ISSN 0006-2979, Biochemistry (Moscow), 2022, Vol. 87, No. 5, pp. 413-424. © Pleiades Publishing, Ltd., 2022.
Russian Text © The Author(s), 2022, published in Biokhimiya, 2022, Vol. 87, No. 4, pp. 459-473.

REVIEW

Oxidative Stress and Redox-Dependent Signaling in Prostate Cancer

Elena V. Kalinina[1,a]*, Ludmila A. Gavriliuk[1], and Vadim S. Pokrovsky[1,2]

[1]*Peoples's Friendship University of Russia (RUDN University), 117198 Moscow, Russia*
[2]*N. N. Blokhin National Medical Research Center of Oncology, 115478 Moscow, Russia*
[a]*e-mail: kalinina-ev@rudn.ru*

Received January 24, 2022
Revised March 20, 2022
Accepted March 20, 2022

Abstract—Tumor emergence and progression is complicated by the dual role of reactive oxygen species (ROS). Low concentrations of ROS are essential for many intracellular metabolic processes and cell proliferation, while excessive ROS generation disrupts the mechanisms of cancer suppression, leading to the cell damage and death. A long-term imbalance in the ROS/antioxidant ratio and upregulation of the ROS generation due to the reduced efficacy of the antioxidant defense system cause chronic oxidative stress resulting in the damage of proteins, lipid, and DNA molecules and cancer development. Numerous data demonstrate that prostate cancer (the most common cancer in males) is associated with the development of oxidative stress. However, the reasons for the emergence of prostate cancer, as well as changes in the redox signaling and cellular redox homeostasis in this disease, are still poorly understood. The review examines the role of prooxidant and antioxidant enzyme systems, the imbalance in their activity leading to the oxidative stress development, changes in the key components of redox signaling, and the role of microRNAs in the modulation of redox status of cancer cells in prostate cancer.

DOI: 10.1134/S0006297922050030

Keywords: prostate cancer, oxidative stress, antioxidant and prooxidant enzymes, transcription factors, Nrf2, NF-κB, redox-dependent signaling, microRNA

INTRODUCTION

According to the WHO reports, morbidity associated with various diseases of prostate has been posing a serious problem in many countries in recent decades. Prostate cancer (PCa) is the most common type of cancer, which ranks second after lung cancer as the cause death in oncological disorders [1]. Oxidative stress, inflammation, and androgen receptor (AR) signaling are of critical importance in the initiation, development, and progression of PCa. Reactive oxygen species (ROS) play a dual role in the development of malignant neoplasms – they can either initiate oncogenesis and maintain tumor cell proliferation or cause death of cancer cells. Genetic changes ensure survival of cancer cells in the presence of high ROS concentrations via activation of redox-dependent transcription factors or increase in the NADPH content through the pentose phosphate pathway activation [2]. Multiple publications corroborate existing relations between oxidative stress and inflammation, pointing out the role of antioxidant deficiency during the development of inflammation and PCa [3, 4].

PCa cells are characterized by the elevated oxidative stress that emerges due to the imbalance between the prooxidants and antioxidants and plays a critical role in PCa development and progression [5, 6]. Tumor cells at the early stages of carcinogenesis are subjected to a severe oxidative stress because of the downregulation of antioxidant enzymes resulting in a higher-than-normal ROS/antioxidant ratio [7].

PCa development is associated with altered intracellular signaling, including MAPK, Nrf2, NF-κB, and AR pathways that are coupled to the ROS levels and control multiple signaling cascades in cancer cells [3, 6].

Abbreviations: AR, androgen receptor; COX, cyclooxygenase; JNK, c-Jun N-terminal kinase; LOX, lipoxygenase; NF-κB, nuclear factor κB; NOX, NADPH oxidase; Nrf2, nuclear factor-erythroid factor 2-related factor 2; PCa, prostate cancer; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3.

* To whom correspondence should be addressed.

However, the crosstalk between these pathways and cell redox status remains poorly investigated. Redox-dependent regulation of cellular events is now envisioned as a multilevel system including proteins and enzyme complexes, as well as noncoding RNAs, in particular, numerous microRNAs (miRNAs). miRNAs play an essential role by acting as oncogenes or onco-suppressors, e.g., via regulation of the prooxidant/antioxidant ratio in cancer cells [8, 9], This activity of miRNAs has gained a special interest in the studies of changes in the cell redox status during PCa development.

Here we analyzed the emergence of the imbalance between the activities of the prooxidant and antioxidant enzyme systems that results in the development oxidative stress in cancer cells, the status of the key components of the redox-dependent signaling, and the involvement of miRNAs in the modulation of cell redox status in PCa.

ANTIOXIDANT AND PROOXIDANT ENZYMES AND DEVELOPMENT OF OXIDATIVE STRESS IN PROSTATE CANCER CELLS

ROS formed in the process of cell metabolism play an important role in the cell signaling, regulation of cell differentiation, proliferation, and bioenergetics. The major sources for ROS are electron leak in the mitochondrial electron transport chain and electron transport chain of the endoplasmic reticulum with the involvement of cytochromes *P450* and *b5*, activity of prooxidant enzymes [NADPH oxidase (NOX), xanthine oxidase, L-amino acid oxidases, monoamine oxidase, lipoxygenase (LOX), etc.], and aerobic redox reactions with metal ions (Fenton reaction). Disruption of the ROS/antioxidant balance accompanied by the rise in the intracellular ROS content can result in the development of cellular oxidative stress may followed by the adaptive activation of the antioxidant defense mechanisms aimed to restore the balance [10]. Long-lasting disruptions of the ROS/antioxidant ratio and markedly elevated ROS levels along with the downregulation of the antioxidant system lead to the chronic oxidative stress accompanied by the damage of protein, lipid, and DNA molecules and development of cell pathologies including malignant neoplasms [11-13].

Development of oxidative stress in PCa is related to the antioxidant deficiency due to a number of reasons (comorbid chronic inflammatory processes, deficit of nutrients with antioxidant properties, etc.), aging being one of the most important among them. The risk of developing PCa is significantly elevated in males above 65 years of age and is related to the reduced activity of the antioxidant defense system [7, 10]. According to the free-radical theory of aging, the balance between the prooxidants and antioxidants is shifted with age towards the oxidative state in most body tissues [14], which increases the risk of oncogenesis [15].

Aging is accompanied by the decrease in the expression of the *GSTP1* gene coding for the glutathione S-transferase (GST) isoform highly active against products of DNA oxidative damage and lipid peroxidation, which is related to the increased DNA methylation [16]. It was found that the CpG-rich promoter region of the pi-class *GSTP1* gene is methylated at single restriction endonuclease sites in the majority of PCa cells vs. normal cells [17]. The loss of the *GSTP1* expression due to the hypermethylation of its own promoter is the most common case of epigenetic modulation observed in human PCa. Reduced *GSTP1* expression may contribute to the elevation in the ROS production and DNA damage.

Malignant transformation of cells altera the oxidant/antioxidant ratio due to the adaptive activation of redox-dependent transcription factors and related increase in the expression of the ROS-neutralizing antioxidant enzymes, which allows cancer cells to sustain their high proliferative activity. PCa cells are characterized by the upregulated gene expression and higher activity of key antioxidant enzymes. PCa progression renders cancer cells more dependent on the antioxidant enzymes, in particular, superoxide dismutase (SOD), which catalyzes dismutation of superoxide anion to H_2O_2 [18]. The data of *in vivo* experiments suggest that expression of SOD2 between the early and advanced PCa stages is regulated by p53 [19].

An important source of ROS in PCa cells is the activity of NOX isoforms [20]. The NOX family consists of seven isoforms (NOX1-5, DUOX1, DUOX2) that transfer electrons from NADPH across the plasma membrane to molecular oxygen followed by formation of superoxide anion.

Although the pivotal role of NOX in developing PCa has been demonstrated in many studies (Table 1), the role of enzyme isoforms in this process remains controversial. Thus, it was demonstrated that xenografts of DU145 cells (human PCa cell line) in Balb/c nude mice were characterized by the *NOX1* gene overexpression that correlated with the tumor growth [21]. Higher *NOX1* expression was found in the high-grade vs. low-grade prostate intraepithelial neoplasia (as well as vs. normal prostate tissue) in the transgenic adenocarcinoma mouse prostate (TRAMP) model [22]. It was found that the activity of NOX1 is related to the VEGF-mediated angiogenesis in the xenografts of DU145 cells [21]. The relation between the NOX1 activity and oncogenesis and development of PCa, was demonstrated in animal models [23]. Moreover, it was found that NOX1 is involved in PCa metastasis [24]. Human PCa cells display higher levels of *NOX1* expression compared to healthy prostate tissue [24]. However, some studies revealed no significant differences in the levels of NOX1 mRNA in benign and malignant PCa cells [25, 26].

