ORIGINAL CONTRIBUTION

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IMMUNOHISTOCHEMICAL STUDY OF CD44 AND OCT3/4 EXPRESSION IN COLORECTAL CANCER SAMPLES OF IRAQI PATIENTS

Background. Colorectal cancer (CRC) is one of the most common cancer types diagnosed globally with high rates of morbidity and mortality. Several biomarkers are associated with cancer stem cells present in various solid tumors, including CRC. **Aim.** This study aimed to investigate the expression of CD44 and OCT3/4 cancer stem cell markers in samples of CRC biopsies and benign colon tumors of Iraqi patients using the immunohistochemical (IHC) technique. **Materials and Methods.** The IHC analysis was used to determine CD44 and OCT3/4 expression levels in tissue samples of 42 CRC cases and 18 benign neoplasms. **Results.** The findings revealed a significant increase in high expression levels of CD44 in CRC cases (81%) vs 23% in benign tumor tissue samples. Similarly, a significant rise in OCT3/4 expression was observed in CRC cases (66%) compared to benign tumors (29%). The expression levels of CD44 and OCT3/4 were significantly associated with the CRC stages. **Conclusion.** Our data indicated that CD44 and OCT3/4 may play a role in CRC progression.

Keywords: cancer stem cells, biomarkers, colorectal cancer, CD44, OCT3/4, immunostaining.

Colorectal cancer (CRC, C18-20) is one of the most common cancer types diagnosed globally with high rates of morbidity and mortality and by 2040 is expected to reach 3.2 million new cases from 1.9 million new cases in 2020 according to the GLOBOCAN database. CRC comes in rank 3 of new cases (10%) after breast cancer (11.7%) and lung cancer (11.4%), and rank 2 by the death rate (9.4%) after lung cancer (18%) [1].

The CRC incidence rate in Iraq in 2019 was 6.18 per 10^5 population and the percentage of cases was 6.5%, the rate of mortality was 1.7 per 10^5 population. The authors suggested the increasing incidence and mortality rate of colon cancer could be related to the lack of a database in Iraq's registry of cancer due to several challenges [2].

Several barriers like the public lack of awareness, insufficient information about the disease and symptoms, and the lack of training resources for the medical staff required for public screening in Iraq might lead to the CRC diagnosis at late stages [3].

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Various cancer stem cell markers have been identified on the surface of CRC cells, and their roles were identified in tumor initiation, development, recurrence, metastasis, and treatment resistance. All these items could be used as targets for treatment, prognosis, and diagnosis of CRC [4]. The identified cancer stem cell markers for colon adenocarcinoma are CD133, CD144, CD24, CD166, CD44, CD29, ALDH, CXCR4, and LGR5 [5].

We have chosen two cancer stem cell markers CD44 and OCT3/4. CD44, also referred to as homing-associated cell adhesion molecule (HCAM), is a membrane protein that plays an essential function in different cellular functions such as cell proliferation, differentiation, migration, and motility [5]. CD44 participates in the metastasis of tumor cells via the link between cell-to-cell and cell-to-microenvironment interaction due to its capability to bind with hyaluronic acid (HA), a transmembrane glycosaminoglycan [6], in addition to other ligands like collagen, fibrinogen, fibronectin, serglycin, mucosal vascular addressin, chondroitin sulfate, laminin, osteopontin, L and E-selectin, and class II histocompatibility complex invariant chain [7].

OCT3/4 (POU5f1) is a transcription factor that is a member of a large homeobox family. This cancer stem cell marker plays a crucial role in undifferentiated embryonic stem cells in a condition of self-renewal and pluripotency [8]. The function of OCT3/4 is activated through a special sequence called AGTCAAAT, which is linked to various genes, which can either enhance or reduce expression levels in unfertilized oocyte cells, the domestic cell mass of blastocyst formation, and embryonic and germ stem cells [9].

Cancer stem cell proteins c-MYC, Oct3/4, NANOG, LGR5, and SOX2 were found to be highly expressed in the established CRC cancer cell line (P6C) [10]. In the study [11], the expression of CD44 was found in the normal mucosa and superficial regions of the cells, whereas in most of the carcinomas, the staining was localized in the basolateral region of the cells and its expression was correlated with the tumor stage.

