BRIEF COMMUNICATION

Follicle Stimulating Hormone Receptor (FSHR) Gene and Postmenopausal Epithelial Ovarian Cancer (EOC)

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Abstract

Objective: Follicle stimulating hormone receptor (FSHR) is expressed not only in granulosa cells of ovary but also in ovarian surface epithelium (OSE) and in benign and malignant epithelial ovarian tumors. The significance of this expression has remained unexplained so far. This transmembrane receptor is involved in G protein linked signal transduction and causation of neo-plasia. These findings have lead us to critically assess the mutation and single neucleotide polymorphism (SNP) of FSHR gene by an extensive search of concerned literature.

Materials and Methods: A systematic review of reports from Medline/Pubmed was performed from May 2005 to May 2006 on the mutation of FSHR gene, their significance in OSE and ovarian cancer. Many reports were collected from journals and additional reports were perused from the reference lists of retrieved articles.

Results: Expression of FSHR in OSE is a comparatively new finding. Some have found mutation in FSHR in granulosa cell tumor and one team could not find any in epithelium ovarian cancer. But SNP, though studied extensively in relation to infertility of various reasons, has not been looked into in such cancers except by a single group of pathologists from Hong Kong.

Keywords: follicle stimulating hormone receptor (FSHR) gene, point mutation, single neucleotide polymorphism (SNP), ovarian surface epithelium (OSE), epithelial ovarian cancer (EOC), sex cord-stromal tumors

Özet

Postmenopozal Epitelyal Over Kanserinde Folikül Stimülan Hormon Reseptör Geni

Amaç: Folikül stimülan hormon reseptör geni (FSHR), overde granüloza hücreleri yanında, over yüzey epitelinde ve benign-malign epitelyal over tümörlerinde eksprese edilmektedir. Bu ekspresyonun sebebi henüz tam olarak bilinmemektedir. Bu transmembran reseptör hücresel sinyal iletimi ve neoplazilerin gelişiminde etkisi olduğu bilinen G proteinleri ile bağlantılıdır. Tüm bu bilgiler, FSHR genindeki mutasyon ve tek nükleotid polimorfizmini literatürü tarayarak araştırmamıza yönlendirdi.

Materyal ve Metot: Mayıs 2005 ile Mayıs 2006 tarihleri arasında FSHR geni, over yüzey epiteli ve kanserindeki önemi Medline/Pubmed içinde sistematik olarak araştırıldı. Konu ile ilgili birçok makale ve bunların kaynaklarında yer alan yayınlara ulaşıldı.

Sonuçlar: Folikül stimülan hormon reseptör geninin over yüzey epitelinde ekspresyonu nispeten yeni bir bulgudur. Bazı araştırmacılar granüloza hücre tümöründe FSHR geninde mutasyon saptarken, bazıları da epitelyal over kanserlerinde herhangi bir bozukluk saptayamamışlardır. Ancak, infertilite ve değişik birçok sebepten dolayı yoğun ilgi odağı olan tek gen polimorfizmi, Hong Kong'daki bir patoloji grubu haricinde epitelyal over kanserinde yeterince araştırılmamıştır.

Anahtar sözcükler: folikül stimülan hormon reseptör geni, nokta mutasyon, tek nükleotid polimorfizmi, over yüzey epiteli, epitelyal over kanseri, seks kord stromal tümörler

Introduction

Gonadotrophin and receptors in epithelial ovarian cancer

A number of *in vivo* and *in vitro* studies have supported the suggestion by Biskind and Biskind (1), that elevated gonadotrophin concentrations may contribute to the development of malignant ovarian tumours. The highest incidence of ovarian cancer, most of which are of epithelial variety, thus occurs in the postmenopausal period, when gonadotrophin concentrations are high in the blood, due to the lack of feedback from ovarian steroid hormones (2-5).

Zheng et al. (6) found FSHR in normal ovarian surface epithelium (OSE). Later it was found in benign and malignant epithelial ovarian tissue (7-10). LHR could also be detected in benign and malignant ovarian epithelial tissue (7,11). Though regulation of gonadotrophin stimulation is poorly

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understood in humans, it seems likely that FSHR and LHR act synergistically and play a pivotal role not only in human reproductive physiology but in precipitation of epithelial ovarian cancer as well (9). By G protein linked signal transduction, this FSHR is capable of neoplastic transformation in OSE. That is why it has gained much importance in recent years (12).

Fallacy of serum FSH

Suppression of endogenous gonadotrophin has no effect in poorly differentiated late stage ovarian cancer (13). Hence, many (14,15) have challenged the gonadotrophin theory. But before we can come to any such conclusion it will be convenient to see the relationship of ovarian cancer with hypothalamo pituitary ovarian (HPO) axis. Jan Blaakaer et al. (16), and more recently others (17,18), have detected quite interesting, selective and significant lowering of serum FSH concentrations in post-menopausal patients with epithelial ovarian cancer. LH was not disturbed in those studies. Helzlsouer et al. (19) has shown that this lowering of FSH even predates ovarian cancer. There is no consistent report of either human chorionic gonadotrophin (HCG) stimulation or oestradiol/androstenedione negative feedback to explain the significant lowering of FSH, while luteinizing hormone (LH) should remain unchanged. