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RESEARCH ARTICLE

Immunohistochemical study of fibroblast activation protein and α-smooth muscle actin expression and distribution in triple negative breast cancer

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ABSTRACT

Introduction: Triple negative breast cancer constituting 10-20% of all breast cancers, and are more frequently in younger patients with poor prognostic outcome , The tumor microenvironment is formed of activated fibroblasts which known as Cancer associated fibroblasts, which can be detected by fibroblast activation protein [FAP] and α- smooth muscle actin [α-SMA]. **Aim of the work**: evaluation of the expression and distribution of FAP and α-SMA in triple negative breast cancer. **Material and methods**: this study was carried on 100 paraffin blocks from pathologically proved triple negative invasive breast cancer patients and subjected to immunostaining of SMA and FAP antibodies, Evaluation of antibodies expression according to its distribution in tumor margin and in tumor center. **Results**: There were significant differences between FAP as well as SMA expression in tumor center and tumor margin, FAP and SMA expression in the tumor center was positively correlated with tumor size and grade. In contrast to tumor margin FAP and SMA expression was negative correlated with tumor size and lymph node metastasis. **Conclusion**: We speculated that high FAP expression and α-SMA expression in the tumor center, but not the tumor margin, is correlated with poor patient's clinicopathological parameter.

Keywords: Breast cancer, FAP, Triple negative

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INTRODUCTION

Breast cancer is considered to be the most frequently diagnosed cancer and is the second leading cause of death in women (Allison 2012). Breast cancer that lack expression of ER , PR and HER2 is considered as a subtype of breast cancer and termed as triple negative breast cancer (TNBC) (Tavassoli and Devilee 2003). After researches, its proved that Triple negative breast cancer constituting 10-20% of all breast cancers, and are more frequently in younger patients with poor prognostic outcome (Carey et al., 2006 and Morris et al., 2007). The tumor microenvironment (TME) is formed of extracellular matrix (ECM) with cellular players which can be divided into neuroendocrine (NE) cells, immune-inflammatory cells, adipose cells, vascular networks and activated fibroblasts which known as Cancer associated fibroblasts (CAFs) (Wang et al.,2017).

Cancer associated fibroblasts can be detected by the immunohistochemical expression of various markers as tenascin C,α-smooth-muscle actin (α-SMA), neuron glial antigen-2 (NG2), fibroblast activation protein (FAP), periostin, vimentin, fibroblast specific protein-1 (FSP-1) and platelet derived growth factor b (PDGFR-b) (Luo et al., 2015, Togo et al., 2013 and Shiga et al., 2015).

Fibroblast activation protein expression have been identified to be expressed by many cell types in the context of the tumor microenvironment (TME) such as tumor associated macrophages, CAFs and mature adipocytes which undergo rapid de-differentiation during carcinogenesis and it is proved that this process was associated with induction of FAP expression (Lessard et al., 2015) .

In TME, the stromal fibroblasts proliferate and differentiate into myofibroblasts which express α-SMA. So the most traditionally and widely used immunohistochemical marker for detection of CAFs is α-SMA (Tomasek et al., 2002). One of the hallmarks of malignancy is tumor heterogeneity. Heterogeneity inside the tumor could be due to the presence of heterogeneous cell populations within an individual tumor (Ellsworth et al., 2016). Tumorigenicity, treatment resistance, and metastatic potential could be different characteristics to defined tumor heterogeneity (Fidler and Kripke, 1977). In this study we evaluated the expression and distribution of FAP and α-SMA in triple negative breast cancer.

MATERIALS AND METHODS

This is a retrospective study was done on 100 paraffin's blocks from pathologically proved triple negative invasive breast cancer patients, the paraffin blocks were collected during the period between January 2018 and December 2019. And the patient characteristics were taken from pathology report. This study was approved by The Ethics Committee in Faculty of Medicine, Tanta University, H&E sections from paraffin blocks was done for confirmation of pathological types, classification as well as grading of the tumor.

