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REVIEWS

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THE FUNCTION OF POLIAMINE METABOLISM IN PROSTATE CANCER

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In many developed countries prostate cancer is the second leading cause of cancer related death in human population. Prostate tissue is characterized by the highest level of polyamines among organs in human body, and it is even higher in prostate carcinomas. These ubiquitous molecules are synthesized by prostate epithelium and are involved in many biochemical processes including cell proliferation, cell cycle regulation and protein synthesis. In this review we made the attempt to discuss the functions of polyamines, their involvement in apoptosis and potential role as molecular biomarker for prostate cancer. Also we present recent data on generation of drugs, in particular, cyclin dependent kinase inhibitor, developed for therapy of prostate cancer.
Key Words: **prostate cancer, polyamines, CDK inhibitors, olomoucine, bohemine, roscovitine.**

Since prostate cancer (Pca) is a heterogeneous disease, it becomes clear that a defined set of markers will become important for early diagnosis, monitoring and prognosis of Pca. Polyamines (PAs) (putrescine (Put), spermidine (Spd) and spermine (Spm)) which play a significant role in the regulation of growth and development of different cell types [1–3] are among potential biomarkers. Elevated PAs levels are not specific for Pca only, but they are good indicators for monitoring of the disease and may serve as biomarkers for rapidly proliferating cells. PA content is regulated by many events such as biosynthesis and catabolic processes, genetic control of key enzymes at transcriptional and translational stage, regular diet. The induction of PA synthesis by any stimulus results in increased rate of DNA, RNA and protein synthesis [1–6].

Ornithine decarboxylase (ODC) is a key enzyme that catalyzes the conversion of ornithine to Put. Then Put is converted to Spd and Spm by Spd-synthetase and Spm-synthetase respectively [1, 2, 7, 8]. PAs are very important cationic molecules for cell homeostasis. If an excess amount of PA is accumulated in the cells, these molecules undergo oxidation in peroxisomes with involvement of monoamine oxidases, in particular PA oxidase (PAO). Oxidation of Spd and Spm occur only after N1-acetylation by spermidine/spermine N^1-acetyltransferase (SSAT) present in cytoplasm [8, 10, 11]. PAs may be degraded also by diamine oxidase (DAO), a copper/quinone containing serum amine oxidase. This enzyme is generally responsible for the cytotoxicity of PAs in *in vitro* models in the presence of fetal calf serum, but its physiological role is not clearly understood [12, 13]. Arginase catalyzes the oxidation of PAs such as Spm and Spd, to much less active compound called Put (Fig. 1) [14].

The content of PAs depends on two main sources: external (consumption-dependent PAs or usage of deposit PA from red blood cells) and synthesis that is regulated by ODC under the control of *c-Myc* gene [1, 9]. The excess amounts of PAs are excreted via efflux mechanism after conversion to N^1-acetylspermine and N^1-acetylspermidine. PAs may affect cell death by modulating the release of cytochrome *c* from mitochondria, which triggers activation of caspases and induction of apoptosis. PAs may also affect signal transduction pathways mediated by the nuclear transcription factor-B (NFkB), mitogen activated protein kinase (MAPK) family members and, possibly, other kinases which modulate the expression of genes implicated in the control of cell growth and cell death. The proposed hypothesis postulates that NFkB may modulate both growth and death mechanisms using PPARγ and polyamine response element (PRE). ODC plays the central role in this network, quickly transforming external signals (growth promoting stimuli, hormones, drugs, growth factors, mitogens) in biological activity. The data demonstrated that overexpression of ODC leads to transformation of cells [15–19].

ODC expression is controlled at the transcriptional, translational and posttranslational level [20]. ODC degradation is regulated by regulatory enzyme called antizyme (AZ) that is induced by PA-mediated shifting of translational frame [21]. AZ binds to ODC monomers and stimulates their proteolytic degradation in proteosomes. AZ also down-regulates PA's uptake by cells. In turn, activity of AZ is regulated by special inhibitor homologous to ODC [22].

