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Original paper

Xanthine oxidase activity and its relation to oxidative stress in human colorectal and prostate cancer

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Summary. Colorectal cancer (CRC) and prostate cancer (PC) are the most often diagnosed cancers and the main reason for mortality connected to tumor diseases. There is still a shortage of examination of mechanisms including the influence of xanthine oxidase (XO) activity in progressiveness and invasion of the cancers. Therefore, present study investigated the role of XO activity, in correlation to thiobarbituric acid-reactive substances (TBARS) and advanced oxidation protein products (AOPP), as markers of oxidative stress in progression and invasion of human CRC and PC. We took tissue specimens from 30 patients with CRC and 18 patients with PC, in all four clinical stages of the disease. They were divided in 3 groups: cancer tissue, tissue surrounding the tumor and healthy control tissue group. The activity of XO in tumor tissue and tissue adjacent to the tumor was significantly higher when compared to healthy colon tissue. The highest activity of XO was in T2 and T3 tumor stadiums. TBARS and AOPP also showed higher concentration compared to control healthy tissue. There was a positive correlation between XO activity and prostate specific antigen (PSA) levels in PC. Presented results suggest that one of the possible causes of oxidative stress in CRC and PC could be high XO activity. XO may be involved in the malignant transformation, in the progression and invasion of human CRC and PC. XO could represent a theranostic biomarker, whereas using XO inhibitors such as allopurinol, could be a promising adjuvant therapy.

Keywords: colorectal cancer, oxidative stress, prostate cancer, xanthine oxidase.

INTRODUCTION

Colorectal cancer (CRC) and prostate cancer (PS), are the most frequent tumours in the human population. They are among the most often diagnosed cancers and the main reason for high mortality connected to tumour diseases (Bray et al. 2018; Siegel et al. 2018). Despite the possibility of early diagnosis and novel treatment strategies, the five-year survival in those tumors remains poor, mostly because of recurrence and metastasis. However, the precise mechanisms resulting in the initiation and development of the carcinoma are still unclear. A great number of evidence has shown that oxidative stress (OS) is included in the pathogenesis and progression of CRC and PS. Reactive oxygen species (ROS) can be involved in all parts of cancer growth, especially the process of cancer initiation and progression (Glei et al. 2002). Hyper-methylation and blocking of transcription of the gene promoter region, as well as oxidative damage to nuclear DNA (oxidative stress), are the two main mechanisms in the initial stages of the carcinogenesis (Garfinkel and Mushinski 1999; Girgin et al. 2000).

While a moderate increase in ROS level can promote cell proliferation and differentiation, a higher accumulation of radicals induces oxidative damage to lipids, proteins and can attack DNA directly forming mutagenic lesions (Assi 2017; Chio and Tuveson 2017).

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There are three main sources of ROS in the cell. The electron transport chain in mitochondria, NADPH oxidase enzymes and peroxisomes. The initial ROS is always superoxide radical anion ($O\cdot_2^-$) which is generated by the reduction of oxygen (Guichard et al. 2008). Since they have xanthine oxidase activity, peroxisomal ROS consists predominantly of superoxide anion radicals (Bonekamp et al. 2009).

XO is an enzyme that can be responsible for oxidative damage in cancers. Its function is to catalyse the terminal degradation of purine bases that generate uric acid, as the last product of purine catabolism (Kimoloi 2018).

It is well known that XO is an enzyme present in two interconvertible forms: dehydrogenase and oxidase. Results of the previous studies have shown that in cancer tissue, through oxidation of sulfhydryl groups or limited proteolysis, dehydrogenase XO activity is converted to oxidase form, which can produce $O\cdot_2^-$ and further hydrogen peroxide (Chen et al. 2016).

So, simultaneously with the purine catabolism, XO activity liberates hydrogen peroxide and $O\cdot_2^-$, which are one of the main ROS and oxidative stress-inducers. DNA damage induced by ROS plays an essential role in the carcinogenic transformation of the cell (Solomon et al. 2010). There are a lot of pathological conditions during which increased plasma XO present, like ischaemia-reperfusion injury, cholecystitis, shock, acute viral infections, adult respiratory distress syndrome (Nath et al. 1994). It has not been clarified yet whether the activity of XO increases or declines in CRC and PC.

