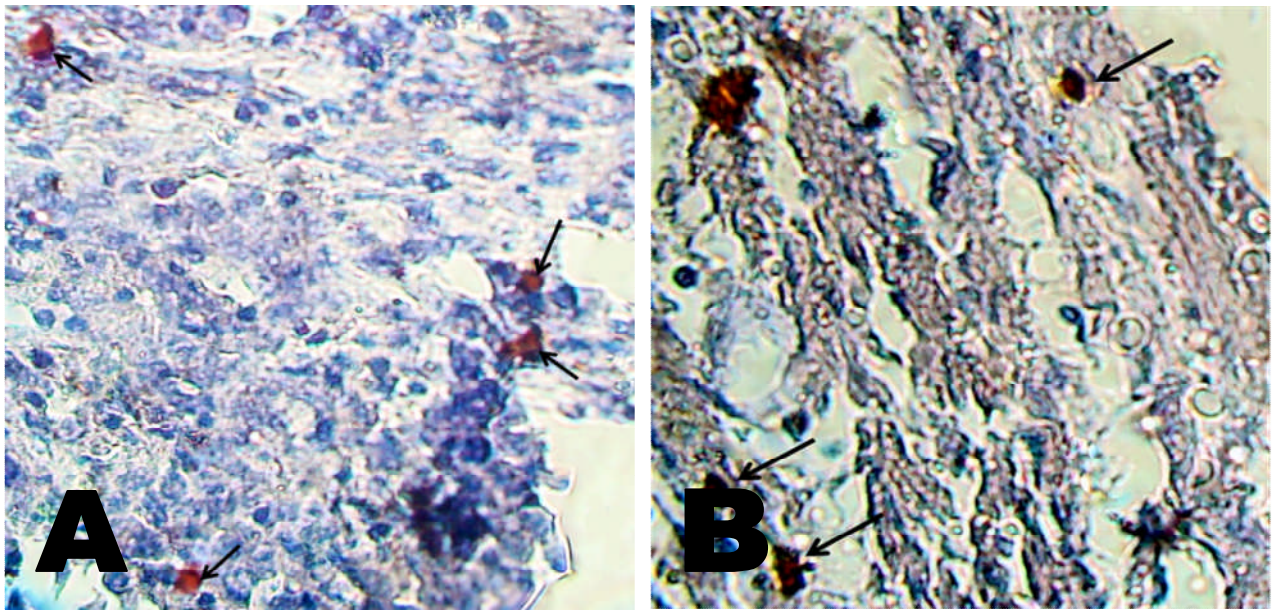

Figure 1: Detection of HCMV early protein by immunohistochemistry in Colorectal Adenocarcinoma. Immunostaining of HCMV by DAB chromogen (dark brown nuclear staining) counterstained with Mayer's heamatoxylin. (**A**) Poorly differentiated, grade III, stage C, colorectal adenocarcinoma show tumor cells positive for the virus early protein. (**B**) Well differentiated, grade II, stage C, colorectal adenocarcinoma show tumor cells positive for the virus early protein. Magnification power of A and B (X400).

Discussion

Despite the rapid advance in the understanding of molecular pathways underlying human colorectal carcinogenesis, the causes that initiate dysregulation of the pathways remain largely unknown. Human cytomegalovirus (HCMV) has been implicated as a potential pathogenic agent [(12)].

In the present study we examined 32 colorectal adenocarcinomas among which five were positive for HCMV early protein which could be supported by many studies and evidences showing that many viral genes and proteins are carcinogenic or participate in the process of carcinogenesis (4-10). One of the viral morphologic transforming regions, mtrII, encodes a 79 amino acid protein that is capable of binding to tumor suppressor p53 to inhibit p53-activated transcription [(13)]. In addition, it was recently reported that the CMV UL82 gene product pp71 stimulates cell cycle progression by inducing protein degradation of another important tumor suppressor Rb and its family members p107 and p130 [(14-16)]. Taken together, these experimental observations strongly suggest CMV to be a potential carcinogenic agent.

Despite the accumulation of in vitro evidence, the role of CMV infection in the development of human cancers has not been established. This is in contrast with other members of the herpes virus family, such as Epstein-Barr virus and human herpes virus 8, that are linked convincingly to several human malignant neoplasms [(17-18)]. The association of CMV with human cancers has been studied in the uterine cervix, prostate, and colorectum, but the data have been conflicting and inconclusive [(5, 12, 19)].

CMV infects a wide range of human cells [(20)], including colonic epithelial cells that give rise to adenomas and adenocarcinomas. The possible association of CMV with human colorectal adenocarcinomas was reported first in 1978 by Huang and Roche [(21)], who detected CMV DNA in 4 of 7 colonic adenocarcinomas by membrane complementary RNA-DNA hybridization. It is interesting that CMV DNA also was detected in 1 of 2 cases of familial adenomatous polyposis but not in normal colonic tissues from the same patients or control cases of Crohn disease [(22, 23)].

In conclusion, HCMV might play a role in the process of colorectal carcinogenesis because it is evidenced now that some of the CMV proteins might have mutagenic potential, which might be expressed only transiently in host cells to induce mutations in cellular genes leading to oncogenic transformation [(24)].

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