Despite numerous studies, the specific role of the ODC-PA system in cellular physiology is still not clarified yet.

ROLE OF POLYAMINES IN CELL GROWTH AND DIFFERENTIATION

PAs are able to bind to macromolecules such as nucleic acids, proteins and phospholipids at physiological pH. Consequently, it has been suggested that PAs are necessary for stabilization of these molecules. Spd and Spm cause condensation and aggregation

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Abbreviations used: AZ – antizyme; AZP – monoaziridinylputrescine; BOH – bohemine; BPH – benign prostate hyperplasia; CDKs – cyclin-dependent kinases; CDKIs – CDK inhibitors; DAO – diamine oxidase; DFMO – difluoromethylornithine; 5-FU – 5-fluorouracil; NAcSpd – N1-acetylspermidine; NAcSpm – N1-acetylspermine; OC – olomoucine; ODC – ornithine decarboxylase; PAO – PA oxidase; PAs – polyamines; Pca – prostate cancer; PSA-5 – Prostate specific antigen; Put – putrescine; Spd – spermidine; Spm – spermine; SSAT – spermidine/spermine N^1 – acetyltransferase.

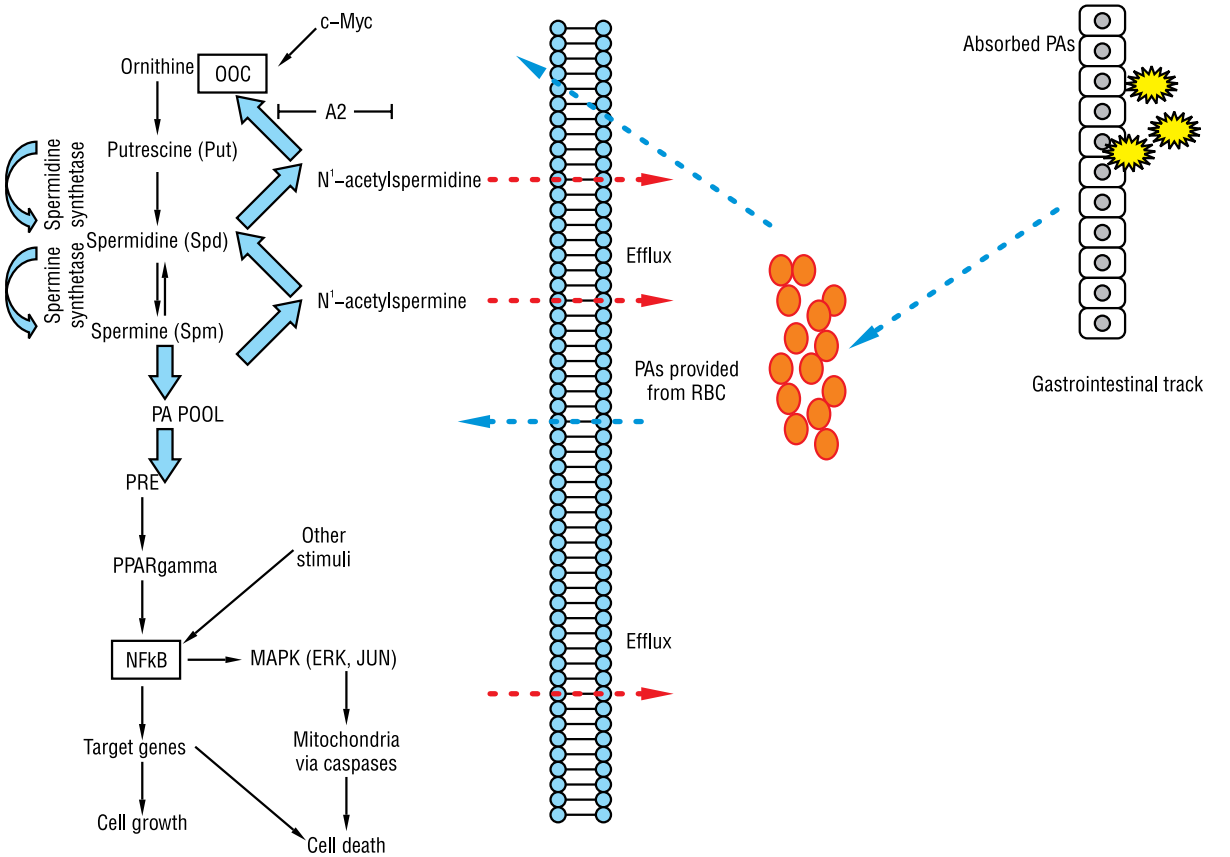

Figure. The amount of PAs has two sources inside the cell. One of them is external PAs sources such as absorption from diet or usage of deposit PA from red blood cells or synthesis. PA synthesis is regulated by ODC under the control of c-Myc. The excess amount of PAs is excreted via efflux mechanism after conversion with N1-acetylespermine and N1-acetylspermidine. Their involvement in signal transduction network is under control of cellular death and growth balance. PA may affect cell death by modulating the release of cytochrome c from mitochondria, which triggers the activation of caspases and the induction of apoptosis. PAs may also affect signal transduction pathways mediated by the nuclear transcription factor-B (NFkB), mitogen activated protein kinase (MAPK) family members and, perhaps, other kinases which modulate the expression of genes implicated in the control of cell growth and cell death. The proposed hypothesis is NFkB may modulate both growth and death mechanism using PPARγ and polyamine response element (PRE) and has dual effect. However, the manager molecule in this network is determined as ODC because of c-Myc relationship

of DNA and induce B-Z and B-A transitions in certain DNA sequences. PA-DNA interaction and resultant structural changes in DNA may provide the molecular basis by which PAs regulate cell proliferation. It was proposed that major function of cationic PAs in the process of cell division may be the stabilization of replication complexes between DNA and nuclear matrix, condensation and packaging of newly synthesized DNA into nucleosomes and chromatin [23–25]. PAs are also involved in stabilization of RNA [26–28], in protein synthesis and endogenous modification of NMDA receptor ion channel and voltage-dependent Ca^{+2} and K^{+} channels [29, 30].