Immunohistochemistry

Sections from paraffin blocks with Four micrometers thickness was placed on positive charged slides then deparaffininzed in xylene, using descending alcohol grades in rehydration of sections, then using antigen retrieval by microwave incubation in 6.1 PH citrate buffer for 20 minutes. Endogenous peroxidase by H2O2 is used for blocking. Sections were incubated in blocking solution for 5 min. Then, sections were incubated with primary antibodies of FAP (clone 427819, 1:50 dilution) and α-SMA (clone 1A4, 1:100 dilutions). Visualization of FAP and α-SMA obtained by streptavidin biotin ABC detection kit (Catalog # TA-015-HP, Lab-Vision Corporation Fremont, USA) and counterstaining with haematoxylin. Evaluation of antibodies expression and distribution was done in the fibroblasts that located tumor margin (in the stroma adjacent to the invasive tumor margin) and tumor center (fibroblasts located in the stroma within the tumor mass). Evaluation of FAP expression was done according to Cao et al., (2017) by using the product of multiplying of proportion score and intensity score. Estimation of proportion score of positively stained fibroblasts: 0: (≤25%) 1: (>26 % & ≤ 50%) 2: (>51% & ≤75%) and 3: (>75) of fibroblasts stained positive. The intensity score of positive stained fibroblasts 0: Negative staining. 1: weak staining. 2: moderate staining .3: strong staining. Then the expression is classified as low expression when the score was (1-3) and high expression when the score was (4-9). Epithelial and macrophages staining were not analyzed. α- smooth muscle actin staining was evaluated as positive only when more than 10% of stromal fibroblastic cells showed cytoplasmic expression.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp).Comparisons between groups for categorical variables were assessed using Chi-square test (Fisher or Monte Carlo). Significance of the obtained results was judged at the 5% level.

RESULTS

One hundred cases were included in this study, they can be classified histologically into 66 cases NST, 12 cases were metaplastic carcinoma, including 3 cases of adenosquamous carcinoma and 8 cases of squamous cell carcinoma], 15 cases were of medullary carcinoma (Tables 1 & 2).

Table 1. Relation between FAP expression between tumor center and tumor margin (n=100)

	FAP Negative	FAP low expression	FAP high expression	χ^2	p
Tumor center	24(24%)	30(30%)	46(46%)	8.964*	0.011*
Tumor margin	44(44%)	21(21%)	35(35%)		

χ^2: Chi square test , *: Statistically significant at p ≤ 0.05

Table 2. Relation between SMA expression between tumor center and tumor margin (n=100)

	SMA Negative	SMA Positive	χ^2	p
Tumor center	24(24%)	76(76%)	18.916*	<0.001*
Tumor margin	54(54%)	46(46%)		

χ^2: Chi square test , *: Statistically significant at p ≤ 0.05

Table 3. Relation between FAP expression and clinic pathological data in the center of the tumor (n=100)

Clinic pathological data	Total (n=100)	FAP expression Negative (n=24)	Low expression (n=30)	High expression (n=46)	χ^2	p
Age (years)						
<45	23(23%)	2 (8.3%)	6(20%)	15(32.6%)	5.466	0.065
>45	77(77%)	22(91.7%)	24(80%)	31(67.4%)		
Tumor size						
T1	10(10%)	8(33.3%)	2(6.7%)	0(0%)		
T2	26(26%)	6(25%)	8(26.7%)	12(26.1%)	17.833*	MCp=0.001*
T3	64(64%)	10(41.7%)	20(66.7%)	34(73.9%)		
Grade						
I	7(7%)	5(20.8%)	1(3.3%)	1(2.2%)		
II	21(21%)	9(37.5%)	8(26.7%)	4(8.7%)	18.842*	MCp<0.001*
III	72(72%)	10(41.7%)	21(70%)	41(89.1%)		
Lymph node status						
N0	34(34%)	19(79.2%)	9 (30%)	6 (13%)		
N1	14(14%)	1(4.2%)	7(23.3%)	6(13%)	36.349*	<0.001*
N2	22(22%)	2(8.3%)	8(26.7%)	12(26.1%)		
N3	30(30%)	2(8.3%)	6(20%)	22(47.8%)		
Histological types						
NST	66(66%)	14(58.3%)	22(73.3%)	30(65.2%)		
Met aplastic	12(12%)	0(0%)	2(6.7%)	10(21.7%)	21.903*	MCp=0.001*
Medullary	15(15%)	10(41.7%)	3(10%)	2(4.3%)		
Others	7(7%)	0(0%)	3(10%)	4(8.7%)		

