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Original Article

Molecular Interplay of *John Cunningham* Virus with Interleukin 1 Beta in Colorectal Carcinomatous Tissues from a Group of Iraqi Patients

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Abstract

Colorectal cancer is ranked to have high mortality among most malignancies worldwide. In the adult population, the seroprevalence rates of the *John Cunningham* virus (JCV) range from 70% to 90%. Recently the association for *JCV* in many malignant tumours have been reported worldwide, including colonic and rectum cancers. Interleukin-1β (IL-1β) can promote tumour growth where it is abundant in the tumour microenvironment, and its up-regulation is considered a poor prognostic feature in different types of solid tumours, including colon malignancies. One hundred tissue biopsies belonged to 50 patients with colorectal cancers and 30 benign colonic tumour patients, and 20 colorectal control tissues were enrolled in this study. *JCV* was detected via chromogenic in situ hybridization (CISH), while IL-1 beta was detected by immunohistochemistry (IHC). The recorded data showed that 21 out of 50 (42%) tissue samples with colorectal carcinoma showed positive CISH reactions for *JCV* DNA in this study. The benign colorectal tumours group revealed positive signals in 2 out of 30 tissues representing 6.7% of this group. Lastly, no control tissues showed positive signals for the *JCV* -CISH test. The positive signals of IL-1 Beta-IHC detection were found in 26 out of 50 (52 %) colorectal carcinoma tissues, while in the benign colorectal tumour was 43.3% (13 out of 30) and in AHC was 20% (4 out of 20 tissues). The high rates of *JCV* infection in this group of Iraqi patients with colonic adenocarcinoma in concordance with IL-1 Beta expression could play an essential role in the development and progression of these malignant tumours along with benign colonic tumours. To analyze the concordant expression of IL-1 beta gene and *JCV* in issues from a group of Iraqi patients with colonic adenocarcinomas.

Keywords: In situ hybridization, IL1 beta, Immunohistochemistry

1. Introduction

Colorectal cancers rank highest in incidence and mortality among all malignancies in western countries. Globally, these cancers rank fourth in men and third in women, where the primary pathological type is adenocarcinoma (1). CancerCare multifactorial diseases and their initiation and progression are related to several genetic alterations and exogenous agents, including chemicals and some infectious agents, including viruses and bacteria (2).

Genomic sequences and oncogenic T-antigen expression of *John Cunningham* Virus (*JCV*) have been detected in various human malignancies, including brain tumours, colon cancer, gastric cancer, and esophageal cancer (3). However, the etiologic contribution of *JCV* to cancer development is complicated by its widespread infection and adaptation to humans. It is well known that *JCV* is a human neurotropic polyomavirus associated with neurological diseases, has been infecting a wide range of cell types, and was detected in several human tumours, including colorectal cancers (4).

It was noticed that the frequency of the T-antigen sequence of *John Cunningham Virus* in CRCs displayed contradictory results, ranging from zero%to 77% of patients. These discrepancies might relate to an ethnic-related factor of this virus or no reliable tests for *JCV* DNA (5). Different cytokines, chemokines and growth factors contribute to tumour-related inflammation in most tumour microenvironments that alter tumour growth and progression, invasion, and metastasis (6).

The IL-1 family consists of 11 agonist and antagonist molecules (including IL-1α, IL-1β, IL-1Ra, IL-18, IL-33, IL-36α, IL-36β, IL36γ and IL-38 [reviewed in .These molecules are secreted by various cell types upon inflammatory or stress conditions to be centrally involved in the regulation of inflammatory responses and have recently been found as one of the prominent tumorigenic inflammatory cytokines and targeted to develop novel IL-1 blockers for cancer therapy (7). The role of IL-1 in CRC showed controversy. It was found that IL-1β increased in patients with metastatic CRC and polymorphisms of the IL-1 receptor antagonist gene associated with CRC (8).

IL-1β induces intestinal epithelial cells and tumour cell proliferation (9) and promotes myeloid-derived suppressor cell recruitment to support cancer progression (10). Furthermore, IL-1 may up-regulate the angiogenesis process within tumours (11). All the signalling pathways that associate the complexion of these IL-1 molecules with their receptors are essential keys in intestinal tumorigenesis CRC pathogenesis (12).

