Leziak Milena, Niedobylski Sylwiusz, Żak Klaudia, Skórzyńska-Dziduszko Katarzyna, Krasowska Danuta. Prolactin – friendly lactation hormone or hostile cancerogenic factor? Journal of Education, Health and Sport. 2019;9(9):247-252. eISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3401873
http://ojs.ukw.edu.pl/index.php/johs/article/view/7390

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 25.08.2019. Revised: 30.08.2019. Accepted: 07.09.2019.

Prolactin – friendly lactation hormone or hostile cancerogenic factor?

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Abstract

Prolactin is a hormone secreted by lactotrophic cells of the pituitary gland and its main function is stimulating lactation. Binding prolactin by its membrane receptor leads to the activation of signalling pathway that enables cell proliferation and differentiation. Due to this mechanism, the potential oncogenic role of the hormone is of great interest. Prolactin and its receptor have many forms and a complicated signalling pathway, that is why defining prolactin's specific role in cancerogenesis is difficult and poses a serious challenge. Researches also indicate an important role of extra-pituitary prolactin synthesised in many

other tissues in the process of cancerogenesis. This article focuses on connection between prolactin and breast cancer, as it is the most common cancer in women. In several studies, prolactin and its receptor were significantly associated with an increased breast cancer risk. Recent research papers focus also on the treatment of breast cancer, using knowledge about prolactin and its role in the development of the tumour.

Key words: prolactin; breast cancer;

Prolactin and its function

Prolactin (PRL) is a hormone produced by lactotrophic cells of the anterior pituitary. It is composed of 198 amino acids. In post-translational processing, prolactin may take different forms and it may also aggregate. Prolactin isoforms, of different molecular mass, are classified as monomers (mPRL -23 kDa), big PRL (bPRL – 45-60 kDa) and macroprolactin (bbPRL > 100 kDa). The mPRL isoform is usually prevalent, consisting 80% of all isoforms. (1). The mPRL is cleaved into 8 and 16-kDa forms, while the second variant exhibits an antiangiogenic activity (2).

Prolactin stimulates lactation. During pregnancy its concentration significantly increases, preparing the mammary gland for lactation. During the foetal period and in the first months of the newborn's life, prolactin concentration is physiologically very high. It has been observed that prolactin level increases during sleep. Moreover, PRL concentration also increases after stress, physical activity, injuries or surgical intervention (especially in the chest region), myocardial infarction or after nipple irritation (1).

Prolactin secretion is controlled by hypothalamic factors. The predominant control is negative regulation mediated by dopamine. As a result, any damage to the infundibulum that connects the hypothalamus and the pituitary gland such as trauma or tumor will increase PRL secretion. Dopamine antagonists and psychotropic drugs also stimulate PRL secretion, decreasing the activity of the pituitary tuberoinfundibular dopaminergic system. (3,4)

Prolactin receptor

The prolactin receptor (PRLR) has the structure of cytokine class-1 receptors. Receptors of this type share a common structure, consisting of an extracellular domain, transmembrane domain and an intracellular domain. The receptor chains are already dimerized in the absence of ligand. The intracellular chain has different domains, which interact with different signaling pathway members. It leads to regulation of cell differentiation, proliferation,

survival, cell's skeleton or the overall function or activity of PRLR signaling (negative regulation)(5).

Several forms of the human prolactin receptor have been identified. There are three major isoforms (long - LF; short 1a and 1b - SF1a and SF1b, respectively) which are regulated by PRL itself. LF signals for many functions including growth and differentiation, whereas SF1a and SF1b act as dominant-negatives for differentiation (6). A low ratio of short-to-long form of the PRLR was associated with cancerous breast tissue rather than normal matching breast tissue, indicating that the reduction in dominant negative regulation may result in unrestrained PRLR signaling in cancerous breast tissue (7). In addition to the membrane anchored prolactin receptors variants there is a soluble isoform (prolactin receptor binding protein - PRLRBP) that is generated by proteolytic cleavage of membrane bound prolactin receptor (8).

The presence of these different types of PRLR creates difficulty in determining the exact function and signalling pathway. It is clear that also the cellular context and microenvironment play a crucial role in selection or predominance of a specific pathway.