χ^2: Chi square test, MC: Monte Carlo, *: Statistically significant at p ≤ 0.05

Table 4. Relation between FAP expression and clinic pathological data in the margin of the tumor (n=100)

Clinic pathological data	Total (n=100)	FAP expression Negative (n=44)	Low expression (n=21)	High expression (n=35)	χ^2	p
Age (years)						
<45	23(23%)	8(18.2%)	0(0%)	15(42.9%)	14.642*	0.001*
>45	77(77%)	36(81.8%)	21(100%)	20(57.1%)		
Tumor size						
T1	10(10%)	1(2.3%)	3(14.3%)	6(17.1%)		
T2	26(26%)	3(6.8%)	8(38.1%)	15(42.9%)	26.591*	MCp <0.001*
T3	64(64%)	40(90.9%)	10(47.6%)	14(40%)		
Grade						
I	7(7%)	1(2.3%)	1(4.8%)	5(14.3%)		
II	21(21%)	10(22.7%)	6(28.6%)	5(14.3%)	5.248	MCp=0.247
III	72(72%)	33(75%)	14(66.7%)	25(71.4%)		
Lymph node status						
N0	34(34%)	21(47.7%)	0(0%)	13(37.1%)		
N1	14(14%)	1(2.3%)	2(9.5%)	11(31.4%)	45.376*	MCp<0.001*
N2	22(22%)	4(9.1%)	9(42.9%)	9(25.7%)		
N3	30(30%)	18(40.9%)	10(47.6%)	2(5.7%)		
Histological types						
NST	66(66%)	26(59.1%)	15(71.4%)	25(71.4%)		
Met aplastic	12(12%)	3(6.8%)	3(14.3%)	6(17.1%)	10.116	0.089
Medullary	15(15%)	12(27.3%)	1(4.8%)	2(5.7%)		
Others	7(7%)	3(6.8%)	2(9.5%)	2(5.7%)		

χ^2: Chi square test, MC: Monte Carlo, *: Statistically significant at p ≤ 0.05

Table 5. Relation between SMA expression and clinic pathological data in the center of the tumor (n=100)

Clinic pathological data	Total (n=100)	SMA expression Negative (n=24)	Positive (n=76)	χ^2	p
Age (years)					
<45	23(23%)	4(16.7%)	19(25%)	0.715	0.398
>45	77(77%)	20(83.3%)	57(75%)		
Tumor size					
T1	10(10%)	6(25%)	4(5.3%)		
T2	26(26%)	8(33.3%)	18(23.7%)	10.220*	0.006*
T3	64(64%)	10(41.7%)	54(71.1%)		
Grade					
I	7(7%)	5(20.8%)	2(2.6%)		
II	21(21%)	2(8.3%)	19(25%)	11.052*	0.004*
III	72(72%)	17(70.8%)	55(72.4%)		
Lymph node status					
N0	34(34%)	9(37.5%)	25(32.9%)		
N1	14(14%)	6(25%)	8(10.5%)	6.196	0.102
N2	22(22%)	6(25%)	16(21.1%)		
N3	30(30%)	3(12.5%)	27(35.5%)		
Histological types					
NST	66(66%)	14(58.3%)	52(68.4%)		
Met aplastic	12(12%)	2(8.3%)	10(13.2%)	4.564	MCp=
Medullary	15(15%)	7(29.2%)	8(10.5%)		0.194
Others	7(7%)	1(4.2%)	6(7.9%)		

χ^2: Chi square test, MC: Monte Carlo, *: Statistically significant at p ≤ 0.05

Table 6. Relation between SMA expression and clinic pathological data in the margin of the tumor (n=100)

