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The interplay between paraoxonase-1 and epigenetic changes in colorectal carcinoma

El-Tokhy Amira Kamel¹*, Zin El-deen Doaa Hussein¹, Foda Abd allah Mahmoud¹, Moussa Gamal Ibrahim² and Abo El-Noeman Saad El-Din Abd el-fatah¹

¹Department of Medical Biochemistry, Faculty of Medicine, Tanta University, Egypt. ²Department of Gastrointestinal and Laparoscopic Surgery, Faculty of Medicine, Tanta University, Egypt.

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Colorectal cancer (CRC) is the third leading cause of cancer-related death. Colorectal mucosa has high levels of oxidative stress (OS) landmarks. OS has deleterious effect on cell structures as lipids, proteins and DNA. Markers of protein oxidation are named as advanced oxidation protein products (AOPPs) which have been considered as novel disease biomarkers. OS may also induce DNA damage which leads to mutation of chromosomes. Paraoxonase 1 (PON1) and Arylesterase (ARE) metabolize different substrates and act as antioxidant enzymes. Disruption of epigenetic processes can lead to altered gene function and malignant transformation. Altered expression of genes that encode histone deacetylase (HDACs) are linked to tumor development. The aim of this study was to evaluate the PON1 and ARE activities in CRC patients and to assess the epigenetic fingerprint via estimation of HDAC. The study was carried out on 30 CRC patients. After excision of tumor, segments were divided into two groups: group A (Control group) included parts taken from safety margin; Group B: (CRC group) subdivided into 3 grades, grade I: well differentiated tumor, grade II: moderately differentiated tumor, and grade III: poor differentiated tumor. CRC groups showed elevation of OS landmarks (AOPPs and DNA damage), HDACs activity and significant decrease in the level of PON1 and activities of PON1 and ARE. The histopathological results were correlated with the laboratory results. It was concluded that the damage of AOPPs and DNA is novel biomarkers in diagnosis of CRC; PON1 is important protective antioxidant enzyme and HDAC activity estimation is a promising line in CRC diagnosis.

Key words: Colorectal cancer, epigenetics, oxidative stress, advanced oxidation protein products, paraoxonase 1, arylesterase, histone deacetylase enzyme.

INTRODUCTION

Colorectal cancer (CRC) is a global public health concern, with an increasing incidence and mortality rates in many countries. Various estimates indicate that CRC incidence is increasing in countries with limited healthcare.

*Corresponding author. E-mail: dramirakamel86@gmail.com.

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CRC is the third leading cause of cancer mortality in men and second in women (Ferlay et al., 2015). It was found that human colorectal mucosa has elevated rates of different markers of oxidative stress (OS), such as reactive oxygen species (ROS) which may also play a role in development of CRC (Aiello et al., 2011). OS is known to have a pathogenic role in ulcerative colitis (UC) and colitis-associated colorectal cancer (CAC) development. In such inflammatory conditions (ROS), as superoxide anion free radical (O$_2^-$), hydrogen peroxide (H$_2$O$_2$), and hydroxyl radical (HO·), are produced at higher levels and accumulate causing protein dysfunction and DNA damage, leading to gene mutations. Accumulated ROS act as chemical messengers that activate signaling pathways that affect cell proliferation, differentiation and apoptosis (Wang et al., 2016).

In comparison to normal cells, malignant cells seem to function with higher levels of endogenous OS as they have higher levels of ROS, which seems to be essential for malignant initiation and progression. Cellular targets affected by OS include DNA, phospholipids, proteins, and carbohydrates on the cell membrane. Oxidized and injured DNA has the potential to induce genetic mutation. Some telomere genes are highly susceptible to mutation in the presence of ROS; it is apparent that tumor suppressor genes (TSG) such as p53 and DNA repair genes may suffer DNA damage. In addition, oxidized lipids react with metals to produce active substances (for example, epoxides and aldehydes) or synthesize malondialdehyde, which has the ability to induce mutation (Morry et al., 2017). DNA repair genes that maintain the integrity of genomic DNA are important in preventing carcinogenesis, so their mutations are associated with cancer predisposition syndromes (Figueroa-González and Pérez-Plasencia, 2017). DNA is the primary target following exposure to stimuli such as ultraviolet (UV) radiation, DNA alkylators, certain environmental carcinogens, OS and chemotherapeutic drugs. All these damaging factors produce lesions on DNA and a base alteration promoting a break in the DNA structure. Double-strand breaks (DSBs) are lethal to cells, as they affect both strands of DNA and promote the loss of genetic information, so DNA damage may promote genomic instability and aid in the development of many cancers (Li et al., 2015).

