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THE POTENTIAL ROLE OF HDAC1 AND HDAC3 IMMUNOEXPRESSION IN P53 DOWNREGULATION AND TUMOR AGGRESSIVENESS OF COLON AND RECTUM CARCINOMAS PATIENTS

Background. Colorectal cancer, ranking second place in global cancer mortality, arises from diverse causes. There is growing recognition of the substantial involvement of the epigenetic modifications of histones at the DNA level in the occurrence of CRC. **Aim**. To assess the expression of p53, HDAC1, and HDAC3 proteins in a cohort of CRC patients and to analyze potential relationship between their expression and the stages of CRC progression. **Materials and Methods**. The retrospective investigation was carried out on 95 paraffin-embedded CRC tissue samples. The expression of p53, HDAC1, and HDAC3 was assessed immunohistochemically. **Results**. Notably, the expression of the p53 protein in CRC tissue samples exhibited a prominent correlation with the protein expression of both HDAC1 ($p < 0.001$, rho = 0.522) and HDAC3 ($p < 0.001$, rho = 0.411), as well as the advanced TNM staging of CRC ($p = 0.002$, rho = 0.313). Downregulation of p53 was correlated with underexpressed HDAC1 and HDAC3. Nevertheless, the observed expression of p53 exhibited a significant negative correlation with the age of the patients. **Conclusion**. The data on HDACs-p53 co-expression suggest a possible mechanism of interaction between the expression of these proteins.

Keywords: colorectal cancer, TNM, expression, HDACs, P53.

Colorectal cancer (CRC) is a form of epithelial malignancy originating in the mucosa that lines either the colon or rectum. The characteristic feature of CRC is the uncontrolled growth of epithelial cells in the last segments of the gastrointestinal tract. This disease is heterogeneous in terms of etiology [1, 2].

Globally, CRC holds third position among the most common cancers [3], with an approximate annual incidence of 1.9 million cases. The projections indicate a significant surge in both the CRC incidence and deaths, which are expected to nearly double from 1.9 million to 3.2 million cases and from 0.9 million to 1.6 million deaths, respectively, between the years 2020 and 2040 [4, 5]. CRC can be caused by various factors, including family history of cancer, infections, and inflammation in the digestive tract, as well as other medical conditions

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like diabetes [6]. Factors such as gut microflora alteration, variation in age, sex, and other demographic characteristics may play a role in contributing to this malignancy [7—9]. Additionally, people who adopt unhealthy habits such as smoking, consuming excessive alcohol, or maintaining an unbalanced diet, are at an increased risk of susceptibility to CRC [6, 10].

It is established that genetic variations in specific genes have shown a strong association with CRC in different populations. Due to the recent advancements in sequencing techniques, along with the investigation of the human exome, many studies have identified distinct genes of interest [11, 12]. Yet, CRC may develop because of the accumulation of acquired genetic and epigenetic alterations. In the last decade, the value of the role of epigenetics in cancer development has gained prominence [13]. It is firmly established that epigenetic events can act as driving forces in the pathogenesis of CRC. These events work in collaboration with gene mutations, playing a role in the transition from normal colon mucosa to the development of CRC [14]. In this context, histone modifications which are known as post-translational modifications (PTMs) have been shown to play a crucial role in tumorigenesis and prognosis, alongside a variety of other factors influencing gene expression in numerous cancers [15, 16], including CRC [17].

Within the histones modification scenario, histone acetyltransferase (HAT) regulates the reversible acetylation of histones, occurring on lysine residues, by transferring acetyl-CoA. This process results in the loosening of nucleosome framework and enhancing the potency of transcription. On the contrary, histone deacetylases (HDACs) deacetylate histones, tightly binding to anionic DNA [18], leading to the dense compaction of chromatin and suppressing gene transcription. HATs, often termed as histone "writers," and HDACs, known as histone "erasers," constitute the two categories of enzymes responsible for regulating acetylation rates. The controlled balance between these two classes of enzymes serves as a crucial regulatory mechanism for gene expression, influencing various physiological processes and disease development [19] including CRC [20].