Clinic pathological data	Total (n=100)	SMA expression Negative (n=54)	Positive (n=46)	χ^2	p
Age (years)					
<45	22(22%)	17(31.5%)	5(10.9%)	6.150*	0.013*
>45	78(78%)	37(68.5%)	41(89.1%)		
Tumor size					
T1	10(10%)	1(1.9%)	9(19.6%)		
T2	26(26%)	8(14.8%)	18(39.1%)	20.299*	<0.001*
T3	64(64%)	45(83.3%)	19(41.3%)		
Grade					
I	7(7%)	1(1.9%)	6(13%)		MCp=
II	21(21%)	9(16.7%)	12(26.1%)	6.764*	0.036*
III	72(72%)	44(81.5%)	28(60.9%)		
Lymph node status					
N0	34(34%)	5(9.3%)	29(63%)		
N1	14(14%)	11(20.4%)	3(6.5%)	33.328*	<0.001*
N2	22(22%)	18(33.3%)	4(8.7%)		
N3	30(30%)	20(37%)	10(21.7%)		
Histological types					
NST	66(66%)	34(63%)	32(69.6%)		
Met aplastic	12(12%)	6(11.1%)	6(13%)	1.305	MCp=
Medullary	15(15%)	9(16.7%)	6(13%)		0.757
Others	7(7%)	5(9.3%)	2(4.3%)		

χ^2: Chi square test, MC: Monte Carlo, *: Statistically significant at p ≤ 0.05

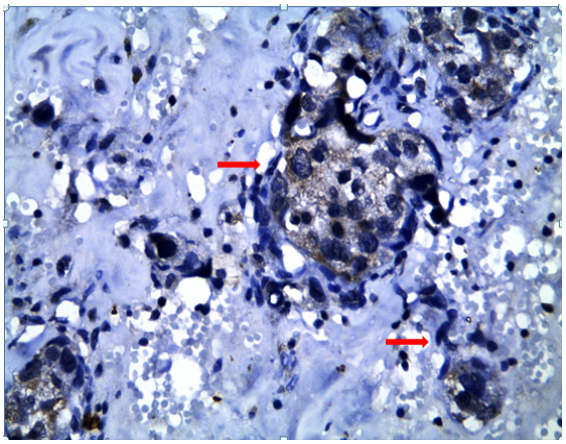

Figure 1. Negative FAP expression in the tumor center [marked by red arrows x400]

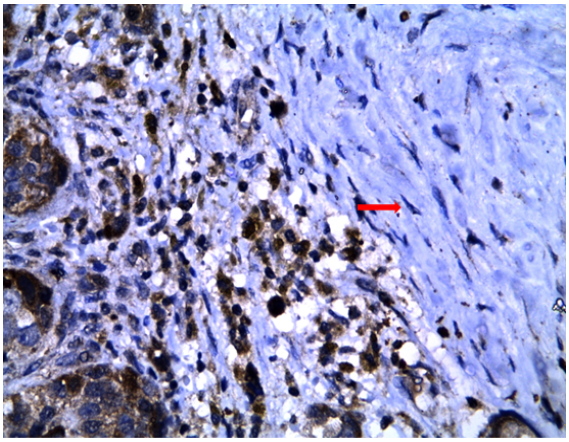

Figure 4. Negative FAP expression in the tumor margin [marked by red arrow x400]

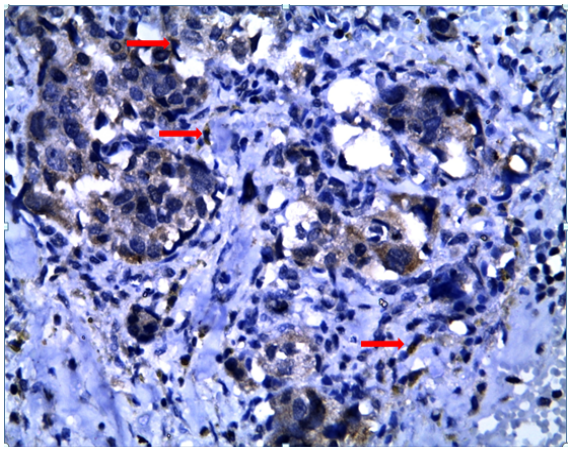

Figure 2. Low FAP expression in the tumor center [marked by red arrows x400]

