ORIGINAL ARTICLE

Expression of CD47, Aldehyde Dehydrogenase, and SOX4 Stem Cells in Different Colonic Lesions

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Abstract

Background: ***Colorectal cancer (CRC) patients have a higher likelihood of a favorable outcome when diagnosed early.***
Aime: ***This study aimed to evaluate the expression of CD47, Aldehyde Dehydrogenase (ALDH), SOX 4 stem cells in cancerous and precancerous colonic lesions.***
Patients and methods: ***A cross-sectional study was conducted on 100 patients at Al-Azhar University and Theodor Bilharz Research Institute. Patients were categorized into three groups: normal colonic mucosa (n=20), precancerous lesions (n=40), and CRC (n=40). Immunohistochemical staining was performed for CD47, ALDH, and SOX4. Results: The expression levels of CD47, ALDH, and SOX4 were significantly higher in CRC patients compared to normal and precancerous groups (P ≤ 0.001). Sox4 was positive in 72.5% of CRC cases compared to 27.5% in polyps, while ALDH and CD47 were highly expressed in CRC (82.5% and 70%, respectively).***
Conclusion: ***The study reveals significant differences in pathological characteristics between normal, precancerous, and colorectal cancer groups. Elevated Sox4, ALDH, and CD47 expression in colorectal cancer patients suggests their potential as biomarkers for cancer progression and early detection, offering potential therapeutic targets in colorectal cancer management.***

Keywords: CD47; Aldehyde Dehydrogenase; SOX 4; Colonic Lesions; CRC; Ulcerative colitis

1. Introduction

Colorectal cancer (CRC) is one of the most prevalent cancers in the world, with increasing incidence and high mortality rates.[1] Since the 1980s, the incidence of CRC has been steadily rising, with projections estimating it will reach more than 2.2 million cases by 2030 in the next few years.[2]

Colorectal cancer (CRC) patients have a significantly better prognosis when diagnosed at an early stage. However, the disease often remains asymptomatic until it reaches an advanced stage. [3]

Statistically, only 39% of CRC cases are detected at a localized, less-invasive stage, where the five-year survival rate is approximately 90% and is associated with better outcomes. [4]

Genetic alterations are fundamental to cancer formation, causing disruptions in the expression of critical regulatory components, such as tumor suppressor genes, various gene regulators, and oncogenic genes. Extensive research has identified genetic alterations in CRC that contribute to tumor progression. Some of these genetic markers have shown potential as indicators of tumor chemoresistance and prognostic factors for patient outcomes. [5]

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Aldehyde Dehydrogenase (ALDH) is involved in the oxidation of aldehydes to carboxylic acids and has been linked to cancer stem cell (CSC) properties. Several clusters of differentiation (CD), including CD47, are critical in tumor and colony formation, survival rate, and tumor metastasis. These markers also contribute to tumor aggressiveness by enhancing cell migration and invasiveness. [5]

This study aimed to evaluate the expression of CD47, Aldehyde Dehydrogenase, SOX 4 stem cells in cancerous and pre- cancerous colonic lesions.

2. Patients and methods

This cross-sectional study was carried out on 100 patients at the Department of Hepatology, Gastroenterology, and Infectious Diseases, Al-Azhar University, in collaboration with Theodor Bilharz Research Institute. The study was conducted from December 2022 to December 2024. Patients were classified into three groups: Group (A) included (20) patients with no obvious lesions at colonoscopy, Group (B) included (40) patients with precancerous lesions such as colorectal polyps, inflammatory bowel disease, and Group (C) included (40) patients with colorectal cancer proven by histopathological examination.

Sample size

The sample size was determined using Epi-Info Version 7, considering a 90% confidence level, a 14% expected colorectal cancer frequency, a 5% confidence limit, and a population size of 1500. This resulted in a minimum of 100 patients, divided into the aforementioned three groups.

Inclusion criteria: Patients aged more than eighteen years old with cancerous and precancerous colonic lesions, in addition to patients with no obvious lesions noted at colonoscopy.

Exclusion criteria: Patients aged less than 18 years, patients who refuse to be enrolled in the study, and patients with a history of previous surgery for colorectal neoplasia, chemotherapy, radiotherapy, or other malignancies.

Methods

All the patients were subjected to the following:

A comprehensive preoperative evaluation included a detailed history, clinical examination, and laboratory investigations. Laboratory tests comprised a complete blood count, kidney function, and liver function tests.