A recent study [12] concluded that CD44 correlated with aggressive metastatic CRC behavior and contributed to the earlier progression of the disease.

Moreover, OCT3/4 has also been identified as an oncogene in several cancer types. For example, high OCT3/4 expression level was observed to play a role in the progression of cervical cancer [13]. This gene was also overexpressed in both prostate and testicular cancer cell lines [14]. In mouse embryos, OCT3/4 knockout results in the loss of stemness properties, highlighting its pivotal role in cell differentiation and regulation of the potential pluripotency of stem cells during cellular development. Furthermore, high OCT3/4 expression level was linked with tumor progression, metastasis, and chemo- and radiotherapy resistance [15, 16]

This study used immunostaining techniques to investigate the expression of CD44 and OCT3/4 cancer stem cell markers in the samples of CRC biopsies and different benign tumors.

Materials and Methods

Patients' selection criteria and tumor characteristics. We have studied histologically confirmed 42 CRC cases and 18 benign colon neoplasms collected between November 2016 and September 2017 at the Alyarmook Medical Hospital in Baghdad, Iraq. CRC cases that had undergone neoadjuvant therapy and radiotherapy were excluded. Mass biopsy, hemicolectomy, and total colostomy were employed to identify the tumors in patients. In each case, the following clinicopathological data were recorded: age, gender, tumor size, tumor grade, and lymph node metastasis. All samples were fixed in formalin, and paraffinized tumors and benign tissues were prepared for the immunohistochemical (IHC) analysis.

The present study was approved by the Research Ethics Committee of the Cancer Research Center and performed according to the ethical standards of the Declaration of Helsinki. The ethical committee permission was obtained from the Health Research Unit and Protocol Review Committee of the Ministry of Health, Iraq (#15/1/2016).

Immunohistochemical staining. The tissue sections, both benign and cancerous, were embedded in paraffin wax. The section thickness was 4 μm. The tissue sections of cancer and benign tumors were mounted on the same slide to ensure resembling conditions. After deparaffinization with xylene, the tissues were subjected at 121 °C to heat-induced retrieval antigen (HIRA). After the sections were washed twice, bovine serum albumin (BSA) was added and incubated at room tempera-

ture, and then the slides were incubated overnight at 4 °C with anti-CD44 (US-bio, USA) and anti-OCT3/4 (US-bio, USA) antibodies. Following the incubation with the secondary antibody (Dako, Denmark), avidin-biotin was incubated for 30 min at room temperature. The slides were treated with 3,3′-diaminobenzidine (DAB), countered with hematoxylin, and dehydrated in serial ethanol solutions. Finally, coverslips were mounted with DPX medium and examined under a microscope. The tissue section from the placenta was considered a positive control.

Table 1. **Clinicopathological parameters of the studied cases**

Clinical feature	CRC cases (n = 42)	Benign neoplasms (n = 18)
Age		
≤ 50 years	17 (40%)	5 (27%)
> 50 years	25 (60%)	13 (72%)
Sex		
Women	23 (55%)	10 (55%)
Men	19 (45%)	8 (45%)
Tumor size		
T1	8 (19%)	
T2	20 (48%)	
T3	10 (24%)	
T4	4 (9%)	
Tumor stage		
Stage 1	10 (24%)	
Stage 2	19 (35%)	
Stage 3	13 (41%)	
Lymph node metastasis		
Positive	12 (24%)	
Negative	30 (76%)	

Table 2. **CD44 and OCT3/4 expression in adenocarcinoma CRC and benign tissues**

Cases	CD44 expression		*p*
	High, n (%)	Low, n (%)	
Cancer (n = 42)	33 (81%)	6 (19%)	**0.001**
Benign (n = 18)	5 (36%)	13 (64%)	
	OCT3/4 expression		
Cancer (n = 42)	28 (66%)	14 (34%)	**0.001**
Benign (n = 18)	6 (38%)	12 (62%)	

For the CD44 expression analysis, cytoplasmic membranous and intraglandular debris staining was taken as positive staining, and nuclear localization staining for Oct 3/4 expression. The cells were categorized based on their positive staining, with zero indicating no staining, and scores of 1, 2, and 3 indicating staining levels of 1%—10%, 11%—50%, and 51%—100%, respectively. For the qualitative analysis, the positive stain intensity was classified into four categories: none, weak, moderate, and strong expression. Scores of zero and 1 were considered to represent low expression, whereas scores of 2 and 3 were grouped as high expression.

