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The influence of quantitative alterations of steroid hormones on energy metabolism of prostate tumors

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Quantitative changes of steroid hormones in prostate tumor tissues and their influence on energy metabolism represents a critical factor in cancer progression and development of hormone-resistant malignant tumor. All distinguishing features of cancer must be one way or other related to specific metabolism that is characteristic to tumor cells. The aim of the work was to study the influence of the alterations in steroid hormone levels on key processes of energy metabolism in the tumor tissues of men with prostate tumors. Based on the data obtained from our research, it can be concluded that: i) A significant change in the amount of steroid hormones in tumor tissue of men with prostate adenocarcinoma have a considerable influence on the unique metabolic mechanisms characteristic to prostate cancer which contributes to the progression and aggressiveness of the tumor; and ii) A significant alteration in energy metabolism of prostate cancer was also established, which revealed through the activation of oxidative phosphorylation in case of benign tumor. It can therefore be implicated that in parallel to the progression of the disease, malignant prostate cells switch again to the increased glycolysis (activation of glycolytic pathway).

Keywords: Benign prostate hyperplasia, Energy metabolism, Glycolysis, Prostate cancer, Steroid hormones

Prostate tumors belong to hormone-sensitive tumors[1]. It is well known that steroid hormones are responsible for normal development of prostate gland in men; however, the steroids including androgens, also contribute to the development and metastasis of prostate tumors. Notably, steroid hormones ensure the running of specific reactions when they bind to their specific receptors in prostate cancer cells and promote the expression of particular genes. Besides, these hormone-receptor complexes have also been involved in specific physiological responses inside the cancer cells[1].

Growing interest in tumor metabolism research is known due to the fact that remodelling of tumor cell metabolism must be closely related with certain signaling pathways[2,3]. It should also be noted that Hanahan and Weinberg considered tumor metabolism as a key feature of cancer[4], but Kroemer and Poyssegeur suggested that all hallmarks of cancer should be related to the specific metabolism of a tumor cell in one way or other[5]. Additionally, Pavlova and Thompson outlined several different characteristics of cancer metabolism, particularly, the enhanced ability to absorb nutrients, selection of relatively acceptable metabolic pathways and remodelling these pathways[6].

Although development of most tumors traditionally occurs according to Warburg effect[2,7], there are also some exceptions[8]. The metabolism of normal prostate tissue is known to be unique, as the differentiated tissue is glycolytic (and not oxidative). As for the cancerous transformation of prostate tissue, during the latter cases, there is a metabolic switch in the direction to oxidative phosphorylation (OXPHOS), which is further transformed into glycolysis again in parallel to the progression of cancer and the formation of a hormone-resistant phenotype[9].

The studies revealed that a significant mechanism for regulation of the metabolic processes should be the hormonal regulation of the genes that are related to the transcription and translation of the enzymes involved in this metabolism[10]. Moreover, it is proved

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that a unique metabolic pathway of normal prostate epithelial cells is regulated by steroid hormones, which regulate the so-called "metabolic genes" in normal as well as in malignant cells[10].

Based on the above noted facts, our work aimed to study the quantitative changes of steroid hormones - [*i.e.*, Estradiol (E), Progesterone (P), and Testosterone (T)] in prostate tumor tissues as well as the alterations in the activities of some key enzymes of energy metabolism.

Material and Methods

Samples

Tumor tissue samples from men with benign and malignant prostate tumors (15 cases in each group) served as materials for the study. The age of all subjects ranged from 60-75 years in each group. The disease status and clinical stage of the subjects was determined based on the rectal, histomorphological and ultrasound examinations of the prostate at the L. Managadze Urology National Center, Tbilisi, Georgia. The study was approved by the National Council on Bioethics of Georgia, and written informed consent was obtained from all subjects.

Methods

200 mg of tumor tissues were washed in phosphate buffer saline (PBS) 1 mM solution (pH 7.4) and then homogenized. Subsequently, 2 mL methanol (100%) was added to the pellets and samples were stored overnight at -20 °C in freezer until further use. Enzyme-linked immunosorbent assay (ELISA) was performed for the quantitative determination of hormones in the supernatant of the samples using the appropriate reagent kits (Human ELISA kits of Progesterone, Estradiol, and Testosterone (Catalog #: 82105, 82130, and 82110, respectively), obtained from Human Diagnostics Worldwide.

Spectrophotometric method was used to determine the enzymatic activities of hexokinase (Catalog # k789-100, BioVision Inc., Milpitas, CA, USA) and m-aconitase (Catalog # k716-100, BioVision) at 450 nm, as well as for quantitative determination of citrate (Catalog # K655-100, BioVision) at 570 nm in the samples using appropriate reagent kits.

The obtained data were processed and analyzed using variation statistical methods and Graphpad prism 6 computer programs. *P*-value of ≤0.05 was considered statistically significant.

Results and Discussion

Our experimental observations showed that the level of free estradiol was elevated in prostate tumor tissue (Fig. 1); the significantly increased level of E (~4-fold) was observed within the prostatic benign hyperplasia tissue, while ~2.5-fold increase was observed in the prostate adenocarcinoma as compared to the control subjects[11].

Estrogens play an important role in male sex hormone secretion as well as in the growth, differentiation, and homeostasis of normal prostate tissues[12,13]. Besides, a high level of estradiol, in case of low testosterone level, promotes the development of inflammatory processes and induces the pre-condition for cancer development in prostate tissue[13]. In conditions of low estradiol levels, high testosterone can lead to hypertrophy and hyperplasia of the prostate[14]. Furthermore, it is known that in case of inhibition of the enzyme aromatase (that carries out the biochemical conversion of androgens into

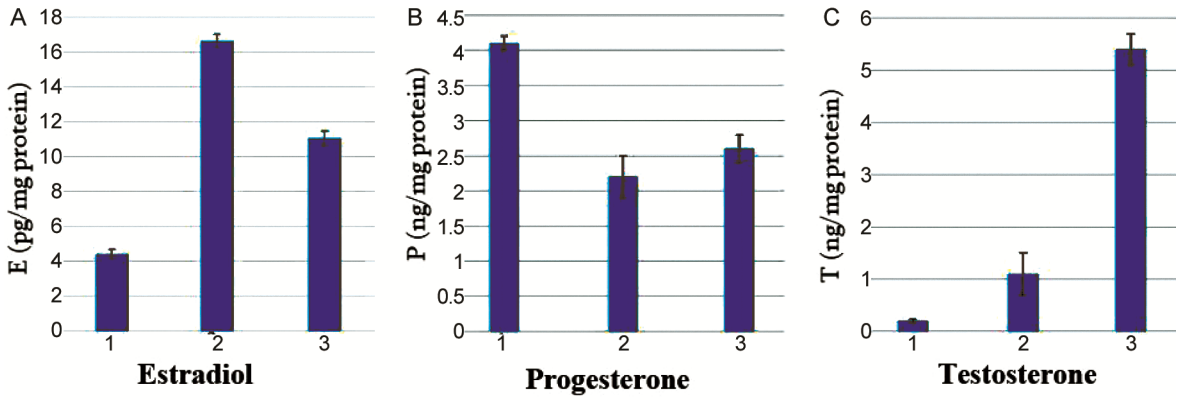

Fig. 1 — Alterations in the level of steroid hormones in prostate tumor tissue samples. 1. Control group[11]; 2. Benign prostatic hyperplasia (BPH); and 3. Prostate adenocarcinoma (PCa). n=15, number of patients in each study group; $P< 0.05$ between the groups; and the age range of the patients: 60-75 years

estrogens) the amount of estradiol decreases, and the level of testosterone increases. The activation of the mentioned enzyme caused the opposite effect[15]. As noted earlier, aromatase is an enzyme that produces estrogen from androgens; therefore, its aberrant expression plays a critical role in the development of prostate tumors[16]. The expression of aromatase in the stroma of benign tumor tissues is characteristic to prostate, while in case of malignant tumor, there is an induction in aromatase expression[16]. Accordingly, an increase in aromatase expression in benign tissue should lead to increased estradiol levels, that has already been confirmed by our previous studies[17].

Thus, a significant increase in the level of estradiol in the prostate tissue of men with benign hyperplasia compared to the control group (as well as compared to patients with malignant adenocarcinoma) can also be caused by an increase in the activity of the enzyme aromatase in response to the demand of benign tumor cells - to increase the amount of estradiol, unlike prostate malignant cells which mainly increase demand for androgens[12].