In humans, HDACs form a group of 18 enzymes categorized into 4 classes: class I includes types 1—3 and HDAC8, class II comprises types 4—9 and HDAC10, class III encompasses SIRTs 1—7, and class IV — HDAC11. Due to the abnormal activity and heightened expression of HDACs in various cancer subtypes, they have been identified as effective therapeutic targets. Inhibitors of HDACs indirectly enhance the therapeutic impact of anticancer agents [21].

The primary role of the p53 protein is related to suppression of tumorigenesis [22]. When the wild-type p53 protein becomes attached to specific DNA response regions, it triggers the expression of numerous genes that are pivotal in preventing the initiation and advancement of cancer [23]. In normal conditions, the p53 signaling pathway becomes active when cells encounter various stress signals. This activation allows cells to initiate sundry transcriptional strategies, such as apoptosis, DNA repair, senescence, and cell cycle arrest [24]. These programs collectively contribute to the suppression of tumor formation [25]. Between 40%—50% of CRC cases are caused by the mutations in the *TP53* gene. The course and outcome of CRC are vigorously correlated with the existence or absence of *TP53* mutation [26].

The dynamic regulation of p53 and histones acetylation levels is supposed to be a key aspect of the relationship between HDACs and p53 in cancer. Suppressing the expression of class I HDAC or utilizing HDAC inhibitors has been proven to hold efficient anti-proliferative impact and to have the potential to induce apoptosis [27]. In a related manner, a specific molecular mechanism was proposed by Mrakovcic et al. [28], indicating that HDAC inhibitors can affect the TP53 expression by reducing its transcription through the involvement of HDAC8 and HoxA5. Moreover, the novel HDACs inhibitor known as depsipeptide FR901228 has been shown to initiate the upregulation of p21 through the p53 pathway. Following treatment with the depsipeptide, acetylation of p53 at lysine residues 373/382 takes place. The acetylated form of p53 exhibits an extended half-life and reduces ubiquitination, consequently resulting in the induction of cell cycle arrest in lung cancer cells *in vitro* [29].

Due to the lack of sufficient local research on the epigenetic alterations in CRC and their correlation with a known effective factor in cancer pathogenicity, this work aimed at immunohistochemical

study of the expression of HDAC1 and HDAC3 in a cohort of CRC patients. Additionally, we explored potential relationship between the expression of p53 and HDAC1 and HDAC3, examining their correlation with the stages of CRC progression.

Materials and Methods

Study samples. This retrospective investigation was carried out on 95 paraffin-embedded CRC tissue samples. The study included patients aged 22 to 79 years (60 males and 35 females). Tumor staging revealed that most patients had an advanced disease, primarily classified as T3 or higher, indicating substantial tumor size and local invasion. Lymph node involvement was common, with many patients classified as N1, while metastatic status varied from M0 to M1. Histological examination showed a predominance of grade 2 tumors, indicating moderate differentiation, with some cases classified as grade 1 or grade 3. These specimens were sourced from the records of the Gastrointestinal and Liver Teaching Hospital in Baghdad, covering the period from October 2021 to December 2022. The CRC grades and stages were determined by a pathologist using the internationally approved TNM staging system [30]. The Ethical Committee of the Leading National Cancer Research Centre in the University of Baghdad (Ref. NCRCEC/01/005) granted approval for this study.