Statistical analysis. The difference between the tissues of CRC and benign tumors was analyzed using Graph Pad Prism version 6 (Graphic Pad Software Inc., USA). The results were expressed as mean, median, standard deviation, percentage, frequency, and proportion. A chi-square ($\chi 2$) statistic was used to determine the expression levels between benign and malignant colon tissues. A p value < 0.05 was considered statistically significant.

Results

Clinicopathological data. The clinicopathological data of 60 cases analyzed in this study are shown in Table 1. The patients' ages ranged between 22 and 80 years, with a mean age of 57 years. The study population was comprised of 19 (45%) males and 23 (55%) females.

Expression of cancer stem cell markers in CRC tissues. IHC analysis was implemented to identify the CD44 and OCT3/4 expression levels in all samples of CRC and benign colon neoplasms. We revealed that CD44 was expressed in the cell membrane and the cytoplasm of tumor cells at a high level in 81% of the CRC samples and at a low level in 19% CRC samples while in benign tissues, high and low CD44 expression levels were found in 36% and 64% of cases respectively (Table 2, Fig. 1).

The IHC analysis revealed OCT3/4 expression in the nuclei of the cells in both cancer and benign tissues (Fig. 2). A high expression level of OCT3/4 was found in 66% of CRC samples, and its low expression — in 34% of CRC cases (p = 0.001). In benign tissue samples, a high OCT3/4 expression

level was found in 38% and its low expression — in 62% of cases (Table 2, Fig. 2).

Association of CD44 and OCT3/4 expression levels with clinicopathological parameters. The relation between CD44 and OCT3/4 expression levels and clinicopathological parameters is presented in Table 3. Our study showed a significant relationship between CD44 and OCT3/4 expression levels and tumor stages (p = 0.026) and (p = 0.031), respectively (Table 3). No significant variations were found between the expression levels of both cancer stem cell markers and other features including patients' age, gender, tumor size, and lymph node metastasis (Table 3).

Discussion

Current research has demonstrated that cancer stem cell markers CD44 and OCT3/4 are expressed at significantly higher levels in CRC tissue samples than in benign colon tissues and show a significant relationship with the tumor stage.

CD44 was originally identified as a surface marker of cancer stem cells and has since been widely used as a marker for identifying and isolating cancer stem cells in various solid tumors [17—20], including CRC [21—30].

The heterogeneity of the tumor cells confirms the presence of cancer stem cells that are responsible for