2. Materials and Methods

2.1. Sample Collection and Study Design

Tissue sectioning of each obtained paraffin-embedded tissue block was conducted at the histopathological department of Teaching laboratories, Baghdad Medical City, for confirmatory histopathological re-evaluation by a consultant pathologist. A 4 μm thick-tissue section was prepared, followed by a trimming process, then mounted on an ordinary glass slide and stained with hematoxylin and eosin. Another 4 μm thick-tissue section was stuck onto a positively charged slide used for detection of *JCV* by chromogenic in situ hybridization (CISH) kit (ZytoVision GmbH. Fischkai, Bremerhaven. Germany) using a digoxigenin-labelled oligo-nucleotides probe that targets *JCV* DNA as well as for detection of IL-1 Beta – antigen using mouse and rabbit Specific HRP/DAB (ABC) IHC- detection kit (Lot. Number: ab64264; purchased from Abcam, UK), and specific Mouse Monoclonal primary IL-1 Beta antibody [Lot. Number: [OTI3E1]; ab156791 purchased from Abcam, UK**]**. The detailed methods for performing both CISH and IHC reactions were done according to the instructions of manufacturing companies which were conducted in the Research Laboratory of the Clinical Communicable Diseases Research Unit at the College of Medicine, University of Baghdad and College of Science, University of Babylon.

2.2. Study Group Characteristics

Patients with colorectal tumours have ages ranging from seven to eighty-five years. The mean age of colorectal carcinoma patients (CRC) (53.595 years) was slightly higher than the benign colorectal tumour patients (BCT) (50. 095 years), whereas the mean age of the control group (AHC) was (49.766 years). The distribution of male gender in this study were 60%, 53.3% & 55% for patients with CRC, BCT & AHC, respectively; while, 40% ,46.7%& 45% were female patients with CR, BCT & AHC ,respectively. This study revealed well-differentiated carcinoma in 48% of the CRC group, while 40% and 12% of CRC have moderate and poorly differentiated grades, respectively. Anatomically, 7 cases of colorectal carcinoma were in

the cecum (14%), 12 cases in the transverse colon (24%); 3cases in the ascending colon (6%); 3 cases in the descending colon (6%); 13 cases in the sigmoid (26%), and 12 cases in the rectum (24%) (Table 1).

Table 1. The study group characteristics

		Malignant colorectal tissues (CRC), N= 50(%)	**Benign colorectal tissues (BCT), N = 30(%)**	**Healthy colorectal tissues (AHC) N=20(%)**
Age	Mean of Age (%)	53.595	50.095	49.766
	Range of Age	17 – 85	24 -74	38 – 75
Gender	Male	30 (60)	16 (53.3)	11 (55)
	Female	20 (40)	14 (46.7)	9(45)
Grade	Poorly	6 (12)		
	Moderately	20(40)		
	Well	24(48)		
Site of tumours	Cecum	7 (14)		
	Transverse colon	12 (24)		
	Ascending colon	3 (6)		
	Descending colon	3 (6)		
	Sigmoid	13 (26)		
	Rectum	12 (24)		

2.3. Statistical Analysis

The statistical analysis of the obtained results using SPSS (Version 22), T-test, ANOVA, and Chi-square was applied in the statistical analysis.

3. Results

3.1. John Cunningham Viral (*JCV*)-Associated Colorectal Cancers

Twenty-one out of fifty (42%) tissues with colorectal carcinoma showed positive chromogenic in situ hybridization reactions for *JCV*- DNA in this study. The high signal scores were found in moderate grade scores (Score II) (22%; 11/50). While the high-intensity signals were found in weak (intensity I) 16% (8/50) (Table 2 and Figure 1). The benign colorectal tumours group revealed 6.7% positive signals, which represented 2 out of these 30 tissues. Lastly, no control tissues revealed positive signals for the *JCV*-CISH test. The differences between the patients with colorectal carcinoma and each of these groups were statistically significant (P-value≤0.0001).