Immunohistochemical analysis. The sections from paraffin-embedded blocks were cut to 4 μm and stained with hematoxylin and eosin (H&E). For immunohistochemistry (IHC), the additional sections on the charged slides were treated with the rabbit monoclonal antibodies against HDAC1 (ab150399), HDAC3 (ab32369), and p53 (ab32049) from Abcam. The process included deparaffinization with xylene, rehydration, and washing. An endogenous peroxidase activity was blocked, and the slides were rinsed with phosphate-buffered saline (PBS), protein-blocked, and incubated at 37 °C. The primary antibodies (1:50 dilution) were applied for 1 h followed by the secondary antibodies for 15 min and streptavidin-HRP for 10 min. After washing, the slides were stained with DAB for 20 min and counterstained with hematoxylin for 30 s. Finally, the slides were air-dried, mounted with DPX, and examined under a microscope at 10x and 40x magnifications. A pathological scoring system, which is a semi-quantitative method, was used to estimate the protein expression and localization. Immunopositive cells were defined as having a brown color in the cytoplasm or nucleus, whereas uncolored cells were classified as immunonegative. The scoring system was applied using the guidelines provided in [32], allocating the following scores: 0 (0%), 1 (< 10%), 2 (10—50%), and 3 (> 50%) [32].

Statistical analysis. Using the Statistical Package for the Social Sciences (SPSS, V22), a Spearman's test was employed for the statistical analysis to assess the correlation coefficient (rho) between the clinicopathological characteristics of the CRC patients under examination and expression of the proteins p53 and HDACs 1 and 3, along with associated two-tailed p-values. Additionally, pertinent data from The Cancer Genome Atlas (TCGA) was gathered and examined using the tumor analysis platform at TNMplot.com to find out the correlation between p53 expression and HDAC3 genes in both malignant and normal tissues. The Kaplan — Meier method was used to assess the overall survival of CRC patients in relation to the parameters under investigation.

Results

As shown in Fig. 1, p53 protein expression was significantly correlated with the protein expression of both HDAC1 ($p < 0.001$, $\rho = 0.522$) and HDAC3 ($p < 0.001$, $\rho = 0.411$) as well as the advanced TNM staging of the patients ($p = 0.002$, $\rho = 0.313$). It was also obvious that downregulated p53 was correlated with underexpressed HDAC1 and HDAC3. Notwithstanding, p53 expression revealed a negative correlation with patients' age, Table 1.

The results in Fig. 2 show that both variables (p53 expression and advanced TNM staging) have a similar trend within the studied age groups of CRC patients. They represent confirmatory data for our findings shown in Table 1, which prove that expression of p53 protein is associated with advanced TNM staging.

In this research, the relationship mapping analysis was employed to visually represent the connections among the tested values of the multiple study variables. The results in Fig. 3 indicate that the absence of HDAC3 protein expression (represented by the biggest dark green circle 0) is highly related