PAs are involved in cell proliferation, embryonic development, cell cycle. PA biosynthesis deficient mutant cells do not grow if PAs are added to the culture medium. Generally, resting cells contain low levels of PAs but if these cells are stimulated to divide by trophic factors, PAs levels increase. PA reduction causes an aberrated cell cycle progression and accumulation of cells in one of phases of cell cycle [31]. Inhibition of PA biosynthesis also affects cell cycle related features such as DNA sensitivity to DNAses [23]. Benign prostate hyperplasia (BPH) is very frequent age dependent illness in men. According to Liu et al. [32] the increased ODC activity and PA content in prostate tissue may correlate with the pathogenesis of BPH. The high level of ODC activity is induced by overexpression of ODC mRNA. The contents of Put, Spd, and Spm in BPH tissues were 2.2, 3.4, and 6.0 times higher than those in normal tissues, respectively; ODC activity of BPH tissue was 3.2 times higher than in normal tissue. The expression level of ODC mRNA in BPH tissues was higher than that in normal tissues.

PAs also affect cell differentiation. Janne et al. [33] suggested that decrease of Spd/Spm ratio reflects transition from proliferation into differentiation state.

ROLE OF POLYAMINES IN APOPTOSIS

The number of cells in adult human body is steady due the balance between cell proliferation and cell loss. Controlled cell death is known as apoptosis or programmed cell death. Apoptosis include oligonucleosomal DNA degradation, condensation of cytoplasm and nuclei and formation of apoptotic bodies.

Changes in PA homeostasis (elevated PA accumulation) may lead to apoptosis. Moreover, induction of ODC is an early event in the induction of apoptosis [35]. Involvement of ODC in the process of cell death becomes apparent from researches on neuronal cell

death induced by hypoglycemia, neurotoxic agents and traumatic brain injury [36]. These studies revealed a significant increase in *ODC* gene expression, protein synthesis and Put levels. Numerous studies in different cell systems have shown pronounced elevation of ODC activity after induction of apoptosis [35]. The role of ODC in apoptosis was studied by Packham and Cleveland [37, 38] who showed that ODC is an important mediator of c-myc-induced apoptosis, and suppose that c-myc induces ODC-mediated apoptosis and proliferation by different but overlapping pathways.