Advanced oxidation protein products (AOPPs) is protein oxidation by covalent modification which occurs either directly by ROS or indirectly by reaction with OS products. It represents dityrosine-containing cross-linked protein. AOPPs have been considered as a novel marker of oxidant-mediated protein damage. Also, it is considered as mediator of inflammation involved in the pathophysiology of many diseases including inflammatory disorders, premature aging and cancer (Salud et al., 2016). AOPPs are derived from oxidation of albumin, fibrinogen, or lipoproteins and they are formed mainly as a consequence of the action of chlorinated compounds on protein (Hopps and Caimi, 2013). Many studies were planned to assess the levels of AOPPs as a markers of oxidant mediated protein damage, as reliable markers of OS in the body that could be helpful in the early identification and even more significantly, in determining the pre-disposition of the various pre-cancerous lesions, before their transformation to frank cancers (Nayyar et al., 2012), since several studies suggest that the pathogenesis of cancer is increased due to the oxidation or nitration of plasma proteins, hence, the attempt to study the oxidant-antioxidant relationship by estimating the levels of AOPP, DNA damage and antioxidant parameters in cancerous subjects (Mukthapura et al., 2013).

Antioxidant is substance that can eliminate ROS directly or indirectly, acting as antioxidant defense, or by inhibiting the production of ROS. The balance between oxidants and antioxidants (redox balance) is essential in maintaining a healthy cellular microenvironment. Antioxidants may be enzymatic or non-enzymatic. Enzymatic antioxidants are superoxide dismutase (SOD), catalase (CAT) and paraoxonase (PON) family including PON1, PON2 and PON3 (Salud et al., 2016). PON1 is the most studied family member of PON family, based on its protective role against poisoning by organophosphate (OP) and in many vascular disease and hence its use as biomarker of diseases involving OS, inflammation and liver diseases (Ceron et al., 2014). It is an antioxidant enzyme closely associated with HDL, preserves LDL against oxidation. PON1 catalyzes the hydrolysis of multiple compounds such as arylesters, lactones and hydroperoxides. The AREase activity of PON1 is involved in the detoxification of lipid peroxides, which are related to several clinical diseases (Gupta et al., 2011). Oxidized LDL is the main form of lipid peroxide responsible for OS-related cancers. Conversely, HDL acts as an anti-carcinogen and a powerful antioxidant as it prevents both enzymatic and non-enzymatic generation of ROS. PON1 is implicated in the elimination of carcinogenic lipid-soluble radicals. So, loss of the PON1 care could play an important role in the susceptibility to genomic damage caused by inflammatory oxidants and dietary carcinogens which modulate the progression of cancer (Hussein et al., 2011).

The mentioned mechanisms of carcinogenesis cannot be explained only by genetic alterations, but epigenetic modifications as well. Epigenetics is a phenomenon that changes the final outcome of a locus or chromosome without changing the underlying DNA sequence (Johnson et al., 2012). Disruption of epigenetic processes can lead to altered gene function and malignant transformation. Global changes in the epigenetic landscape are a hallmark of cancer (Shikhar et al., 2010). Histone acetylation is the best understood epigenetic modification. Histone acetylation and deacetylation are the processes by which the lysine residues within the tail protruding from the histone core are acetylated and deacetylated as part of gene regulation. These reactions are typically
catalyzed by "histone acetyl transferase" (HAT) and "histone deacetylase" (HDAC), respectively (Choudhary et al., 2009). Hyperacetylation increase the expression of particular genes and hypoacetylation has the opposite effect (Annemieke et al., 2003). HDACs are receiving considerable attention as a therapeutic target in many cancers, as mutation of various HDACs genes have been observed in many human cancers. HDACs function to deacetylate the lysine on histone tails causing chromatin condensation and subsequent repression of genes. HDACs are of particular importance as their upregulated activity is associated with tumorigenesis and HDAC inhibitors as romidepsin, vorinostat, belinostat and panobinostat are currently approved for clinical use (Ma et al., 2016). The HDAC family of enzymes regulates the acetylation of histones in chromatin and various non-histone substrates, including many proteins involved in tumor progression, cell cycle control, apoptosis, angiogenesis and metastasis (Tandon et al., 2016). Reduced acetylation, due to enhanced expression of HDACs, may lead to transcriptional repression of tumour-suppressive pathways, including cell cycle regulators and DNA repair pathways. For example, the epigenetic repression of the locus encoding the TSG and DNA repair genes such as BRCA1 and ATR. HDAC1 and HDAC2 regulate acetylation of the onco-suppressor p53, thus inhibiting its function (Ceccacci et al., 2016).