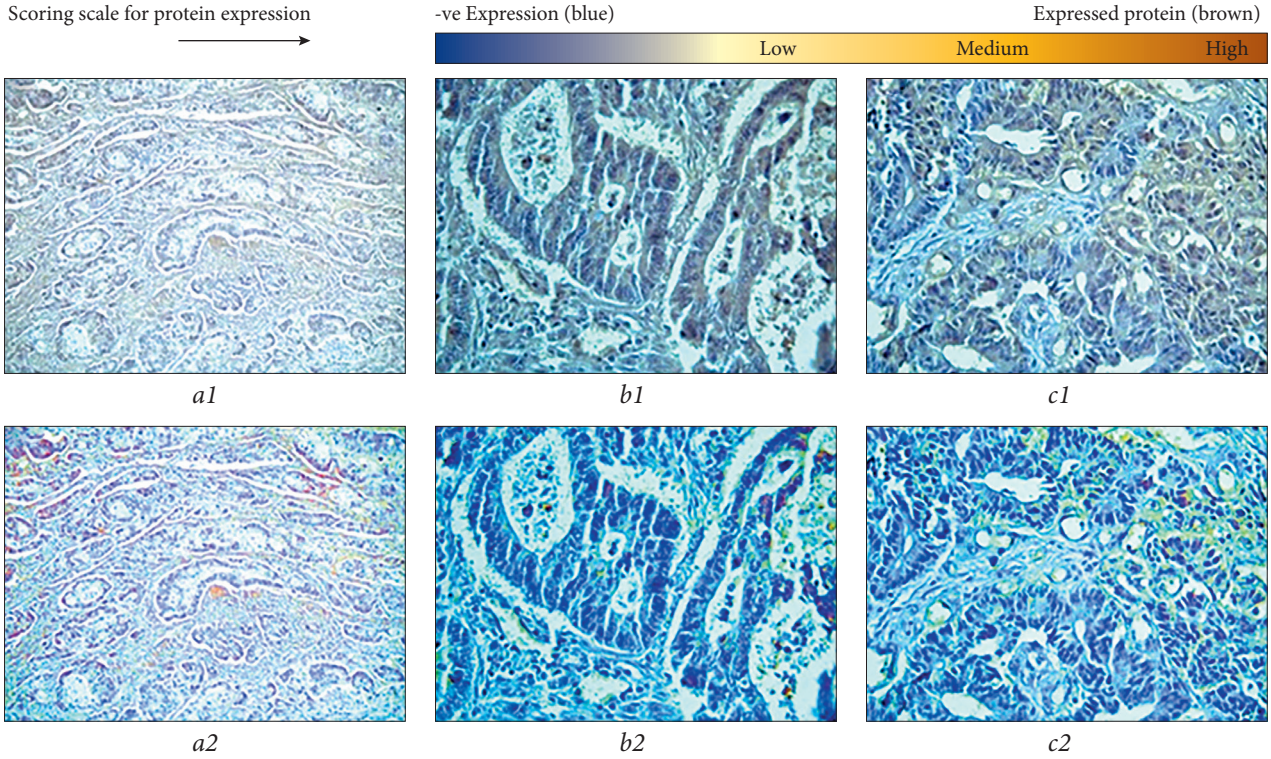

Fig. 1. Images displaying immunohistochemical staining to detect the protein expression levels (brown color) of p53 (*a*), HDAC1 (*b*), and HDAC3 (*c*) in CRC patients. The scoring system indicates increased expression levels of p53 (*a2*), HDAC1 (*b2*), and HDAC3 (*c2*) based on the intensity of brown color, ranging from low to high, with blue indicating genes that are not expressed

Table 1. **The correlation among clinicopathological features of the study sample**

Features	Spearman's test	Sex	TNM stag.	HDAC1 expr.	HDAC1 local.	HDAC3 expr.	HDAC3 local.	p53 expr.
Age	[1] rho (ρ)	–0.369**	–0.214*	–0.06	–0.12	0.01	–0.572**	–0.280**
	[2] p-value (*p*)	< 0.001	0.04	0.56	0.31	0.96	< 0.001	0.01
	[3] Number	95	95	95	70	95	55	95
TNM staging	[1] rho (ρ)			–0.212*	–0.534**	0.204*	0.10	0.313**
	[2] p-value (*p*)			0.04	< 0.001	0.05	0.45	0.002
	[3] Number			95	70	95	55	95
HDAC1 expression	[1] rho (ρ)				0.252*	0.414**	0.06	0.522**
	[2] p-value (*p*)				0.04	< 0.001	0.68	< 0.001
	[3] Number				70	95	55	95
HDAC3 expression	[1] rho (ρ)						–0.468**	0.411**
	[2] p-value (*p*)						< 0.001	< 0.001
	[3] Number						55	95

Notes: * Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (two-tailed). [1] Correlation coefficient (rho), [2] two-tailed significant *p* value, [3] sample size where the missing values of the handling samples numbers were excluded listwise.