It is established that prostate normal, as well as tumor tissue, expresses both types of estrogen receptors (ER), *i.e*., estrogen receptor alpha (ER-α) and estrogen receptor beta (ER-β). The ER-α is mostly expressed in stromal cells and basal prostate epithelial cells, whereas ER-β is predominantly expressed in prostate epithelial cells, particularly luminal cells. Thus, they reveal different tissue localizations in prostate[13]. Since these two types of receptors differ in heterodimerization, as well as in activation and transactivation in response to estrogens, therefore their imbalance may determine the nature of the action of estrogens on prostate tumor cells[13,20].

It is established that in case of benign prostate tumor, ER-α receptor is upregulated in response to the increased amount of estradiol and contributes to cellular proliferation and inflammation. It has also been found to be upregulated in malignant epithelial prostate tissue that causes increased proliferation of tumorous cells. There are studies regarding high-grade prostatic intraepithelial neoplasia (HGPIN) indicating that ER-α protein and mRNA levels are upregulated, and its expression spreads from basal to luminal cells[18,19].

It is important to note that in case of prostate cancer cells, the ER-β receptors which exhibits anti-proliferative, anti-invasive, and pro-apoptotic effects is also activated, however its expression declines during the development of prostate cancer. It is supposed that ER-β inhibits cell proliferation directly or by inhibiting ER-α. Consequently, when the ER receptors are inhibited or partially lost in malignant cells, which allows these cells to progress and acquire malignant phenotype[18,20]. We therefore suggest that inhibition of the corresponding receptors or their lost reduces the demand of cancer cells for estrogens. In turn, this should lead to decreased levels of estrogens, particularly estradiol, in prostate adenocarcinoma compared to benign hyperplasia, which is confirmed by our experimental results (Fig. 1). Thus, the loss of ER-β gene expression may be considered as a prognostic risk factor for prostate cancer. However, the precise mechanism as to how *ESR2* is regulated in prostate cancer cells remains widely unknown[18].

Next, we investigated the quantitative alterations of progesterone in prostate tumor cells. Studies have shown that level of progesterone was decreased compared to control group in case of benign, as well as in malignant tumor. It should be noted that the quantitative change of progesterone differs slightly between benign and malignant tumors (Fig. 1).

There are controversial opinions regarding the role of progesterone in the development of prostate tumors. Some researchers report that progesterone reduces the uptake of androgens by prostate cancer cells, thus reducing their amounts in tumor tissue - it also inhibits androgen receptors and reduces their amounts in cancer cells[21]. In contrast, another group of researchers believe that using progesterone as anti-tumor hormone therapy increases the risk of developing hormone-resistant cancer, since it reveals oncogenic effects under some circumstances[22,23].

According to the recent data, prostate stromal cells contain three isoforms of progesterone receptor (PR): (*viz*., PRA, PRB, and PRC). The stromal PR is also known to play an important role in both normal development of prostate as well as in the development of tumor pathology[24]. It was initially assumed that PR suppresses cell proliferation by inhibiting the cell cycle pathways that contribute to the development of benign prostatic hyperplasia. In particular, there is an inhibition of the synthesis of tumor promoter cytokines such as interleukin-6 (IL-6) and stromal cell-derived factor 1 (SDF-1); also to inhibit the formation of reactive stroma (RStr) by inhibiting the trans-differentiation of stromal cells[25]. According to the data available currently, it is considered that

progesterone and its receptors prevent the cancerous transformation of the prostate[24]. Accordingly, in the benign and malignant tumors, reduced amount of progesterone should contribute to cell proliferation and progression, which is confirmed by our findings (Fig. 1).

As noted earlier, another representative of steroid hormones - testosterone (T) and its metabolites[26] play a vital role in prostate malignant transformation. Therefore, we studied the alteration of T level in prostate tumor tissues on the following stage. Our study showed an increased level of T as compared to the control group in case of benign as well as prostate malignant tissues. This increase was more pronounced in case of malignant tumor (~5-fold increase) (Fig. 1) as compared to a benign hyperplasia.