MATERIALS AND METHODS

Chemicals

PON1 ELISA was supplied by Sunred (Biotechnology) company. Potassium iodide, glucal acetic acid, chloramine T crystalline, phenyl acetate, and paraoxon (diethyl p-nitrophenylphosphate) were supplied by Sigma (USA). Nuclear cytoplasmic protein extraction kit and HDACs activity were supplied by Biovision USA. Blood DNA extraction kit supplied by Vivantis technologies Sdn, Bhd Diagnostic Company (Malaysia). Reproducibility of the data presented in this article was confirmed by repeating the experiments at least three times. The data presented here are typical experimental data.

Subjects

The study was carried out on 30 newly diagnosed CRC patients admitted to the outpatient clinic of surgery and laparoscopic department, Tanta University Hospital. All patients were submitted to:

(1) Demographic data taking: age (45-65), sex (18 male and 12 female), social state, risk factors (smoking, obesity, family history of GIT malignancy and inflammatory bowel diseases).
(2) Symptoms: Bleeding per rectum, weight loss, chronic constipation or diarrhea and abnormal bowel habits.
(3) Clinical examination: Full abdominal and rectal examination.
(4) Routine laboratory investigations: Stool analysis, CBC, Prothrombin time and INR.
(5) Tumor markers: carcinoemoberic antigen, alfa feto protein.
(6) Other investigations: MRI, CT and Ultrasound.

(7) The diagnosis was confirmed by the microscopic evaluation of colonoscopic biopsy.

Exclusion criteria

Patients of renal, cardiac, metabolic and other colonic diseases such as ulcerative colitis and chronic inflammatory bowel diseases were excluded from the study. Also, any other suspected malignancies were excluded from the study. CRC patients who had undergone previous colectomy or radiofrequency ablation were excluded from this study.

Research ethics

An informed consent was obtained from all the participants in this research. There was adequate provisions to maintain privacy of participants and confidentiality of the data obtained from the patients and there was code number for every patient file, which includes all investigations.

Experimental

After total excision of tumor, segments were collected and divided into two groups: control group which included parts of safety margin and colorectal tumor tissues divided according to histopathological grading into Group I: well differentiated tumor tissues (grade I), Group II: moderately differentiated tumor tissues (grade II) and Group III: poorly differentiated tumor tissues (grade III). The nature of all tissues was confirmed by histopathological study.

Tissue segments in each group were divided into two parts one for histopathological examination (was kept in 10% formalin solution and fixed for histopathological examination) and the other used for preparation of tissue homogenate.

Preparation of tissue homogenates

Lysis buffer preparation

After adding 100 ml of 0.5 Tris HCl (pH 8), 10 ml of 100 Mm EDTA, 100 ml of glycerol, 30 ml of 5 M NaCl, 10 ml of 1M sodium pyrophosphate and 5 ml of Triton X-100, volume was adjusted for 1 L by adding double distilled water. Pieces of tissue were homogenized in lysis buffer (pH 8) in a ratio of 1/5 w/v. The crude homogenate was centrifuged at 15000 rpm at 4°C for 15 min and the supernatants was diluted with lysis buffer to result in a protein concentration of approximately 2 mg/ml (Prasad et al., 2011).

Paraoxonase1 (PON1) level

By double-antibody sandwich (ELISA). The tissue homogenates were separated and specific antibodies against PON1 were used by an optimized ELISA method according to the manufacturer's procedure (Garin et al., 1994).