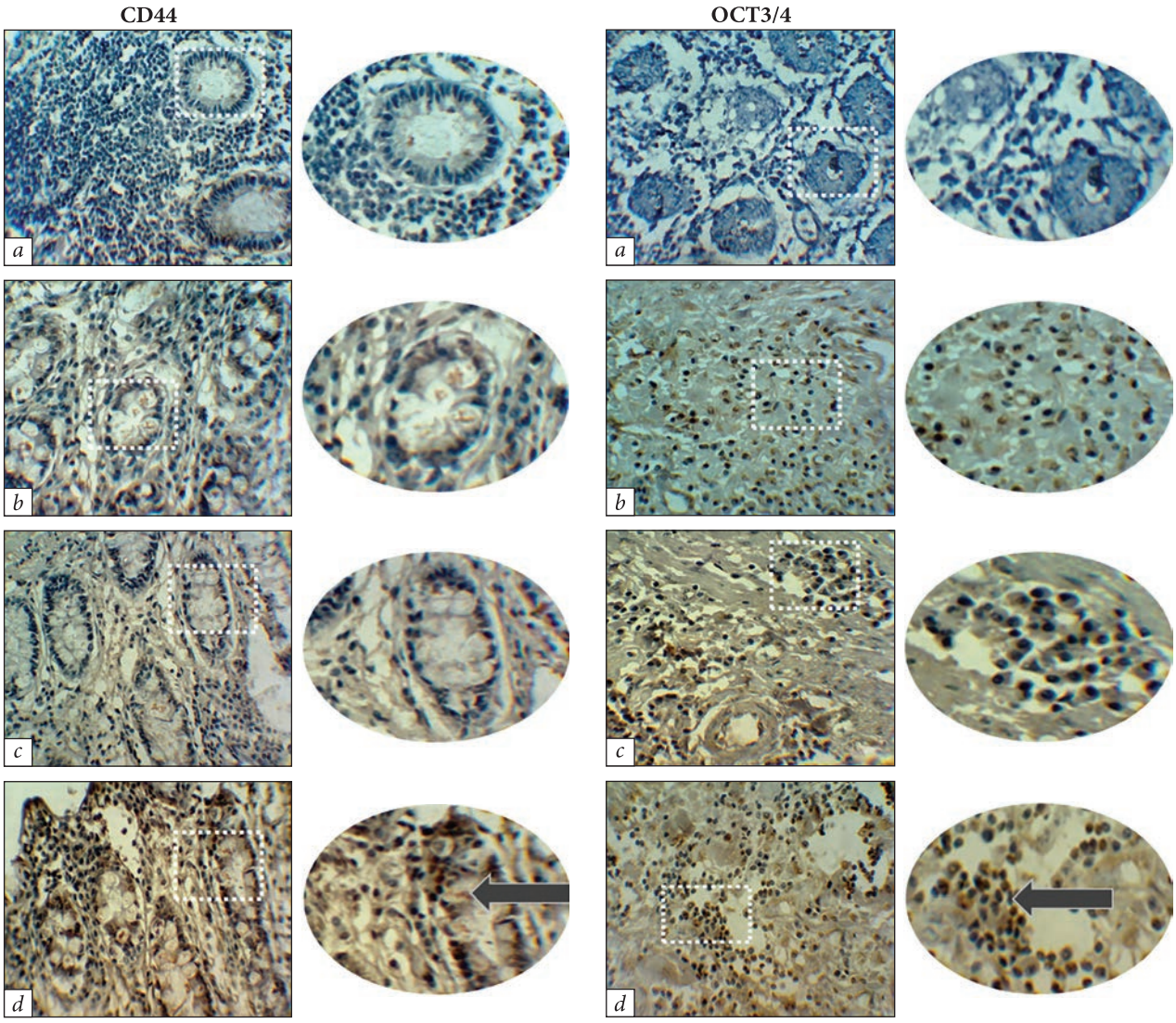

Fig. 1. Immunostaining of CD44 in benign tissue and CRC tissue samples (×400): (*a*) benign colon tumor; (*b*) stage I CRC with positive CD44 expression in the cytoplasm and cell membrane of tumor cells; (*c*) stage II CRC with elevated CD44 expression; (*d)* stage III CRC with high expression of CD44

Fig. 2. Immunostaining of OCT3/4 in benign tissue and CRC tissue samples (×400): (*a*) benign colon tumor, (*b*) stage I CRC with positive OCT3/4 expression in cytoplasm and cell membrane, (*c*) stage II CRC with elevated OCT3/4 expression level, (*d*) stage III CRC with high OCT3/4 expression

