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Molecular genetic aspects of prostate cancer radioresistance

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ABSTRACT

Radioresistance of prostate cancer is a complex therapeutic problem. Biochemical recurrence after radiation therapy occurs in 22–69% of patients with prostate cancer. Nearly half of these patients progress to a clinical relapse within 15 years, and a third progress to castration-resistant prostate cancer. This review analyzes literature data on radioresistance mechanisms in prostate cancer cells. We searched for literature published in eLibrary, PubMed, and Scopus databases by key words: prostate cancer, radioresistance, markers. In total, 568 foreign and 178 national articles published between 1975 and 2020 were found. Of these publications, 77 articles were selected (published in 2001–2020), which reveal the molecular basis of tumor radioresistance.

Modern understanding of the origin of radioresistant cancer cells focuses on processes leading to enhanced DNA repair, activation of anti-apoptotic signaling pathways, and a decrease in the level of endogenous and exogenous reactive oxygen species. The state of a tumor microenvironment, autophagy, and epithelial-mesenchymal transition also play an important role in radioresistance. Currently, the mechanisms of resistance to radiation therapy are explained by the existence of tumor stem cells, which provide genetic heterogeneity and activation of carcinogenesis signaling pathways. The tumor can also be protected from radiation by a hypoxic microenvironment. Since cancer stem cells can acquire plasticity in response to radiation therapy, search for markers of radioresistance for screening and identification of radioresistant prostate cancer is relevant.

Key words: prostate cancer, radioresistance, cancer stem cells, DNA repair, reactive oxygen species, epithelial-mesenchymal transition, microenvironment, autophagy.

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Молекулярно-генетические аспекты радиорезистентности рака предстательной железы

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РЕЗЮМЕ

Радиорезистентность рака предстательной железы представляет собой сложную терапевтическую проблему. После проведения лучевой терапии 22–69% больных раком предстательной железы

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сталкиваются с биохимическим рецидивом. Почти половина таких пациентов прогрессирует до клинического рецидива в течение 15 лет, а у трети наблюдается прогрессия до кастрационно-резистентного рака. Настоящий обзор посвящен анализу данных литературы о механизмах развития радиорезистентности в онкотрансформированных клетках предстательной железы. Осуществлен поиск литературных источников, опубликованных в базах eLibrary, PubMed, Scopus по ключевым словам: рак предстательной железы, радиорезистентность, маркеры. Всего найдено 568 иностранных и 178 отечественных работ, опубликованных в период 1975–2020 гг., из которых отобрано 77 статей, раскрывающих молекулярную основу радиорезистентности и вышедших в печать в 2001–2020 гг.

Современные представления о происхождении устойчивых к радиации злокачественных клеток концентрируются на процессах, приводящих к усиленной репарации ДНК, активации антиапоптотических сигнальных путей, снижению уровня эндо- и экзогенных активных форм кислорода. Также немаловажную роль играют состояние микроокружения опухоли, аутофагия и эпителиально-мезенхимальный переход. Механизмы развития устойчивости к радиационному лечению на сегодняшний день объясняются наличием стволовых клеток опухоли, которые обусловливают генетическую гетерогенность и возможность ухода от воздействия терапии с помощью активации сигнальных путей канцерогенеза. Также опухоль может быть защищена от радиации гипоксической микросредой. Ввиду возникающей пластичности опухолевых стволовых клеток в ответ на лучевую терапию актуальным представляется поиск их маркеров с целью скрининга и идентификации радиорезистентного рака предстательной железы.

Ключевые слова: рак предстательной железы, радиорезистентность, опухолевые стволовые клетки, репарация ДНК, активные формы кислорода, эпителиально-мезенхимальный переход, микроокружение, аутофагия.

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INTRODUCTION

Prostate cancer (PC) is the second most common malignant disease diagnosed in men worldwide. It is also the fifth leading cause of cancer death [1, 2]. According to GLOBOCAN estimates, 1,276,106 new cases of PC were reported worldwide in 2018, with higher prevalence in developed countries, which reflects differences in diagnostic capabilities. PC incidence and mortality rates are strongly related to age: the highest incidence is seen in men over the age of 65 [3].