Table 2. **Correlation between p53 and HDAC3 gene expression in normal and CRC tissues (according to the TNMplot data)**

	Tumor				Normal			
Analysis type	TP53 (No.)	HDAC3 (No.)	ρ	*p*	TP53 (No.)	HDAC3 (No.)	ρ	*p*
Spearman test	1450	1450	0.4	<0.01	377	377	0.37	<0.01

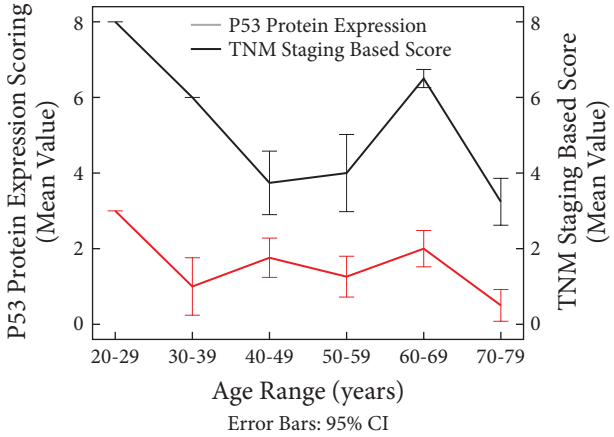

Fig. 2. A line graph depicting the mean p53 protein expression (red line) and advanced TNM staging (green line) across various age groups of CRC patients over a 10-year period. Each data point represents the mean value from five replicates of visualized score readings. Error bars indicate 95% confidence intervals, reflecting the variability and reliability of the mean scores. The graph highlights potential correlations between p53 expression and TNM staging in relation to patients' age

to the absence of p53 protein expression (represented by magenta colored circle 0). The decreased levels of both p53 and HDAC1 gene products are also related as shown by the second biggest blue circle 1 and dark green circle 1 respectively. This finding further confirmed their significant association ($p = 0.02$, $\rho = -0.243$) shown in Table 1. However, weaker relations were demonstrated at the higher scoring of expression of p53 and both HDACs. These results may indicate that HDAC1 and HDAC3 co-expression plays a slight interchangeable role in expression of p53 protein.

Based on our results, we considered it appropriate to analyze the correlation between *TP53* and *HDAC3* mRNA levels. For this purpose, we used the online tool TNMplot.com developed by Bartha and Gyorffy [33] that uses data from The Cancer Genome Atlas (TCGA). The scatter-plotted data in Fig. 4 and the corresponding statistical analysis in Table 2 exhibit a significant correlation between the expressed *TP53* and *HDAC3* genes in either malignant ($p < 0.001$, $\rho = 0.4$) or normal tissues ($p < 0.001$, $\rho = 0.37$). The correlation of p53 and HDAC3 expressions in the malignant tissues agrees and, thus, confirms our findings of the positive significant correlation between expressions of p53 and HDAC3 in the CRC patients ($p < 0.001$, $\rho = 0.411$) as shown in Table 1.

