Żak Klaudia, Niedobylski Sylwiusz, Leziak Milena, Maliszewska Karolina, Czapska Mirella, Skórzyńska-Dziduszko Katarzyna. Have thyroid hormones an impact on ovarian cancer? Journal of Education, Health and Sport. 2018;8(12):803-809. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.2537850
http://ojs.ukw.edu.pl/index.php/johs/article/view/6460
https://pbn.nauka.gov.pl/sedno-webapp/works/897265

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 20.12.2018. Revised: 20.12.2018. Accepted: 31.01.2018.

Have thyroid hormones an impact on ovarian cancer?

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Abstract

Thyroid hormones show not only genomic, but also nongenomic activity, which is related to specific membrane, cytoplasmic and organelle receptors. The best known receptors are located on the alpha-V-beta-3 integrin of cell membrane. Their stimulation results in an activation of mitogen-activated protein kinases (MAPKs) or

phosphoinositide 3-kinase (PI3K), which directly leads to an inhibition of apoptosis and increased proliferation of tumor cells, as well as promotes angiogenesis and metastasis formation. In ovarian cancer cells L-thyroxine is proven to be involved in MAPK activation as well as in the up-regulation of expression and enhanced cellular accumulation of programmed death ligand 1 (PD-L1), which results in an inhibition of neoplastic cells apoptosis.

Key words: thyroid hormones; ovarian cancer.

Introduction

Thyroid hormones (TH) have two different mechanisms of action: genomic and nongenomic. Triiodothyronine (T3), which is produced from conversion of prohormone L-thyroxine (T4), affects virtually every cell in the body by genomic mechanism, due to its high binding affinity to the nuclear thyroid hormone receptors (THRs) [1] One of the most important physiological effects of T3 is an increase in the production of enzymatic proteins, which leads to increased metabolism. In addition, T3 is involved in the regulation of growth and development processes, increased catecholamine effect, metabolism of glucose, breakdown of cholesterol and increase of the number of LDL receptors. The final effect of T3 action is an increase in oxygen consumption as well as an elevation of the cellular glucose level [2] In contrast, the nongenomic mechanism is exerted primarily by thyroxine that has the higher affinity to specific receptors. located in the cytoplasm, as well as on cellular membranes or mitochondrial membrane. One of the best known non-nuclear receptors is a receptor on the alpha-V-beta-3 integrin (αVβ3). Nongenomic mechanisms are involved in the proliferation of tumor cells, promotion of angiogenesis, formation of the actin

cytoskeleton and regulation of cell motility [3,4] This review is focused on nongenomic effect of the thyroid hormones action that is possibly related to the development and progression of ovarian cancer.

Nongenomic mechanism of thyroid hormones

Nongenomic action of thyroid hormones may be initiated by the plasma membrane or a cytoplasmatic receptor or receptors on mitochondrial membrane. The best known receptor is the one on the integrin αVβ3 on plasma membrane. As a result of interaction of T3 with the αVβ3 integrin receptor, PI3K is being activated which leads to proliferation of the neoplastic cells and inhibition of apoptosis [6] In comparison, the connection of T4 to receptors on the integrin αVβ3 makes MAPK activated - this is possible due to two enzymes: phospholipase C (PLC) or protein kinase C-α (PKC-α). One of the effects is nuclear receptor activation: estrogen receptor alpha (ERα) and thyroid hormone receptor beta 1 (TRβ1), and in consequence, altered transcriptional activity [4] Another action is modulation of the activity of the Na^+/H^+-antiporter or exchanger (sodium/hydrogen ion exchanger, NHE) [4] In comparison, the connection of T4 to receptors on the integrin αVβ3 makes MAPK activated - this is possible due to two enzymes: phospholipase C (PLC) or protein kinase C-α (PKC-α).

Moreover, TH can not only activate receptors on the αVβ3 integrin, but also they can influence on cytoplasmatic thyroid hormones receptors: TRα1 and TRβ1. Activation of the first one stimulates converting soluble actin into fibrous (F) and regulates cell motility, what is well-characterized in CNS cells [4,13] TRβ1, as TRα1, exists in the cytoplasm and is involved in transduction of the TH through a specific gene expression among others hypoxia-inducible factor 1A gene (HIF1A). Hypoxia inducible factor 1 (HIF1), encoded by HIF1A, regulates proliferation, angiogenesis and glucose transport [4,7] Generally angiogenesis is stimulated by expression of specific genes - the most important one is vascular endothelial growth factor (VEGF), which induces endothelial mitosis and migration.

In summary, thyroid hormones influence gene transcription, MAPK or PI3K activation, which finally results in tumor cell proliferation and angiogenesis.