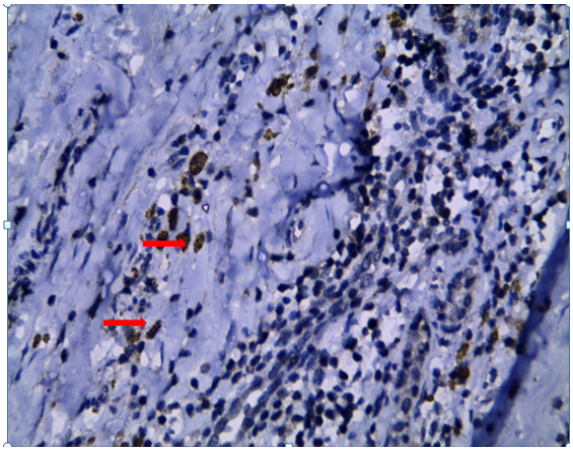

Figure 5. Low FAP expression in tumor margin [marked by red arrows x400]

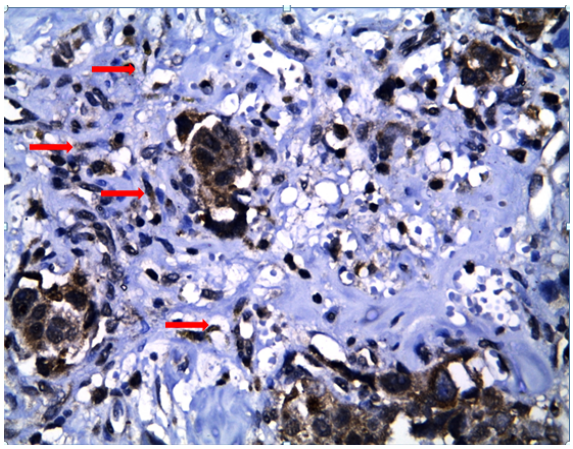

Figure 3. High FAP expression in the tumor center [marked by red arrows x400]

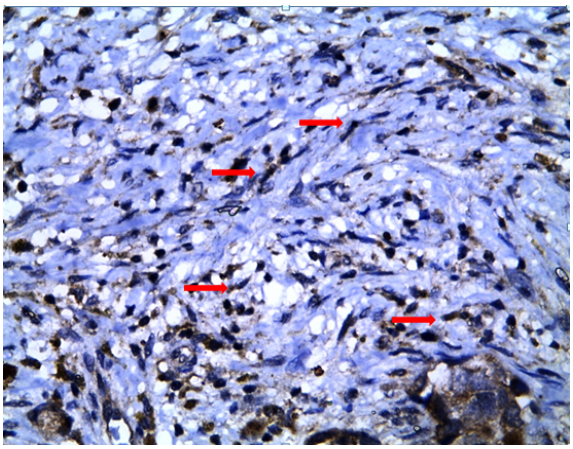

Figure 6. High FAP expression in the tumor margin[marked by red arrows x400]

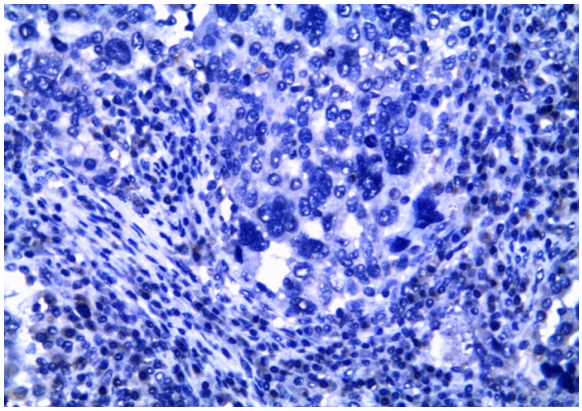

Figure 7. Negative SMA expression in the tumor center[x400]