Lower gastrointestinal endoscopy and biopsy sampling procedure

All the included patients underwent full ileocolonoscopic examination, except those with obstructing lesions preventing endoscope advancement. Bowel preparation included oral magnesium citrate or polyethylene glycol one day prior, alongside 24-36 hours of fasting (allowing water and fiber-free juices). Endoscopy was performed under conscious sedation at the gastrointestinal unit after obtaining written informed consent. Biopsies were taken from cancerous and precancerous lesions, preserved in 10% formalin, and processed under gastrointestinal pathology supervision. Histopathological examination and immunohistochemical staining for CD47, ALDH, and SOX4 were conducted on all samples. Patients diagnosed with colorectal cancer underwent metastatic evaluation using contrast-enhanced CT of the chest, abdomen, and pelvis.

Histopathological technique

For histopathological evaluation, four μm sections from formalin-fixed paraffin blocks were deparaffinized, rehydrated, and stained with H&E for examination by two independent pathologists. For immunohistochemical staining, five μm formalin-fixed, paraffin-embedded sections were mounted on Dako REAL Capillary Gap slides, dried, deparaffinized, and rehydrated. Heat-induced epitope retrieval was made in EDTA-Tris buffer (pH 9.0) using a pressure boiler. Immunostaining was conducted with Dako Autostainer using EnVision/HRP and primary mouse monoclonal antibodies (CD47, ALDH, Sox4, Santa Cruz, USA) at 1:100 dilution. Slides were stained with the DAB detection system, rinsed under running water, and prepared for analysis.

Evaluation of Immunohistochemical Staining

For immunohistochemical analysis, ten high-power fields were examined per section in each case, and the average count was calculated.

The CD47 expression was performed by the Allred scoring system, which was determined according to a predefined formula.

SOX4 immunoreactivity was evaluated based on both the proportion of stained cells and staining intensity. The extent of SOX4 staining was graded semi-quantitatively as follows: 0 = negative, I = 1-25%, II = 26-50%, III = 51-75%, and IV > 76% and up to 100% positive cells. Staining intensity was scored as 0, which is considered negative; I = weak, II = moderate, III = strong, and IV very strong. The final staining score was obtained by summing the intensity and extent scores.

ALDH1 expression was detected in the cytoplasm and semi-quantitatively scored based on the percentage of positive tumor cells by a four-tier grading system: 0 (<5%), 1 (5–20%), 2 (20–50%), and 3 (>50%). A median cutoff value of 55% was

used to categorize expression levels into low (≤55%) and high (>55%) groups. Negative cases were included in the low-expression category for statistical analysis. Notably, both scoring methods yielded consistent results without significant discrepancies.

Statistical analysis:

Data analysis was performed using SPSS version 24. Qualitative variables were represented as numbers and percentages, while quantitative data were expressed as means and standard deviations (SD). For statistical analysis, the Chi-square test was used to compare qualitative variables between groups. The independent t-test was employed to compare two independent groups with a parametric distribution, while the One-Way ANOVA test was utilized to compare more than two independent groups with quantitative data and a parametric distribution. A P-value of less than 0.05 was regarded as statistically significant.

3. Results

There was no statistically significant difference among the studied groups in terms of sex and special habits (P > 0.05). However, the CRC group showed a significantly higher age compared to precancerous and normal groups (P < 0.05). (Table 1)

ALDH positivity is highest in colorectal cancer (82.5%), followed by UC (72.7%) and colorectal polyps (34.5%). There is a strong association between ALDH-positive results and CRC mass, as indicated by the high percentage of positive results in this category table (2). Sox4 is significantly linked with the presence of CRC (72.5% positive) compared to ulcerative colitis (UC) 63.60%) and polyps (27.5%), with negative percentage of Sox4 in normal tissue (0%) table (2). Aso, table 2 indicates that CD47 positivity is highest in colorectal cancer (70%), followed by ulcerative colitis (36.4%) and polyps (27.5%), with no expression observed in normal tissues (0%).

Table 3 demonstrates a statistically significant increase in the immunohistochemical expression of Aldehyde Dehydrogenase (ALDH), Sox4, and CD47 in colorectal cancer (CRC) patients compared to normal and precancerous groups (P ≤ 0.001). ALDH expression was absent in normal tissues, moderately expressed in precancerous lesions (Mean ± SD: 47.77 ± 21.01), and highest in CRC cases (Mean ± SD: 61.06 ± 18.48).

Similarly, Sox4 was absent in normal tissues, moderately expressed in precancerous lesions (Mean ± SD: 32.53 ± 10.12), and significantly elevated in CRC patients (Mean ± SD: 47.58 ± 12.7). CD47 expression followed the same trend, with no expression in normal tissues, moderate levels in precancerous lesions (Mean ± SD: 37.5 ± 11.38), and the highest expression in CRC cases (Mean ± SD: 62.32 ± 17.45).