Patients with moderately differentiated prostate adenocarcinoma demonstrated low *NOX2* expression levels

Table 1. Expression of NOX isoforms in PCa cell lines and tissues

Cell line/tumor tissue	Isoform							References
	NOX1	NOX2	NOX3	NOX4	NOX5	DUOX1	DUOX2	
PC-3	↑	↑		↑	↑	↑	↑	[2-29, 93, 94]
DU145	↑	↑		↑	↑	↑	↑	[27-29, 94, 95]
DU145, mouse xenograft	↑							[21]
VCaP	↑	↑			↑			[27-29]
U251		↑						[93]
LNCaP	↑	↑		↑	↑			[24, 27, 28, 94]
C4-2		↑						[96]
RWPE1, human prostate benign epithelial cells		↑				↑	↑	[28, 29]
EP156T, cancer cells, human prostate benign epithelial cells		↑				↑	↑	[29]
Human prostate adenocarcinoma	↑			↑		↑	↑	[20, 24, 28]
TRAMP, C57BL/6 mice	↑							[22]

[25]. However, no difference in the *NOX2* expression was found between the malignant and benign prostate cells [26]. Although some publications reported upregulated *NOX2* expression in PCa vs. non-cancer cells, numerous *in vivo* studies suggest that both NOX2 and NOX3 play no role in developing PCa.

On the contrary, expression of the *NOX4* gene in PCa cells (DU145, PCa-3, and LNCaP) was upregulated compared to normal prostate cell lines [27]. In particular, the content of *NOX4* mRNA in PCa cells was markedly higher than in benign prostate tumor cells [26].

Due to the lack of differences in the *NOX5* mRNA expression between normal prostate tissue and PCa cells, it was concluded expression of this gene cannot be used as a marker of malignant transformation of prostate cells [28]. Similar data were obtained in [26], which allowed to conclude the absence of significant difference in the expression of *NOX5* gene in malignant vs. benign tumor tissues.

DUOX1 is a dual-activity NOX isoform and is one of the major sources of H_2O_2. It is highly expressed in both in human prostate normal and PCa cells. However, in some patients with PCa, expression of *DUOX1* was higher in PCa vs. normal cells [25]. In addition, upregulated expression of the *DUOX2* gene was found in DU145 cells [26]. Although the role of DUOX in PCa remains poorly understood, it was found that the high content of ROS in PCa-3 cells is largely sustained due to the activity of DUOX1 and DUOX2 enzymes and that ROS generation may lead to the development of resistance to apoptosis in cancer cells via activation of Akt signaling [29].

Androgens upregulate expression of genes coding for the NOX subunits p22phox and gp91phox in PCa cells and activate ROS generation by NOX2 and NOX4 in the androgen-sensitive 22Rv1 cell line [30]. Similar to androgens, adiponectin triggers marked elevation in the *NOX2* and *NOX4* expression in DU145 and 22Rv1 cells [31].

Cyclooxygenase (COX) and lipoxygenase (LOX) also contribute to the oxidative stress development. These enzymes generate hydroperoxides of polyunsaturated higher fatty acids that are further transformed into highly reactive bifunctional electrophiles – 4-hydroxynonenals and 4-oxo-nonenals, which form crosslinks in proteins and DNA, thus contributing to the emerging oxidative stress [32]. The role of metabolism of arachidonic and linoleic acids catalyzed by LOX in developing malignant neoplasms has been convincingly demonstrated [33-35]. Fatty acid hydroperoxides generated in the metabolism of arachidonic or linoleic acids affect cell growth and survival, angiogenesis, cell invasion, metastasis, and immunomodulation.

Based on the data obtained in PCa experimental models, it was proposed that 5-LOX and 12-LOX, whose

inhibitors exhibit the anti-proliferative activity, can be used as PCa biomarkers [36, 37]. 12-LOX promotes PCa progression and metastasis. It was found that 12(S)-hydroxyeicosatetraenoic acid produced from arachidonic acid in 12-LOX-catalyzed reaction stimulates the PI3K/AKT/mTOR signaling pathway that upregulates expression of the transcription factor HIF-1α gene. This results in the upregulated expression of the vascular endothelial growth factor (VEGF) gene, thereby contributing to the activation of its angiogenic potential [36].

5-LOX also plays an important role in the survival and proliferation of PCa cells by maintaining high expression levels of the *C-MYC* gene. Inhibition of LOX-5 suppresses expression of the c-Myc oncogene in tumor cells [37].

PCa cells demonstrate higher expression levels of the 15-LOX-1 isoform compared to the normal prostate tissue; higher expression of this gene was linked to the tumor Gleason score. In contrast, expression of the 15-LOX-2 gene expression in the tumor was suppressed compared to the healthy tissue [38]. Studying effects of 15-LOX-1, 15-LOX-2, and relevant metabolites on the EGF (epidermal growth factor)-dependent signaling in PC3 cells revealed 13-(S)-hydroxyoctadecadienoic acid (product of 15-LOX-1 activity) activated MAP kinase, whereas 15-(S)-hydroxyeicosatetraenoic acid (product of 15-LOX-2 activity) inhibited this enzyme, which in turn promoted or suppressed, respectively, PPARγ phosphorylation [38]. Hence, it was concluded that 15-LOX-1 and 15-LOX-2 have different or even opposing functions in the prostate.

Despite the difference in the mechanisms of action, the role of LOX isoforms in the PCa development in humans has been elucidated (Table 2). Thus, 12-LOX is considered as a PCa prognostic marker [39]. Analysis of the tumor samples from PCa patients revealed a significant increase in *12-LOX* expression that correlated with the tumor malignancy, which indicated that 12-LOX can be used as a marker of aggressive PCa phenotype and an indicator of poor prognosis [40]. Upregulated expression of *5-LOX* and *12-LOX* was found in PC3 and DU-145 cells [41]. Similar to human PCa tissues, PC-3 cells display an elevated *15-LOX-1* expression that correlates with the extent of cell malignancy [34, 42, 43].

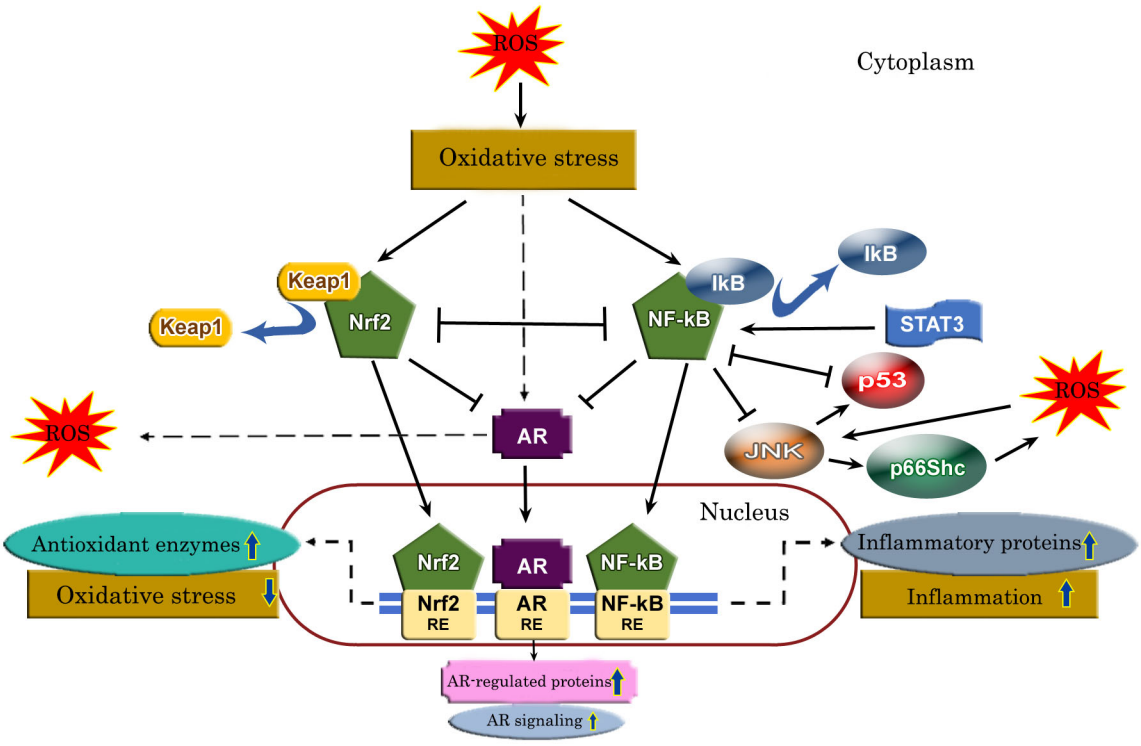
Table 2. Expression of LOX isoforms in human PCa cell lines and prostate cancer tissue

Cell line/ tumor tissue	Isoform			References
	15-LOX-1	12-LOX	5-LOX	
PC-3	↑	↑	↑	[34, 41-43]
DU145	↑	↑	↑	[34, 41, 43]
LNCaP			↑	[37]
PCa, tumor tissue		↑		[40]
$CD133^+$, PCa stem cells			↑	[97]
$CD44^+$, PCa stem cells			↑	[97]

REDOX-DEPENDENT SIGNALING IN PROSTATE CANCER CELLS. THE ROLE OF NRF2, NF-κB, JNK, AND AR SIGNALING PATHWAYS

Nrf2 signaling cascade. Development of chronic oxidative stress in PCa (due mostly to the high ROS content) results in some adaptive alterations in cell signaling that are accompanied by the emergence of the so-called aggressive cancer cell phenotype. Transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2) is the most important regulator of genes encoding enzymes of the antioxidant and detoxification systems in normal and tumor cells [44-46]. Nrf2 is encoded by the *NFE2L2* gene from the family of CNC (Cap'n'collar leucine zipper) transcription factors that also includes NF-E2, Nrf1, Nrf3, BACH1, and ACH2 proteins. Nrf2 controls gene expression of both antioxidant and detoxifying enzymes and, therefore, is an essential element of the cell defense against oxidative stress [46].