Since there is still a limited number of data including influence of XO in progressiveness and invasion of CRC and PC, the present study investigated the role of XO activity in relation to oxidative stress and progression of CRC and PC. Also, better and specific biomarkers are always wanted, especially those which can help not only with diagnosis but also with the prediction of cancer growth, the degree of malignancy and a marker which can be a possible therapeutic target.

MATERIALS AND METHODS

Patients and tissue samples

We conducted investigations on 30 patients with CRC, which were operated at the Clinical Center in Niš, Serbia. Among them 20 were male patients, and 10 were female patients. There were 2 patients in stadium T1, 7 patients in stadium T2, 19 patients in T3 stadium and 2 patients in T4 stadium of the CRC. Also, we included 18 patients with PC, which were operated at the Clinics for Urology. All patients gave their written consent to include in the study. The study was conducted under the Declaration of Helsinki, and the Ethics Committee of Faculty of medicine approved the proper protocols in Nis, and Ethical Committee of Clinical Center in Niš. The exclusion criteria from the study were: liver dysfunction, secondary malignancies, in-operability, previous chemotherapy, or radiation therapy, heart failure or renal failure, smoking and oral antioxidant supplementation before the operation. Patients with diagnosed gout, who were taking allopurinol, were also excluded from the study. Tissue specimens used in the study were obtained during the surgery as soon as possible after resection of the carcinoma. In all patients, pathohistological diagnosis confirmed adenocarcinoma. Also, as a control, we collected the same amount of sample from the macroscopically unchanged region farthest from cancer. Also, we collected adjacent tissue, healthy tissue surrounding the tumor with no macroscopic or pathohistological manifestations of the tumor disease. Every specimen of the tumor and healthy samples were investigated by a pathologist to confirm that the appropriate part of the tissue is collected.

Preparation of tissue samples

We removed tissues quickly during the process of surgery. All samples were placed in iced 0.15 mol/L NaCl solution, cleaned with an isotonic solution to get rid of blood cells and tissue residues. Afterwards, the tissue was cut into smaller pieces and washed with de-mineralized water to remove RBC as much as possible and, subsequently, with 0.15 M phosphate-buffered (30 HIM) saline (pH7.5). We homogenized the tissue with a homogenizer with teflon pestle; We added 90% of isotonic solution to 10% of tissue and we homogenized it. Those 10% homogenates were centrifuged at 3,000 x g for 15 min. The supernatant was frozen at -80 C and kept until assayed.

Biochemical assays

Xanthine oxidase activity

XOD and XO activity in the tissue homogenate were estimated by the amount of uric acid produced by using xanthine as substrate, in the presence of NADH (for XOD) or absence of NADH (for XO) only O_2 as an electron acceptor, for the fixed time interval. XOD and XO were measured in tissue according to the liberation of uric acid by using xanthine as substrate, in the presence of NADH (to measure XOD) or absence of NADH (to measure XO) when only molecular oxygen was electron acceptor. The activity of XDH was calculated by substracting XO activity from the XOD. The molar extinction coefficient of 7.6×10^{-3} M cm^{-1} was used for this purpose XO and XDH activity activity was expressed as U/mg tissue protein in the homogenate (Spiekermann et al. 2003).

Thiobarbituric acid-reactive substances (TBARS) concentration

The amount of TBARS- the final product of lipid per-oxidation in the homogenate was determined using the slightly modified method of Nabavi et al (2012). The quantity of TBA- reactive lipid per-oxidation products was measured at 532 nm against a blank. The concentration was expressed in nmol/mg of protein.

Advanced oxidation protein products (AOPP) concentration

The concentration of AOPP was determined by spectrophotometric method according to Witko-Sarsat et al. (1996). 200 microliters of supernatant from tissue homogenates were diluted in 1:5 in PBS; chloramine-T was used as standard and placed in wells of a 96-well microtiter plate. Then we added 20 *μl* of acetic acid, followed by ten microliters of 1.16 M potassium iodide. At the end 20 *μl* of the glacial CH3COOH was added to wells. The mixture absorbance was read at 340 nm in a micro-plate reader. Blank contained all reagents. We concentration of the AOPP was calculated based on the standard curve of chloramine T (0–100 μmol/L) and was expressed in *μmol* /mg of chloramine T.