Table 4 reveals that ALDH and Sox4 expression were significantly higher in colorectal polyps compared to ulcerative colitis (UC) (P ≤ 0.001 and P = 0.03, respectively). ALDH showed a mean expression of 60 ± 20.5 in polyps versus 32.5 ± 7.07 in UC, while Sox4 had a mean expression of 36 ± 8.81 in polyps compared to 28.57 ± 10.69 in UC. However, CD47 expression did not show a statistically significant difference between polyps (38.75 ± 12.46) and UC (35 ± 10) (P = 0.37).

In Table 5, Sox4 and CD47 expressions were significantly higher in CRC compared to colorectal polyps (P ≤ 0.001 for both markers). Sox4 had a mean expression of 47.58 ± 12.7 in CRC versus 36 ± 8.81 in polyps, while CD47 was 62.32 ± 17.45 in CRC compared to 38.75 ± 12.46 in polyps. In contrast, ALDH expression did not show a significant difference between CRC (61.06 ± 18.48) and polyps (60 ± 20.5) (P = 0.82), suggesting that ALDH may be involved in both early and advanced stages of colorectal carcinogenesis.

Table 6 demonstrates that ALDH, Sox4, and CD47 expressions were significantly higher in CRC compared to ulcerative colitis (P ≤ 0.001 for all markers). ALDH showed a mean expression of 61.06 ± 18.48 in CRC versus 32.5 ± 7.07 in UC, Sox4 was 47.58 ± 12.7 in CRC compared to 28.57 ± 10.69 in UC, and CD47 had a mean expression of 62.32 ± 17.45 in CRC versus 35 ± 10 in UC.

Table 1. Distribution of demographic features between studied groups.

VARIABLES		GROUP A (NORMAL) N=20 MEAN ±SD	GROUP B (PRECANCEROUS LESIONS) N=40 MEAN ±SD	GROUP C (CRC) N=40 MEAN ±SD	TEST	P VALUE
AGE		37.55± 17.19	36.4± 14.1	59.6 ± 9.2	F=36.41	<0.001
		PI = 0.94	PII < 0.001	PIII <0.001		
SEX		N (%)	N (%)	N (%)		
MALE		8 (40%)	21 (52.5%)	23 (57.5%)	X^2=1.643	0.44
FEMALE		12 (60%)	19 (47.5%)	17 (42.5%)		
SPECIAL HABITS	Smoking	6 (30%)	13 (32.5%)	14 (35%)	X^2=0.158	0.92
BMI		26.92±2.76	27.25±2.14	27.45±3.24	F= 0.820	0.06

PI: p value between group A & group B, PII: p value between group A & group C, PIII: p value between group B & group C, SD: Standard Deviation; BMI: Body Mass Index p value < 0.05: statistically significant, X^2: Chi Square test, F: Anova test.

Table 2. Correlation between Aldehyde, Sox4 and CD47 in the studied groups

BIOMARKERS		GROUP A (NORMAL)	GROUP B		GROUP C (CRC)	TEST X^2	P VALUE
			Polyp	UC			
ALDEHYDE DEHYDROGENASE	negative	20	19	3	7	41.943	0.001
		100.00%	65.50%	27.30%	17.5%		
	positive	0	10	8	33		
		0.00%	34.50%	72.70%	82.5%		
SOX4	negative	20	21	4	11	33.792	0.001
		100.00%	72.5%	36.40%	28.5%		
	positive	0	8	7	29		
		0.00%	27.5%	63.60%	72.5%		
CD47	negative	20	21	7	12	30.256	0.001
		100.00%	72.5%	63.60%	30%		
	positive	0	8	4	28		
		0.00%	27.5%	36.40%	70%		

p value < 0.05: statistically significant, X^2: Chi Square test.

Table 3. Immunohistochemical expression (positive percentage) of Aldehyde dehydrogenase, Sox4 and CD 47 in different studied groups.

BIOMARKERS	GROUP A (NORMAL) N=20 MEAN ±SD	GROUP B (PRECANCEROUS LESIONS) N=40 MEAN ±SD	GROUP C (CRC) N=40 MEAN ±SD	F	P VALUE
ALDEHYDE DEHYDROGENASE	0	47.77 ±21.01	61.06 ±18.48	80.8617	≤0.001
SOX4	0	32.53 ±10.12	47.58 ±12.7	142.4209	≤0.001
CD 47	0	37.5 ±11.38	62.32 ±17.45	149.5057	≤0.001

p-value < 0.05: statistically significant, F: Anova test.