PC may be asymptomatic at early stages [3]. 58.5% of patients are diagnosed with localized PC which is characterized by a low-to-intermediate risk [4]. Patients without distant metastases respond successfully to treatment, in particular, to radiation therapy [5]. Radiation therapy can be an alternative to surgical treatment as a primary monotherapy for low- and intermediate-risk PC, as well as for treatment of locally advanced PC in combination therapy. Patients diagnosed with locally advanced PC (pT3a or pT3b) often require additional adjuvant radiation therapy after radical prostatectomy. Radiation therapy for oligometastatic PC is possible, but at the moment it is used only in clinical trials and requires further discussion [6, 7].

Radioresistance of a subpopulation of prostate cancer cells may be one of the possible reasons for continued tumor growth after radiation therapy [2]. Tumor progression and spread of distant metastases disable the use of classical therapy regimens [5]. Treatment recommendations differ depending on the time of the biochemical relapse onset. When it occurs after radical prostatectomy, radiation therapy is an option. When the relapse is detected after radiation therapy, alternative treatments are used [8].

Deciphering the mechanisms of PC radioresistance onset seems to be necessary due to the recurrence risk. The main mechanisms underlying radioresistance include disruption of DNA repair processes, activation of anti-apoptotic signaling pathways, a decrease in

intracellular reactive oxygen species (ROS), and epithelial – mesenchymal transition (EMT). Hypoxia of a tumor microenvironment and autophagy also contribute to the development of radioresistance. Currently, it is assumed that these processes take place not in all cancer cells, but only in the so-called cancer stem cells [9]. Presumably, they promote recurrence and metastasis both due to the reasons stated above and due to their unique ability to reproduce the heterogeneity of the primary tumor [10]. Searching for prostate cancer stem cell markers for identification, prognosis, and targeted treatment is critical for improving therapeutic and clinical outcomes.

CANCER STEM CELLS

Cancer stem cells (CSCs) have fundamental properties that distinguish them from other malignant cells: the ability to initiate carcinogenesis, unlimited self-renewal, and the ability to differentiate into all cell populations present in the primary tumor. The last two features underlie growth and progression of malignant neoplasms [11]. More evidence is emerging to support the dynamic nature of cancer stemness. The epithelial – mesenchymal transition (EMT) reflects plasticity of CSCs and determines the degree of tumor invasion and metastasis. Activation of the Notch, Hedgehog, WNT / β-Catenin, JAK / STAT, and NFκB signaling pathways is observed in regulation of plasticity of both healthy and cancer stem cells [12, 13].

There are two concepts in the CSC origin. The first concept postulates their formation from postnatal stem cells; another hypothesis explains their occurrence by reprogramming of differentiated tumor cells [13], and EMT is the most representative process of cell reprogramming [12]. CSCs are characterized by changes in the activity of many signaling cascades; however, the importance of transcription factors OCT3/4, SOX2, KLF4, and cMYC, which regulate the work of genes responsible for pluripotency, is especially emphasized [14].

In addition to genetic reprogramming, the mechanisms of epigenetic reprogramming similar to processes taking place in embryonic stem cells play an important role in CSC formation [11]. In particular, genes of the Polycomb recessive complex, which provide pluripotency of stem cells through histone post-translational modifications, are overexpressed in prostate cancer [15]. DNA methylation is also an epigenetic feature of CSCs. DNA methyltransferases DNMT1 and DNMT3, which are required to maintain existing patterns of methylation and *de novo* methylation in CpG islands, are factors in CSC reprogramming [16].

Radioresistant subpopulations of prostate cancer cells are proved to have many properties in common with prostate CSCs, in particular, increased expression of CD133, CXCR4, ABCG2, OCT4, and NANOG. In addition, exposure of prostate cells to ionizing radiation stimulates constitutive activation of stem cell markers, which reprogram them epigenetically and mediate radioresistance formation. In particular, increased methylation of the H3 histone in the *ALDH1A1* promoter stimulates its transcription [17]. Inhibition of methylation causes apoptosis and decreased radioresistance in prostate cancer cells [18].

The most well-known markers of prostate CSCs are αvß3-integrin, E-cadherin, N-cadherin, vimentin, NANOG, OCT4 and SOX2, as well as markers of EMT, for example, CD44.

Experimental studies use CD44, CD133, and α2β1 markers to isolate a population of prostate CSCs. Caveolin-1, a membrane protein involved in receptor-independent endocytosis [19], and aldehyde dehydrogenase 1A1 (*ALDH1A1),* which catalyzes oxidation of retinal to retinoic acid, a signaling molecule of cell differentiation and self-renewal of stem cells [9], are considered as potential predictors of PC radioresistance.