Extrapituitary prolactin

Lactotrophic cells constitute about 20% of the functional cells of the anterior pituitary gland, but it is not the only place where prolactin is synthesized. The first data about extrapituitary origin of prolactin dates from 1986, when the patients after hypophysectomy showed normal prolactin concentration in CSF (9). In this study, as a potential source of PRL, the neurons of CNS and tuberal adenyhypophysial cells were indicated. In 1996, a review of extrapituitary prolactin (ePRL) was published, in which the reproductive system (ovaries, placenta, decidua, mammary glands, testes, prostate gland), nervous system (brain, spinal cord), lungs, cardiac muscle, immune system (thyroid, bone marrow, tonsils, lymph nodes, spleen), skin, adipose tissue, kidneys and lacrimal and sweat glands were also indicated as the place where the prolactin is produced (10). Recently discovered ePRL production sites are hair follicles and the inner ear.

Further studies showed differences in regulation and functioning of ePRL compared to prolactin produced by the pituitary gland (pPRL), while the structure and the receptor for both versions of the hormone were found to be the same (11).

Prolactin and breast cancer

Prolactin has for long been connected with galactorhhoea and infertility in women. Since its well-known function is promoting cell growth and proliferation and its expression has been discovered in many other than pituitary gland tissues, prolactin is considered to have an impact on cancerogenesis. The connection between prolactin and cancer has been suspected for many years, but never conclusively proven. Recent research has underlined the role of PRL and PRLR in breast and prostate cancer most importantly, but in a variety of other cancers as well (12).

Breast cancer is the most common cancer in women. It is also the second leading cause of cancer death in women. This is the reason why searching for factors causing it and also the means of counteraction are so crucial. Recent studies have brought to fore, a few critical

concepts regarding the role of PRL in breast cancer. First of all, even high-normal circulating levels of PRL increase breast cancer risk. Secondly, locally produced prolactin acts as an autocrine/paracrine factor in breast cancer evolution. What is more, a causal relationship between prolactin receptor expression and breast cancer has also been recognized (12).

In several studies, high PRL levels were significantly associated with increased breast cancer risk. In a pooled analysis of three studies, higher plasma prolactin concentration prior to diagnosis was associated with the higher risk of cancerogenesis. The risk did not vary by menopausal status (13). Further study showed that this association is also observed after diagnosis of breast cancer and it is most importantly observed within 10 years of diagnosis. This indicates that prolactin has a role in tumor development once a preclinical lesion has been established (14).

High levels of prolactin may be induced as a side effect by antipsychotics. These drugs activate JAK-STAT5 signalling pathway, which induces cell differentiation and suppresses apoptosis. Research revealed that some hyperprolactinemia-inducing antipsychotic drugs may prompt precancerous lesions to progress to breast cancer. The same study showed that inhibitors of this signalling pathway prevent from early lesion progression and may be used as chemoprevention regime in women who have or likely have already developed precancerous lesions while also requiring hyperprolactinemia-inducing antipsychotics (15).

As extra-pituitary prolactin produced in breast tissue is claimed to increase the risk of breast cancer formation, lowering its level or neutralizing it could provide a good form of therapy. The local production of prolactin cannot be controlled by conventional dopamine agonists that act at the pituitary level. Autocrine prolactin in breast cancer cell lines can be antagonized by prolactin-neutralizing antibodies (16).

Studies showed that breast tumors express higher levels of PRLR when compared to healthy tissue (17). Also impaired turnover of the prolactin receptor in breast cancer cells results in accelerated proliferation and increased invasive growth (18). This has very important implication in chemotherapy of breast cancer. The possible way of treatment is to block the PRLR rather than target the action of prolactin itself.

Another mechanism of cancerogenic effect of PRL which is plausible, is inhibition of the tumor suppressive function of BRCA1. PRL activates STAT5, which results in formation of a complex with BRCA1. This complex binds to the p21 promoter in the nucleus, but cannot activate it. As a result the function of BRCA1 as a tumor suppressor is compromised (19).

What is more, recent research has indicated significant interaction between estrogen and prolactin systems. Estrogen stimulates prolactin secretion and can also up-regulate human prolactin receptor gene expression and stimulate tumorigenesis (20). PRL has also been shown to exert some of its effects on mammary tumor cells by stimulating the estrogen receptor. On the other hand, hyperprolactinemia results in hypogonadism, which suppresses the ovarian reproductive cycle, and reduces estrogen. Due to complex interactions between PRL and estrogen pathways, more studies are required.

Conclusion

Prolactin has always been considered as a lactation promoting hormone. Recently, some new functions of prolactin have been revealed. It's clear that it plays an important role in cancerogenesis, especially in breast cancer, which is the most common cancer in women. Due to many forms of PRL and PRLR and it's complicated signalling pathway, defining prolactin's specific role in cancerogenesis is an important challenge. Unraveling these unknown factors will help define the therapeutic targets in the future.

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