Table 4. Immunohistochemical expression (positive percentage) of Aldehyde dehydrogenase, Sox4 and CD 47 in colorectal polyps and ulcerative colitis (UC).

BIOMARKERS	COLONOSCOPY FINDINGS		T	P VALUE
	Polyps (N=29) Mean ±SD	UC (N=11) Mean ±SD		
ALDEHYDE DEHYDROGENASE	60 ±20.5	32.5 ±7.07	4.3224	≤0.001
SOX4	36 ±8.81	28.57 ±10.69	2.2461	0.03
CD 47	38.75 ±12.46	35 ±10	0.8928	0.37

p value < 0.05: statistically significant, T: Independent t-test.

Table 5. Immunohistochemical expression (positive percentage) of Aldehyde dehydrogenase, Sox4 and CD 47 in colorectal polyps and group C (colorectal cancer, CRC).

BIOMARKERS	COLONOSCOPY FINDINGS		T	P VALUE
	Polyps, N=29 Mean ±SD	CRC, N=40 Mean ±SD		
ALDEHYDE DEHYDROGENASE	60 ±20.5	61.06 ±18.48	6.7572	0.82
SOX4	36 ±8.81	47.58 ±12.7	4.2245	≤0.001
CD 47	38.75 ±12.46	62.32 ±17.45	6.2107	≤0.001

p value < 0.05: statistically significant, T: Independent t-test.

Table 6. Immunohistochemical expression (positive percentage) of Aldehyde dehydrogenase, Sox4 and CD 47 in UC and group C (colorectal cancer, CRC).

BIOMARKERS	COLONOSCOPY FINDINGS		T	P VALUE
	UC, N=11 Mean ±SD	CRC, N=40 Mean ±SD		
ALDEHYDE DEHYDROGENASE	32.5 ±7.07	61.06 ±18.48	4.9953	≤0.001
SOX4	28.57 ±10.69	47.58 ±12.7	4.5335	≤0.001
CD 47	35 ±10	62.32 ±17.45	4.9504	≤0.001

p value < 0.05: statistically significant, T: Independent t-test.

4. Discussion

The current study investigated the expression of CD47, Aldehyde Dehydrogenase (ALDH), and SOX4 in normal, precancerous, and colorectal cancer (CRC) tissues to assess their potential role as biomarkers for cancer progression and early detection. The results demonstrated a statistically significant increase in the expression of these markers in CRC cases compared to precancerous and normal tissues, supporting their relevance in colorectal carcinogenesis.

There was no significant difference between normal, precancerous, and CRC groups regarding sex and special habits; however, CRC patients were significantly older than those with normal or precancerous lesions. It has been reported that the individual risk of CRC is influenced by non-modifiable factors, such as age, sex, and family history.6 The incidence rate of CRC increases rapidly with age, doubling with every 5-year increment until the age of 50, after which it increases by 30% in individuals aged 55 years and older.[4]

Our result showed that Sox4 expression was significantly elevated in CRC tissues (72.5%) compared to precancerous lesions (27.5%), with no expression in normal tissues. The increased level of Sox4 in colorectal cancer is consistent with findings from Pan S et al,[7] and Liu et al.[8], who reported significantly higher Sox4 levels in CRC tissues as demonstrated through immunohistochemistry, PCR, and western blot analyses in comparison to normal tissues. Furthermore, elevated Sox4 levels were observed in CRC cell lines (DLD1, HCT116, T84, and SW480) relative to normal tissues. Similarly, Wang X et al,[9] reported that SOX4 mRNA levels were higher in CRC tissues compared to surrounding normal colonic mucosal tissues. SOX4 protein expression was also significantly upregulated in CRC tissues, supporting the link between Sox4 overexpression and CRC progression.

Our results revealed that ALDH was highly expressed in CRC tissues (82.5%) compared to precancerous lesions (34.5%), further supporting its role in colorectal carcinogenesis. The elevated level of ALDH among CRC patients has been well-established in several studies, further supporting its role in CRC progression, Zedan EM et al,[10] reported a strong correlation between elevated ALDH expression and aggressive tumor characteristics in colorectal carcinoma.

CD47 expression was significantly higher in CRC cases (70%) compared to precancerous lesions (27.5%) and was absent in normal tissues. The elevated level of CD47 among CRC patients is well-documented in multiple studies, emphasizing its critical role in CRC progression. Oh HH et al,[11] demonstrated that CD47 contributes to CRC progression by enhancing tumor cell resistance to apoptosis and promoting angiogenesis. Their study found significantly higher CD47 expression in CRC tissues and metastatic lymph nodes compared to the normal tissues and lymph nodes, reinforcing its role in tumor immune evasion and metastasis.