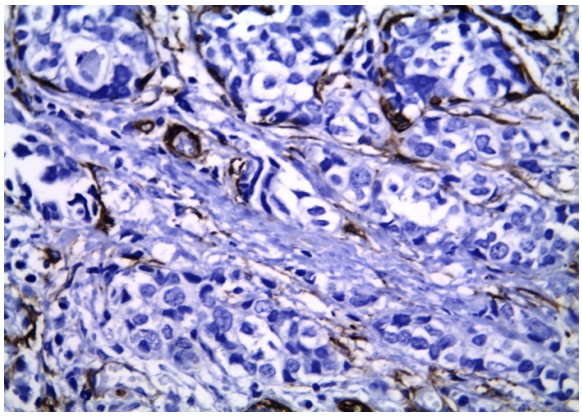

Figure 8. Positive SMA expression in the tumor center[x400]

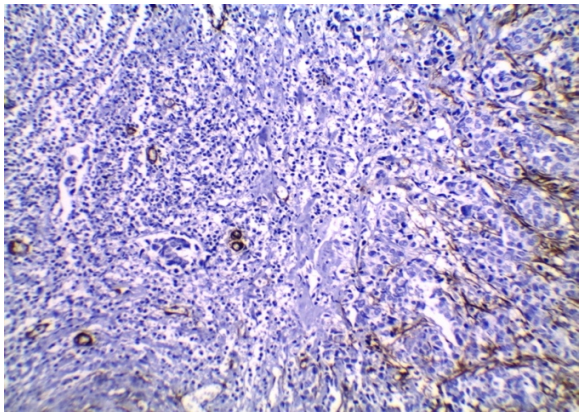

Figure 9. Negative SMA expression in the tumor margin [x100]

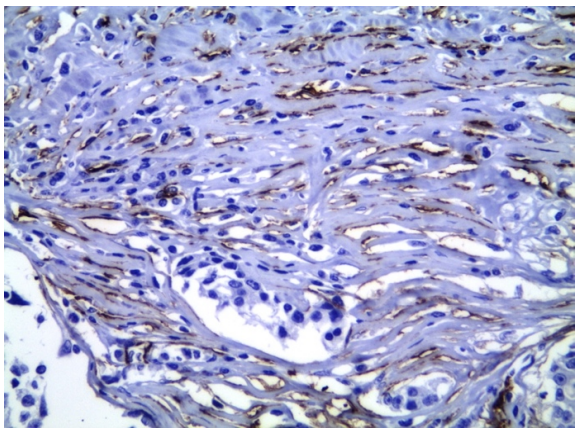

Figure 10. Positive SMA expression in the tumor margin [x400]

Also there were 4 cases of pleomorphic lobular carcinoma, 2 cases of mucinous carcinoma and 1 case of apocrine adenocarcinoma, which are collected together to facilitate statistical analysis (Table 1&2).

The distribution of studied antibodies in the tumor

There were significant differences between FAP expression in tumor center and tumor margin as there were 24 of cases were negative for FAP expression in the tumor center. Thirty of cases showed low expression while 46 of cases showed stromal FAP high expression , while on examination of the tumor margin there were 44 cases were negative, 21 cases showed low expression and 35 cases showed high stromal FAP expression (Figs. 1-6). Also, there were significant differences between α-SMA expression in tumor center and tumor margin as there were 24 cases were negative for expression of α-SMA in the tumor center and 76 cases showed positive expression. In contrast to tumor margin 54 cases were negative, 46 cases showed positive expression (Figs. 7-10).

Correlation with clinicopathological data

Fibroblast activation protein expression in the tumor center was positively correlated with histopathological types, tumor size, grade and lymph node metastasis. In contrast to tumor margin FAP expression was negative correlated with tumor size and lymph node metastasis. On examination of α-SMA expression in the tumor center, there were positive correlation with tumor size and grade, while in tumor margin there were negative correlation with tumor size, grade and lymph node metastasis (Tables 3-6).

DISCUSSION

Triple negative breast cancer when compared to other types of breast cancer, it is a unique subgroup of breast cancers with heterogeneous presentation, behavior, grade, and response to the therapy (Brouckaert et al., 2012).