Both up-regulation and down-regulation of PA levels may be associated with apoptotic events. For example, treatment of HL-60 cells with etoposide, a classic inducer of apoptosis, resulted in early and transient increase of ODC content, which may initiate apoptosis, followed by its decrease, which would sustain this process [40]. ODC induction and Spd accumulation have been related to the progression of the cell cycle until a checkpoint from which apoptosis is triggered in the presence of cell death-inducing signals or negative growth factors [35, 41].

The involvement of PAs in apoptosis-related pathways at the level of mitochondria has been investigated in different cell models. Some research groups have initially studied the effects of PAs on events directly related to the activation of the caspases. PAs, particularly Spm, can trigger the activation of caspases in cell-free models of apoptosis and PAs can directly induce the release of cytochrome *c* from mitochondria and activate the death program [42].

The release of cytochrome *c* from mitochondria may be modulated by Bcl-2 family proteins (Bax and Bid), which influence opening of mitochondrial permeability transition pores and the subsequent release of cytochrome *c* into cytosol [43]. In intestinal cell line, PA depletion antagonizes camptothecin-induced apoptosis by preventing translocation of the proapoptotic Bcl-2 family member Bax to mitochondria and inhibiting the release of cytochrome *c* [44]. Moreover, in ODC-overproducing murine myeloma cells, accumulation of Put provokes apoptotic death that is inhibited by DFMO and involves the release of cytochrome *c* from mitochondria, followed by the activation of caspase cascades [45]. On the other hand, in various lymphoid cell lines, the complete depletion of PAs provoked by the combined use of ODC and SAMDC inhibitors causes the disruption of the mitochondrial membrane potential, resulting in caspase activation and apoptotic cell death [46]. A recent study [47] has shown that Spm inhibits the release of cytochrome *c* from mitochondria of the dexamethasone-treated thymocytes, but it does not totally prevent the dexamethasone-induced DNA fragmentation.

POLYAMINES AS BIOMARKERS IN PROSTATE CANCER AND TARGETS FOR ANTICANCER THERAPY

The increasing awareness of the role of PAs in cell behavior has attracted the attention to the PA as biomarkers and potential targets in the treatment of cancer and other diseases. *In vitro* and *in vivo* studies have revealed that ODC activity and PAs metabolism are fundamental for malignant transformation of cells [15, 17–19]. In prostate adenocarcinoma, acute lymphoblastic leukemia and brain tumors PAs and their metabolic enzymes appear to be of diagnostic value. Spermidine/spermine N^1-acetyltransferase (SSAT) was shown to serve as a reliable biochemical marker for proliferation of bladder epithelium [48, 49]. Recently PAs content was found to be a promising biomarker for cervical malignancies [50].

Since PAs play important role in tumor cell growth, interference in PA metabolism provides a possible mean for chemotherapy of cancer. Different compounds inhibiting the activity of enzymes related to PA metabolism have been described and their anticancer properties have been analyzed [51–53]. However, these compounds are active only *in vitro*, but not *in vivo*. The reasons of the failure were determined as follow: 1) rapid turnover of PA biosynthetic enzymes; 2) compensatory elevation of other PA-related enzymes not targeted by inhibitor; 3) compensatory increase of external uptake of PA; 4) compensatory retroconversion of intracellular PA pool, because single inhibitor cannot reduce all PA pools.