The analysis of colonoscopy findings and biomarker expression (Sox4, ALDH, and CD47) demonstrated significant associations, emphasizing their potential diagnostic value in colorectal pathology.

Sox4 positivity was predominantly associated with the presence of colorectal cancer (72.5%), while normal findings showed no Sox4 positivity (0% each). These findings align with Pan S et al,[7] and Liu et al.[8], who reported elevated Sox4 expression in CRC tissues compared to surrounding normal tissues and its critical role in promoting tumor progression and metastasis.

ALDH positivity was highest in colorectal cancer (82.5%), followed by ulcerative findings (72.7%) and polyps (34.5%). This strong association with masses is supported by Zedan EM et al,[10] who demonstrated that ALDH expression correlates with tumor aggressiveness, lymphovascular invasion, and nodal metastasis in colorectal cancer.

CD47 positivity was most prevalent in colorectal cancer (70%). Moderate levels of positivity were observed in polyps (27.5%) and ulcerative findings (36.4%). This pattern is consistent with Oh HH et al,[11] and Arai H et al,[12] who identified CD47 as a key factor in tumor immune evasion, angiogenesis, and advanced disease stages. CD47 expression was significantly associated with lymphovascular invasion, metastasis, and worse prognosis in colorectal cancer patients.

Sox4, ALDH, and CD47 positivity were significantly higher in CRC patients compared to Group B (precancerous lesions), demonstrating its strong association with malignant transformation and tumor progression. The statistically significant differences in these biomarkers between precancerous and cancerous groups validate their potential as diagnostic and prognostic tools, as well as therapeutic targets for colorectal cancer.

These findings are consistent with existing literature. Sox4 has been reported as a key regulator of cancer cell invasion and metastasis in colorectal cancer.[7, 13]

The current study showed a statistically significant difference between polyp and ulcerative findings regarding the immunohistochemical expression of Sox4 and aldehyde dehydrogenase (ALDH), with both markers showing a significant increase in polyps compared to ulcerative lesions. However, there was no statistically significant difference between these two findings in terms of immunohistochemical expression of CD47.

Sox4 and ALDH exhibited elevated positivity in polyp cases, suggesting their prominent role in the early stages of colorectal neoplastic transformation. The lack of significant difference in CD47 positivity between polyps and ulcerative findings may indicate that CD47 expression is more strongly associated with advanced malignancy rather than precancerous or inflammatory conditions.

These data suggest that Sox4 and ALDH may serve as valuable biomarkers for distinguishing between different precancerous conditions, while CD47 may be more indicative of advanced cancer progression.

The current study revealed no significant difference in the immunohistochemical expression of aldehyde dehydrogenase between polyps and masses. However, a statistically significant increase in the immunohistochemical expression of Sox4 and CD47 was observed in CRC masses compared to polyps.

Pan S et al,[7] showed that Sox4 is overexpressed in both colorectal adenomas and carcinoma tissues, implying its role in the progression of colorectal cancer and suggesting that its expression may not be significantly elevated between polyp and mass stages.

Studies by Zedan EM et al,[10] and Mohamed ND et al,[14] found high ALDH expression in both colorectal adenomas and carcinomas, suggesting that ALDH may not be sufficient to distinguish between early-stage polyps and advanced tumors in colorectal cancer.

The absence of significant changes in the expressions of ALDH between polyps and masses may reflect the involvement of this marker in both early and advanced stages of colorectal carcinogenesis. These biomarkers play a vital role in colorectal neoplasia rather than serving as clear differentiators between precancerous lesions

and established cancers. The elevated expression in both polyps and masses may indicate their potential utility as early biomarkers for CRC, but not necessarily as indicators of tumor progression in this context.

However, colorectal neoplasia exhibited a statistically significant higher in the immunohistochemical expression levels of Sox4 and CD47 compared to polyps, highlighting the potential of these markers as reliable predictors for the initiation and progression of colorectal cancer.

Study limitations: The main limitations of this study include its single-center design, which may affect the generalizability of findings, and a relatively small sample size that limits subgroup analyses. The study primarily focused on pathological and biomarker findings, without assessing treatment responses. Additionally, further research incorporating additional biomarkers is needed for a more comprehensive understanding of colorectal cancer progression.

4. Conclusion

The study reveals significant differences in clinical and pathological characteristics between normal, precancerous, and CRC groups. Elevated Sox4, ALDH, and CD47 expressions in CRC patients suggest their potential as biomarkers for CRC progression, early detection, and prognosis, offering potential therapeutic targets in CRC management. Further studies are needed to explore the therapeutic potential of targeting these biomarkers in colorectal cancer treatment.

Disclosure

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