Under physiological conditions, Nrf2 binds to the cytosolic repressor protein Keap1 (Kelch-like ECH-associated protein 1) that promotes Nrf2 degradation via the ubiquitin–proteasome pathway. Stress promotes oxidation of cysteine residues in Keap1, thus preventing Nrf2 ubiquitination [47] and facilitating Nrf2 nuclear translocation. In the nucleus, Nrf2 together with small Maf proteins binds to the antioxidant responsive elements (AREs) or MAF recognition elements (MAREs) in the promoter regions of more than 250 target genes. Among currently identified Nrf2-regulated ARE-containing genes there are genes encoding the (i) antioxidant enzymes Mn-SOD (*SOD2*), catalase (*CAT*), heme oxygenase 1 (*HO1*), (ii) enzymes maintaining the level of the intracellular lower-molecular-weight antioxidant glutathione (GSH) via its *de novo* production or GSSG reduction, such as γ-glutamylcysteine synthetase H and L subunits (*γ-GCSH*, *γ-GCSL*), γ-glutamyl transferase (*γ-Gt*), and glutathione reductase (*GSR*), (iii) redoxin proteins involved in the redox-dependent regulation, such as thioredoxin 1 (*TRX1*), thioredoxin-reductase 1 (*TRXRD1*), peroxiredoxin 1 (*PRDX1*), peroxiredoxin 2 (*PRDX2*), and (iv) other enzymes participating in deactivation of oxidative stress products, in particular, GST isoforms GSTP1-1 (*GSTP1*), GSTA4-4 (*GSTA4*), NAD(P)H:quinone oxidoreductase 1 (*NQO1*), and ferritin H and L subunits (*H-Ferritin*, *L-Ferritin*). Activation of Nrf2 along with other



Redox-dependent regulation in PCa cells involving Nrf2, NF-κB, and AR. The type of redox-dependent signaling in PCa depends on the ROS level and developing oxidative stress. The effects of middle-level ROS ensure Nrf2 activation, whereas higher ROS concentrations "switch on" NF-κB and suppress expression of the *NFE2L2* gene. PCa progression is related to the activation of STAT3 in the presence of elevated ROS concentrations. p53 and NF-κB can suppress each other's transactivation. Inactivation of p53 and activation of NF-κB promote resistance to apoptosis. NF-κB activation suppresses activation of JNK necessary for the stimulation of p53. However, ROS can activate JNK via phosphorylation. In turn, JNK activation promotes ROS generation via phosphorylation of p66Shc protein. JNK activation and suppression of Nrf2 facilitate AR activation. Activated by ROS growth, NF-κB can directly bind to the AR site, suppressing AR binding to DNA and its effect on the transcription of target genes

redox-sensitive transcription factors (e.g., AP-1 and NF-κB) can result in the redox-dependent changes in their expression, which ensures shaping of coordinated cell response to oxidative stress. According to the rheostat model of the response against oxidative stress, Nrf2 activation is the first tier in the defense against to moderate ROS concentration, whereas higher amounts of ROS induce the switch to the transcription factors AP-1 and NF-κB, so that further ROS elevation activates apoptosis [2]. It is believed that the final response to the extremely high ROS concentrations is enabled by the transcription factor p53, which controls cell cycle, aging, and apoptosis. It should be noted that during extensive oxidative stress, an excessive amount of accumulated nuclear Nrf2 may bind to the regulatory element in the *Klf9* (Kruppel-like factor 9) gene promoter and activate its expression, resulting in the downregulated expression of the antioxidant enzymes due to the Klf9 binding to the relevant repressor sites, and thus cause cell damage due to the elevated ROS generation [48].

NF-κB signaling pathway. PCa development is often accompanied by the decrease in the Nrf2 activity. In particular, lower Nrf2 levels were observed in the TRAMP progression [49]. Downregulated *NFE2L2* expression in PCa cells is accompanied by the extensive oxidative stress and DNA damage [50]. Low Nrf2 levels can contribute to oncogenesis, since disruptions of the cell defense mechanisms are associated with the development of inflammation. To a certain extent, this is accounted for by the fact that the decreased Nrf2 activity may elicit activation of the inflammation-promoting transcription factor NF-κB. A crosstalk between Nrf2 and NF-κB is a critical element in the integration between oxidative stress and inflammation [51]. Suppression of the *NFE2L2* expression elevates NF-κB activity and cytokine production, whereas NF-κB itself can regulate NRF2 transcriptional activity both positively and negatively [51, 52].

The family of NF-κB transcription factors includes proteins formed by the homo- or heterodimerization of the p50, p52, p65/RelA, RelB, and c-Rel subunits. The binding to DNA is mediated by the N-terminal domain of Rel (~300 amino acid residues). In the cytoplasm, NF-κB is bound to its cognate inhibitor IκB. Activation of the IκB kinase (IKK) complex consisting of the IKKα and

IKKβ subunits results in IκB phosphorylation leading to the proteolytic degradation of the latter accompanied by the nuclear translocation of the NF-κB dimer. NF-κB controls expression of genes encoding cytokines, chemokines, matrix metalloproteinases, pro-inflammatory enzymes (such as cyclooxygenase 2, COX2), cyclins, anti-apoptotic and pro-angiogenic proteins, as well as antioxidant (*SOD1*, *SOD2*, *HO1*) and prooxidant (*CYP2E1*, *NOX2*, *XOR*, *NOS2*, *COX2*, *ALOX5*, and *ALOX12*) genes [53] that can contribute to the development of the redox-dependent adaptation [2].

NF-κB activation occurs in different types of malignant neoplasms, including PCa, and correlates with cancer progression, chemoresistance, and metastasis [54]. In many cases, activation of target gene by the binding of NF-κB dimers to specific DNA motifs requires participation of other transcription factors, such as STAT, AP1, IRF, as well as kinases involved in various (e.g., mTOR, ERK1/2, JNK, p38, PI3K, AKT, and WNT) signaling pathways [53].

Transcription factors NF-κB and STAT3 (signal transducer and activator of transcription 3) may interact both positively and negatively and regulate, e.g., expression of pro-inflammatory factors (cyclin D1, MYC), anti-apoptotic proteins (Bcl-X_L, Bcl-2), and inducible nitric oxide synthase (NOS2) [55]. STAT family proteins are transcription factors; they are activated by cytokines and growth factors and then activate transcription of their target genes. Downregulation of the *STAT3* gene expression is associated with the reduced PCa tumor size and prevents disease recurrence [56]. Inhibition of the Jak-1/STAT3 pathway *reduces cell proliferation and activates apoptosis* of *PC3 cells* [57].

At the same time, it was found that the content of interleukin-8 (IL-8) is significantly increased in PCa cells, where this inflammatory mediator exhibits carcinogenic and pro-angiogenic activity, stimulates cell proliferation, and suppresses apoptosis due to the activation of the STAT3/AKT/NF-κB axis [58]. IL-8 activates phosphorylation of AKT kinase, which, in turn, triggers canonical NF-κB pathway resulting in the increased phosphorylation of the inhibitory IκB subunit followed by its separation from p50-p65-IκBα complex and subsequent p50-p65 nuclear translocation.

STAT3 also can affect the content of ROS in tumor cells. In particular, epidermal growth factor (EGF) contributes to the PCa progression via the ROS/STAT3/HIF-1α/TWIST1/N-cadherin pathway, which is related to the STAT3 activation and elevated ROS levels. According to the authors, these results can indicate new cancer biomarkers and therapeutic targets. Also, it was demonstrated that STAT3 inhibition may result in the increased ROS generation and activation of the endoplasmic reticulum stress leading to the PCa cell apoptosis [59].