In recent years it has become obvious that structural analogues of PAs can act as antineoplastic agents. PA analogues down-regulate the enzymes of biosynthesis, deplete the PA pools and therefore inhibit cell growth. So far, the most effective for cell growth inhibition are PA analogues bis(ethyl)-analogues of Spm and bis(ethyl)-analogues of Spd [54, 55]. Growth inhibitory effects of these analogues have been established in a number of transformed cell lines [52], and inhibition of ODC and SAMDC activities, depletion of the PA pools and increase of SSAT activity upon their action have been established. Currently, some of the structural analogues of PAs are under Phase I or II of clinical trials and show promising results.

Although the findings are based on an artificial system (i.e. conditional overexpression of SSAT), there are many pharmacological examples of SSAT induction by the classes of drugs other than PA analogues [56]. Anticancer drugs unrelated to PAs can also elicit the significant increase of expression of *SSAT* gene. Using cDNA gene profiling, Maxwell et al. [57] have found that in MCF-7 cells treated with 5-fluorouracil, *SSAT* gene expression is affected at the highest degree among > 3000 genes studied. Similar results were obtained if the DNA-alkylating platinum compounds, oxaliplatin and cisplatin were applied [58]. Finally, SSAT transgenic mice that are genetically predisposed to develop prostate cancer (i. e. TRAMP mice) markedly suppressed genitourinary tumors [59]. These findings support the possibility that selective small molecule inducers of SSAT may have therapeutic and/or preventive potential against prostate cancer.

In many developed countries, Pca is the second leading cause of cancer related death among men.

Radical surgery and radiotherapy are curative options for Pca. Early diagnosis is pivotal to prolonged survival and quality of life. Prostate specific antigen (PSA) is the first widespread accepted biomarker for Pca. However it's use has many limitations: over-diagnosis of clinically insignificant Pca will cause over-treatment, including incontinence, impotence that are side effects of radical surgery and radiotherapy, and will negatively affect the patients' quality of life; from other hand, PSA screening fails to detect a small proportion of highly aggressive Pca. Therefore new Pca biomarkers need to be discovered [60].

The considerable number of patients is diagnosed at a time when the disease already is wide-spreaded. These patients ultimately require androgen ablation therapy that means surgical or medical castration. Androgen ablation induces an apoptosis in the androgen-dependent Pca cells [61], but it's hardly ever curative [62]. The main reason for the failure of androgen ablation is heterogeneity of Pca cells population. Compounds active against androgen-independent Pca cells are required.

Prostate tissue is characterized by the highest concentrations of PAs. In rats, the content of PAs is the highest in ventral, dorsal and lateral prostate, but lower in coagulating glands and seminal vesicles [63], and Spd is the dominant PA. In human body, ODC was found in prostate fluid, seminal plasma and sperm [64, 65], and Spm is the dominant PA in prostate tissue. It was shown that prostate PAs content is under the control of androgens [63, 66, 67]. Upon castration-induced apoptosis of prostate epithelial cells, ODC activity and PA levels decrease significantly, but SSAT activity increases [35]. Regeneration of prostate tissue by androgens support correlates with a marked increase of ODC activity and PAs level. It was reported that ODC activity and ODC mRNA level are stimulated by androgens treatment, and ODC activity is especially high in the epithelial cells of the prostate [66]. *In vitro* studies [68, 69] have revealed that androgen regulation of ODC is directly related to androgen receptor. Inhibition of ODC activity by difluoromethylornithine (DFMO) reduces the development of prostate and retards testosterone-induced re-growth of prostate in castrated rats [70].

It is clear now that in prostate tissue ODC and PAs are involved in cell proliferation and secretory activities via an androgen-regulated Spm-binding protein [71, 72].

Functional importance of seminal PAs is not clear still. Spm molecules are localized in the middle and top parts of the acrosome and possibly alter sperm fertilization competence and the acrosome reaction [73]. In sperm cells Spm may originate from endogenous PA biosynthesis, because ODC activity is associated with spermatogenesis [74]. Seminal PAs may also regulate seminal clotting or prevention of bacterial growth in urinary tract [75].

Monitoring of PAs and ODC content in prostate tissue may be useful for the diagnosis and prognosis of prostate cancer. Researches on rat prostate derived tumor cell lines demonstrated that ODC activity was elevated in quickly growing cells [76]. Similar data were obtained on human prostate cancer cell lines (PC-3, TSU-prl, DU-145 and JCA-1) [35]. Malignant PC-3 and TSU-prl prostate cell lines possess the high level of PAs associated with high ODC and low SSAT activities [35]. Moreover, significantly elevated ODC expression on mRNA and protein level in tumor tissue compared to the benign tissue of prostate was revealed [65, 77]. Graaf et al. [78] have shown correlation between Spm level and degree of differentiation in prostate tumors, and indicated that normal and benign hyperplasic prostate tissues have high content of Spm whereas in tissue of prostate carcinoma with metastases Spm levels are reduced.

PAs or their acetylated forms are secreted by cells, and these circulating molecules can be re-used by PA-requiring cells. Moulinoux et al. [79] revealed that circulating Spd and Spm are transported by red blood cells (RBC), and RBC PA level correlates with tumor development in tumor-graft model. Analysis of PAs levels in Pca cell lines with different degrees of differentiation has shown that less-differentiated cell lines contained lower Spm concentrations. Similar correlation between Spm levels and the degree of differentiation of prostate tumors was established by Shipper et al. [35] in the study of biopsy materials. These authors also indicated that in normal and benign hyperplastic prostate tissues a high content of Spm occurs, whereas in tumor tissue, especially in prostate carcinoma with metastases, Spm levels are reduced. Hence, a dramatic decrease of the prostate Spm content could indicate a conversion of prostate tissue from a benign to a malignant phenotype. *In vitro* studies [80, 81] demonstrated differential sensitivity of prostate tumor cell lines to Spm. Exposure of cells to Spm induced cell cycle arrest and apoptosis in the weakly metastatic AT-2.1 cell line but not in the highly metastatic AT-3.1 cell line. We also have established that total PA content was higher in highly metastatic rat prostate cancer cell lines (MAT-Lylu) than AT-2 cell line, which is low metastatic one (unpublished data). A possible explanation these facts may be in the different induction of antizyme in Spm-sensitive and Spm-insensitive cells. In the Spm-insensitive cells, ODC antizyme levels were not up-regulated, thereby failing to inhibit and degrade ODC [82].

As it is mentioned above, PAs are important for prostate cell growth and function, for this reason interference with PA homeostasis offer a promising target for chemotherapy of prostate cancer. Inhibitors of PA biosynthesis and PA analogues can affect PA homeostasis. Different compounds are able to inhibit the PA biosynthetic enzymes activities [52].

DFMO is the most widely studied ODC inhibitor causing depletion of Put and Spd pools without significant effect on Spm levels [83–85]. DFMO treatment has remarkable inhibitory effects on cell growth of cultured prostate cancer cells, and this inhibition may

be reversed by the addition of PAs or their acetylated derivatives in PC-3, PC-82 and androgen-stimulated LNCaP cells [85]. However, DFMO was ineffective *in vivo*, perhaps due to the compensatory uptake of PAs from extracellular sources [76, 86]. Another ODC inhibitor, methylacetylenic putrescine (MAP) inhibited the growth of PC-3 and some other cell lines, and slowly growing cells were more sensitive to its action [87]. Also, *in vitro* inhibitory effect on ODC activity of the naturally occurring garlic derivatives [88] and green tea polyphenols were demonstrated [89].

Experimental studies showed that PA analogues have significant antitumor activity in solid tumors. (Table). The prostate tissue preferentially takes up Put and this uptake can be enhanced by DFMO. Put analogues have chemotherapeutic potential, especially in combination with DFMO. Monoaziridinylputrescine (AZP) inhibited growth of PC-3 human prostate cells, while co-treatment with DFMO increased the growth inhibitory effect [94].