Radioresistance of CSCs is now believed to be a complex set of complementary mechanisms. The presence of CSCs in the total tumor mass partially explains the phenomenon of cell resistance to ionizing radiation. Processes that promote resistance to radiation therapy occur in CSCs and include enhanced DNA repair, activation of apoptosis suppressors, EMT, decreased ROS levels, autophagy, and the state of the tumor microenvironment.

DNA REPAIR

Activation of cell cycle checkpoints, which cause its intermittence to correct defects in the nucleotide sequence, is an integral part of a cellular response to DNA damage caused by radiation [20]. Adaptation to replication stress involves repairing single- and double-strand breaks in DNA, which leads to increased activation of replication after radiation therapy [21]. Cells use two main mechanisms to repair DNA damage: non-homologous end joining (NHEJ) and homologous recombination (HR). HR is induced in the S and G2 phases of the cell cycle, while NHEJ can be activated at any point in the cell cycle with the greatest efficiency at the G2 stage of mitosis and pre-

dominance in the G0, G1, and early S phases [23]. The greatest radioresistance is observed in the late S phase and explained by increased replication, which promotes HR [24].

Dysregulation of the signaling cascades EGFR, PI3K / Akt / mTOR, ATM-Chk2, WNT, Notch, and Hedgehog is associated with CSC radioresistance [25–27]. Radioresistant prostate stem cells are characterized by increased phosphorylation of Chk2 and AKT. These modifications cause arrest of cell proliferation through the ATM-Chk2 pathway and enhancement of DNA repair through activation of the PI3K signaling cascade [17]. In their model experiment, S. Yadav et al. showed overexpression of *SMC1A* in prostate cancer cell lines DU145 and PC3. Knockdown of *SMC1A* increased the efficiency of radiation therapy in these cells, which could be associated with ATM-mediated repair of DNA double-strand breaks [27]. Ionizing radiation causing this effect leads to a delay in the S phase of DNA repair [28]. In contrast to the rest of the tumor mass, stem cells are characterized by reduced activation of the p53 signaling pathway after radiation therapy. As a result, normal functioning of the cell cycle and apoptosis is disrupted and, ultimately, mutations accumulate. Over time, mutational load increases intratumoral heterogeneity and leads to the disease progression [29].

Radioresistance supported by a high level of DNA repair is also determined by indirect mechanisms, and one of them is a decrease in ROS production causing DNA damage and ROS-dependent apoptosis [30]. Other mechanisms include increased expression of APE1 / Ref-1 and activation of the NNMT pathway, which decreases intracellular ROS levels [30, 31].

ACTIVATION OF APOPTOSIS SUPRESSORS

Radiation therapy involves death of tumor cells due to activation of apoptotic signaling pathways in response to single- and double-strand breaks in DNA. Apoptosis disruption can be one of the reasons for radioresistance. Activation of the Wnt / β-catenin signaling pathway is excessive in prostate CSCs. This allows cells to activate their repair mechanisms when avoiding apoptosis [32]. A model experiment on the DU145 cell line showed that overexpression of the *SOX2* gene increased resistance to apoptosis, delaying cleavage of caspase-3 and decreasing supply of Ca2+ ions. The subsequent knockdown of *SOX2* increased sensitivity to apoptosis, which suggests an association between *SOX2* overexpression and radioresistance [33]. In turn, resistance to apoptosis may be due to the differentiation status of stem cell differentiation, external factors of the microenvironment, and hypoxic conditions [9].

PRODUCTION OF REACTIVE OXYGEN SPECIES

Exposure to ionizing radiation causes excessive production of ROS, which are formed either directly through water radiolysis or indirectly through mitochondrial damage or metabolic changes [34]. The produced ROS molecules damage not only DNA, but also proteins and lipids, which complicates the process of cell repair after radiation-induced damage. Cancer cells, in contrast to non-malignant cells, have higher ROS levels due to the increased metabolic rate and the use of glycolysis for energy production. Despite the cytostatic effect of ionizing radiation, the production of ROS creates a favorable environment for acquisition of stemness properties by cancer cells [18]. Given the low proliferation rate of CSCs, they demonstrate lower levels of endogenous ROS, and, therefore, can neutralize their production more efficiently [21]. Oxygen-dependent production of free radicals can contribute to resistance to radiation therapy [35].

Radioresistant prostate tumors are characterized by lower baseline levels of intracellular ROS, which indicates implementation of another mechanism of radioresistance through their increased absorption. This is confirmed by studies that demonstrated increased expression of ROS acceptors in prostate CSCs [36]. In the DU145 and PC3 PC cell lines, an increase in intracellular ROS levels and a decrease in glutathione levels during repression of *SMC1A* were demonstrated, which leads to radiosensitization of cells in response to radiation therapy [27]. In addition, some transcription factors can affect the level of antioxidant proteins. For example, NF-kB is required to resist oxidative stress, while NRF2 in combination with ARE is capable of stimulating radioresistance [37, 38].

Hypoxia of the microenvironment contributes to the development of radioresistance of PC cells through impaired ROS production and activation of hypoxia-inducible factor (HIF). The HIF-2α subunit regulates the transcriptional activity of genes responsible for tolerating hypoxia and maintaining an undifferentiated phenotype, which stimulates selection of a radioresistant population of cancer cells [39]. The effect of a hypoxic microenvironment on CSCs is currently a promising area of research.

EPITHELIAL – MESENCHYMAL TRANSITION

The phenotype of CSCs is quite plastic and associated with EMT, which can be caused by exposure to radiation and hypoxic conditions of the microenvironment [40]. EMT is characterized by cell motility, inhibition of adhesion, loss of polarity, and interaction with the extracellular matrix. The key features of EMT, namely, a decrease in E-cadherin and an increase in N-cadherin and vimentin, are significantly more pronounced after radiation therapy for PC [41]. Induction of EMT and acquisition of stemness properties by cells are associated with activation of the PI3K / AKT / mTOR pathway. Studies of CSCs isolated from a human PC cell line obtained after prostatectomy also showed the presence of CD44 expression, which is an EMT marker [33].

The mechanism of radioresistance acquisition through EMT is implemented mainly through activation of the TGF-β, Wnt / β-catenin, Hedgehog, Notch, NANOG, and STAT3 signaling pathways [42]. EMT mediated by ionizing radiation and signaling through the TGF-β pathway plays a crucial role in enhancing the migratory and invasive capabilities of cancer cells [43]. EMT partially contributes to maintenance of the CSC phenotype [44]. In particular, activation of the main transcription factors of EMT signaling cascades, such as Snail, HIF, ZEB1 / 2, and Twist1, mediates stemness features of the tumor [45]. Snail plays a decisive role not only in migration and invasion of cancer cells, but also in the radiation-induced EMT [46]. Constitutive activation of Snail, which mediated acquisition of mesenchymal properties by the tumor, was revealed in a model of human PC cells [47]. The transcription factor ZEB1 represses miR-183, miR200c, and miR203, which exhibit antitumor activity [48]. Finally, Twist1 positively regulates the proto-oncogene *BMI1*, thereby provoking EMT and forming tumor microenvironment niches [49].

Thus, EMT is a dynamic process with many transients. The presence of stem cells is a favorable condition for maintaining the vital activity of the tumor and avoiding radiation therapy by balancing between the epithelial and mesenchymal stages.

AUTOPHAGY

Autophagy is a natural process that allows cells to cope with stress by recycling damaged cellular components. Prolonged autophagy induction can lead to cell death due to excessive degradation of key intracellular components [50]. Therefore, autophagy performs a double paradoxical function – it suppresses tumor growth at early stages by removing damaged proteins, but promotes tumor growth and survival at later stages under conditions of nutrient deficiency and hypoxia [51].

The role of autophagy in the survival and death of cancer cells seems to differ depending on a disease and is not completely clear in PC [52]. The data on the effect of autophagy suppression in prostate CSCs are very contradictory. S. Paglin et al. found that inhibition of autophagy leads to radiosensitization of LNCaP cells [53]. In contrast, Yao et al. showed improvement of the viability of PC cells with inhibition of autophagy in PC3 and LNCaP cells and xenograft mouse models [54]. The unidentified role of autophagy determines the relevance of a more detailed study of its contribution to the development of PC radioresistance.

TUMOR MICROENVIRONMENT

In addition to the internal mechanisms of radioresistance, the fate of tumor cells after radiation therapy depends on a variety of signals emanating from the tumor microenvironment. The latter consists of components that include, in addition to the extracellular matrix, fibroblasts and inflammatory, immune, vascular, and endothelial cells. All these components interact through cytokines, chemokines, and growth factors, creating a hypoxic, inflammatory, and immunosuppressive microenvironment. Ionizing radiation can act as a modifier of mechanisms that cause release of growth factors, activation of tumor-associated fibroblasts, and induction of inflammation and hypoxia [11]. These conditions are favorable for tumor growth, progression, and metastasis [55].

