



The roles of p53 and XPO1 on colorectal cancer progression in Yemeni patients

Mohammed Aladhraei¹, Eman Al-Salami², Naravat Pongvarin³, Prasit Suwannalert¹

¹Department of Pathobiology, Faculty of Science, Mahidol University, Bangkok, Thailand; ²Department of Pathology, Faculty of Medicine and Health Sciences, University of Sana'a, Sana'a, Yemen; ³Clinical Molecular Pathology Laboratory, Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Contributions: (I) Conception and design: M Aladhraei, P Suwannalert, N Pongvarin; (II) Administrative support: P Suwannalert, N Pongvarin; (III) Provision of study material or patients: M Aladhraei, E Al-Salami; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Prasit Suwannalert, PhD. Department of Pathobiology, Faculty of Science, Mahidol University, Bangkok, Thailand. Email: prasit.suw@mahidol.ac.th; parasit109@yahoo.com.

Background: The colorectal cancer (CRC) tumorigenesis is driving by genetic alterations leading to changes in protein expression such as p53. The p53 is frequently expressed in CRC and its association with clinicopathological features is still controversial. Moreover, accumulated evidence suggests that both p53 and nuclear exporter protein, exportin 1 (XPO1), are working in reciprocal manner may lead to loss of p53 nuclear localization and enhance cancer progression through hyperactive nuclear export. Accordingly, the present study aimed to evaluate the expression of p53 in CRC Yemeni patients and to explore the association between the p53 and XPO1 coexpression in relation to clinicopathological features.

Methods: A series of 40 formalin fixed paraffin embedded (FFPE) tissue blocks taken from CRC patients that diagnosed as adenocarcinoma were prospectively collected and then analyzed for p53 and XPO1 expression by immunohistochemistry (IHC). The patients and tumor clinicopathological characteristics were retrieved from the histopathology reports and the P value <0.05 were considered statistically significant.

Results: The p53 expression was observed in 60% (24/40) of CRC tumor samples. Significantly, the p53 expression was noted in 72.4% (21/29) of the left side compared to 27.3% (3/11) of the right side colon tumors (P=0.014). Furthermore, p53 expression was positively and significantly correlated with well-but not moderate- or poorly-differentiated tumors (P=0.023). No significant difference was observed between the p53 expression and age, gender and tumor size. Regarding the XPO1 expression, the p53 expression didn't show an association with XPO1 expression. The coexpression of p53 and XPO1 analysis revealed that 100% (11/11) tumors with negative p53 and positive XPO1 coexpression was noted with lymph node metastasis with significant difference (P=0.003) and more frequently observed in moderate-or poorly- differentiated tumors.

Conclusions: The loss of p53 accompanied with increased XPO1 expressions was associated with the progression of histopathological features of CRC Yemeni patients. Further studies are needed to elucidate the p53 genetic mutations in relation to the XPO1 coexpression in CRC prognosis.

Keywords: Colorectal cancer (CRC); p53; exportin 1 (XPO1); Yemen

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Introduction

Colorectal cancer (CRC) is a major health dilemma, rating as the third most frequently diagnosed cancer with higher mortality worldwide (1). The development of CRC is a complex process based on the accumulation of genetic mutations such as tumor suppressor genes, which may lead to disruption of cellular homeostasis (2). *TP53* mutation was reported in all types of cancer with different rates, which lead to changes in the p53 protein expression within the cell and may eventually lose its function that involved in the regulation of cell cycle, DNA repair and apoptosis (3). In CRC, the p53 protein expression is frequently observed and its prognostication role and association with clinicopathological features still controversial (4). Recently, Cao *et al.*, 2017, reported that the loss of p53 expression was frequently noted in CRC tumors and was associated with aggressive clinicopathological characteristics such as positive lymph node metastasis and advanced tumor stage (5). Although some studies failed to find any association between the p53 expression and clinicopathological characteristics (6), other studies indicated that the p53 expression was associated with metastatic stage (7) and the p53 protein overexpression may act as an independent predictor of tumor recurrence in CRC (8).

In addition to its function as guardian of the genome, the p53 predominantly works as a transcription factor and its function crucially depends on its nuclear localization, which is regulated, into some extent, by nuclear transport machinery such as exportin 1 (XPO1). The XPO1, also known as chromosomal maintenance 1 (CRM1), is a nuclear export chaperone, mediates the nuclear export of several proteins which are essential for growth regulation and tumor suppression such as p53, leading to cytoplasmic degradation (9). Overexpression of XPO1 is identified in CRC (10) and the accumulated evidence suggests that both p53 and XPO1 are working in reciprocal manner, while the *XPO1* gene has a binding site for p53 and its transcription activity may be repressed by p53, the increased activity of XPO1 can cause the p53 mislocalization and dysfunction in cancers (11,12). From the above indications and because of individual marker expression has a limited prognostic value, we aimed to evaluate the association between the expression of p53 and clinicopathological features in CRC Yemeni patents, which is still unknown, and tried to explore the ambiguous relationship between the coexpression of p53 and XPO1 in CRC tissue samples in relation to histopathological features.

Methods

Patients and tissue samples

Total of 40 formalin fixed paraffin embedded (FFPE) tissue blocks from CRC patients diagnosed as adenocarcinoma were collected prospectively from the National Oncology Center (NOC), Sana'a, Republic of Yemen, after the informed consent taken from each patient. The study was approved by the Ethics Committee of the Ministry of Public Health and Population, the National Health and Medical Research Committee (NHMRC) (Reference: B2/10-2017). The patients' age, gender and other tumor clinicopathological characteristics were retrieved from the patient's histopathology report with the following inclusion criteria. Tumor stages were classified according to the TNM staging system, the American Joint Committee of Cancer (AJCC). The size of tumor was taken as the maximum diameter of the tumor in centimeters. The locations of the tumors were grouped into right (beginning from the cecum extending to the hepatic flexure and transverse colon) or left (starting from splenic flexure extending to the sigmoid colon and rectum). Binary system of lymph node (LN) metastasis as positive (N1) or negative (N0) was used. Paraffin tissue blocks representing the diagnosed tumor cells with adjacent normal epithelium were cut for hematoxylin and eosin (H&E) and selected for further immunohistochemistry (IHC) staining.

Immunohistochemical analysis

Consecutive 4- μ m sections were cut from the FFPE tissue blocks adhered onto positive charge slides and deparaffinized sections bring to phosphate buffered saline (PBS) at pH 7.4. For antigen retrieval, the slides were placed in a container containing citric acid (pH 6.0) and heated in a microwave oven for 15 minutes at maximum power and then 3% H₂O₂ in methanol was used to block endogenous peroxidase activity. The tissue sections incubated overnight at 4 °C with monoclonal antibodies against p53 (dilution 1:500, DO-7; Cell Marque) and XPO1/CRM1 (dilution 1:400, sc-74454; Santa Cruz Biotechnology). Then, the antibodies were amplified by HiDef Detection™ HRP Polymer detection system (Cell Marque) for 10 minutes for each step. The color was developed with the chromogen substrate, liquid diaminobenzidine (DAB, Cell Marque), and the sections counterstained with hematoxylin (13). Sections of colon cancer known as positive for p53 and XPO1 expression were used as positive controls. Negative

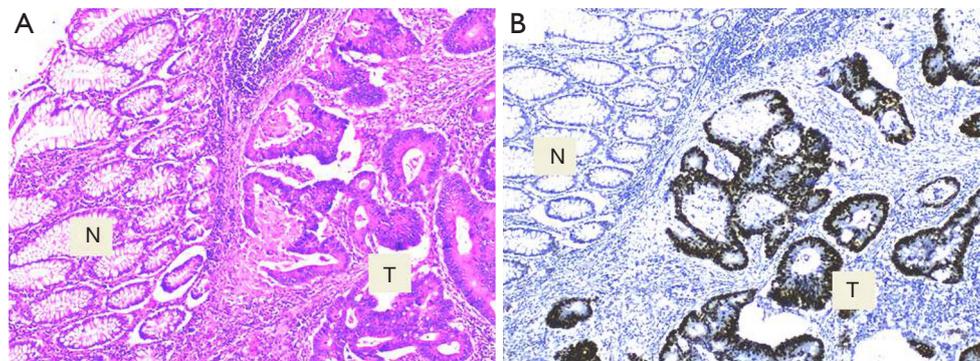


Figure 1 Expressions of p53 in tumor cells and adjacent normal colon epithelium with H&E staining (A) and IHC staining (B). Tumor areas [T] and adjacent normal epithelium [N] at magnification 100x.

control also used in every IHC batch experiment.

Each section was evaluated by two independent investigators according to the following criteria. Nuclear expression of the p53 protein was evaluated and classified as negative (<10% of tumor cells) or positive (\geq 10% of tumor cells) according to the percentage of 500-tumor cells count (14). For the XPO1 expression, we used immunoreactive score (IRS) system according to the formula; the index of immunoreactive score (IRS) = (percentage of positive cells score) \times (staining intensity score). Accordingly, the percentage of positive cells (nuclear and/or cytoplasmic) scored as 0 (0%), 1 (<10%), 2 (11–50%), 3 (51–80%), or 4 (>80%); while the intensity of staining scored as 0 (negative), 1 (weak), 2 (moderate), or 3 (strong). The resulting IRS values between 0–12 were further divided in to 0 (no staining) or 1–3 (weak) which considered as negative, while 4–8 (moderate) or 9–12 (strong) were considered as positive XPO1 expression in CRC tumors (15).

Statistical analysis

The associations between the p53 expression and the clinicopathological variables as well as the XPO1 expression were analyzed using Chi-square and Fisher's exact tests. Spearman rank test was also used. The SPSS 18.0 software was used for data analysis and the P values <0.05 was considered statistically significant difference.

Results

Association between the p53 expression and clinicopathological features

The p53 expression was observed in 60% (24/40) of

CRC tissue samples while no immunostaining was seen in the adjacent normal epithelial colon cells (*Figure 1*). The association between the p53 expression and clinicopathological characteristics of the patients' tumors is summarized in *Table 1*. Briefly, all of age, gender and tumor size groups didn't show significant difference by the p53 expression. Significantly, the p53 positive expression was noted in 72.4% (21/29) of the left side colon tumors compared to 27.3% (3/11) in the right side ($P=0.014$), and according to the evaluated tumor differentiation, a significant positive correlation of p53 expression was observed with well- but not moderate- or poorly-differentiated tumors ($P=0.023$). Most of positive p53 expression, 66.7% (16/24), was correlated to well differentiate tumors. Even though the frequency of the positive p53 expression was similar in both positive and negative lymph node metastasis tumors (12/24 of each), the negative p53 expression with 75% (12/16) were observed in tumors with positive lymph node metastasis.

Coexpression of p53 and XPO1 in CRC

The positive expression of XPO1 was identified in 72.5% of the CRC tumors. Although there was no association between the expression of p53 and XPO1 ($P=0.728$), the frequency of negative p53 expression was more than doubled in tumors with XPO1 positivity (68.75%, 11/16) compared to the negative one (31.25%, 5/16) (*Table 1*). Further evaluation of the p53 and XPO1 coexpression in relation to clinicopathological characteristics revealed that the tumors with negative p53 expression and an increase of XPO1 expression were observed as moderate- or poorly-differentiated while combined positive of p53

Table 1 Association between the p53 expression, clinicopathological features and XPO1 expression

Clinicopathological features and XPO1	Total No. (%)	p53 expression		P
		Positive	Negative	
Age				0.604
<50 years	22 (55.0)	14	8	
≥50 years	18 (45.0)	10	8	
Gender				0.436
Female	22 (55.0)	12	10	
Male	18 (45.0)	12	6	
Tumor location				0.014
Right	11 (27.5)	3	8	
Left	29 (72.5)	21	8	
Tumor size				0.329
≤5 cm	14 (35.0)	10	4	
>5 cm	26 (65.0)	14	12	
Tumor stage				0.148
I-II	11 (27.5)	9	2	
III-IV	29 (72.5)	15	14	
Lymph node metastasis				0.114
Positive	24 (60.0)	12	12	
Negative	16 (40.0)	12	4	
Tumor differentiation				0.023
Well	19 (47.5)	16	3	
Moderate	7 (17.5)	1	6	
Poorly	14 (35.0)	7	7	
XPO1 expression				0.728
Positive	29 (72.5)	18	11	
Negative	11 (27.5)	6	5	

and XPO1 expression was predominantly observed in well differentiated tumors (*Table 2, Figure 2*). Furthermore, 100% (11/11) tumors with negative p53 and positive XPO1 expression was associated and identified with positive lymph node metastasis with significant difference ($P=0.003$) (*Table 3*). Other clinicopathological characteristics such as age, gender and tumor location didn't show a significant difference according to the p53 and XPO1 coexpression.

Table 2 CRC-differentiated tumors and coexpression of p53 and XPO1

P53 and XPO1 coexpression	Tumor differentiation		
	Well	Moderate	Poorly
P53+/XPO+	12	1	5
P53+/XPO-	4	0	2
P53-/XPO+	1	5	5
P53-/XPO-	2	1	2
Total	19	7	14

CRC, colorectal cancer.

Discussion

Although the molecular and cellular biomarker trends make the CRC more understandable, CRC still harvests the lives of many of its victims around the world with different rates. In Yemen, 17.1% of total cancers were raised in the digestive system and one-third of them were observed as CRC (16). The early onset of CRC in Yemeni people in their thirties and forties with high frequency at the left sided colon tumors (17) urged to evaluate the biology of CRC among these patients which is still poorly understood.

In spite the association between the p53 expression and reliable prognostic clinicopathological characteristics such as age, tumor location, tumor grade as well as lymph node metastasis had been studied in many nations, revealed controversial results; such association still unknown in CRC Yemeni patients. Moreover, the ambiguous relationship of p53 with the XPO1 nuclear cytoplasmic transporter persuaded us to evaluate their coexpression association with histopathological characteristics in CRC tissue samples.

Published literature reveals that the rates of the p53 expression in CRC range from 27% to 76% (18), while in our series the p53 positivity was detected in 60%. However, the frequency of p53 expression among Yemeni patients was far from that reported in China (19) and Turkey (20) but close to the prevalence reported in Saudi Arabia (21) and Iran (22) with 43%, 82.1%, 57.5%, and 59% respectively. These differences may attribute to ethnic and technicality (4). No p53 immunostaining was detected in the adjacent normal epithelial colon cells supporting the hypothesis of that the CRC carcinogenesis occurs through nonfunctional mutated p53 protein.

The assumption of CRC pathogenesis variation between the left and right side was significantly implied in our

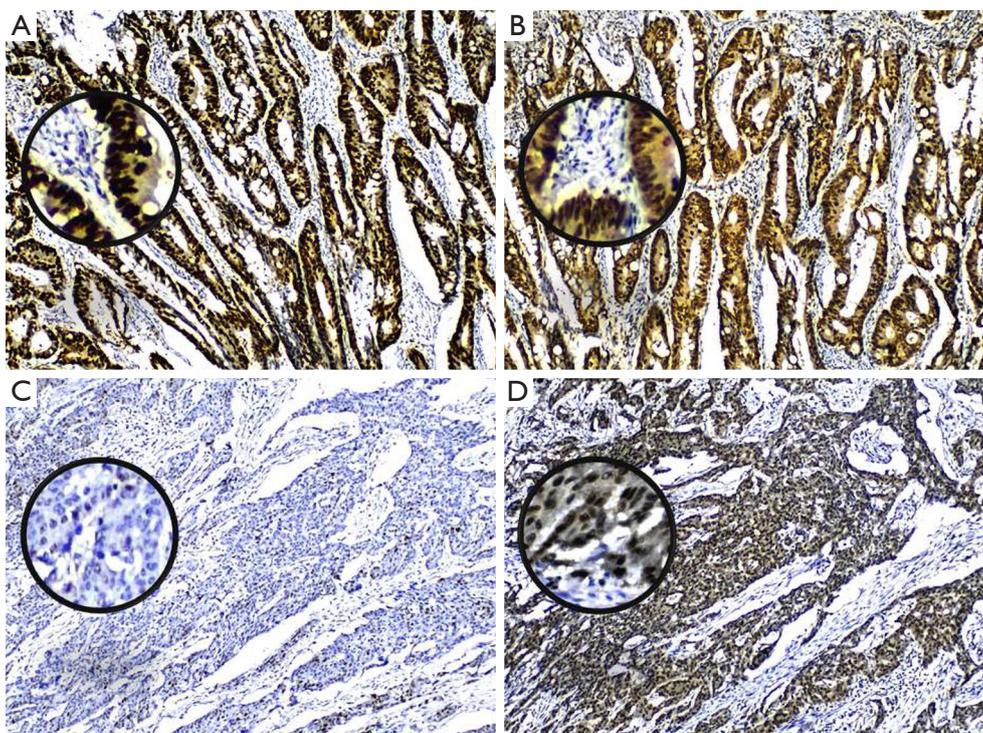


Figure 2 CRC tumor differentiation with p53 and XPO1 coexpression. Positive immunostaining coexpression of both p53 (A) and XPO1 (B) in well differentiated CRC tumors, while p53 expression loss (C) is accompanied with increase XPO1 expression (D) in poorly differentiated tumors, at magnification 100 \times . CRC, colorectal cancer.