In many tumor types, transcription factors NF-κB and p53 antagonistically regulate each other's activity [60]. p53 and NF-κB suppress each other's transactivation and ability to stimulate gene expression. p53 inactivation suppresses apoptosis, whereas NF-κB activation promotes cell resistance to apoptosis [61]. According to the data of clinical studies, expression of NF-κB/p65/RelA, NF-κB/p50/RelB, and c-Rel is increased, while activity of p53 is decreased in PCa primary and metastatic tumor samples [62]. Despite the fact that mutations in the p53 gene are found at the early stages of PCa, the number of such mutations at the advanced and metastatic stages is higher than in the localized tumors [63]. p53 mutations impair cell cycle control, resulting in abnormal cell proliferation and malignant transformation [64]. Moreover, the high content of p53 protein in PCa cells is closely related to cell proliferation, migration, and adhesive potential. In DU145 cells, p53 activates the FAK/Src pathway and increases the levels of JNK and ERK phosphorylation [65]. At the same time, the polyphenolic compound resveratrol induces apoptosis in TRAMP cells via HIF-1α/ROS/p53 signaling, which is related to the elevated levels of the p53 and ROS [66].

JNK signaling pathway. The rise in the NF-κB activity suppresses JNK activation due to the activation of GADD45β, XIAP, and A20 proteins [67]. JNK as a component of MAPK signaling, is essential for the growth of PCa cells both *in vitro* and *in vivo*, which makes it a new target in the PCa therapy [68]. The JNK family of protein kinases, also known as stress-activated MAP kinases (SAPK), includes JNK1, JNK2, and JNK3 isoforms. JNK1 and JNK2 are expressed at low-to-moderate levels in healthy prostate cells; however, their expression is highly upregulated in PCa [68, 69].

JNK controls a wide range of cellular processes including apoptosis, proliferation, migration, survival, differentiation, and inflammation. Cytokines, pathogens, growth factors, and ROS can activate JNK via phosphorylation [70]. The two upstream MKK protein kinases, MKK4 and MKK, activate JNK by phosphorylation at Thr183 and Tyr185 [71]. In turn, MKK4 and MKK7 are activated by serine/threonine protein kinases, such as MEKKs, mixed lineage kinases (MLKs), apoptosis signal-regulating kinases (ASKs), TAK1, and TPL2 [72]. Among the target proteins able to activate JNK there are transcription factors STAT1 and STAT3, p53, c-Myc, Elk1, ATF-2, NFAT, and mitochondrial apoptosis-controlling proteins from the Bcl-2 family (Bcl-2, Bad, Bim, Bax) [68].

The role of JNK signaling in PCa is controversial and seems to depend on the ROS level and developing oxidative stress. It was found that the decrease in the intracellular NOX5 content results in the reduced JNK1/3 phosphorylation, which suppresses the ROS-dependent proliferation of PC3 cells. Similar effect was also observed for the JNK1 inhibitor SP600125 that exhibited strong antiproliferative activity in PC3 cells [26]. It was also demonstrated that lanthionine synthase C-like protein 1

(LanCL1) from the LanCL family protects LNCaP and PCa-3 cells against oxidative stress and promotes cell proliferation by reducing cell death via suppression of JNK signaling [73].

JNK1 can suppress PCa by regulating the anti-proliferative activity. In particular, it was shown that the knockdown of serine/threonine protein phosphatase 5 contributes to the JNK1 phosphorylation that results in the inhibition of proliferation of PC3, DU145, and 22RV1 cells [74]. On the other hand, JNK kinases can be directly translocated to mitochondria under various stressful conditions and activate ROS generation followed by cell death [75]. Rigosertib (synthetic benzylstyrylsulfone also known as ON01910 or Estybon) activates JNK1/2, which, in turn, activates p66Shc protein and promotes mitochondrial ROS generation in PC3 and DU-145 cells [76]. Phosphorylation of p66Shc (prooxidant isoform from the SchA family of adaptor proteins) at Ser36 by JNK1/2 results in the increased electron transport from cytochrome *c* to molecular oxygen, which activates ROS generation [77]. p66shc can also escalate ROS production by elevating NOX levels and/or altering the intracellular antioxidant enzyme ratio via suppression of the transcription factor FOXO activity [78].

AR signaling pathway. Activation of the JNK pathway results in increased AR phosphorylation at Ser650 in LNCaP cells. This promotes AR cytosolic export, but lowers its nuclear translocation [68]. The activity of AR as a transcription factor is crucial for the PCa progression. Androgen binding to AR promotes tumor growth and metastasis and suppresses apoptosis. The activity of AR can change the ROS level in PCa cells in a dual manner: on one hand, ROS stimulate AR nuclear translocation and transcriptional activity; on the other hand, AR-activated intracellular signaling stimulates the prooxidant enzyme systems [79]. AR-responsive elements and NF-κB-binding sites in gene promoters are known to overlap, so that ROS-activated NF-κB can directly bind to the AR-responsive motif and alter its activity, thus affecting transcription of the AR-regulated target genes [80]. Elevated ROS levels increase the content of AR by upregulating expression of the *AR* gene, increasing AR mRNA stability, and promoting Prx1-mediated AR protein stability [81]. Significant elevation in the Nrf2 content results in the suppression of the AR gene expression and AR activity in PCa cells by decreasing the level of ROS [82].

THE ROLE OF microRNAs IN THE REGULATION OF CELL REDOX HOMEOSTASIS IN PROSTATE CANCER

Currently, the role of microRNAs in pathogenesis of various diseases attracts a special interest. MicroRNAs are a class of short single-stranded non-coding RNAs that suppress gene expression post-translationally via complementary pairing with the 3′-untranslated regions (UTRs) in the target mRNAs. They inhibit translation of target mRNAs and/or cause their degradation [83]. Taking into account that microRNAs participate in the regulation of principal events ensuring cell viability, such as proliferation, differentiation, and programmed cell death, investigation of their role in the mechanisms underlying development of diseases, including malignant neoplasms, has become of particular importance [83]. It has been increasingly evident that microRNAs have a significantly impact on the regulation of cell redox homeostasis in cancer cells by modulating the growth of malignant cell at different stages of oncogenesis [84]. The relation between microRNAs and intracellular redox system in PCa is also relevant for searching new targets for the therapeutic interventions in cancer, especially in the case of aggressive drug-resistant PCa (Table 3). High metabolic rate is typical for rapidly proliferating cancer cells with an elevated content of intracellular ROS generated by the prooxidant enzymatic systems, mostly complexes I and III of the mitochondrial respiratory chain. Mitochondrial enzymes, such as Mn-dependent superoxide dismutase (SOD2), glutathione peroxidase 2 (Gpx2) and thioredoxin reductase 2 (TrxR2), constitute the primary antioxidant defense system and contribute significantly to the maintenance of redox balance necessary for the mitochondrial function. It was found that miR-17-3p suppresses activity of all the three enzymes in PCa cells. PCa-3 cells (aggressive PCa type) transfected with miR-17-3p demonstrate a markedly decrease content of these enzymes and exhibit an increased sensitivity to ionizing radiation [85]. Moreover, upregulated expression of the *miR-17-3p* gene suppressed induction of *SOD2*, *GPX2*, and *TXNRD2* expression (delayed cell response to ionizing radiation) and therefore, reduced cancer cell proliferation due to substantially elevated ROS levels and decreased mitochondrial respiration [85]. One of the mechanisms in cancer therapy is based on the activation of ROS generation by radiation exposure or chemotherapy. Thus, administration of the antitumor drug LQB-118 (pterocarpanquinone) capable to induce ROS generation in the PC3, LNCaP and LAPC4 cell lines and subcutaneous PC-3 xenografts in Balb/c nude male mice resulted in the adaptive elevation of the SOD1 activity, while introduction of miR-206, miR-1, and miR-101 decreased the intracellular content of SOD1 [86]. However, the efficacy of each microRNA in lowering the SOD1 activity and sensitizing cells to the cytostatic effects of LQB-118 varied greatly between different PCa cell lines.

The target of miR-193a-5p in PCa cells is presumably heme oxygenase (HO-1) that plays an important role in the antioxidant defense and redox-dependent signaling. PCa cell lines demonstrated the elevated levels of miR-193a-5p that correlate with the HO-1 activity [87].