Symmetrically substituted bis(ethyl) analogues of Spm and Spd are highly effective in cell growth inhibition [53]. Some of these analogues BE-3-3-3, BENSpm or DENSpm are assessed in clinical tests [90, 91, 93, 95, 96]. BE-3-3-3 has different effects on cell growth and PA homeostasis in different prostate carcinoma cells: androgen independent cells were the most sensitive, whereas androgen-dependent cells were insensitive. Generally, degree of cell growth inhibition correlated with SSAT stimulation. BE-4-4-4-4 was more effective compared to BE-3-3-3 in inhibiting the growth of DU-145, Tsu-Pr-1 and DuPro-1 cells [90]. In all tumors treated with the BE-4-4-4-4, the levels of Spd and Spm were shown to decrease whereas Put level was not affected. The reason of the lack of PA depletion *in vivo* is probably uptake of PAs via food consumption.

Recently, the effect of a Spm analogue BIS has been studied on DU-145 and PC-3 cells [92]. BIS showed dose-dependent cytotoxic effect on prostate cancer cells *in vitro* and this effect was realized via apoptotic pathway. Besides, combination of treatment of BIS with irradiation strikingly increased the number of apoptotic cells. Therefore, application of BIS results in increased radio-sensitivity of human prostate cancer

The key enzymes involved in the cell cycle machinery belong to the group of homologous serine/threonine protein kinases known as cyclin-dependent kinases (CDKs), which typically contain cyclin as a regulatory subunit. Up to date, nine CDKs have been identified in human and animals [97]. These enzymes preferentially phosphorylate lamins, vimentin, caldesmon, and histon H1, which play a key role in cell division during the G2/M phase of the cell cycle, as well as proteins RBs, E2Fs, DP-1, RNA-polymerase II, EF-2 implicated in activation of the S-phase-specific genes involved in G1/S boundary [98].

It is well known that there both ODC and PA concentrations during the cell cycle are changed [99]. There is an early peak in ODC content at G1-phase, followed by an increase in PA content, and the second increase during G2-phase and prior to mitosis [100]. Thus, both PAs and cyclin/CDKs show phased changes throughout the cell cycle, but the interaction between these two sets of regulatory molecules remains to be defined. One suggestion is that PAs regulate cyclin degradation [101]. Intracellular PA concentrations have been reported to determine both up- and down-regulation of important cellular check points within the cell cycle, and this may in part, explain why their concentrations are controlled throughout the cycle [102, 103].

The enzymatic activity of CDKs in normal somatic cells is precisely regulated by several mechanisms. The natural CDK inhibitors (CDKIs) play an important role in this process [104]. Recently, natural peptide CDK inhibitors have been shown to play an important regulatory role in cell differentiation, proliferation, senescence, and programmed cell death [105]. It has also been demonstrated that the effects of these endogenous inhibitors may be partly mimicked by several different types of synthetic inhibitors including butyrolactone I, flavopiridol, 2,6,9-trisubstituted purines such as olomoucine (OC), roscovitine, and purvalanol, paullones, indirubins, and others [106–108]. These proteins bind to the cyclin-CDK complex and inhibit its activity. Consequently, the entry of the cell into the cell cycle is blocked. Due to the fact that the families of natural CDKIs or genes that control CDKIs transcription (e. g., p53) belong to the most frequently mutated proteins in cancer cells, the molecules that could mimic their biological activities are attractive candidates for anticancer treatment [109, 110].

Upon the study of plant hormones, cytokinins, specific inhibitors of the CDKs were identified, in particular 6-benzylamino-2-(2-hydroxyethylamino)-9-methylpurine (OC). At micromolar concentrations OC selectively blocks CDK1, CDK2 and CDK5 kinases [111]. OC does not exert an inhibitory effect on the major cellular kinases such as cAMP- and cGMP-dependent kinases, protein kinase C and Src kinases, however, it is able to block cells at the G1/S and G2/M boundaries [111]. OC has low cytotoxicity *in vitro* [111]. Another purine derivative, roscovitine, induces apoptosis under normal growth conditions. Roscovitine is a novel substance with potent inhibitory activity towards CDK1, high selectivity and antimitotic activity [112]. It was revealed that OC and roscovitine act as competitive inhibitors of in ATP-binding sites of kinases. The study of specificity of these inhibitors has shown that only the cell cycle regulating cdc2/cyclin B, CDK2/cyclin A and CDK2/cyclin E kinases, the brain CDK5/p25 kinase and ERK1 are inhibited by OC and roscovitine. Structure-activity studies and analysis of OC/CDK2 and roscovitine/CDK2 co-crystal structures confirmed that OC and roscovitine bind in the ATP-binding pocket of CDK2, but showed that the purine rings of OC/roscovitine and ATP are located in a totally different orientation. The antimitotic effects of

