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Evaluation of (PARP-1) Expression in Gastric Carcinoma by Immunohistochemistry and Quantitative Real-Time PCR and its Relation to HER2 Status

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Abstract

Background: PARP-1 overexpression has been identified in several malignancies. Few studies have handled the expression of PARP-1 protein in gastric carcinoma and its associations with outcome.

Aim of Study: This study aimed at exploring the significance of PARP-1 expression in gastric adenocarcinoma and correlation with HER2 status.

Subjects and Methods: Quantitative expression of PARP-1 proteins was assayed by Immunohistochemistry in 40 cases of gastric adenocarcinoma. PARP-1 mRNA was moreover evaluated by Quantitative Real-Time Polymerase Chain Reaction.

Results: The level of expression of mRNA expression level was significantly increased in 25 of 40 (62.5%) of gastric adenocarcinoma tissues compared with the corresponding adjacent non cancer tissues (p<0.001). Positive expression of PARP-1 protein was detected in 23/40 (57.5%) of gastric adenocarcinoma. PARP-1 expression in cancer tissues was significantly higher than adjacent non-cancerous tissue (p<0.001). The aberrant high expression of PARP-1 showed significant correlation with depth of invasion (p<0.001), advanced stage (p<0.001), nodal (p<0.05) and distant metastasis (p<0.001). Positive correlation was detected between PARP-1 and positive HER2 status (p<0.001).

Conclusion: PARP-1 level is up regulated significantly in gastric adenocarcinoma tissue. PARP-1 is positively correlated with positive HER2 status and poor prognostic factors. PARP-1 might be potential prognostic marker for gastric adenocarcinoma.

Key Words: *PARP-1 – HER2 – Gastric carcinoma – Immunohistochemistry – Quantitative real-time PCR.*

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Introduction

GASTRIC Carcinoma (GC) is ranking as the fourth most common malignancy and the third leading cause of cancer related mortality worldwide [1]. Most of gastric carcinomas are frequently discovered in an advanced stage [2]. Hence, it is necessary to identify novel biomarkers for early detection of gastric carcinoma.

Poly (ADP-ribose) polymerases (PARPs) are multitasking protein translation enzymes. PARPs are believed to be activated by damaging DNA fragments. The PARP family includes multiple members, PARP1/4, PARP5a and PARP50 plus PARP6 [3].

PARP1 is ranking the most abundant member of the PARP family and is considered a key DNA repair factor involved in base excision repair occurring in response to DNA damage [4]. Beside the well-known function of PARP 1 in DNA damage repair, all recent studies have revealed that PARP1 play much wider role in malignancy as transcriptional regulation, chromatin remodeling and miRNA processing [5].

PARP1 expression has been detected to be increased significantly in a variety of cancers, including uterine, breast, ovarian, lung, and skin cancers [6]. PARP1 was believed to act as an oncogenic gene in breast cancer [7] and prostate cancer [8]. PARP1 protein expression was elevated in HER2+ breast tumors and correlation between PARP 1 and HER2 in breast cancer was documented in various studies [9].

This made us curious to investigate the relation between PARP1 expression and HER2, status in

gastric adenocarcinoma. Moreover, the present study aimed for assessment of PARP1 expression in gastric carcinoma and adjacent non-cancerous tissue by Quantitative Real-Time PCR and Immunohistochemistry and to correlate it with different clinicopathological factors.

Subjects and Methods

Subjects:

This is a retrospective controlled study carried upon 40 specimens of formalin-fixed, paraffin-embedded gastric adenocarcinoma. They were collected from Archives of Pathology Department, Benha Faculty of Medicine during the years 2013-2018. In each case, clinicopathologic findings, including age, gender, lymph node and distant metastasis status, were obtained from pathology reports and hospital records after approval by the Ethical Committee at Benha Faculty of Medicine. The study cases were previously stained immunohistochemically by HER2 and the HER2 status was revised.

Quantitative real-time RT-reassessment of PARP1 mRNA:

Total RNA was extracted from cancerous and adjacent non-cancer gastric tissues using the RNeasy extraction kit (Qiagen-USA) according to the manufacturer's protocol. The RNA concentration was measured using nanodrops pectrophotometer (Biowave II Germany). Then RNA was reverse transcribed into cDNA using the iScriptcDNA Synthesis Kit (Bio-Rad, USA). Quantitative PCR was applied using the Ready Mix PCR Reaction Mix kit (iScriptTM One-Step RT-PCR Kit with SYBR® Green (Bio-Rad, USA). PCR thermal cycling conditions were: 10min at 50ºC, 5min at 95ºC then 40 cycles (10sec at 95ºC 30sec at 55ºC, 1min at 55ºC) using Rotorgene real time PCR system and the related software for analysis and interpretation (Qiagen-S. Korea). P-actin used as the reference gene for internal control. The PCR primers sequences are shown in (Table 1), data were analyzed using the comparative Ct (2- AACT) method.

Table (1): The PCR primers sequences.

Gene	Forward primer	Reverse primer
PARP 1	5' TGCAGCTAGGGATGTGAATCTTC-3'	5' GGAGCCCAGTCCATCAGAACT-3'
P-actin	5' GTGACATCCACACCCAGAGG-3'	5' ACAGGATGTCAAAACTGCCC-3'

Histopathological study:

Conventional hematoxylin and eosin (H & E) stain was performed for all cases. Each case was examined by two specialists for (1) confirmation of the previous diagnosis, (2) assessment of tumor grade according to the WHO (2010), (3) assessment of Pathological T stage (depth of invasion) (4), assessment of other histopathological features as lymph node and distant metastasis. Stage was defined according to AJCC on Cancer Criteria (2017).

Immunohistochemical study:

Sections were prepared and immunostained for PARP1 Rabbit polyoclonal antibody (clone- ab 194586) (cat. ab6079; Abcam, Cambridge, UK) at a dilution of 1:100.DAP was utilized as a chromogen. IHC staining was performed, using detection kit (Thermoscientific, USA) according to the manufacturer's data. Positive control for PARP1 was human placental tissue. For negative controls, the primary antibody was replaced with phosphate-buffered saline.

Immunohistochemical assessment:

PARP1: Expression was detected mainly in the nucleus of positively stained cells. The intensity of staining was classified to four groups: 0 indicate no staining; 1 indicate weak staining; 2 indicate moderate staining and 3 indicate strong staining. The percentage was scored as follow: 0 if <5%, 1 if (5%-25%); 2 if (25%-50%). 3 if (51%-75%). 4 if >75%. After multiplication the percentage by intensity of stained cells, score of 0-4 was considered negative immunoreactivity, while score greater than 4 was considered positive immunoreactivity **[10]**.

HER2: HER2 scoring was divided into 4 groups, dependent on the extension and intensity: 0, with no positivity or positivity in the cell membrane in <10% of the cells; 1+, weak or hardly perceptible stain in >10% of the cells; 2+, weak to moderate, complete or in the basolateral membrane in >10% of the cells; 3+ complete, intense, positive or in the basolateral membrane in >10% of the cells. Only the cases of the 3+ group were considered positive for HER2 overexpression **[11]**.

Statistical analysis:

Analysis of the collected data was performed by SPSS version 16 software (Spss Inc, Chicago, ILL Company). Chi square (X^2) or Fisher's Exact Test (FET) were applied during the analysis of

categorical data. Differences between 2 groups were tested using student "*t*" test. Correlations among non-parametric variables were evaluated by Spearman's correlation coefficient (rho). The accepted level of significance in this work was stated at 0.05 (p<0.05 was considered significant).

Results

Patient clinicopathologic data:

The present retrospective study included 40 cases of gastric adenocarcinoma. The clinicopathological data were summarized in (Table 2).

Table (2): Clinicopathologic data of study cases.

Study groups	Number	Percent
Sex:		
Female	16	40
Male	24	60
Type:		
Tubular Adenorcarinom	22	55
Mucinous carcinoma	6	15
Signet ring carcinoma	12	30
Grade:		
Grade II	17	42.5
Grade III	23	57.5
Depth of invasion:		
T2	5	12.5
T3	14	35
T4	21	52.5
LN metastasis:		
Absent	7	17.5
Present	33	82.5
Distant metastasis:		
Absent	25	62.5
Present	15	37.5
TNM stage:		
Stage II	8	20
Stage III	17	42.5
Stage IV	15	37.5
Tumor size:		
<5cm	30	75
>5cm	10	25
Total	40	100

qRT-PCR results:

The mRNA level of PARP 1 was measured by qRT-PCR in 40 gastric adenocarcinoma tissue and adjacent non cancer tissues. The level of expression of mRNA expression level was significantly increased in 25 of 40 (62.5%) of gastric adenocarcinoma tissues compared with the corresponding adjacent non cancer tissues (p<0.001), as shown in Fig. (1).

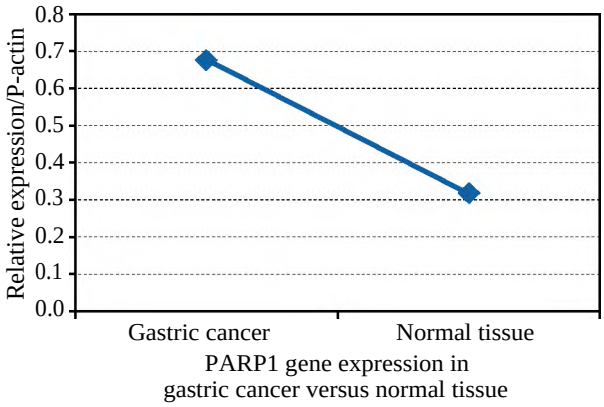

Fig. (1): PARP1 Gene expression in gastric adenocarcinoma tissue versus non-cancerous tissues by RT-PCR (PARP1/β actin, n=40, p<0.001).

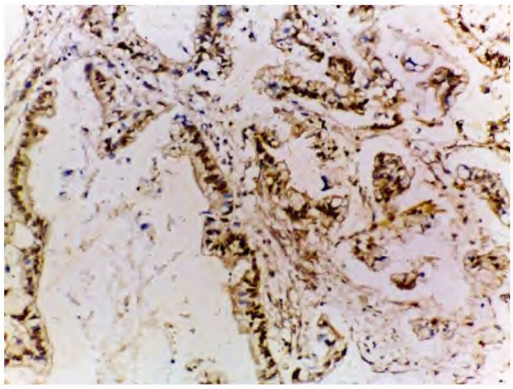

Fig. (2): Nuclear expression of PARP1 score (8) in gastric mucinous adenocarcinoma (IHC, X200).

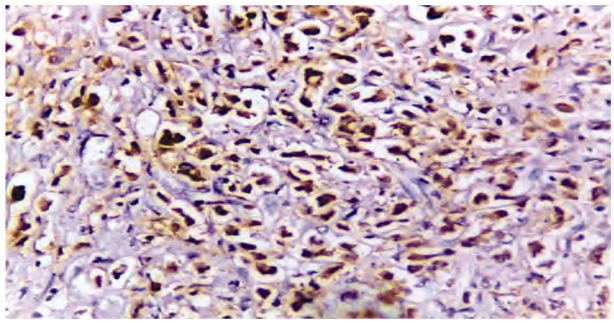

Fig. (3): Strong nuclear expression of PARP1, score (9) in signet ring gastric carcinoma (IHC X400).

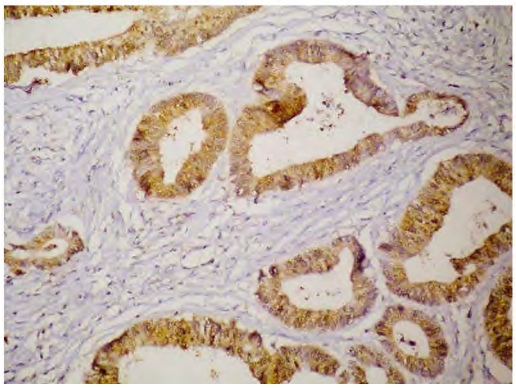

Fig. (4): Strong membranous expression of HER2, score (3) in gastric tubular adenocarcinoma (IHC, X200).