Table 3. MicroRNAs regulating redox status in PCa cells

MicroRNA	Target	Enzyme activity	Cells/tumor tissue	Effect	References
miR-17-3p	GPx2 TrxR2 SOD2	↓ ↓ ↓	PC-3	pro-oncogenic	[85]
miR-521	SOD2	↓	LNCaP	pro-oncogenic	[98]
miR-206, miR-1, miR-101	SOD1	↓	PC-3, LNCaP, LAPC4 PC-3, mouse xenograft	pro-oncogenic	[86]
miR-193a-5p	HO-1	↑	PC-3 human PCa-cancer tissue PC-3, mouse xenograft	pro-oncogenic	[87]
miR-101	COX-2	↑	LNCaP, PC-3	pro-oncogenic	[91]
miR-205	COX-2	↑	human PCa tissue, PC-3	pro-oncogenic	[99]
miR-21	NOX (p47)	↑	PC-3M-MM2	pro-oncogenic	[88]
miR-137	NOX4	↑	PC-3	pro-oncogenic	[100]
miR-23b	NOX4	↑	LNCaP	pro-oncogenic	[90]

In human PCa cells (LNCap, PCa-3, and DU145), expression of the *miR-193a-5p* gene is associated with the higher HO-1 content compared to normal prostate epithelial RWPE cells, whereas miR-193a-5p inhibitor causes decline in the HO-1 level. Examination of the action of the anticancer drug docetaxel (commonly used in therapy of patients with metastatic PCa) on the subcutaneous PC3 xenograft in Balb/c nude mice revealed that the drug triggered oxidative stress accompanied by upregulated *miR-193a-5p* expression and elevated HO-1 synthesis due to the reduced expression of the *HO1* gene repressor caused by the miR-193a-5p binding to the 3′-UTR in Bach2 mRNA [87]. miR-21, which is one of the oncogenic microRNAs promoting invasive tumor growth, was identified in PCa cells. Tumor tissues from patients with the metastatic PCa demonstrated high levels of miR-21, p47 (phox), and ROS together with the decreased expression of PDCD4 (programmed cell death 4) protein [88].

Androgen-independent PCa cells (PCa-3M-MM2) exhibit high *miR-21* and *p47* (cytosolic NOX subunit) expression. Cell transfection with the anti-miR-21 and anti-p47 (si-p47) siRNAs resulted in the downregulation of *miR-21* and *p47* expression accompanied by the increase in the PDCD4 level and decrease in the PCa invasiveness. Moreover, knocking out the *p22phox* gene (membrane-bound NOX subunit) led to the reduced miR-21 content and suppression of PCa metastatic potential. Diphenyleneiodonium chloride (DPI; NOX inhibitor) or N-acetylcysteine (antioxidant) decreased expression of the *miR-21* gene [88].

Low levels of *miR-137* and, on the contrary, high content of NOX4 found in PC-3 cells are considered as important features of PCa progression [89]. An elevated content of miR-137 promoted decrease in the content of NOX4 and Bcl-2 in PC-3 cells, resulting in the increased amounts of caspases-3, -8, and -9, PARP, and Bax, as well as suppressed proliferation and activated apoptosis of cancer cells [89]. NOX4 may be also targeted by miR-23b in PCa. In particular, reduction in the miR-23b content in PC-3 cells resulted in the upregulation of NOX4 expression [90].

Chronic inflammation is associated with oxidative stress and oncogenesis and may often precede them. As a key regulator of prostaglandin content, COX-2 contributes to cell proliferation and growth; upregulated expression of the *COX-2* gene is often observed in PCa tissues. It was found that miR-101 suppresses COX-2 synthesis via binding to the 3′-UTR in the COX-2 mRNA [91]. There is an inverse correlation between the levels of miR-101 and COX-2 protein in the PCa cell lines BPH^{CAFTD}, LNCap, and PCa-3. miR-101 not only lowers the content of COX-2 protein, but also decreases EGFR (epidermal growth factor receptor) expression in cultured $BPH1^{CmiR101}$ cells and xenografts [91]. EGFR is a ligand-activated surface receptor that initiates EGFR-dependent DNA synthesis and cell proliferation. High expression levels of the *EGFR* gene are observed in multiple types of malignancies including PCa. Upregulated expression of the *COX-2* gene results in the EGFR-stimulated cell proliferation, in which PGE2 (a product of COX-2 activity) activates EGFR-mediated signaling that promotes

tumorigenesis. For instance, it was found that in the androgen-independent PC-3 cells, intracellular poroncogenic PGE2 initiates EGFR-dependent activation of COX-2 [92]. Hence, these data suggest a close interplay between miR-101, COX-2, PGE2, and EGFR, which accounts for proliferation of PCa cell.

In conclusion, numerous data indicate an importance of developing oxidative stress and altered redox-dependent regulation of malignant growth in PCa, that are related to the disruptions in the regulation of ROS content due to the activation of some prooxidant systems and reduced antioxidant defense. A significant role in the modulation of cell redox balance belongs to microRNAs. An increase in the ROS content results in the altered redox-dependent regulation involving Nrf2, NF-κB, JNK, and AR signaling pathways in cancer cells and can affect tumor progression. However, the mechanism and regulatory factors underlying redox-dependent signaling in benign and malignant tumors still remain poorly investigated. Further investigation of their role, as well as the search for efficient modulators of prooxidant enzymes, antioxidant defense enzymes, and enzymes transmitting redox-dependent signals may be a promising approach for developing novel chemotherapy strategies to suppress tumor growth in PCa.

Funding. The study was supported by the RUDN Strategic Academic Leadership Program.

Ethics declarations. The authors declare no conflicts of interest. This article does not contain description of studies with the involvement of human or animal subjects performed by the any of the authors.

REFERENCES

1. Rawla, P. (2019) Epidemiology of prostate cancer, *World J. Oncol.*, **10**, 63-89, doi: 10.14740/wjon1191.
2. Hayes, J. D., Dinkova-Kostova, A. T., and Tew, K. D. (2020) Oxidative stress in cancer, *Cancer Cell*, **38**, 167-197, doi: 10.1016/j.ccell.2020.06.001.
3. Staal, J., and Beyaert, R. (2018) Inflammation and NF-κB signaling in prostate cancer: mechanisms and clinical implications, *Cells*, **7**, 122, doi: 10.3390/cells7090122.
4. Tan, B. L., and Norhaizan, M. E. (2021) Oxidative stress, diet and prostate cancer, *World J. Mens Health*, **39**, 195-207, doi: 10.5534/wjmh.200014.
5. Shukla, S., Srivastava, J. K., Shankar, E., Kanwal, R., Nawab, A., et al. (2020) Oxidative stress and antioxidant status in high-risk prostate cancer subjects, *Diagnostics (Basel)*, **10**, 126, doi: 10.3390/diagnostics10030126.
6. Fahmy, O., Alhakamy, N. A., Rizg, W. Y., Bagalagel, A., Alamoudi, A. J., et al. (2021) Updates on molecular and biochemical development and progression of prostate cancer, *J. Clin. Med.*, **10**, 5127, doi: 10.3390/jcm10215127.
7. Szewczyk-Golec, K., Tyloch, J., and Czuczejko, J. (2015) Antioxidant defense system in prostate adenocarcinoma and benign prostate hyperplasia of elderly patients, *Neoplasma*, **62**, 119-123, doi: 10.4149/neo_2015_015.
8. D'Souza, L. C., Mishra, S., Chakraborty, A., Shekher, A., Sharma, A., et al. (2020) Oxidative stress and cancer development: are noncoding RNAs the missing links? *Antioxid. Redox. Signal*, **33**, 1209-1229, doi: 10.1089/ars.2019.7987.
9. Kalinina, E. V., Ivanova-Radkevich, V. I., and Chernov, N. N. (2019) Role of MicroRNAs in the regulation of redox-dependent processes, *Biochemistry (Moscow)*, **84**, 1233-1246, doi: 10.1134/S0006297919110026.
10. Snezhkina, A. V., Kudryavtseva, A. V., Kardymon, O. L., Savvateeva, M. V., Melnikova, N. V., et al. (2019) ROS generation and antioxidant defense systems in normal and malignant cells, *Oxid. Med. Cell Longev.*, **2019**, 6175804, doi: 10.1155/2019/6175804.
11. Sajjaboontawee, N., Supasitthumrong, T., Tunvirachaisakul, C., Nantachai, K., Snabboon, T., et al. (2020) Lower thiol, glutathione, and glutathione peroxidase levels in prostate cancer: a meta-analysis study, *Aging Male*, **23**, 1533-1544, doi: 10.1080/13685538.2020.1858048.
12. Martignano, F., Gurioli, G., Salvi, S., Calistri, D., Costantini, M., et al. (2016) GSTP1 methylation and protein expression in prostate cancer: diagnostic implications, *Dis. Markers*, **2016**, 4358292, doi: 10.1155/2016/4358292.
13. Debelec-Butuner, B., Bostanci, A., Ozcan, F., Singin, O., Karamil, S., et al. (2019) Oxidative DNA damage-mediated genomic heterogeneity is regulated by NKX3.1 in prostate cancer, *Cancer Invest.*, **37**, 113-126, doi: 10.1080/07357907.2019.1576192.
14. Liguori, I., Russo, G., Curcio, F., Bulli, G., Aran, L., et al. (2018) Oxidative stress, aging, and diseases, *Clin. Interv. Aging*, **13**, 757-772, doi: 10.2147/CIA.S158513.
15. Zhang, L., Wang, X., Cueto, R., Effi, C., Zhang, Y., et al. (2019) Biochemical basis and metabolic interplay of redox regulation, *Redox Biol.*, **26**, 101284, doi: 10.1016/j.redox.2019.101284.
16. Mohammadi, M., Irani, S., Salahshourifar, I., Hosseini, J., Moradi, A., et al. (2020) Investigation of GSTP1 and epigenetic regulators expression pattern in a population of Iranian patients with prostate cancer, *Hum. Antibodies*, **28**, 327-334, doi: 10.3233/HAB-200424.
17. Yang, Y., Fuentes, F., Shu, L., Wang, C., Pung, D., et al. (2017) Epigenetic CpG methylation of the promoter and reactivation of the expression of GSTP1 by astaxanthin in human prostate LNCaP cells, *AAPS J.*, **19**, 421-430, doi: 10.1208/s12248-016-0016-x.
18. Fukai, T., and Ushio-Fukai, M. (2011) Superoxide dismutases: role in redox signaling, vascular function, and diseases, *Antioxid. Redox Signal*, **15**, 1583-1606, doi: 10.1089/ars.2011.3999.
19. Dhar, S. K., Tangpong, J., Chaiswing, L., Oberley, T. D., and Clair, D. K. (2011) Manganese superoxide dismutase is a p53-regulated gene that switches cancers between early and advanced stages, *Cancer Res.*, **71**, 6684-6695, doi: 10.1158/0008-5472.CAN-11-1233.
20. Roy, K., Wu, Y., Meitzler, J. L., Juhasz, A., Liu, H., et al. (2015) NADPH oxidases and cancer, *Clin. Sci. (Lond)*, **128**, 863-875, doi: 10.1042/CS20140542.
21. Arbiser, J. L., Petros, J., Klafter, R., Govindajaran, B., McLaughlin, E. R., et al. (2002) Reactive oxygen generated by Nox1 triggers the angiogenic switch, *Proc. Natl. Acad. Sci. USA*, **99**, 715-720, doi: 10.1073/pnas.022630199.
22. Deep, G., Kumar, R., Jain, A. K., Dhar, D., Panigrahi, G. K., et al. (2016) Graviola inhibits hypoxia-induced

NADPH oxidase activity in prostate cancer cells reducing their proliferation and clonogenicity, *Sci. Rep.*, **6**, 23135, doi: 10.1038/srep23135.

23. Tamura, R. E., Hunger, A., Fernandes, D. C., Laurindo, F. R., Costanzi-Strauss, E., et al. (2017) Induction of oxidants distinguishes susceptibility of prostate carcinoma cell lines to p53 gene transfer mediated by an improved adenoviral vector, *Hum. Gene Ther.*, **28**, 639-653, doi: 10.1089/hum.2016.139.
24. Lim, S. D., Sun, C. Q., Lambeth, J. D., Marshall, F., Amin, M., et al. (2005) Increased Nox1 and hydrogen peroxide in prostate cancer, *Prostate*, **62**, 200-207, doi: 10.1002/pros.20137.
25. Juhasz, A., Ge, Y., Markel, S., Chiu, A., Matsumoto, L., et al. (2009) Expression of NADPH oxidase homologues and accessory genes in human cancer cell lines, tumours and adjacent normal tissues, *Free Radic. Res.*, **43**, 523-532, doi: 10.1080/10715760902918683.
26. Höll, M., Koziel, R., Schäfer, G., Pircher, H., Pauck, A., et al. (2016) ROS signaling by NADPH oxidase 5 modulates the proliferation and survival of prostate carcinoma cells, *Mol. Carcinog.*, **55**, 27-39, doi: 10.1002/mc.22255.
27. Kumar, B., Koul, S., Khandrika, L., Meacham, R. B., and Koul, H. K. (2008) Oxidative stress in inherent in prostate cancer cells and is required for aggressive phenotype, *Cancer Res.*, **68**, 1777-1785, doi: 10.1158/0008-5472.CAN-07-5259.
28. Brar, S. S., Corbib, Z., Kennedy, T. P., Hemendinger, R., Thornton, L., et al. (2003) NOX5 NAD(P)H oxidase regulates growth and apoptosis in DU145 prostate cancer cells, *Am. J. Physiol. Cell Physiol.*, **285**, 353-369, doi: 10.1152/ajpcell.00525.2002.
29. Pettigrew, C. A., Clerkin, J. S., and Cotter, T. G. (2012) DUOX enzyme activity promotes AKT signalling in prostate cancer cells, *Anticancer Res.*, **32**, 5175-5181.
30. Lu, J. P., Monardo, L., Bryskin, I., Hou, Z. F., Trachtenberg, J., et al. (2010) Androgens induce oxidative stress and radiation resistance in prostate cancer cells though NADPH oxidase, *Prostate Cancer Prostatic Dis.*, **13**, 39-46, doi: 10.1038/pcan.2009.24.
31. Lu, J. P., Hou, Z. F., Duivenvoorden, W. C., Whelan, K., Honig, A., et al. (2012) Adiponectin inhibits oxidative stress in human prostate carcinoma cells, *Prostate Cancer Prostatic Dis.*, **15**, 28-35, doi: 10.1038/pcan.2011.53.
32. Speed, N., and Blair, I. A. (2011) Cyclooxygenase- and lipoxygenase-mediated DNA damage, *Cancer Metastasis Rev.*, **30**, 437-447, doi: 10.1007/s10555-011-9298-8.
33. Pidgeon, G. P., Lysaght, J., Krishnamoorthy, S., Reynolds, J. V., O'Byrne, K., et al. (2007) Lipoxygenase metabolism: roles in tumor progression and survival, *Cancer Metastasis Rev.*, **26**, 503-524, doi: 10.1007/s10555-007-9098-3.
34. Saboormaleki, S., Sadeghian, H., Bahrami, A. R., Orafaie, A., and Matin, M. M. (2018) 7-Farnesyloxycoumarin exerts anti-cancer effects on a prostate cancer cell line by 15-LOX-1 inhibition, *Arch. Iran Med.*, **21**, 251-259.
35. Iranpour, S., Al-Mosawi, A. K. M., Bahrami, A. R., Sadeghian, H., and Matin, M. M. (2021) Investigating the effects of two novel 4-MMPB analogs as potent lipoxygenase inhibitors for prostate cancer treatment, *J. Biol. Res. (Thessalon)*, **28**, 10, doi: 10.1186/s40709-021-00141-w.
36. Krishnamoorthy, S., Jin, R., Cai, Y., Maddipati, K. R., Nie, D., et al. (2010) 12-Lipoxygenase and the regulation of hypoxia-inducible factor in prostate cancer cells, *Exp. Cell Res.*, **316**, 1706-1715, doi: 10.1016/j.yexcr.2010.03.005.
37. Sarveswaran, S., Chakraborty, D., Chitale, D., Sears, R., and Ghosh, J. (2015) Inhibition of 5-lipoxygenase selectively triggers disruption of c-Myc signaling in prostate cancer cells, *J. Biol. Chem.*, **290**, 4994-5006, doi: 10.1074/jbc.M114.599035.
38. Hsi, L. C., Wilson, L. C., and Eling, T. E. (2002) Opposing effects of 15-lipoxygenase-1 and -2 metabolites on MAPK signaling in prostate. Alteration in peroxisome proliferator-activated receptor gamma, *J. Biol. Chem.*, **277**, 40549-40556, doi: 10.1074/jbc.M203522200.
39. Gondek, T., Szajewski, M., Szefel, J., Aleksandrowicz-Wrona, E., Skrzypczak-Jankun, E., et al. (2014) Evaluation of 12-lipoxygenase (12-LOX) and plasminogen activator inhibitor 1 (PAI-1) as prognostic markers in prostate cancer, *Biomed. Res. Int.*, **2014**, 102478, doi: 10.1155/2014/102478.
40. Gao, X., Porter, A. T., and Honn, K. V. (1997) Involvement of the multiple tumor suppressor genes and 12-lipoxygenase in human prostate cancer. Therapeutic implications, *Adv. Exp. Med. Biol.*, **407**, 41-53, doi: 10.1007/978-1-4899-1813-0_7.
41. Matsuyama, M., Yoshimura, R., Mitsuhashi, M., Hase, T., Tsuchida, K., et al. (2004) Expression of lipoxygenase in human prostate cancer and growth reduction by its inhibitors, *Int. J. Oncol.*, **24**, 821-827, doi: 10.3892/ijo.24.4.821.
42. Goftari, S. N., Sadeghian, H., Bahrami, A. R., Maleki, F., and Matin, M. M. (2019) Stylosin and some of its synthetic derivatives induce apoptosis in prostate cancer cells as 15-lipoxygenase enzyme inhibitors, *Naunyn Schmiedebergs Arch. Pharmacol.*, **392**, 1491-1502, doi: 10.1007/s00210-019-01689-0.
43. Hosseinymehr, M., Matin, M. M., Sadeghian, H., Bahrami, A. R., and Kaseb-Mojaver, N. (2016) 8-Farnesyloxycoumarin induces apoptosis in PC-3 prostate cancer cells by inhibition of 15-lipoxygenase-1 enzymatic activity, *Anticancer Drugs*, **27**, 854-862, doi: 10.1097/CAD.0000000000000399.
44. Robertson, H., Dinkova-Kostova, A. T., and Hayes, J. D. (2020) NRF2 and the ambiguous consequences of its activation during initiation and the subsequent stages of tumourigenesis cancers, *Cancers*, **12**, 3609, doi: 10.3390/cancers12123609.
45. Zimta, A.-A., Cenariu, D., Irimie, A., Magdo, L., Nabavi, S. M., et al. (2019) The role of Nrf2 activity in cancer development and progression, *Cancers*, **11**, 1755, doi: 10.3390/cancers11111755.
46. Sekine, H., Motohashi, H. (2021) Roles of CNC transcription factors NRF1 and NRF2 in cancer, *Cancers (Basel)*, **13**, 541, doi: 10.3390/cancers13030541.
47. Taguchi, K., and Yamamoto, M. (2021) The KEAP1-NRF2 system as a molecular target of cancer treatment, *Cancers (Basel)*, **13**, 46, doi: 10.3390/cancers13010046.
48. Zucker, S. N., Fink, E. E., Bagati, A., Mannava, S., Bianchi-Smiraglia, A., et al. (2014) Nrf2 amplifies oxidative stress via induction of Klf9, *Mol Cell*, **53**, 916-928, doi: 10.1016/j.molcel.2014.01.033.
49. Barve, A., Khor, T. O., Nair, S., Reuhl, K., Suh, N., et al. (2009) Tocopherol-enriched mixed tocopherol diet inhibits