One of the favorable prognostic factor of breast cancer is the presence of mature fibrosis with dense collagen fibers and spindle-shaped fibroblasts, which are reported to inhibit the spread of cancer cells, however the presence of

immature desmoplasia with large, plump myofibroblast-like cells could promote cancer invasion, and are considered as one of the undesirable prognostic factors (Son et al., 2019). As such, the existences of fibroblasts around cancer cells which are called cancer-associated fibroblasts (CAFs) in tumor microenvironment are important factor for cancer invasion and metastasis (Shi et al., 2017). FAP and α-SMA has been described to be expressed in the CAFs in tumor microenvironment of epithelial cancers (Garin et al., 1990 and Rettig et al., 1994).

In the present study we examined the distribution of FAP and α-SMA antibodies in different tumor areas in TNPC and their expression in relation to clinicopathological parameters. FAP expression in the tumor center was negative in 24% of cases, showed low expression in 30% of cases and showed high expression in 46% of cases, while it was negative in the tumor margin in 44% of cases, showed low expression in 21% of cases and high expression in 35% of cases. There were significant differences between FAP expression in tumor center and tumor margin

On examination of α-SMA in the tumor center there was negative expression 24% of cases and positive expression in 76% of cases, while in tumor margin there was negative expression in 54% of cases and positive expression in 46% of cases. There were significant differences between α-SMA expression in tumor center and tumor margin.

This could be explained by the study of Maria et al., (2013) on colonic cancer, they stated that FAP expression by CAFs in the tumor margin may reflect a stress effect to the tumor microenvironment at the invasive margin, while FAP expression in the more sheltered tumor center might be an indicator of the inherent invasive potential of the tumor.

As regards to clinicopathological parameter FAP expression in the tumor center was positively correlated with tumor size, grade, lymph node metastasis and histological types, while α-SMA expression in tumor center was positively correlated with tumor size and grades

Fibroblast activation protein expression in the tumor margin was negatively correlated with tumor size and lymph node metastasis, while α-SMA expression in tumor margin was negatively correlated with tumor size, grade and lymph node metastasis

This results was similar to Tchou et al., (2013) in their study using breast cancer tissues and reported FAP expression in breast cancer stroma is heterogeneous and may correlate with clinicopathologic parameters such as size, grade, axilla nodal involvement and tumor histological types especially TNBC. So, FAP may represent a potentially targetable by therapy especially for tumor that lacks targeted therapy such as TNBC

Maria et al ., (2013), have reported that FAP and α-SMA expressing CAFs produce fibroblast growth factor 1, that increase the invasion of cancer cells and could explained the poor prognosis seen in patients with high FAP expression in the tumor center.

As well as Henry et al., (2007), who concluded that FAP and α-SMA expressing CAFs in the tumor margin are of importance during early invasion and metastasis , which might be similar to our finding of high FAP expression and positive α-SMA expression in the tumor margin is correlated with small tumor size, low lymph node metastasis and low histological grade cases . Once the invasive carcinoma is established, there are other factors affecting clinical outcome.

In conclusion, we speculated that high FAP expression and α-SMA expression in the tumor center, but not the tumor margin, is correlated with poor patient's clinicopathological parameter. This study is important in studying cancer microenvironment presented in activated fibroblasts in order to find treatment against it to prevent tumor progression.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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EACR is an NGO society that was declared by the Ministry of Social Solidarity (Egypt) No. 1938 in 19/11/2014 based on the initiative of Prof. Mohamed Labib Salem, the current Chairman of EACR. EACR aims primarily to assist researchers, in particular young researchers in the field of cancer research through workshops, seminars and conferences. Its first international annual conference entitled "Anti-Cancer Drug Discovery" was successfully organized in April 2019 (http://acdd.tanta.edu.eg). Additionally, EACR aims to raise the awareness of the society about the importance of scientific research in the field of cancer research in prediction, early diagnosis and treatment of cancer. EACR is also keen to outreach the scientific community with periodicals and news on cancer research including peer-reviewed scientific journals for the publication of cutting-edge research. The official scientific journal of EACR is "International Journal of Cancer and biomedical Research (IJCBR: https://jcbr.journals.ekb.eg) was successfully issued in 2017 and has been sponsored by the Egyptian Knowledge Bank (EKB: www.ekb.eg).

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