3.2. The Results of IL-1 Beta-IHC Signal Scoring and Intensity Signalling in Colorectal Tumors

Table 3 shows the positive results of IL-1 Beta-IHC detection, where 52 % (26 out of 50 tissues) from the colorectal carcinoma group showed positive signals, including 24 % (12 out of 50 tissues) in the average score (II) and the intensity of IL-1 Beta-IHC reactions showed 28.5 % (12 out of 50 tissues) in the weak intensity (I). The percentage of the benign colorectal tumour was 43.3% (13 out of 30) that showed positive signals, including 23.3 % (7 out of 30 tissues) in the low score (I) and 22.7 % (5 out of 22 tissues) in the weak intensity score (the score I). Lastly, in AHC, 20% (4 out of 20 cases) showed positive signals, including 10 % (2 out of 20 tissues) in the low score (I) (Figure 2).

Statistically, significant differences were noticed between IHC-scoring & -intensities of tissues at (P<0.05) in the colorectal tumours group.

3.4. Correlation between *JCV* and IL-1 Beta among Colorectal TumorsTissues

The *JCV* was statistically significantly correlated with the malignant colorectal tumour group when compared with healthy tissues (control group) (P<0.001, OR=1.33). The IL-1 Beta gene expression was significantly correlated with the malignant colorectal group when compared with the healthy tissues (control group) (P<0.001, OR= 27.8). The IL-1 Beta gene expression was significantly correlated with the benign colorectal group when compared with the healthy colorectal tissues (P<0.001, OR 24.6) (Table 4).

3.5. Spearman's Rho Testing of the Studied Markers in Colorectal Tissues

A highly significant correlation found between *JCV* and IL-1 Beta (r= 0.428, P= 0.003) as well as highly significant correlation between IL-1 Beta and grade of colorectal tissues (r= 0. 517; P= 0.002). No significant correlations between *JCV* and other markers (Table 5).

Table 2. The percentage of *JCV*-CISH score and intensity signalling in Colorectal Tumors

JCV-CASH		Colorectal carcinoma (n=50)		Benign colorectal tumours (n=30)		AH control (n=20)		*P*-value (χ^2test)
		No.	%	No.	%	No.	%	
Negative		29	58	28	93.3	20	100	0.0001
Positive		21	42	2	6.7	0	0.00	
Signal Score	I	6	12	1	3.35	0.00	0.00	0.002
	II	11	22	1	3.35	0	0.00	
	III	4	8	0	0	0	0.00	
Signal Intensity	Weak	8	16	2	6.7	0	0.00	0.001
	Moderate	7	14	0	0	0	0.00	
	Strong	6	12	0	0	0	0.00	

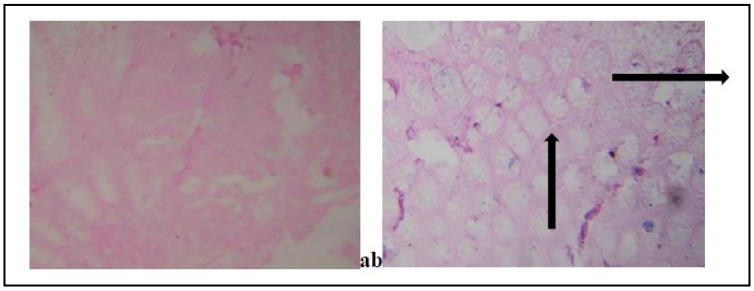

Figure 1. Chromogenic *Insitu hybridization*(CISH) for *JCV* detection in colorectal carcinoma using Digoxigenin-Labeled *JCV* - Probe; Stained with NBT\BCIP (Blue) and Counter stained by red nuclear solution (Red)
(a) Colorectal cancer with no *JCV*–CISHreactions (40×).
(b) Positive *JCV*-CISH reactions (40×).

Table 3. The percentage IHC- score and intensity signalling of IL-1 Betain Colorectal Tumors

IL-1 Beta-IHC		Colorectal carcinoma (n=50)		Benign colorectal tumours (n=30)		AH control (n=20)		*P*-value (χ^2test)
		No.	%	No.	%	No.	%	
Negative		24	47.6	17	56.7	16	80	0.008
Positive		26	52	13	43.3	4	20	
Signal Score	I	8	16	6	20	1	5	0.04
	II	12	24	4	13.3	2	10	
	III	4	8	3	10	1	5	
Signal Intensity	Weak	13	26	8	26.7	2	10	0.03
	Moderate	6	12	4	13.3	1	5	
	Strong	5	10	1	3.3	1	5	

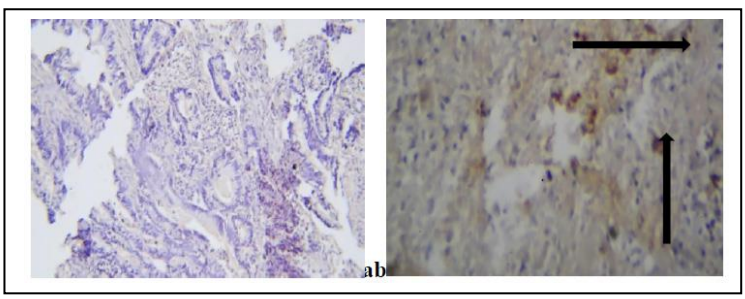

Figure 2. Infiltrative colorectal carcinoma showing immunohistochemistry stinging of IL-beta protein Over Expression Using Biotinylated Anti – IL-1 Beta antibody stained by DAB-chromogen (brown) and counterstained by Mayer's Haematoxylin (Blue).
(c) Colorectal cancer with negative stinging for IL-beta (40X).
(d) IL-1 Beta -IHC-reaction with high signal score and vigorous signal intensity (40x).

Table 4. The association between *JCV* and IL-1 Beta among Colorectal Tumor Tissues

	Malignant (n=50)	**Control (n=20)**	***P*-value**	**OR(95%CI)**
JVC	21 (42%)	0 (0.00%)	<0.001	1.33 (0.5)
IL-1 Beta	26 (52%)	4 (20%)	<0.001	27.8 (4.2)
	Benign (n=22)	**Control (n=17)**	***P*-value**	**OR(95%CI)**
JVC	2 (6.7%)	0 (0.00%)	0.001	3.4 (2.7-48)
IL-1 Beta	26 (52%)	26 (52%)	<0.001	24.6 (3.4)

Table 5. Spearman's Rho statistical testing of the studied markers

Spearman's rho		**Age groups (years)**	**Grade**	**JVC**
Grade	R	-0.123		
	P	0.459		
JVC	R	0.020	0.163	
	P	0.876	0.365	
IL-1 Beta	R	0.130	0.517	0.428
	P	0.228	0.002*	0.003*

*Correlation is highly significant (*P*<0.01)

4. Discussion

The age distribution of a population is considered the most critical factor in determining the overall incidence (13). The results of this study revealed that the mean age of patients in colorectal carcinoma was higher (53.595 years) than the mean age of the benign colorectal tumours group (50.062 years), while the male to female ratio was 1.3:1. The present results might indicate the age as a relevant risk could affect colorectal tissues. Similar observations have been made in many other previous studies in Iraq (14, 15). In this study, well-differentiated carcinomas were 52.38% of the CRC group, 40.48% with moderately graded-carcinomas and poorly differentiated graded carcinomas were seen in 7.14%**.** These results contradicted Kifah (15) and Ava (14).

Almohana, Alhelu (16) found that the mean age of CRC was 50 years. The present high percentage of CRC that increased with the increase of the patient's age could be related to many other factors that enhance the appearance of malignant colorectal tumours in the young age group through the proceeding of age, such as genetic predisposition, hormonal factors and changes in lifestyle which in turn are supported by many previous studies done by Mármol, Sánchez-de-Diego (17) and Wong, Ding (1).

The incidence and mortality rates of colorectal cancer are 35% to 40% higher in men than in women. It might reflect a complex interaction among gender-related differences with exposure to hormones and other risk factors, yet, the reasons are not entirely understood (18).