Table 3 Association between the coexpression of p53 and XPO1 in lymph node metastasis

P53/XPO1 coexpression	Lymph node metastasis		Total	P
	Positive	Negative		
P53 positive				0.640
XPO1 positive	8	10	18	
XPO1 negative	4	2	6	
P53 negative				0.003
XPO1 positive	11	0	11	
XPO1 negative	1	4	5	

findings as higher proportion of p53 positivity in the left colon tumors compared to the right side which congruent with many studies (23,24).

In our series, most of the patients' tumors with positive lymph node metastasis were poorly differentiated indicating that these aspects of aggressive tumor behavior (25) may be a marker of poor prognosis in this study. Analysis of

the p53 expression revealed that the p53 expression was strongly associated with well differentiated tumors while some interesting high frequency of the p53 loss expression was predominated in moderate- or poorly-differentiated tumors as well as in positive lymph node metastatic tumors. Therefore, there was a strong trend of p53 loss related to more aggressive tumors behaviors than overexpression among CRC patients' tumors. These aspects were in concordance and supported by Cao *et al.*, 2017, who reported that the loss of p53 expression level was associated with aggressive clinicopathological characteristics such as lymph node and distant metastasis as well as with advanced tumor stages in patients with colon cancer (5). Trends of the p53 loss expression with worsening histological grade were also noted by Rambau *et al.* (26) while the in vivo study by Schwitalla *et al.* strongly suggested that the loss of p53 triggers the NF- κ B activation and epithelial-mesenchymal transition occurrence leading to colonic tumor invasion and lymph node metastasis (27).

The signaling complexity and diverse roles of the p53 protein in cellular regulation may be lost either through

the nuclear mislocalization or gene mutation leading to increase of its oncogenic properties in cancer (28). Therefore, the clarification of the association between p53 and other proteins expression such as XPO1 in tissue samples may help to define the prognostic value of p53 in CRC. Previously, a report indicated that while the *XPO1* gene expression is regulated negatively by p53 (11), the XPO1 induces loss of the p53 function through nuclear-cytoplasmic transport and then degradation through MDM2-mediated ubiquitination (9).

Although our findings showed that there was no significant association between the p53 and XPO1 expression, an inverse relationship was noted between the loss of p53 and increase of XPO1 expressions. Accordingly, the trends of p53 loss expression accompanied with increased intensity of the XPO1 expression conceded to evaluate their coexpression in relation to histopathological features. The results showed almost all the tumors with negative p53 expression and increases of the XPO1 expression were moderate- or poorly-differentiated tumors. In this study, most of the patients' tumors with worsening histological grade were positive for lymph node metastasis, which spurred us to study the association between these aspects of aggressive tumor behavior and the p53/XPO1 coexpression. Consistently, the *in vitro* studies showed that the XPO1 inhibitor increases the expression and nuclear localization of p53 through the inhibition of p53 nuclear export by the XPO1 (29,30), which indicate that the XPO1 may have an indirect effect on cancer behavior through p53. In our study, further interesting finding was that all tumors with loss p53 expression and an increase of the XPO1 expression were significantly observed with positive lymph node metastasis and mainly seen in TNM advance stage (III and IV) tumors. The XPO1 activity may abrogate the function of p53 by inhibiting its access to the nucleus through nucleo-cytoplasmic transport mechanism, which may lead to decrease the p53 activity and tumor progression (31). Cytoplasmic sequestration of mutant or wild-type p53 has been reported in a variety of tumors including CRC (32). Moreover, Sun *et al.* reported that the cytoplasmic expression of p53 but not nuclear was associated with poor survival in CRC patients (33). On the other hand, an association between the p53 overexpression and better survival of CRC patients has been reported occasionally (34,35). Taken together, the loss of the nuclear p53 expression accompanied with increase XPO1 expression may be considered as a factor of aggressive histopathological features among patients in this study. Therefore, further

investigations are needed considering molecular defining of functional p53 and its prognostic role in relation to XPO1 status in CRC patients.

Conclusions

As Yemeni patients with CRC, the loss of p53 in combination with increased of XPO1 expression was associated with aggressive histopathological features with poorly differentiated tumors and lymph node metastasis. Further studies are needed to elucidate the *TP53* mutations in relation to XPO1 coexpression in CRC prognosis.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the National Health and Medical Research Committee (NHMRC), the Ethics Committee of the Ministry of Public Health and Population, Republic of Yemen (Reference: B2/10-2017). Informed consent was obtained from all patients for being included in the study.

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