Protein content

The amount of protein was determined by Lowry method et al. using bovine serum albumin as a standard (Lowry et al. 1951).

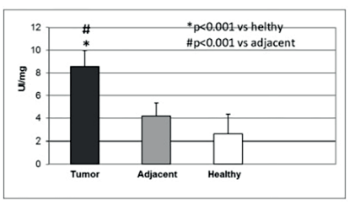
Statistical data processing

The values of the obtained parameters were expressed as X ± SD (mean value ± standard deviation). The examination of obtained results was assessed by the t-test comparing the enzyme activity of samples with pathological manifestations or tissue adjacent to tumor tissue with the activity of corresponding further healthy tissue as well as with the activity of obtained tissue from patients without pathological manifestations.

The statistical significance of differences between TNM stadiums of the tumour was calculated using the ANOVA test. The value of $p < 0.05$ was considered statistically significant.

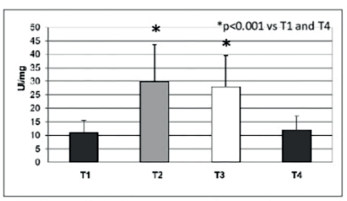
RESULTS

The results are presented in Figs 1 and 2.



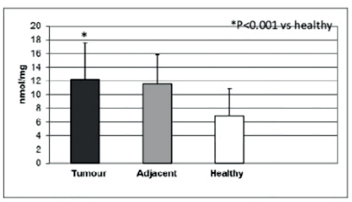
The XO Activity in tumour, adjacent and healthy colon tissue

The activity of XO in tumour tissue was significantly higher when compared to healthy colon tissue ($p < 0.001$). Also, tumour tissue had higher activity of XO when compared to tissue surrounding the tumour ($p < 0.001$).



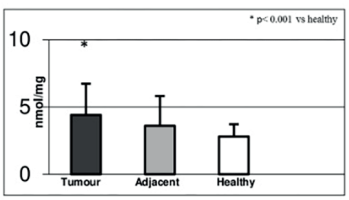
The XO activity in tumour tissue of patients with T1, T2, T3, and T4 stadium

T3 and T4 tumour stadiums have a significantly higher XO activity when compared to T1, T2 tumour stadiums ($p < 0.001$)



TBARS levels in tumour tissue, adjacent and healthy

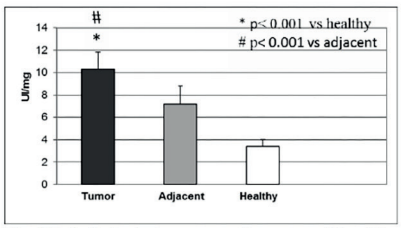
TBARS levels in the tumour tissue were significantly higher in comparison to the healthy colon tissue ($p<0.001$) Also, the tissue surrounding the tumour had higher



AOPP levels in tumour tissue, adjacent and healthy

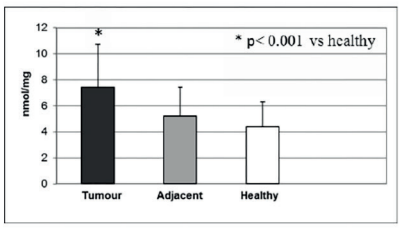
AOPP level in the tumour tissue were significantly higher in comparison to the healthy colon tissue ($p<0.001$).

Fig. 1. XO activity, TBARS and AOPP concentration in CRC.



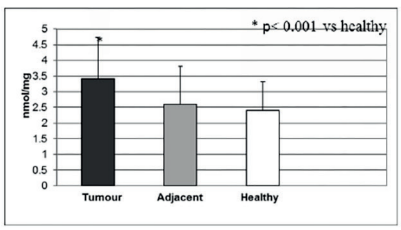
The XO Activity in tumour, adjacent and healthy prostate tissue

The activity of XO in tumour tissue was significantly higher when compared to healthy colon tissue ($p < 0.001$). Also, tumour tissue had higher activity of XO when compared to tissue surrounding the tumour ($p < 0.001$).