Paraoxonase1 (PON1) activity

PON1 converts paraoxon (diethyl-p-nitrophenylphosphate) to p-nitrophenol, a yellow compound that can be measured spectrophotometrically at 405 nm. 50 μl of tissue homogenate was added to 700 μl of Tris HCl solution, 150 μl CaCl2 of solution and 100 μl of paraoxon in each test tube. The rate of generation of P-
nitrophenol was determined at 37°C, 405 nm using spectrophotometer within 1 min. The enzyme activity was calculated using a molar extinction coefficient of P-nitrophenol = (1829 M⁻¹ cm⁻¹) at 405 nm and normalized to protein concentration for crude tissue homogenate. PON1 activity (U/mg protein/min) = (∆ A405/min) / 0.018 x (TV/SV in ml) / protein concentration in mg/ml (Eckerson et al., 1983).

Arylesterase (ARE) activity

The enzyme converts phenyl acetate to phenol that can be measured spectrophotometrically at 270 nm. 125 µl of diluted sample was added to 750 µl of reagent 1 (prepared by dissolving 1.16 g of phenyl acetate in 1 L of distilled water). The rate of generation of phenol was determined at 37°C, 270 nm using spectrophotometer within 1 min. The enzyme activity was calculated using a molar extinction coefficient of phenol = (1.31 m.mol/L/cm) at 270 nm and normalized to protein concentration for crude tissue homogenate (Kilic et al., 2005).

ARE activity (U/mg protein/min) = (∆ A270/min) / 0.00131

Advanced oxidation protein products (AOPPs)

AOPPs were determined spectrophotometrically using semi-automated method on a microplate reader and were calibrated with chloramines-T solutions in the presence of potassium iodide. 200 µl of diluted tissue homogenate (1/5) in phosphate buffer saline (PBS) 50 mM (pH 7.4), was placed, then 10 µl of 1.16 potassium iodide was added followed by 20 µl of acetic acid. In standard tube 10 µl of 1.16 potassium iodide was added to 200 µl of Chloramine T (0-100 µLmol/L) followed by 20 µl of acetic acid. The absorbance of the reaction mixture was immediately read at 340 nm against a blank containing 200 µl of PBS, 20 µl of acetic acid and 10 µl of KI using a microplate reader at 340 nm. A standard curve was plotted and AOPPs concentration in samples was determined by comparing the OD of the samples to the standard curve. AOPP concentrations were expressed as micromoles per liter of chloramine-T equivalents (Blandin et al., 2004).

DNA damage

Genomic DNA was purified using GF-1 Tissue, Blood DNA Extraction Kit, a specially treated glass filter membrane fixed into a column to efficiently bind DNA in the presence of high salt. A mini-column spin technology and the optimized buffers were used to ensure that only DNA was isolated while cellular proteins, metabolites, salts and other low molecular weight impurities were removed during the subsequent washing steps. Genomic DNA release from the tissue by lysis and protein precipitation buffer coupled with the selective adsorption of the genomic DNA to a column. The purified genomic DNA was eluted in a low salt Tris buffer which enhanced DNA solubility and helped to protect the high molecular weight DNA against subsequent nuclease degradation.

Agarose gel electrophoresis

Prepared samples were then resolved in the wells. The gel was run at 88 V for 75 min. A VC 100 bp plus DNA ladder (100 to 3000 bp) with concentration of 0.1 µg/µl served as reference for DNA fragment size. Ultraviolet trans-illuminator was used for visualization of DNA bands and they were photographed (Schaffer et al., 1981).

Nuclear extracts

Cytoplasmic protein extraction was added to the sample to provide hypotonic condition that broke cell membrane and released proteins followed by centrifugation for collection of the nucleoli. Then, the nuclear proteins were extracted by adding nuclear protein extraction (NEB) followed by centrifugation. An additional protease inhibitor cocktail was included to maintain protein integrity and high activity. In addition, DTT helped to maintain the reduced state of the environment, by avoiding the false interaction between the cysteines (Ouyang et al., 2009).

HDAC activity

HDAC substrate was incubated with a sample containing HDAC activity. Deacetylation of the substrate sensitized the substrate, so that treatment with the Lysine Developer produced a chromophore. The chromophore was analyzed using microplate reader.

Procedure

Samples (50 to 200 µg of nuclear extracted protein) were diluted to 85 µl (final volume) using distilled H₂O. 10 µl of the 10X HDAC assay buffer was added to each well, 5 µl of the HDAC colorimetric substrate was added to each well and mixed thoroughly. The plate was incubated at 37°C for 1 h. The reaction was stopped by adding 10 µl of lysine developer and mixed well. The plate was incubated at 37°C for 30 min. Samples were read in a microplate reader at 405 nm. The concentration of the samples was calculated from HDAC standard curve (Li et al., 2012).