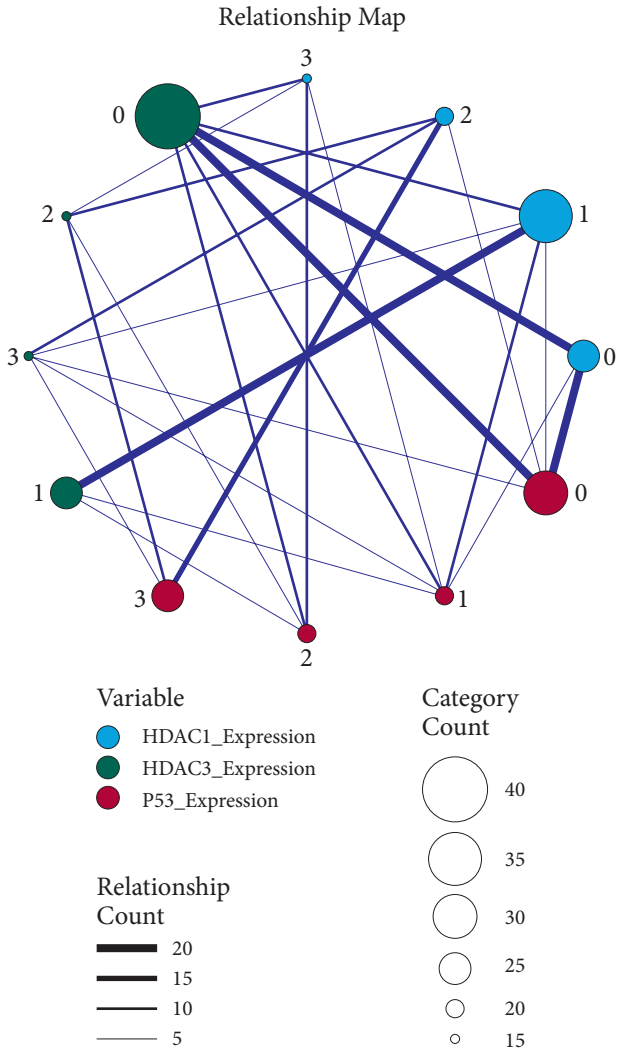

Fig. 3. The presented diagram illustrates a relationship map depicting the interconnections among the assessed variables of p53, HDAC1, and HDAC3 protein expression scores. The map visually represents the correlations between the expressed proteins through circles denoting their impacts and interconnecting lines. The size of the circles indicates the categorical count of expressed p53, HDAC1, and HDAC3 proteins, with larger circles reflecting a higher frequency of occurrence, regardless of the expression score. The thickness of the interconnecting lines elucidates the degree of impact relation between the expressed proteins — thicker lines indicating a larger co-occurrence

To determine the prognostic value of *TP53*, *HDAC1*, and *HDAC3* expression in colorectal cancer tissue, we analyzed overall survival using the online tool KMplot developed by Lanczky and Gyorffy [34]. The OS curves exhibit that higher transcripts levels of *TP53*, *HDAC1*, and *HDAC3* are significantly associated with good prognosis of female CRC patients (Fig. 5), whereas data analysis of both

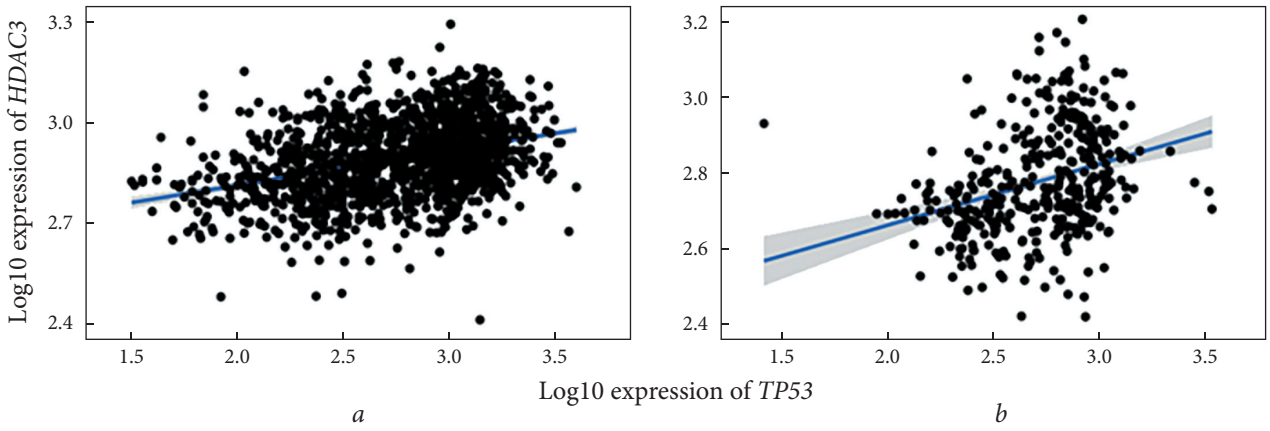

Fig. 4. Scatter plots demonstrating the relations between the studied *TP53* and *HDAC3* gene expression in normal (*a*) and CRC (*b*) tissues (according to the TNMplot data)