Hypoxia causes significant changes in tumor metabolism due to nutrient deficiency, low oxygen concentration, and dysregulation of carrier proteins and metabolic enzymes [56]. Persistent hypoxia can trigger mechanisms including activation of the HIF-1α signaling pathway, autophagy, and EMT. Their importance in the development of radioresistance is explained by the possibility to maintain the vital function of CSCs [57].

CSCs are located in specific areas of the microenvironment, called niches, that provide autocrine signaling, as well as signals from tumor-associated fibroblasts, immune and endothelial cells, and components of the extracellular matrix [58]. Despite poor understanding of the composition of niches and their signaling interaction with the tumor, the microenvironment is known to supply CSCs with oxygen and nutrients

and support their functions protecting them from such effects as radiation [59].

Perivascular and hypoxic CSC niches are the most studied types. The perivascular niche is located in the immediate vicinity of blood vessels, supplying cells with nutrients, growth factors, and cytokines. This environment can induce secretion of stem cell factors, such as OCT4 and NANOG, to initiate transformation of cancer cells into cancer stem cells [60].

Hypoxia is another mechanism used by the niche to protect CSCs. Oxygen is a potent radiosensitizer, and it is required for radiation-induced ROS production and, as a consequence, for cell death. A lack of oxygen increases radiation resistance of cells and is associated with an early relapse after radiation therapy [61]. In addition, ROS neutralization is increased in the hypoxic niches [11]. Radiation therapy induces production of PDGF, IL-1β, IL-6, TNFα, TGFβ, CXCL12, and MMPs in the tumor microenvironment, which leads to activation of ROS acceptors and the STAT3 signaling cascade, promoting self-renewal and survival of cancer cells [62, 63].

In addition to the above-mentioned mechanisms, CSCs are supposed to be able to exist in a quiescent state which provides the basis for new micrometastases or initiation of a tumor relapse [30].

MARKERS OF PROSTATE CANCER RADIORESISTANCE

Defining prognostic determinants of a response to radiation therapy is an important task of research on PC radioresistance. Signaling pathways PI3K / Akt, MAPK / ERK, and VEGF and glucose metabolism are essential for radioresistant PC [64, 65].

The metastatic capability of radioresistant PC cells is also explained by increased expression of heat shock protein 90 (HSP90) [36]. PC resistance to radiation therapy may arise due to nuclear translocation of β-catenin induced by HIF-1 overexpression [57]. The ineffectiveness of radiation therapy can most likely be indicated by expression of PCSC1- and PCSC2-RAN. The CXCR4 and CXCR12 chemokine receptors are also recognized as biomarkers of radioresistant PC cells [64]. A recent study revealed an association between differential expression of 14 genes and radioresistance of PC cell lines [66]. PC cells were shown to respond to ionizing radiation by increasing the expression of *BRCA1*, *FANCG,* and *RAD51* [67]. The epithelial cell adhesion molecule (EpCAM) is a potential biomarker, as its overexpression is associated with radioresistance both *in vitro* and *in vivo* [68]. S.G. Zhao et al. created a diagnostic panel of gene expression (PORTOS), which predicted the outcomes of postoperative radiation therapy. The results of this study could predict the risk of distant metastases [69]. *RAD9* is considered to be a potential biomarker of PC radioresistance. Its contribution to regulation of the cell cycle, repair, and apoptosis, as well as to migration and invasion was proven. The role of this molecule as a transcription factor for androgen receptors is also undeniable [70]. Increased expression of markers of neuroendocrine differentiation CD133 and CD138 is presumably associated with increased expression of pluripotency genes and, ultimately, with subsequent development of radioresistance [71].