Table (3): PARP1 immunostaining in gastric adenocarcinoma cases.

Variable	Adjacent non-cancerous tissue		Cancerous tissue		Test of significance	*p*	Cut out point	Sensitivity %	Specificity %	AUC
PARP1:										
Negative	40	100.0%	17	42.5%	χ^2=25.7	<0.001	>2	80.5%	85.4%	0.896
Positive	0	0.0%	23	57.5%		(HS)*				

*(HS): Highly Significant.

Table (4): Correlation of PARP1 with clinicopathological variables.

Variable	N	PARP 1				Test of sig.	*p*
		Negative (n=17)		Positive (n=23)			
		No.	%	No.	%		
Age (ys): (Mean ± SD)	40	13.5±51.5		12.6±54.9		Z_{MWU}=0.62	0.53 (NS)
Sex:							
Female	15	7	41.2	8	37.5	χ^2=0.06	0.81 (NS)
Male	25	10	58.8	15	62.5		
Type:							
Adenocarcinoma	22	8	47.1	14	62.5	FET=1.97	0.38 (NS)
Mucoid carcinoma	6	2	11.8	4	16.7		
Signet ring carcinoma	12	7	41.2	5	20.8		
Grade:							
Grade II	18	8	41.2	10	45.8	χ^2=0.09	0.76 (NS)
Grade III	22	9	58.8	13	54.2		
Depth of invasion:							
T2	5	4	23.5	1	4.2	FET=19.3	<0.001 (HS)**
T3	15	9	52.9	6	25.0		
T4	20	4	23.5	16	70.8		
LN metastasis:							
Absent	10	7	35.3	3	4.2	FET=8.28	<0.05 (S)*
Present	30	10	64.7	20	95.8		
Distant metastasis:							
Absent	25	17	100.0	8	33.3	χ^2=28.5	<0.001 (HS)**
Present	15	0	0.0	15	66.7		
TNM:							
Stage II	8	8	47.1	0	0.0	FET=26.5	<0.001 (HS)**
Stage III	17	9	52.9	8	33.3		
Stage IV	15	0	0.0	15	66.7		
Size:							
≤5cm	21	11	100.0	10	58.3	FET	0.78 (NS)
>5cm	19	6	0.0	13	41.7		

(NS): Non Significant. (S*): Significant. (HS**): Highly Significant.

Immunohistochemical results:

PARP1 immunostaining in studied cases:

Comparing the levels of PARP1 in gastric adenocarcinoma tissues and adjacent non-cancerous tissues revealed significant higher expression in the cancerous group (p<0.001). Concerning predictively of the PARP1 in early diagnosis of cancerous group, sensitivity was (80.5%) and specificity was (85.4%) as shown in (Table 3).

Correlation of PARP1 with clinicopathological variables: PARP1 was significantly correlated with depth of invasion (p<0.001), advanced tumor stage (p <0.001), nodal (p<0.05) and distant metastasis status (p<0.001). Other histopathological factors failed to obtain statistical significant differences as detailed in (Table 4).

Correlation between PARP1 and HER2 in the studied cases: The present study demonstrated a high significant positive correlation between PARP1 and HER2. Out of 23 cases positive for PARP1, 13 cases (56.5%) were positive for HER2 while 10 cases (43.5%) were negative (p<0.001) as detailed in (Table 5).

Table (5): Correlation between PARP1 and HER2.

Markers	PARP 1		Rho	*p*-value
	Negative (17)	Positive (23)		
HER2:				
Negative (26)	16 (94.1%)	10 (43.5%)	0.685	<0.001
Positive (14)	1 (5.9%)	13 (56.5%)		(HS)*

*(HS): Highly Significant.

Discussion

Gastric cancer is ranking one of the most common malignant neoplasms. Gastric cancer is attributed to a high cancer-related mortality worldwide [12]. Most gastric cancer patients are often diagnosed with an advanced stage. Discovery of new diagnostic biomarkers for early detection of gastric cancer remains an urgent need [13].