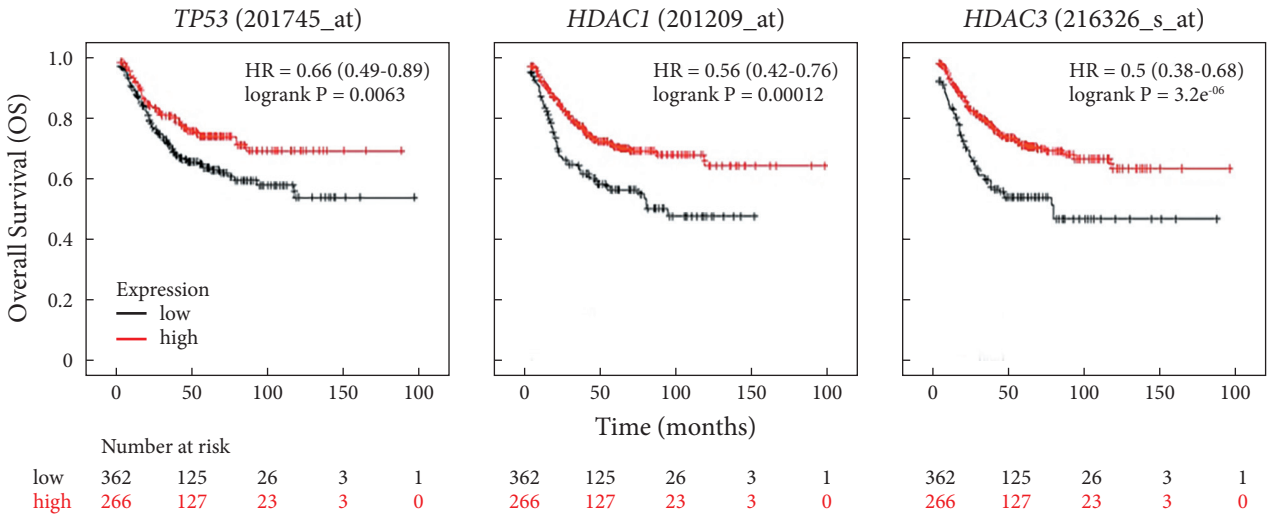

Fig. 5. Kaplan — Meier plots demonstrating overall survival (OS) of CRC patients dichotomized by the median of p53, HDAC1 and HDAC3 mRNA transcripts (according to the KMplot data)

genders collectively show negative correlation between p53 and either of HDAC1 and HDAC3 separately (data not shown). These outcomes further confirmed our findings of the significant association between the expressed *TP53*, *HDAC1*, and *HDAC3* proteins shown in Table 1 but based on the patients' gender.

Discussion

Cells and organisms gradually lose many of their regular biological functions as they age, which is an innate and slow process. Numerous reports have shown that aging negatively affects many functions such as DNA repair, immunological response, and cell proliferation regulation [35, 36]. Our results regarding the decrease in p53 protein expression with age are consistent with several studies that indicated the reduction of both p53 expression and activity in elderly people [37, 38], suggesting that the reduction in p53 expression during aging could potentially contribute to the onset of cancer in an age-dependent manner. Conversely, our results regarding the elevation of p53 expression in relation to CRC progression align with the findings from various cancer studies, including those focused on CRC [39—41]. One way or another, the knowledge of the functions of wild-type and mutated p53 may open avenues for the invention of innovative therapy of CRC [42].