The detection of specific circulating microRNAs, in addition to genetic markers, also seems to be extremely promising. The presence of some microRNAs in PC patients is a more informative indicator than measuring the level of the prostate-specific antigen (PSA) [72]. According to the literature, more than 50 known microRNAs are involved in the pathogenesis of PC. The pattern of microRNA expression is specific in the lines of radioresistant PC cells [73]. Increased clonogenic survival after radiation is associated with significant changes in the expression profiles of miR-221, miR-4284, MiR-31, and miR-200c [74]. Inhibition of miR-521 in the PC cell line provokes a radioresistant phenotype. Overexpression of miR-548c-3p in differentiated cells induces stem-like properties and radioresistance [75]. In radioresistant PC cells, miR-106a expression is elevated, which provides resistance to radiation therapy due to a direct effect on LITAF and increased proliferation [76]. Experiments on PC cells showed an association between increased miR-301a and miR-301b expression and hypoxia, as well as autophagy, which provokes enhanced radioresistance [77]. Aberrant expression of miR-521, miR-95, miR-106b, miR-32, and miR-205 is observed in the establishment of radioresistance [78]. In PC cells, miR-32 suppresses the function of the DAB2IP protein, inducing autophagy and inhibiting radiation-induced apoptosis [79]. Tumor radioresistance is also enhanced by miR-620 and miRNA-95, which target HPGD and SGPP1, respectively [80, 81].

According to our studies, the copy number of genes regulating proliferation and apoptosis can be considered as a factor of resistance of PC cells to radiation therapy. Thus, in a model experiment on PC-3 cells, we found that cells that retained their viability after five days of radiation therapy were characterized by an increased copy number of the *CDK1, CDKN1B,*

H2AX, PTEN, XRCC4, RBBP8, and *EP300* genes and a decreased copy number of the *CCND3, BAX, TP53,* and *BCL2* genes [82]. Table 1 presents the main markers of PC radioresistance.

Table 1

Markers of prostate cancer radioresistance

Markers	Method for determination	Reference
α2β-, αvß3-integrins, E-, N-cadherins, vimentin	IHC	[9]
CD44, CD133	IHC	[9]
NANOG, OCT4, SOX2	RT-PCR	[9]
ALDH1A1	microchip	[17]
Caveolin-1	western blot	[19]
HSP90	ELISA	[35]
HIF-1α	RT-PCR	[56]
PCSC1- RAN, PCSC2-RAN CXCR4 / CXCL12	IHC	[64]
ADAMTS9, AKR1B10, FOXL1, FST, ITGA2, GRPR, SOX17, STARD4, VGF, FHL5, LYPLAL1, PAK7, TDRD6, CXXC5	microchip	[65]
BRCA1, FANCG, RAD51	RT-PCR	[67]
EpCAM	RT-PCR	[68]
DRAM1, KRT14, PTPN22, ZMAT3, BIN2, ARHGAP15, IL1B, ANLN, RPS27A, MUM1, TOP2A, GNG11, CDKN3, HCLS1, DTL, IL7R, UBA7, NEK1, CDKN2AIP, APEX2, KIF23, SULF2, PLK2, EME1	microchip	[69]
RAD9	IHC	[70]
CD133, CD138	RT-PCR	[71]
miR-221, miR-4284, MiR-31, miR-200c	microchip	[74]
miR-521, miR-548c-3p	microchip	[75]
miR-106a	RT-PCR	[76]
miR-301a, miR-301b	RT-PCR	[77]
miR-521, miR-95, miR-106b, miR-32, miR-205	RT-PCR, microchip	[78]
miR-32	RT-PCR	[79]
miRNA-95	RT-PCR	[80]
miR-620	RT-PCR	[81]
CDK1, CDKN1B, H2AX, PTEN, XRCC4, RBBP8, EP300, CCND3, BAX, TP53, BCL2	RT-PCR	[82]

Note: IHC – immunohistochemistry, RT-PCR – real-time polymerase chain reaction, ELISA – enzyme-linked immunosorbent assay.

CONCLUSION

The cancer stem cell model determined the direction of research to explain the mechanisms of prostate cancer radioresistance development. A high degree of tumor heterogeneity and difficult conditions for the emergence of tumor resistance to ionizing radiation suggest detection of specific markers. Their diversity is determined by the main processes occurring during radioresistance development, including increased DNA repair, activation of anti-apoptotic signaling pathways, production of ROS, hypoxia of the tumor microenvironment, epithelial – mesenchymal transition, and autophagy. Assessment of the transcriptional profile of the tumor can serve as a basis for predicting the outcomes of radiation therapy. A combination of the molecular genetic approach with standard biochemical and instrumental diagnostic methods will help to identify patients with radioresistant prostate tumors and select a personalized therapeutic strategy.

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Omelchuk E.P. – drafting of the manuscript. Kutilin D.S. – conception, critical revision of the manuscript for important intellectual content. Dimitriadi S.N., Gusareva M.A. – critical revision of the manuscript for important intellectual content. Timoshkina N.N. – critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication.

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