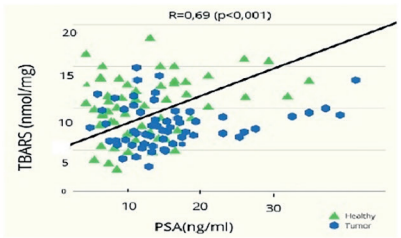
TBARS levels in tumor tissue, adjacent and healthy tissue

TBARS levels in the tumour tissue were significantly higher in comparison to the healthy prostate tissue ($p<0.001$)



AOPP levels in tumour tissue, adjacent and healthy tissue

AOPP level in the tumour tissue were significantly higher in comparison to the healthy colon tissue ($p<0.001$).



Correlation between XO activity in tumour tissue versus serum PSA, The association was estimated using the Pearson correlation coefficient (r) and illustrated using a scatter plot.

A significant positive correlation ($r = 0.63$ ($p = 0.001$)) was observed

Fig. 2. XO activity, TBARS and AOPP concentration, XO and PSA correlation in PC.

DISCUSSION

Alterations in the enzymology of the human colorectal and prostate cancers clearly distinguished it from the healthy tissue of those organs. To get a better understanding of the role of the XO enzyme in cancers, we have paid attention to investigating the interrelations between XO, OS and the carcinogenic process

Despite the available diagnostic methods for those cancers, prediction of its progressiveness and potential to develop, we still don't have an ideal non-invasive biomarker. Can XO be biomarker which can help us in diagnosis, prediction and also possible therapy?

One of the main mechanisms included in carcinogenesis is OS. We define it as alterations in gene expression, cell metabolism, and cell homeostasis caused by overproduction of ROS and disturbances in antioxidant mechanisms (Maciejczyk et al. 2019). It has been documented that oxidative stress causes genetic alterations, which may lead to cance (Wu et al. 2009).

Our aim was to evaluate the importance of XO as an ROS producer since its activity has been involved in ROS-dependent tissue damage under ischemia-reperfusion or hypoxia conditions, which are the hallmarks of the cancer (Anderson et al. 1989; Portugal-Cohen and Kohen 2009).

XO showed twofold higher activity in CRC and PC compared to healthy tissue and also tissue surrounding the tumour. These results are similar to our previous published study, which we conducted on higher number of patients, in which we showed high XO activity in PC (Veljković et al. 2020).

Tissue surrounding the tumor had lower activity when compared to tumor tissue, which implies that XO is not the main reason for tumor proliferation. A very important ques-

tion is the mechanism involved in the higher XO activity. Thus, in PC we examined XDH activity to determine the percentage of conversion of the HDX to XO. By now, it has been noted that xanthine oxidoreductase activity is only regulated at the transcriptional and post-translational levels. Besides proteolytic and cysteine disulphide modifications, XDH/XO protein phosphorylation or even limited proteolysis were also reported in previous studies (Battelli et al. 2014). We related increased XO activity to the conversion of the dehydrogenase form of XO into the oxidase form, by reversible oxidation of thiol groups or by irreversible proteolytic attack caused by elevated peroxy nitrite (Battelli et al. 2016).

Also, the high activity of XO may be explained by the high xanthine levels which are present in the cancer tissue, because it is one substrate of XO. Or high xanthine levels promote the expression of the enzyme. Therefore, higher levels of xanthine raise XO activity, that might be the source of high oxidative stress. It is a main enzyme which links the metabolism of purines and free radicals along with oxidative stress.

Some previous studies have reported lower XO activity in cancers, and suggest that the decreased purine catabolism and increased activity of salvage pathway enzymes would favour tumour cell growth (Ikegami et al. 1986). Some of the previous research has refuted the thesis that XO activity is the source of the oxidative stress (Sun and Cederbaum 1980). The decreased XOR activity observed in highly aggressive cancer cells appears to have unexplained effects on tumour differentiation and leads to cancer growth and metastasis.

However, in another study, liver cancer compared with noncancerous human liver tissues had lower activity of the dehydrogenase form of XOR, but its oxidase form increased (Durak et al. 1998). Significantly higher XOR levels were also reported in meningioma and astrocytoma in comparison with normal brain tissue (Kökoglu et al. 1990). Increased XOR activity was also reported in human laryngeal well-differentiated squamous cell carcinomas compared with the corresponding tumor-free adjacent tissues or normal laryngeal tissues (Durak et al. 1993).

We could relate increased XO activity to the conversion of the dehydrogenase form of XO into the oxidase form, by reversible oxidation of thiol groups or by irreversible proteolytic attack caused by elevated peroxy nitrite levels.