Table 3. **Association of CD44 and OCT3/4 expression with clinical parameters**

Clinical feature	CD44		*p*	OCT3/4		*p*
	High expression	Low expression		High expression	Low expression	
≤ 50 years	9 (52.9%)	8 (47.1%)	0.77	11 (64.7%)	6 (35.3%)	0.63
> 50 years	16 (64.0%)	9 (42.0%)		17 (68.0%)	8 (32.0%)	
Women	12 (52.1%)	11 (47.9%)	0.84	10 (43%)	13 (57%)	0.41
Men	11 (57.8%)	8 (42.2%)	0.61	12 (63%)	7 (37%)	
T1	3 (37.5%)	5 (62.5%)	0.26	2 (25%)	6 (75%)	0.31
T2	13 (65%)	7 (35%)		9 (45%)	11 (55%)	
T3	7 (70%)	3 (30%)		8 (80%)	2 (20%)	
T4	4 (100%)	0		9 (90%)	1 (10%)	
Stage 1	4 (40%)	6 (60%)	0.01	3 (30%)	7 (70%)	0.03
Stage 2	9 (47%)	10 (53%)		11 (57%)	8 (43%)	
Stage 3	10 (78%)	3 (22%)		12 (92%)	1 (8%)	
Positive	10 (83.3)	2 (26.7%)	0.11	8 (67%)	4 (33%)	0.09
Negative	7 (23.3%)	23 (76.7%)		11 (37%)	19 (63%)	

tumorigenesis, metastasis, and resistance to radiochemotherapy [31, 32]. Accumulating evidence illustrated that OCT3/4 as a transcription factor plays a key role in the self-renewal and pluripotency of cancer stem cells, tumorigenicity, and radiochemotherapy resistance. In our study, we found that the expression of CD44 increased in 81% of tumor samples while OCT3/4 is highly expressed in 66% of tumor samples. The presence of such biological markers has been linked to a poorer prognosis in various solid tumors [33, 34]. Conversely, the reduced expression of OCT3/4 has been associated with a lower likelihood of vascular invasion. Furthermore, there appears to be a significant correlation between a decreased expression of OCT3/4 and a reduced incidence of distant metastasis or lymph node involvement. Nevertheless, multiple studies have demonstrated that OCT4 expression is increased in various solid tumors [35, 36].

Previous studies have shown that the OCT4 expression in colon cancer and normal colon tissue reveals no significant correlation with the incidence of cancer [37]. Meanwhile, study [38] has revealed a strong association of OCT4 expression levels with poor prognosis and recurrence in patients undergoing chemotherapy. According to the data [29, 39], an increased expression of OCT3/4 in adult patients with CRC is associated with more advanced stages and a poorer prognosis. The high OCT3/4 expression levels play an important role in the epithelial-to-mesenchymal transition, which leads to the aggressive behavior of cancer cells [40, 41].

In conclusion, the results of this study imply that the studied markers could serve as reliable indicators for detecting cancer stem cells in CRC patients and may provide a promising target for cancer treatment.

Conflict of interests

The authors declare no conflict of interest.

Acknowledgments

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ІМУНОГІСТОХІМІЧНЕ ДОСЛІДЖЕННЯ ЕКСПРЕСІЇ CD44 ТА OCT3/4 В ЗРАЗКАХ ПУХЛИН ХВОРИХ НА КОЛОРЕКТАЛЬНИЙ РАК В ІРАКУ

Стан питання. Колоректальний рак (КРР) є одним з найпоширеніших типів злоякісних пухлин у всьому світі з високими рівнями захворюваності та смертності. Низка біомаркерів, асоційованих із раковими стовбуровими клітинами, виявляється в різних солідних пухлинах, включаючи КРР. **Метою** роботи було вивчити експресію маркерів ракових стовбурових клітин CD44 та OCT3/4 в зразках біопсій КРР та доброякісних пухлин товстої кишки хворих з Іраку за допомогою імуногістохімічного методу. **Матеріали та методи**. Експресію CD44 та OCT3/4 визначали в зразках пухлин 42 хворих на КРР та 18 хворих на доброякісні новоутворення товстої кишки. **Результати**. Виявлено достовірне підвищення експресії CD44 в клітинах КРР (81% у порівнянні з 23% у зразках доброякісних пухлин). Таке ж підвищення виявлено і щодо експресії OCT3/4 (66% у порівнянні з 29%). Показано достовірну асоціацію між рівнями експресії CD44 та OCT3/4 і стадіями КРР. **Висновок**. CD44 та OCT3/4 можуть відігравати роль у прогресії КРР.

Ключові слова: ракові стовбурові клітини, біомаркери, колоректальний рак, CD44, OCT3/4, імуногістохімія.