OC and roscovitine were investigated in a large variety of cellular models. The compounds inhibit both G1/S and G2/M transitions [113, 114].

Recently new groups of CDKIs with high specificity and efficacy have been synthesized [115]. They are strongly cytotoxic toward tumor cell lines *in vitro.* One of them, bohemine (BOH) and OC II were found to be effective *in vivo* [116]. On the other hand, OC II is the most active CDK1 inhibitor *in vitro* against tumor cells [117].

During the experimental studies, Mad'arova et al. [118] discovered that both BOH and OC were potent inhibitors of cell growth and viability, especially for androgen responsive cells; BOH was 2–3 times more effective than OC toward human prostate cancer cell lines. In our research, we estimated that treatment with BOH or OC II inhibited *in vitro* cell growth of highly metastatic (MAT-Lylu) and low metastatic (AT-2) rat prostate cancer cell lines and caused drastic reduction of Put, Spd and Spm levels (unpublished data).

In conclusion, PAs are promising biomarkers for prostate cancer, and the compounds targeting their metabolism should be studied for possible chemotherapeutical application.

Table. *In vitro* effects of polyamine analogues on human prostatic cancer cell lines [35]

	Analogue	DU-145	PC-3	LNCaP	Reference
Apoptosis	BE-3-3-3	not observed	not observed	induced	[91]
	BE-4-4-4-4	not observed	data not	data not avail-	[92]
	CPE-3-3-3	induced	available	able	[91]
	CHE-3-3-3	induced	induced	induced	[91]
	BIS	induced	induced	induced	[93]
			induced	data not available	
Polyamine	BE-3-3-3	increased	decreased	decreased	[91]
Pools	BE-4-4-4-4	decreased	decreased	decreased	[94]
	CPE-3-3-3	decreased	decreased	decreased	[91]
	CHE-3-3-3	not signifi-	decreased	not signifi-	[91]
		cantly		cantly	
		affected		affected	
ODC/	BE-3-3-3	decreased	decreased	data not avail-	[35]
SAMDC	CPE-3-3-3	not signifi-	not signifi-	able	[91]
Activity		cantly	cantly	not signifi-	
	CHE-3-3-3	affected	affected	cantly	[91]
		not signifi-	not signifi-	affected	
		cantly	cantly	not signifi-	
		affected	affected	cantly	
				affected	
SSAT	BE-3-3-3	increased	increased	increased	[91]
Activity	CPE-3-3-3	increased	increased	increased	[91]

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ПОЛИАМИНЫ И РАК ПРЕДСТАТЕЛЬНОЙ ЖЕЛЕЗЫ

Во многих развитых странах рак предстательной железы занимает первое место как причина смертности вследствие онкологических заболеваний. Ткань предстательной железы характеризуется наиболее высоким уровнем содержания полиаминов в сравнении с другими органами человека, причем в ткани карциномы простаты их содержание еще выше. Эти биомолекулы синтезируются эпителиальными клетками предстательной железы и принимают участие во многих биохимических процессах, включая пролиферацию клеток, регуляцию клеточного цикла и синтез белков. В обзоре обсуждаются функции полиаминов в клетке, их участие в процессах апоптоза и потенциальная роль в качестве биомаркеров при раке предстательной железы. Кроме того, приведены новые данные о разработке препаратов, в частности ингибитора циклинзависимой киназы, предназначенных для лечения рака предстательной железы.

Ключевые слова: **рак предстательной железы, полиамины, ингибитор CDK, оломуцин, богемин, росковитин.**