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Review

The controversial role of human chorionic gonadotropin in the development of breast cancer and other types of tumors

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ABSTRACT

Introduction: Breast cancer is the most often diagnosed tumor of women and one of the leading cause of cancer related death. Due to different known risk factors there are epidemiological differences. Beside genetic disorders and patient's age it is especially the age of the first full-term pregnancy and in this context the pregnancy hormone human chorionic gonadotropin that seems to play an important role.
Methods: This review is based on a PubMed research in publications of the last 20 years. Only articles in English language were considered.
Results: The effect of human chorionic gonadotropin on development of cancer is controversial. In fact, for breast cancer there is evidence that this hormone has a protective effect against tumorigenesis due the differentiation of the mammary tissue after a full term pregnancy through the downregulation of estrogen receptors.
Conclusion: Human chorionic gonadotropin has among promoting pregnancy important controversial functions especially in tumor development. The mechanisms that explain the pro- and anti-carcinogenic effects are not fully understood yet. It seems to have a protective effect on breast cancer through increasing differentiation and hereby decreasing susceptibility of the mammary tissue for toxicants. This knowledge might help developing a preventive agent in the next future that uses the anti-carcinogenic effect of human chorionic gonadotropin and thereby decrease the mortality out of breast cancer.

Introduction

Breast cancer

Breast cancer is the most diagnosed malignant tumor and the leading cause of cancer related death of women [1]. In 2012 there were about 1.7 million cases worldwide and about 522 thousand patients died because of this disease [1]. The World Health Organization estimates that the annual death toll will increase further over the next twenty years [2]. Today the five year survival rate is about 89% [3]. The molecular mechanism of breast cancer development is not yet known although diverse risk factors have been identified.

The most popular risk factors are patient's age, family history of breast cancer, early menarche, late menopause, high body mass index, socioeconomic status, ethnicity and a genetic predisposition for breast cancer [4]. The reproductive history has an influence on the development of breast cancer too [4]. Especially a younger age at first full-term pregnancy and a greater number of pregnancies seem to have a protective effect for the development of this malignancy [3,5]. Clinical trials in the past could show that primiparous women younger than 25 years of age with elevated levels of hCG during the first months of pregnancy have a significant decrease in risk of developing breast cancer after the age of 50 [6]. The relationship between breast cancer and pregnancy is very complex and not fully understood yet. Some authors observed that certain perinatal factors as pre-term birth, infant birth weight, pre-eclampsia and multifetal gestation are associated with maternal breast cancer risk. The pattern of these associations offers indirect support for a role of gestational hormones, and

Abbreviations: Lob, lobules; NGF, nerve growth factor; TGFβ, transforming growth factor β; PCNA, proliferating cell nuclear antigen; PDGF-B, platelet-derived growth factor.

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particularly gestational estrogens, in the etiology of breast cancer among young women [7]. The aim of this review is to describe the function of hCG on the development of breast cancer and other type of tumors.

Function and structure of human chorionic gonadotropin

Human chorionic gonadotropin is a pregnancy hormone which is a complex glycoprotein with a molecular mass of about 37 kDa, composed of two glycosylated subunits [8–11]. It is produced in placental syncytiotrophoblasts and in a large number of different tumors [12].

Like the pituitary gonadotropins LH (luteinizing hormone), FSH (follicle-stimulating hormone) and TSH (thyroid-stimulating hormone) hCG is also a member of the glycoprotein hormone family [10]. It is a heterodimer and composed of an alpha-subunit, which is characteristical for the glycoprotein family and a target specific β-subunit [5,10].

The two subunits of the holo-hormone are encoded by several independent genes and combine to form the biologically active hCG molecule [13]. This holo-hormone is composed of an α- and a β-subunit and is expressed mainly in the combination of pregnancy and trophoblastic tumors [14]. It is proven that only this combination shows gonadotrophic activity [9]. In non-trophoblastic tumors the β-subunit is usually expressed alone [14].

The common alpha-subunit contains 92 amino acids and has two N-glycosylation sites [11]. The alpha-subunit of hCG is identical to the alpha-subunits of LH, FSH and TSH [11,15,16].

In contrast the β-subunit is specific for the hCG and confers biological activity [16]. The β-subunit contains 145 amino acids and has two N-glycosylation sites and four sites of O-glycosylation [11]. The structure and function of hCG and LH are very similar [17]. They show a very high homology of about 80% [16]. These two hormones exert their effects usually trough a common hCG/luteinizing hormone receptor [17,18].