RESULTS

The study confirmed that OS plays the main role in pathogenesis of CRC as confirmed by results which showed significant increase in DNA damage and AOPPs levels in CRC groups as compared with control one. The results indicated marked DNA damage in all cohorts of CRC patients, as revealed by increased laddering and fragmentation of DNA extracted from colonic homogenates, when compared with those of control subjects. Variable degree of DNA damage was detected among the three CRC groups with the highest damage observed in group III CRC (Figures 1 and 2). DNA fragmentation was assessed by one densitometry program (Image J), which transforms electrophoresis image into graphic data showing that lanes with multiple fragmentations showed multiple peaks.

As the underlying mechanisms of carcinogenesis cannot be explained only by genetic alterations, but epigenetic modifications as well, the study assessed the epigenetic fingerprint via estimation of (HDAC) activity. The elaborated data indicated that the CRC groups showed statistically significant increase in tissue (HDAC) activities, when compared with control group. There were statistically significant differences in values of (HDAC) activities among the three CRC groups. However, the
Figure 1. (A) Representative electrophoresis image of DNA fragmentation assay showing M: DNA marker (100-300bp), C: control, I: CRC grade I, II: CRC grade II, III: CRC grade III. (B) Representative peaks of fragmented DNA (multiple peaks increased DNA fragmentation) analyzed by Image J software.

Figure 2. Electrophoresis images: M: DNA marker (100-3000 bp), C: control, I: grade I CRC, II: grade II CRC, III: grade III CRC.

highest values were found in group III CRC (Table 1). PON1 is considered not only an antioxidant enzyme but also has been implicated in the development of many cancers. The results showed impairment in defense
mechanisms appeared as significant decrease in level of PON1 and PON1 and ARE activities in CRC groups as compared to control one. Low PON1 activity has been consistently linked to an increased risk of CRC (Table 1).

The correlation matrix showed, positive correlation between AOPPs concentration, HDAC, and negative correlation between (PON1, HDACS) and (AOPPs, PON1 level) (Figure 3).

**Histopathological results of colonic tissue**

The colonic tissue specimens from control group had no noticeable histological changes with normal architecture and normal interstitial spaces. However, colonic tissue specimens from group I CRC showed histopathological changes in the form of irregular displaced glands with scattered mucine lacks lined by malignant cells. While colonic tissue from group II CRC showed histopathological changes in the form of irregular displaced sheets of malignant cells with poorly differentiated glands, scattered mucine lacks lined by malignant cells and muscle cells infiltration. However, colonic tissue from group III CRC showed histopathological changes in the form of irregular displaced sheets of malignant cells showing signet ring appearance. Malignant cells show all criteria of malignancy (hyperchromatism, pleomorphism). There is total loss of glandular architecture, scattered mucine lacks lined by malignant cells and marked muscle fiber infiltration (Figure 4).

**DISCUSSION**

In the previous study, AOPPs were reported as an important OS landmark. Several other studies also demonstrated that new compounds, such as AOPPs may be used as a new basis for early diagnosis of the deleterious effect of ROS (Alani et al., 2014). The present study indicated that the CRC groups showed statistically significant elevations in AOPPs, when compared with control. There were statistically significant differences in values of AOPP concentrations among CRC groups. However, the highest values were found in group III CRC, a finding that had been previously reported by Gonzalez et al. (2015), Zhou et al. (2012), and Xu et al. (2014) who found elevated levels of AOPPs in sera of cardiac and uremic patients, and concluded that OS causes damage to important biological structures and may enhance the inflammatory response. New compounds, such as AOPPs and advanced lipoperoxidation end products (ALEs) may constitute a new basis for the deleterious activity of ROS and they could be considered to be true mediators of the proinflammatory effect of OS (Gonzalez et al., 2015; Zhou et al., 2012; Xu et al., 2014). The results presented herein indicated marked DNA damage in all cohorts of CRC patients, as revealed by increased laddering and fragmentation of DNA extracted from colonic homogenates, when compared with those of control subjects. Variable degree of DNA damage was detected among the three CRC groups with the highest damage observed in group III CRC. This is in line with Júnior et al. (2015), who revealed a marked DNA damage in lymphocytes from patients with breast cancer. They assumed that alkylating member of the nitrogen mustard family induced various types of DNA damage, such as DNA adducts, gene mutations, and chromosomal aberrations leading to cancer development. Similarly, Guo et al. (2016), stated that urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) (a product of oxidative modifications of DNA), is elevated in CRC patients particularly those with distant metastasis highlighting the role played by OS in the development of CRC.