ROS overproduction leads to cancer progression and results in lipid peroxidation and protein oxidative damage (Reuter et al. 2010). To evolve the effect of high xanthine oxidation activity on elevated levels of OS, we determined the concentration of markers of oxidative changes in lipids and proteins. Results of our study in CRC show the highest activity of XO in T3 and T4 stadium and it is in correlation with the TBARS concentration the higher stadium of the disease.

Specifically, ROS induced by XO increase hypoxia-inducible factor 1a expression and activates NF-kB, contributing to cancer-associated inflammatory signalling and to tumour progression by activating angiogenesis, cell migration, and invasion (Romagnoli et al. 2010; Balamurugan 2016). Janion et al. (2020) demonstrated that the intensity of lipid peroxidation processes is correlated with the development of colorectal cancer.

Marked oxidative stress in stage 4 of cancer in our investigation shows the advancement of the disease since the prevalence of oxidative stress gives rise to inflammation. ROS can also act as a secondary messenger by activating intracellular signalling pathways, such as NF-κB, a major modulator of carcinogenesis. Oxidative activation stimulates the expression of many pro-inflammatory cytokines in intestinal epithelial cells, such as TNF-α, IL-1, IL-8, and COX-2, and leads to inflammation and carcinogenesis (Cummins et al. 2013).

In PC, the TBARS levels were significantly higher in cancer tissue. Results of this study are in accordance with the findings of Yilmaz et al. (2004) on the elevated lipid peroxidation with antioxidant depletion in prostate cancer.

Our results also showed increased levels of the AOPP in CRC and PC tissue versus control healthy tissue. AOPP may be formed by the oxidation of a few amino acid side chains via the addition of aldehydes, such as those generated from lipid peroxidation. PCB is an initial and reversible product of protein oxidation, while Pande et al. (2013) reported that patients with PC have higher AOPP levels compared to the healthy control.

Increased XO activity in patients with colorectal cancer in our study suggests that oxidative stress may be increased in cancerous changes and processes, and may affect the course of the disease. Zińczuk et al. (2020) have also reported high XO activity in CRC tissue, and higher concentration of the markers of lipid peroxidation compared to healthy colon tissue. The explosion of XO - mediated RVK in cancerous tissues may be caused by a large increase in substrate formation, which occurs because of rapid nucleotide production during the tumor growth process. Degradation of xanthine XO rather than XOD also leads to the formation of hydrogen peroxide and hydroxyl radicals. Stimulated ROS generation can be potentially responsible for cell membrane damage and lipid peroxidation and leads to tissue and / or organ damage. We may relate increased XO activity in our study to increased levels of TBARS in tumour tissue representing markers of oxidative damage.

Also, the increased XO activity in patients with PC in our study suggests that this parameter might be a useful marker of the disease evolution and it could influence on the pathology of the disease. It is even in strong correlation to PSA values from the serum of the patients. The activity of

xanthine XO rather than XOD also leads to the formation of hydrogen peroxide and hydroxyl radicals. Higher ROS concentration could be responsible for cell membrane damage, lipid peroxidation and leads to tissue and/or organ damage. Despite the fact that further studies in PC patients are required, our results may suggest that we can use the XO in these tissues as a surrogate marker for the individualization of PC prevention and therapy. Further research should be planned to find out whether the XO as a biomarker could be used as a differential diagnostic and prognostic tool for prostate cancer and BPH.

Recently published article has shown XO inhibition can suppress cell migration and metastasis of breast cancer (Oh et al. 2019) so that the use of allopurinol as adjuvant therapy in CRC and PC could be a promising treatment.

CONCLUSION

Presented results suggest that one of the possible causes of oxidative stress in CRC and PC could be high XO activity. This enzyme may be involved in the malignant transformation of the colon and prostate epithelium, as well as in the progression and invasion of the tumors.

The simplicity of measuring activity asserts usefulness of this enzyme in some patients, where cytopathological findings cannot lead to a clear conclusion. This simple test, together with known clinical pathological findings, can have significance in diagnosis, but in prognosis of the disease as well. We could use this enzyme as theranostic biomarker, since using XO inhibitors such as allopurinol as adjuvant therapy could be a promising treatment.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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