There are five major isoforms of hCG known [19]. These are hCG, sulfated hCG, hyperglycosylated hCG, hCG free β-subunit and hyperglycosylated hCG free β-subunit [19]. All of them have their own function although they have the identical amino acid sequence [19].

The two isoforms hyperglycosylated hCG and hCG free β-subunit, which are involved in carcinogenesis, are also binding and antagonizing TGFβ (transforming growth factor β) receptor on the cells that also build these isoforms [19]. That might be responsible for the carcinogenic effect.

One of the most often described functions of hCG is its role in pregnancy. Human chorionic gonadotropin is the first hormonal sign from the trophoblast towards the mother [11]. It is the essential hormone to maintain pregnancy. It controls the implantation of the pregnancy and the development of the placenta [8]. Through the influence of hCG there is a transformation of cyclic ovary corpus luteum to gravid corpus, which in turn obtain the concentration of progesterone and estradiol in the first weeks of pregnancy [11]. The isoform responsible for the pregnancy implantation and placental development is hyperglycosylated hCG [19].

As already described does hCG and LH act trough an common hCG/luteinizing hormone receptor [17,18]. On cellular level hCG binds to the G-protein coupled membrane receptor (hCG/luteinizing hormone (LH) receptor) at the cell plasma membrane and stimulates an adenylate cyclase on the internal membrane resulting in a conversion of adenosine trisphosphate (ATP) into cyclic adenosine monophosphate (cAMP) [10,20]. Cyclic adenosine monophosphate mediates then the hormonal effects [10,20].

Methods

This review is based on publications derived from a PubMed based pursuit of scientific literature in the last 20 years. Only publications in English language were considered. Relevant keywords were used individually and in combination: breast cancer, risk factors, human chorionic gonadotropin (hCG), pregnancy, LH/hCG receptor, hormones and breast cancer, estrogen, cancer statistics, hCG vaccines, TGFβ.

Results

The effect of hCG on tumor development

There are several types of malignancies including bladder carcinoma, lung cancer, colorectal carcinoma, prostate cancer, gastric carcinomas and different gynecological cancers like breast cancer, cervical carcinoma, vulva/vaginal cancer which express hCG or its subunits ectopically [21].

The procarcinogenic and anticarcinogenic effects are discussed controversially and are not fully understood yet.

In breast cancer it has been suggested that beta-HCG/LH receptor may be selectively upregulated in invasive tumor components, increasing sensitivity of ductal cells to hormones that target b-HCG/LH-R thus favoring mammary carcinogenesis.

Past studies on trophoblastic choriocarcinomas showed that the neoplastic tumor cells produce hyperglycosylated hCG [19]. They also demonstrated that the hyperglycosylated hCG in turn is responsible for the promotion of tumor growth and invasion [19]. In accordance with this assumption experiments with antibodies against hyperglycosylated hCG showed an entire suppression of choriocarcinoma cell growth [19]. The stimulating effect of tumor cell growth has also been shown for the hCG free β-subunit for bladder and endometrial cancer [19].

Not all tumors of a specific cancer type usually express hCG. For example bladder cancer is known as one of the cancer types that express hCG free β-subunit ectopically [14]. However this molecule is detected in only 35% of patients with this type of cancer [14]. So there seem to exist subgroups under this aspect. The subgroups which express hCG unfortunately correlate with an increasing risk for metastases and worse prognosis [14,22]. The more aggressive course of tumors which express hCG free β-subunit is not only proven in bladder cancer [23]. This characteristic is also shown in colorectal, pancreatic and renal cancer [23].

There are several theories, which try to explain the procarcinogenic effect of hCG. Some authors suppose that hCG free β-subunit and hyperglycosylated hCG antagonize the TGFβ receptor, which then leads to an antiapoptotic and proliferative effect [19]. Other research focused more on the invasive behavior from tumor cells in connection with hCG [22]. They were able to show a different adhesiveness, migratory and the invasive ability from tumor cells from prostate cancer which are affected by hCG free β-subunit [22]. These different behaviors of tumor cells could be one explanation for the increased metastatic potential of hCGβ positive tumors [22].

In context of the development of cancer and human chorionic gonadotropin other studies focus more on the structure of oligosaccharide which is found in hCG [24]. They were able to prove that the structure of the oligosaccharides differs depending on the source of hCG [24]. Accordingly there is a difference in the oligosaccharide structure of hCG that is purified from the urine of pregnant women to hCG form patients with hCG expressing cancers [24]. Furthermore an interesting study from 2003 concentrated on the expression of the sialyl Lewis carbohydrate epitopes on hCG from different sources [24]. The sialyl Lewis carbohydrate