Taken together, our results indicate that p53 protein expression in CRC patients is associated with the expression of HDAC 1 and 3 proteins. These results are supported by the statistical analysis of plotted data obtained from portals at kmplot.com and TNMplot.com. However, they disagree with

previous reports that p53 expression is dysregulated by HDAC1 [43] and HDAC3 [44]. A potential explanation of our finding is that the p53 protein could be produced in mutated forms, which may associate with HDACs expression [45]. The rationale behind our explanation is based on the fact that p53 may be expressed in variant forms of *TP53* status including the mutated forms in cancer cells [46] and CRC tissues [47]. On the other hand, it is important to point that there is a possibility of another mechanism behind this result, which is that HDACs could directly contribute to the acetylation of p53 and convert it in an inactive form regardless its expression. As an example, HDAC1 has the capacity to undo the acetylation of p53, resulting in its transcriptional inhibition [48]. Additionally, the direct dampening of the p53 function by HDACs has been primarily linked to its C-terminal domain composed of 30 amino acids. This region encompasses the acetylation sites targeted by p300/CBP, where p300/CBP boosts p53 activity not only through histone modification but also by directly adding acetyl groups to p53 at its C-terminal lysines. Given the reversible nature of histone acetylation involving both acetyltransferases and deacetylases [49], it is conceivable that HDACs might participate in the stripping of acetyl groups from non-histone transcription factors like p53. This process could contribute to the inactivation of p53, potentially occurring in CRC. This suggests that the suppressive effect of HDACs on p53 transactivation is not solely associated with histone deacetylation within the promoter region. Notably, HDAC1, -2, and -3 have been observed to directly interact with p53, likely leading to its deacetylation and, consequently, a reduction in its transcriptional activity [50]. HDACs can reactivate signaling pathways related to cell death, such as NF-κB and p53, by directly modifying the acetylation pattern of non-histone proteins, particularly transcription factors, in cancer cells [28]. Additionally, it has been shown that interaction with a complex containing HDAC1 decreases the stable levels of acetylated p53, leading to the repression of p53-mediated transcriptional activation, cell cycle arrest, and programmed cell death [48].

The findings of the current study confirm the importance of p53 expression in CRC prognosis. On the other hand, the co-expression data of HDACs-p53 could pave the way to hypothesize a possible mechanism underlying the expression of these molecules, highlighting the need for further study with the use of advanced molecular techniques (e.g., Whole Transcriptome Sequencing) for the association of p53 variants dysregulation with HDAC1/HDAC3 mediated histone deacetylation in predicting CRC patients' outcomes.

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Conflict of interest

The authors declare that they have no competing interests.

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АСОЦІАЦІЯ МІЖ ЕКСПРЕСІЄЮ HDAC1 І HDAC3 ТА ПРИГНІЧЕННЯМ ЕКСПРЕСІЇ P53 І АГРЕСИВНІСТЮ ПУХЛИНИ У ХВОРИХ НА КОЛОРЕКТАЛЬНИЙ РАК

Стан питання. Колоректальний рак (КРР) посідає друге місце у світі за смертністю від онкологічних захворювань. Це захворювання спричинюється різними факторами. З'являється все більше даних, які вказують на роль епігенетичних модифікацій гістонів у виникненні КРР. В роботи полягала у визначенні експресії білків p53, HDAC1 та HDAC3 в пухлинах хворих на КРР та аналізі можливого зв'язку між їхньою експресією та стадіями прогресування захворювання. **Матеріали та методи**. Проведено ретроспективне дослідження експресії p53, HDAC1 та HDAC3 імуногістохімічним методом у 95 парафінових блоках зразків тканини КРР. **Результати**. Експресія p53 в тканині КРР суттєво корелювала з експресією як HDAC1 ($p < 0,001$, rho = 0,522), так і HDAC3 ($p < 0,001$, rho = 0,411), а також із стадіюванням за TNM ($p = 0.002$, rho = 0.313). Зниження експресії p53 корелювало з меншою експресією HDAC1 та HDAC3. Визначили також суттєву від'ємну кореляцію між експресією зазначених білків та віком хворих. **Висновки**. Дані із сумісної експресії білків HDAC та p53 припускають можливий механізм взаємозв'язку між експресією цих білків.

Ключові слова: колоректальний рак, TNM, експресія, p53, HDAC.