Prostate cancer is known to be closely related to the high levels of testosterone[27]. Moreover, high level of testosterone in prostate cancer cells positively correlates with the progression and metastasis of the pathology[27], which is also confirmed by our results[17]. The significant increase in testosterone levels in prostate adenocarcinoma compared to both control group and benign hyperplasia may be due to several factors. For example, inhibition of the enzyme aromatase in malignant cells probably led to excessive accumulation of unconverted T (as a substrate)[16]. Furthermore, these effects may have been caused by the heterogenity of androgen receptors[28].

Steroid hormones undergo significant quantitative changes during prostate malignant transformation, as development of given pathology is mainly conditioned by hormonal imbalances, which in turn, should contribute to the tumor growth, progression, and aggressiveness.

Next, we evaluated the changes in the activities of the enzymes involved in energy metabolism (*viz.*, hexokinase and m-aconitase). We also investigated the quantitative changes of citrate as the main metabolic product of prostate epithelial cells in prostate tumor tissues (Fig. 2).

We found that there was an increase in hexokinase activity in prostate tumor tissue in case of both benign (≈17 times) and malignant tumors (≈32 times) as compared to the control group[29] (Fig. 2). Notably, the activity of enzyme hexokinase was increased ~1.8 times in the malignant tumor tissue as compared to the benign tumor. It is known that hexokinase, as a glycolytic enzyme, is responsible to carry out the phosphorylation of glucose to convert it into glucose-6 phosphate[30].

oreover, the increased activity of hexokinase in case of benign and malignant prostate tumor tissues can be caused by different possible mechanisms. For instance, the tumor transformation requires an increase in energy consumption, which leads to the activation of certain metabolic pathways[6]. We hypothesize that the elevated hexokinase activity in prostate tumour tissue, both in benign and malignant tumors, as compared to the control subjects may be caused by the activation of energy metabolic pathways.

Additionally, it should be noted that the steroid hormones (e.g., estradiol and progesterone) significantly influence the hexokinase activity. These hormones affect enzyme's functions and causes increase in the activity of hexokinase[31]. Besides, the action of estrogens leads to the activation of the processes in the cell, which requires energy. Accordingly, in order to satisfy the mentioned energy requirement estrogens increase the expression of the gene that encodes for hexokinase and consequently, exspression of the enzyme[31]. We therefore suggest that in case of benign prostatic hyperplasia, a sharp increase in hexokinase activity (compared to control) may be

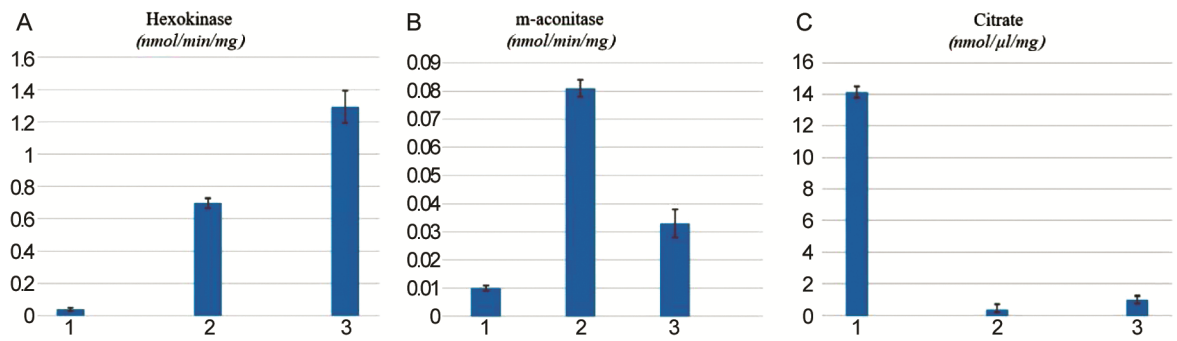

Fig. 2 — Alterations in the activities of hexokinase, m-aconitase and the amount of citrate in prostate tumor tissue samples. 1. Control group[29,34]; 2. Benign prostatic hyperplasia (BPH); and 3. Prostate adenocarcinoma (PCa). n=15, number of patients in each study group; $P< 0.05$ between the groups; and the age range of the patients: 60-75 years

caused by significant increase in estrogen level that is observed in our current study (Fig. 1).