It is well acknowledged that PARP 1, the most abundant member of the PARP superfamily, is a key DNA repair factor involved in base excision repair occurring in response to DNA damage [14]. PARP1 is a highly conserved cell signaling protein that exclusively catalyzes poly ADP-ribosylation of DNA-binding proteins, such as BRCA1, thereby modulating their activity. Overexpression of PARP1 has been identified in different human cancers [15]. However, few papers have studied PARP 1 expression in gastric adenocarcinoma.

The present study aims to detect PARP1 expression at mRNA level using qRT-PCR technique and protein level using immunohistochemistry in gastric adenocarcinoma tissue and compare its level in adjacent non-cancerous tissue. The correlation between PARP1 and HER2 status was also assessed in addition to its correlation with different clinicopathologic parameters.

The current study demonstrated that PARP1 detection at both mRNA level and protein expression was significantly higher in in gastric adenocarcinoma tissues than that in adjacent non-cancerous tissue (p<0.001). PARP1 protein was seen in 57.5% of study gastric adenocarcinoma cases. The level of expression of PARP1 mRNA expression level was significantly detected in (62.5%) of gastric adenocarcinoma tissues (p <0.001).

In addition, the present work revealed that overexpression of PARP1 was correlated with depth of invasion (p<0.001), advanced tumor stage (p <0.001), nodal metastasis (p<0.05) and distant metastasis status (p<0.001) but not correlated with patient age, gender, tumor type or grade of differentiation. Consequently, our results might provide further evidence of PARP1 being a potential biomarker of carcinogenesis, aggressiveness and poor prognosis in gastric adenocarcinoma.

Previous reports have revealed similar results. The study of Park et al., [16] demonstrated that PARP1 proteins was observed in 54% of gastric carcinoma and was correlated with tumor invasion (p<0.001), higher tumor stage (p<0.001, lymph node metastasis (p<0.001), and venous invasion (p=0.017) and more shorter OS (p<0.001). The study of Liu et al., [17] showed that increased PARP-1 expression was associated with lymph node metastasis, advanced TNM stage and reduced DFS and OS in gastric cancer patients.

The recent study of Afzal et al., [10] detected significant up-regulation of PARP 1 in gastric carcinoma (p<0.001) and significant correlation with poor prognostic factors as T stage (p<0.01) and lymph node metastasis and poor survival. Moreover, they found that upregulation of PARP 1 was significantly higher in H. pylori positive gastric cancer (HPGC) cases and they explained that H. pylori is associated by an increased oxygen free radical formation with increased oxidative stress and chronic accumulation of DNA damage.

The study of Wang et al., [18] that increased PARP1 activity in gastric carcinoma cells is responsible for cisplatin resistance and that PARP1 inhibitor can significantly enhance cisplatin induced DNA damage and apoptosis, indicating potential clinical significance of PARP1 activity in gastric carcinoma.

Association of PARP1 with poor prognostic factors had been documented in other types of cancers as breast cancer [19], hepatocellular carcinoma [20], cancer ovary [21] and melanoma [22].

The role of PARP1 in carcinogenesis and cancer progression may be clarified by its dual functions in both DNA repair and transcriptional regulation. PARP1 can modulate the transcription of many oncogenes, as hypoxia-inducible factor 1 α and 2A genes and Vascular Endothelial Growth Factor Receptor 1 (VEGFR1) gene [23]. PARP1 regulates gene expression through different mechanisms as chromatin remodeling, DNA methylation pathways and RNA polymerase II [24].

The study of Pu et al., [25] demonstrated that PARP-1 has a role in regulation of Epithelial-mesenchymal Transition (EMT) in prostate cancer. Moreover, the study of Choi et al., [26] revealed that PARP1 upregulates metastasis of lung cancers

by improving PARP1-mediated transcription of S 1 000A4 and CLDN7.