Thyroid hormones in ovarian cancer

Ovarian cancer is a type of neoplasia, in which the majority of cases are not familial but sporadic. Only 5% to 10% of cases depend on family history [8] It is the reason why researchers are still investigating factors which can have impact on this neoplasia development and progression. There are a number of risk factors: childlessness , a prolonged period of ovulation caused by early first menstruation and late menopause, obesity, hormone replacement therapy, genetic factors: breast cancer-1 gene (BRCA-1) and breast cancer-2 gene (BRCA-2) abnormalities. In addition, the increase of ovarian cancer incidence and mortality in high-income countries is connected with an access to oral contraception among generations born after 1930 [9] Scientists also discovered significant nongenomic role of thyroid hormones in ovarian cancer.

The effect of thyroid hormones is exerted by stimulation of receptors located on the integrin αVβ3 on plasma membrane. In the oncogenesis of ovarian cancer the increased expression of receptors for T3 and T4 is observed [10, 11, 12] In consequence, intensification of tumor cell proliferation, uncontrolled cell growth, metastasis formation and enhanced process of angiogenesis can be seen. A stimulation of receptors activates MAPK and PI3K, which subsequently results in activation of the nuclear receptor TRβ. It is not the primary role of thyroid hormones, but overexpression of this specific receptor induces inhibition of proliferation of certain cells [13] In addition, thyroid hormones also increase expression of ERα, which is associated with the development of epithelial ovarian cancer. The consequence is an expression of basic fibroblast growth factor (bFGF). This could be the explanation why hyperthyroidism is linked with ovarian cancer. The other is hypoxia-inducible factor 1-alpha (HIF1-alpha), which was encoded by HIF1A gene. HIF-1 is known to induce transcription of more than 60 genes, including vascular endothelial growth factor (VEGF), thus it regulates biological processes such as angiogenesis, cell proliferation and cell survival [14] T3 can also stimulate inflammatory effects on ovarian surface epithelial cell due to its influence on genes associated with inflammation expression, including cyclooxygenase-2 (COX-2) and matrix metallopeptidase 9 (MMP9) [14]

The presence of thyroid hormones in ovarian cancer cells in vitro also changes the expression of genes regulating cell cycle and cancer cell apoptosis. The first example of this activity is the decrease of genes expression responsible for tumor suppressor protein: p12 and p16, which plays an important role in cell cycle regulation. The consequence is an inhibition of cancer cell apoptosis [11] The same result is achieved by increasing expression and accumulation of programmed death ligand 1 (PD-L1) [15]

Ovarian cancer has high metastatic potential, which is enhanced by Epithelial-Mesenchymal Transition (EMT). The EMT is a process in which cells lose cell-polarity and adhesion, they can disconnect and migrate to other parts of the body [16] In the conducted research, based on three ovarian cell models: OVAR-3 (type II - high grade serous ovarian tumors), SKOV-3 and A2780 (type I - low-grade tumors of different histology), nine EMT markers were examined. After that, the most important ones were selected: zeb-1, β-catenin, vimentin. The most significant was β-catenin, which regulated the transcription of several EMT markers. Moreover, it was hormonally induced more rapidly in the high-grade ovarian tumors. In addition, the transcription of e-cadherin can be inhibited by both T3 and T4, which in consequence means the loss of adhesion and metastases. In brief: the transcription of the mesenchymal markers: β-catenin, zeb-1, slug, vimentin, and n-cadherin was hardly affected by thyroid hormones, but the epithelial markers: e-cadherin and zo-1 were inhibited. It is a new role of T3 and T4 by αvβ3 integrin in EMT, which gets connected in ovarian cancer metastases [17]

The next research in witch 11 studies from the Ovarian Cancer Association Consortium are pooled shows the association between hyper- and hypothyroidism and medications prescribed for these conditions with 5-year all-cause survival with invasive ovarian cancer. Hazard Ratio (HR) without hyper- or hypothyroidism is 1.00, while juxtaposed with any history of hyperthyroidism is HR= 1.22. What can be seen is the diversity of timing duration of hyperthyroidism: if the hyperthyroidism dures more than 5 years, HR will be 1.07, but if the hyperthyroidism dures 5 years or less than 5 years, then HR=1.97. The hypothyroidism, however changes HR to 1.16. What is very important is that hyperthyroid medications decrease HR to 0.69, that is why

early treatment could mitigate the risk of developing ovarian cancer. In the same research the association of mortality and history of hyperthyroidism and mortality was examined - HR=1.22. In conclusion, the most high Hazard Ratio is with untreated hyperthyroidism, which lasts for less than 5 years [18]

Conclusion

Summarizing, thyroid hormones are very important in pathogenesis of ovarian cancer. T3 and T4 stimulate the receptors on the αVβ3 integrin and activate MAPK and PI3K, which has a number of consequences including . an increased expression of TRβ, ERα, basic fibroblast growth factor, p12, p16, PD-L1, dysregulation of cell cycle, and induction of cancer-related local inflammation. In addition, HT can modify the activity of Epithelial-Mesenchymal Transition.. The highest Hazard Ratio is observed in hyperthyroidism during less than 5 years, that is why exists necessity to take medicament in order to decrease HR. Generally, thyroid hormones affect different mechanisms involved in oncogenesis, including cell proliferation, angiogenesis, and metastasis formation.

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