Genetic variations result in an orchestrated activation of oncoproteins and inactivation of tumour suppressor proteins in the development of tumours in the colon (19). Other factors, such as viral infection, can alter many regulatory processes and are environmentally acquired. Several studies demonstrated JC virus could be found in the kidneys, B lymphocytes, and gut mucosa after primary viral infection. The first report suggested *the JC* virus in human CRC, dated 1999, followed by more reports of an association of JC viral infection with CRC (20).

The JC virus has two proteins in particular, namely large T-antigen and agnoprotein, that interfere with cell cycle control mechanisms as well as those controlling

instability of genome, while further viral proteins also contribute to cell transformation (21). In the present study, viral DNA was found in carcinoma lesions and less frequently in adenomas but not in the normal tissues; herein, the *JCV*- DNA percentage in malignant colorectal tumours (42%) was higher than its percentage (6.7%) in their benign counterparts. In addition, a pathogenic role for this virus in colorectal carcinogenesis might happen, among additional events in cancer progression, supported by the initial studies that observed a transforming ability of *JCV* in specific neural cell types. However, *JCV* can transform many cell culture types and other laboratory animals (22). The colon is the natural human reservoir for *JCV*, where the viral genome has been detected in tonsillar cells, B lymphoid cells, kidney cells, and upper and lower gastrointestinal tract parts (4).

Sinagra, Raimondo (23) reviewed the detecting frequencies of *JCV* DNA that ranged from 26% to 89% of colorectal carcinomas that were positive for *JCV* to zero% of normal colorectal tissue positive for John Cunningham virus. The current results are among this range, too. Casini, Borgese (24) reported 88.9% - positive results for the presence of *JCV* within the primary tumours and Antonic, Stojadinovic (25) identified *JCV* DNA in 86.4% of the CRC tissue samples (25).

This finding could, in turn, indicate a respective role of JCV in colorectal cancer pathogenesis and/or their multi-step carcinogenesis. These results suggest a viral DNA integration could happen in the host cell genome and result in chromosomal damage and malignant transformation. In addition, our results disagree with Enam, Del Valle (26) and Boland (27), who did not support the role of the *John Cunningham* virus as a cause of colon cancer. Colorectal cancers can show chromosome instability, and it was hypothesized that *the John Cunningham* virus might account for some of this instability and be integrated into the colorectal cellular genome. In addition, Ricciardiello, Baglioni (28) reported a high prevalence of *JCV* in gastric and colonic tissue from patients without gastrointestinal neoplasia (>70% of participants).

IL-1β plays a significant role as a pleiotropic pro-inflammatory cytokine in colon inflammation and carcinogenesis. Aberrant production and signalling of IL-1β were found to be tightly linked to tumour generation, growth and metastasis of multiple types of cancers (29).

However, the IL-1 role in CRC has shown controversy. IL-1β cytokine increased in metastatic CRC tissues (30), and *in vivo* block of *IL1B*significantly decreased the tumour development in colon cancers. Further, IL-1β directly induces tumour cell proliferation and supports cancer progression (10).

Most studies highlighted the ability of IL-1β in inducing Th1 and Th17 responses to induce anti-tumorigenic effects, where IL-1β activation of tumour-specific Th1 responses protected against myeloma, lymphoma and colorectal cancers (31).

Other researchers revealed the impact of IL-1 signalling in CRC (32), and other authors reported that ablation of IL-1R1 by T cells decreased inflammation elicited by IL-17 and IL-22 and reduced CRC progression (33).

We conclude that *JCV* infection with IL-1 Beta expression is commonly present in CRC patients and might share as a risk factor for CRC.

Authors' Contribution

Study concept and design: S. H. M. A.
Acquisition of data: S. H. M. A. and M. M.
Analysis and interpretation of data: Z. M. M. A.
Drafting of the manuscript: S. H. M. A.
Critical revision of the manuscript for important intellectual content: H. G. S.
Statistical analysis: A. K. H.
Administrative, technical, and material support: M. J. H.

Ethics

The study was approved by the Ethics Committee of the University of Babylon, Babylon, Iraq.

Conflict of Interest

The authors declare that they have no conflict of interest.

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