Recent data suggest that malignant, progressive prostate cancer cells inhibit the oxidative phosphorylation pathway and return to the glycolytic pathway[30,32], which in turn, should lead to an increase in the activity of the initial enzyme of glycolysis (hexokinase), which is also confirmed by our results (Fig. 2).

Additionally, it is known that the enzyme hexokinase suppresses apoptosis in malignant tumor cells in a conditionally "mitochondrial" way[33]. Hexokinase binds to voltage-dependent channels on the mitochondrial membrane, preventing the release of apoptosis-inducing factors from the mitochondria, and finally inhibiting the apoptosis of tumor cells[33]. We presumed that in case of progressed adenocarcinoma, the increase in hexokinase activity may be due to the mentioned mechanism, inhibiting tumor cell apoptosis and promoting tumor progression.

Next, the changes in the activity of another enzyme (*viz.*, m-aconitase) and the quantitative change of its substrate (citrate) in the tumor tissues of men with benign prostatic hyperplasia and prostate adenocarcinoma were studied. We found that there was an increase in m-aconitase activity in the tumor tissues of men with both benign prostatic hyperplasia and prostate adenocarcinoma (Fig. 2). The tendency of increasement was more pronounced in case of benign hyperplasia. As for prostate adenocarcinoma, the activity of m-aconitase in malignant tumor tissue was increased by ~3.3-fold as compared to the control, although it was found to be decreased as compared to benign hyperplasia (~ 2.45-fold)[34] (Fig. 2).

Our study showed that in case of benign prostatic hyperplasia, the amount of citrate was sharply decreased (~22-fold) as compared to the control group, in parallel with significantly increased m-aconitase activity (Fig. 2). As for the malignant tumor tissue, under the conditions of decreased m-aconitase activity, the amount of free citrate was also decreased (~12 fold); but this change was not so drastic as in case of benign tumor (Fig. 2). It should be noted here that the amount of free citrate in malignant tumor tissue was ~1.8 times higher as compared with the same index of benign tumor tissue (Fig. 2).

It is known that m-aconitase is a Krebs cycle enzyme that oxidizes citrate and converts it to isocitrate[32]. As for citrate, it is produced in the mitochondrial matrix, and at a later stage, citrate can be converted in mitochondria in two different ways: i) it continues to be converted by Krebs cycle enzymes, and ii) it participates in the synthesis of fatty acids[8,32].

It is well-known that prostate cancer is a unique type of tumor in terms of its characteristic metabolic pathways or metabolic switches[8]. As mentioned earlier, normal prostate tissue satisfies its energy requirements through glycolysis, while during tumor transformation, it switches to oxidative phosphorylation[32]. However, recent investigations show that in case of progressing adenocarcinoma, it is common for cancer cells to return to the metabolic pathway of glycolysis[9]. We therefore assume that in our case, the observed changes in the benign and malignant tumor cells (*i.e.*, change in m-aconitase activity) should be due to the above mentioned factors. In addition, it is well known that re-programming of fatty acid biosynthesis occurs during prostate adenocarcinoma. Moreover, tumor cells need citrate to carry out mentioned metabolic switch[32].

Therefore, we suggest that reducing m-aconitase activity in malignant tumors increases the amount of citrate and its inclusion in the re-programmed biosynthesis of lipids. At the same time, an increase in the amount of citrate in malignant tumor cells is considered one of the prognostic markers of the disease progression and the formation of a hormone-resistant phenotype.

Conclusion

Based on the data obtained from our research, it can be concluded that: A) A significant change in the amount of steroid hormones in tumor tissue of men with prostate adenocarcinoma have a considerable influence on the unique metabolic reactions characteristic to prostate cancer, which should contribute to the progression and aggressiveness of the tumor; B) A significant alteration in the energy metabolism of prostate cancer was established, as revealed by the activation of oxidative phosphorylation in case of benign tumor. It is therefore implicated that in parallel to the progression of the disease, malignant prostate cells switch again to the increased glycolysis (*i.e.*, activation of glycolytic pathway).

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Conflict of interests

All authors declare no conflicts of interest.

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