Concerning the correlation between PARP1 and HER2 status, the present study demonstrated positive significant correlation between PARP1 positive expressions and positive HER2 status in gastric carcinoma cases. To our best knowledge, this may be the first study identifying significant correlation between PARP1 and HER2 in gastric carcinoma. This allows us to think about the possibility of combining PARP1 inhibitor therapeutics with anti HER2 therapeutics for gastric carcinoma patients to obtain optimal benefits of chemotherapy.

In consistence with the present results, the study of Stanley et al., **[9]** revealed a statistically significant increase in PARP1 protein levels in HER2+ breast cancers. The study of Wielgos et al., **[27]** clarified that increased PARP1 expression in HER2+ breast cancers is regulated by the let-7a miRNA and that Ectopic expression of the let-7a anti-miRNA resulted in increased PARP1 protein.

On brief, our study provided additional evidence about the potential prognostic role of PARP1in gastric adenocarcinoma and highlighted important information about the link between PARP1 and HER2 pathways during the progression of gastric adenocarcinoma.

Conclusion:

PARP1 may have a potential role in carcinogenesis, and aggressiveness of gastric adenocarcinoma. A significant correlation between PARP1 and HER2 may highlight the role of PARP1in regulation of HER2 in gastric adenocarcinoma. Further research is needed to confirm the role of PARP1-HER2 axis in the progression of gastric carcinoma and possibility of a combined anti PARP 1 and anti HER2 chemotherapy strategy.

Conflict of interest:

No conflict of interest.

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أهمية ظهور الدلالة (PARP-1) فى سرطان المعدة بإستخدام الكيمياء المناعية وتحليل البوليميراز المتسلسل اللحظى المرسال وعلاقته بالدلالة (HER2)

\المقدمة: يعد سرطان المعدة واحداً من أكثر الأورام السرطانية شيوعاً وغالباً ما يتم تشخيص معظم مرضى سرطان المعدة بمرحله متقدمة لذلك هناك ضرورة ملحة لإكتشاف مؤثرات حيوية جديدة للتشخيص المبكر عن سرطان المعدة. يعتبر (PARP-1) جين خاص بإصلاح الحمض النووى وقد أثبتت الدراسات إرتفاع مستوى PARP-1 فى الأورام السرطانية المختلفة.

\الهدف من \البحث: دراسة ظهور PARP-1 بإستخدام الكيمياء المناعية وتحليل البوليميراز المتسلسل اللحظى وتوضيح دورة فى نشأة وتطور سرطان المعدة الغدى وعلاقته بالدلالة HER2.

طريقة \البحث: تم تقييم التعبير الكمى لبروتينات PARP-1 وHER2 بواسطة الكيمياء المناعية وتم أيضاً تقييم الحمض النووى الريبوزى المرسال ل PARP-1 بواسطة تحليل البوليميراز المتسلسل اللحظى فى ٤٠ حالة من سرطان المعدة الغدى.

\النتائج: أظهرت هذه الدراسة أن بروتين PARP-1 يتواجد بنسبة (٥٧.٥٪) فى سرطان المعدة الغدى أما الحمض النووى الريبوزى المرسال ل PARP-1 فقد ظهر بنسبة (٥.٦٢٪) فى سرطان المعدة الغدى وهذه النسب أعلى إحصائياً من الأنسجة غير السرطانية المجاورة لسرطان المعدة (p<0.001). كما كشفت الدراسة أيضاً إيجاد علاقة إحصائية طردية بين إرتفاع مستوى PARP-1 وبين المتغيرات الأخرى مثل إرتفاع درجة الورم ووجود ثانويات فى الغدد الليمفاوية وكذلك تقدم مرحلة الورم وتكوين الثانويات البعيدة. كشفت الدراسة أيضاً عن وجود علاقة طردية بين زيادة مستوى PARP-1 وحالة HER2 الموجبة.

\الإستنتاج: إن دلالة الأورام PARP-1 قد يكون لها دوراً رئيسياً فى نشأة وتقدم وشراسة سرطان المعدة الغدى. يرتبط PARP-1 بشكل إيجابى مع HER2 قد يمكن الإعتماد على PARP-1 كعامل للتنبؤ بالتطور المرضى لسرطان المعدة الغدى.