prostate carcinogenesis in TRAMP mice, *Int. J. Cancer*, **124**, 1693-1699, doi: 10.1002/ijc.24106.
50. Frohlich, D. A., McCabe, M. T., Arnold, R. S., and Day, M. L. (2008) The role of Nrf2 in increased reactive oxygen species and DNA damage in prostate tumorigenesis, *Oncogene*, **27**, 4353-4362, doi: 10.1038/onc.2008.79.
51. Wardyn, J. D., Ponsford, A. H., and Sanderson, C. M. (2015) Dissecting molecular cross-talk between Nrf2 and NF-κB response pathways, *Biochem. Soc. Trans.*, **43**, 621-626, doi: 10.1042/BST20150014.
52. Buelna-Chontal, M., and Zazueta, C. (2013) Redox activation of Nrf2 and NF-κB: a double end sword? *Cell Signal*, **25**, 2548-2557, doi: 10.1016/j.cellsig.2013.08.007.
53. Taniguchi, K., and Karin, M. (2018) NF-κB, inflammation, immunity and cancer: coming of age, *Nat. Rev. Immunol.*, **18**, 309-324, doi: 10.1038/nri.2017.142.
54. Jin, R., Yi, Y., Yull, F. E., Blackwell, T. S., Clark, P. E., et al. (2014) NF-κB gene signature predicts prostate cancer progression, *Cancer Res.*, **74**, 2763-2772, doi: 10.1158/0008-5472.CAN-13-2543.
55. Grivennikov, S. I., and Karin, M. (2010) Dangerous liaisons: STAT3 and NF-κB collaboration and crosstalk in cancer, *Cytokine Growth Factor Rev.*, **21**, 11-19, doi: 10.1016/j.cytogfr.2009.11.005.
56. Jiang, L. H., Hao, Y. L., and Zhu, J. W. (2019) Expression and prognostic value of HER-2/neu, STAT3 and SOCS3 in hepatocellular carcinoma, *Clin. Res. Hepatol. Gastroenterol.*, **43**, 282-291, doi: 10.1016/j.clinre.2018.09.011.
57. Wang, X., Wang, B., Zhou, L., Wang, X., Veeraraghavan, V. P., et al. (2020) *Ganoderma lucidum* put forth anti-tumor activity against PC-3 prostate cancer cells via inhibition of Jak-1/STAT-3 activity, *Saudi. J. Biol. Sci.*, **27**, 2632-2637, doi: 10.1016/j.sjbs.2020.05.044.
58. Guo, Y., Zang, Y., Lv, L., Cai, F., Qian, T., et al. (2017) IL-8 promotes proliferation and inhibition of apoptosis via STAT3/AKT/NF-κB pathway in prostate cancer, *Mol. Med. Rep.*, **16**, 9035-9042, doi: 10.3892/mmr.2017.7747.
59. Chen, W., Li, P., Liu, Y., Yang, Y., Ye, X., et al. (2018) Isoalantolactone induces apoptosis through ROS-mediated ER stress and inhibition of STAT3 in prostate cancer cells, *J. Exp. Clin. Cancer Res.*, **37**, 309, doi: 10.1186/s13046-018-0987-9.
60. Gudkov, A. V., and Komarova, E. A. (2016) p53 and the carcinogenicity of chronic inflammation, *Cold Spring Harb. Perspect. Med.*, **6**, a026161, doi: 10.1101/cshperspect.a026161.
61. Schneider, G., Henrich, A., Greiner, G., Wolf, V., Lovas, A., et al. (2010) Crosstalk between stimulated NF-kappaB and the tumor suppressor p53, *Oncogene*, **29**, 2795-2806, doi: 10.1038/onc.2010.46.
62. Shankar, E., Zhang, A., Franco, D., and Gupta, S. (2017) Betulinic acid-mediated apoptosis in human prostate cancer cells involves p53 and nuclear factor-kappa B (NF-κB) pathways, *Molecules*, **22**, 264, doi: 10.3390/molecules22020264.
63. Dong, J. T. (2006) Prevalent mutations in prostate cancer, *J. Cell Biochem.*, **97**, 433-447, doi: 10.1002/jcb.20696.
64. Meek, D. W. (2015) Regulation of the p53 response and its relationship to cancer, *Biochem. J.*, **469**, 325-346, doi: 10.1042/BJ20150517.
65. Wan, J., Zhang, J., and Zhang, J. (2018) Expression of p53 and its mechanism in prostate cancer, *Oncol. Lett.*, **16**, 378-382, doi: 10.3892/ol.2018.8680.
66. Wang, D., Gao, Z., and Zhang, X. (2018) Resveratrol induces apoptosis in murine prostate cancer cells via hypoxia-inducible factor 1-alpha (HIF-1α)/reactive oxygen species (ROS)/P53 signaling, *Med. Sci. Monit.*, **24**, 8970-8976, doi: 10.12659/MSM.913290.
67. Papa, S., Zazzeroni, F., Pham, C. G., Bubici, C., and Franzoso, G. (2004) Linking JNK signaling to NF-κB: A key to survival, *J. Cell Sci.*, **117**, 5197-5208, doi: 10.1242/jcs.01483.
68. Xu, R., and Hu, J. (2020) The role of JNK in prostate cancer progression and therapeutic strategies, *Biomed. Pharmacother.*, **121**, 109679, doi: 10.1016/j.biopha.2019.109679.
69. Nikoloudaki, G., Brooks, S., Peidl, A. P., Tinney, D., and Hamilton, D. W. (2020) JNK signaling as a key modulator of soft connective tissue physiology, pathology, and healing, *Int. J. Mol. Sci.*, **21**, 1015, doi: 10.3390/ijms21031015.
70. Takata, T., Araki, S., Tsuchiya, Y., and Watanabe, Y. (2020) Oxidative stress orchestrates MAPK and nitric-oxide synthase signal, *Int. J. Mol. Sci., **21***, 8750, doi: 10.3390/ijms21228750.
71. Dou, Y., Jiang, X., Xie, H., He, J., and Xiao, S. (2019) The Jun N-terminal kinases signaling pathway plays a "see-saw" role in ovarian carcinoma: a molecular aspect, *J. Ovarian Res.*, **12**, 99, doi: 10.1186/s13048-019-0573-6.
72. Acosta, A. M., and Kadko, S. S. (2016) Mitogen-activated protein kinase signaling pathway in cutaneous melanoma: An updated review, *Arch. Pathol. Lab. Med.*, **140**, 1290-1296, doi: 10.5858/arpa.2015-0475-RS.
73. Wang, J., Xiao, Q., Chen, X., Tong, S., Sun, J., et al. (2018) LanCL1 protects prostate cancer cells from oxidative stress via suppression of JNK pathway, *Cell Death. Dis.*, **9**, 197, doi: 10.1038/s41419-017-0207-0.
74. Lv, J. M., Chen, L., Gao, Y., Huang, H., Pan, X. W., et al. (2018) PPP5C promotes cell proliferation and survival in human prostate cancer by regulating of the JNK and ERK1/2 phosphorylation, *Onco. Ther.*, **11**, 5797-5809, doi: 10.2147/OTT.S161280.
75. Chambers, J., Pachori, A., Howard, S., Iqbal, S., and LoGrasso, P. (2012) Inhibition of JNK mitochondrial localization and signaling is protective against ischemia/reperfusion injury in rats, *J. Boil. Chem.*, **288**, 4000-4011, doi: 10.1074/jbc.M112.406777.
76. Günther, J. K., Nikolajevic, A., Ebner, S., Troppmair, J., and Khalid, S. (2020) Rigosertib-activated JNK1/2 eliminate tumor cells through p66Shc activation, *Biology (Basel)*, **9**, 99, doi: 10.3390/biology9050099.
77. Galimov, E. R. (2010) The role of p66shc in oxidative stress and apoptosis, *Acta Naturae*, **2**, 44-51, doi: 10.32607/20758251-2010-2-4-44-51.
78. Eid, R. A., Zaki, M. S. A., Eldeen, M. A., Alshehri, M. M., Shati, A. A., et al. (2020) Exendin-4 protects the hearts of rats from ischaemia/reperfusion injury by boosting antioxidant levels and inhibition of JNK/p^{66}Shc/NADPH axis, *Clin. Exper. Pharmacol. Physiol.*, **47**, 1240-1253, doi: 10.1111/1440-1681.13299.
79. Han, C., Wang, Z., Xu, Y., Chen, S., Han, Y., et al. (2020) Roles of reactive oxygen species in biological behaviors of prostate cancer, *Biomed. Res. Int.*, **2020**, 1269624, doi: 10.1155/2020/1269624.
80. Khurana, N., and Sikka, S. C. (2018) Targeting crosstalk between Nrf-2, NF-κB and androgen receptor signaling in