The present study indicated a statistically significant decrease in tissue level of PON1 and ARE activities of CRC patients when compared with control. This is in basic agreement
with previous reports of Elkiran et al. (2007), who declared decreased serum PON1 and ARE activities in patients with lung cancer as compared to the controls. Similar results were obtained by Eldeeb et al. (2017), who evaluated the relation between CRC and PON1 enzyme activity and polymorphism. The study indicated that the serum PON1 and ARE activities were significantly lower in CRC patients as compared to healthy subjects concomitant with significant difference of genotype distribution of PON1 between patients and control groups. These observations suggested the hypothesis that defects in the antioxidant system capacity and altered PON1 activity may be involved in the pathogenesis of CRC.

On the other hand, contradictory results from previous studies of Afsar et al. (2015), who evaluated PON1 and ARE activities and OS in patients with CRC. The PON1 and ARE activities of the patients with CRC were significantly higher as compared to those of the control group. Therefore, the plausibility of using control specimens from the same patient instead of healthy individuals is questionable, particularly when common inherited and exposure factors could lead to a shared cause-effect relationship within the same individual.

In agreement with the present study, previous reports of Ellidag et al. (2014), they determined the phenotype distribution and enzymatic activity of PON1 and ARE in CRC, bladder cancer and multiple myeloma patients as compared to healthy subjects. PON1 and ARE activities were significantly lower in the cancer patients as compared to the control group. However, PON1 phenotypes were similar between the cancer groups and control group. To the best of the authors' knowledge, no previous study has estimated the level and activity of PON1 and ARE in tissue homogenate of CRC tumor segments.

Figure 3. A. Correlation matrix of HDAC and PON1. B. Correlation matrix of HDAC and AOPPs. C. Correlation matrix of PON1 level and AOPPs.
The underlying mechanisms of carcinogenesis cannot be explained only by genetic alterations, but epigenetic modifications as well. Disruption of epigenetic processes can lead to altered gene function and malignant cellular transformation (Figure 5). The elaborated data in this study indicated that the CRC groups showed statistically significant increase in tissue (HDAC) activities, when compared with the control group. There were significant differences in values of HDAC activities among the three CRC groups. However, the highest values were found in group III CRC. The present study is in basic agreement of previous reports of Singh et al. (2012), which stated that HDAC mRNA and protein overexpression was observed in endometrial and ovarian cancers. Numerous in vitro studies have shown that HDAC inhibitors, through their actions on histone and non-histone proteins, are able to reactivate the TSG, inhibit cell cycle progression and induce cell apoptosis in endometrial and ovarian cancer cell cultures. Moreover Jin et al. (2008), estimated that overexpression of HDAC1, HDAC2 and HDAC3 proteins were detected in ovarian cancer tissues implying a significant role of HDACs in ovarian carcinogenesis. The present study is in harmony with previous reports of Marques et al. (2014), who assessed the characteristics of endoscopically resected polyps in patients who underwent colonoscopy and compare histopathology findings according to patient age and polyp size. Similarly, Marzouk et al. (2011) predicted the prognosis of CRC patients through estimation of several factors such as tumor size, histological type and subtype, presence of signet ring morphology and the degree of differentiation as well as the presence of lymphovascular invasion and lymph node involvement.

**Conclusion**

In view of the assessed data, it can be concluded that OS plays the control role in cancer development and thus elimination of multiple ways that increase ROS production and improving lifestyle can enhance the defense mechanisms against OS in the form of
antioxidant enzymes which guard against cancer development. Also, it can be concluded that histone acetylation/deacetylation process has an important role in cancer cell development, and thus early estimation of HDAC activity in cancer cell biopsy may give early diagnostic method. Also, HDAC inhibitors are promising line of treatment in CRC patients.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

REFERENCES


Chronic colorectal cancer and fibrosis: Opportunity for therapeutic intervention with molecular prognostic features in histopathology findings.