prostate cancer, *Cancers*, **10**, 352, doi: 10.3390/cancers10100352.
81. Yu, J., Zhou, P., Du, W., Xu, R., Yan, G., et al. (2020) Metabolically stable diphenylamine derivatives suppress androgen receptor and BET protein in prostate cancer, *Biochem. Pharmacol.*, **177**, 113946, doi: 10.1016/j.bcp.2020.113946.
82. Schultz, M. A., Hagan, S. S., Datta, A., Zhang, Y., Freeman, M. L., et al. (2014) Nrf1 and Nrf2 transcription factors regulate androgen receptor transactivation in prostate cancer cells, *PLoS One*, **9**, e87204, doi: 10.1371/journal.pone.0087204.
83. Uzuner, E., Ulu, G. T., Gürler, S. B., and Baran, Y. (2022) The role of miRNA in cancer: pathogenesis, diagnosis, and treatment, *Methods Mol. Biol.*, **2257**, 375-422, doi: 10.1007/978-1-0716-1170-8_18.
84. Ali Syeda, Z., Langden, S. S., Munkhzul, C., Lee, M., and Song, S. (2020) Regulatory mechanism of microRNA expression in cancer, *J. Int. J Mol. Sci.*, **21**, 1723, doi: 10.3390/ijms21051723.
85. Xu, Z., Zhang, Y., Ding, J., Hu, W., Tan, C., et al. (2018) miR-17-3p downregulates mitochondrial antioxidant enzymes and enhances the radiosensitivity of prostate cancer cells, *Mol. Ther. Nucleic Acids*, **13**, 64-77, doi: 10.1016/j.omtn.2018.08.009.
86. Martino, T., Kudrolli, T. A., Kumar, B., Salviano, I., Mencalha, A., et al. (2018) The orally active pterocarpanquinone LQB-118 exhibits cytotoxicity in prostate cancer cell and tumor models through cellular redox stress, *Prostate*, **78**, 140-151, doi: 10.1002/pros.23455.
87. Yang, Z., Chen, J.-S., Wen, J.-K., Gao, H.-T., Zheng, B., et al. (2017) Silencing of miR-193a-5p increases the chemosensitivity of prostate cancer cells to docetaxel, *J. Exp. Clin. Cancer Res.*, **36**, 178, doi: 10.1186/s13046-017-0649-3.
88. Jajoo, S., Mukherjea, D., Kaur, T., Sheehan, K. E., Sheth, S., et al. (2013) Essential role of NADPH oxidase-dependent reactive oxygen species generation in regulating microRNA-21 expression and function in prostate cancer, *Antioxid. Redox Signal.*, **19**, 1863-1876, doi: 10.1089/ars.2012.4820.
89. Wu, Q.-Q., Zheng, B., Weng, G.-B., Yang, H.-M., Ren, Y., et al. (2019) Downregulated NOX4 underlies a novel inhibitory role of microRNA-137 in prostate cancer, *J. Cell Biochem.*, **120**, 10215-10227, doi: 10.1002/jcb.28306.
90. Kim, H-K., Lee, H-Y., Riaz, T. A., Bhattarai, K. R., Chaudhary, M., et al. (2021) Chalcone suppresses tumor growth through NOX4-IRE1α sulfonation-RIDD-miR-23b axis, *Redox Biol.*, **40**, 101853, doi: 10.1016/j.redox.2021.101853.
91. Hao, Y., Gu, X., Zhao, Y., Greene, S., Sha, W., et al. (2011) Enforced expression of miR-101 inhibits prostate cancer cell growth by modulating the COX-2 pathway *in vivo*, *Cancer Prev. Res. (Phila)*, **4**, 1073-1083, doi: 10.1158/1940-6207.CAPR-10-0333.
92. Madrigal-Martínez, A., Constâncio, V., Lucio-Cazaña, F. J., and Fernández-Martínez, A. B. (2019) Prostaglandine$_2$ stimulates cancer-related phenotypes in prostate cancer PC3 cells through cyclooxygenase-2, *J. Cell Physiol.*, **234**, 7548-7559, doi: 10.1002/jcp.27515.
93. Josson, S., Sung, S-Y., Lao, K., Chung, L. W. K., and Johnstone, P. A. S. (2008) Radiation modulation of microRNA in prostate cancer cell lines, *Prostate*, **68**, 1599-1606, doi: 10.1002/pros.20827.
94. Gandellini, P., Giannoni, E., Casamichele, A., Taddei, M. L., Callari, M., et al. (2014) miR-205 hinders the malignant interplay between prostate cancer cells and associated fibroblasts, *Antioxid. Redox Signal.*, **20**, 1045-1059, doi: 10.1089/ars.2013.5292.
95. Zang, Y., Zhu, J., Li, Q., Tu, J., Li, X., et al. (2020) miR-137-3p modulates the progression of prostate cancer by regulating the JNK3/EZH2 axis, *Onco. Targets Ther.*, **13**, 7921-7932, doi: 10.2147/OTT.S256161.
96. Meitzler, J. L., Antony, S., Wu, Y., Juhasz, A., Liu, H., et al. (2014) NADPH oxidases: a perspective on reactive oxygen species production in tumor biology, *Antioxid. Redox Signal.*, **20**, 2873-2889, doi: 10.1089/ars.2013.5603.
97. Kumar, S., Singh, R. K., and Meena, R. (2016) Emerging targets for radioprotection and radiosensitization in radiotherapy, *Tumour Biol.*, **37**, 11589-11609, doi: 10.1007/s13277-016-5117-8.
98. Sarveswaran, S., Varma, N. R. S., Morisetty, S., and Ghosh, J. (2019) Inhibition of 5-lipoxygenase downregulates stemness and kills prostate cancer stem cells by triggering apoptosis via activation of c-Jun N-terminal kinase, *Oncotarget*, **10**, 424-436, doi: 10.18632/oncotarget.13422.
99. Wartenberg, M., Hoffmann, E., Schwindt, H., Grünheck, F., Petros, J., et al. (2005) Reactive oxygen species-linked regulation of the multidrug resistance transporter P-glycoprotein in Nox-1 overexpressing prostate tumor spheroids, *FEBS Lett.*, **579**, 4541-4549, doi: 10.1016/j.febslet.2005.06.078.
100. Jones, K. J., Chetram, M. A., Bethea, D. A., Bryant, L. K., Odero-Marah, V., et al. (2013) Cysteine (C)-X-C receptor 4 regulates NADPH oxidase-2 during oxidative stress in prostate cancer cells, *Cancer Microenviron.*, **6**, 277-288, doi: 10.1007/s12307-013-0136-0.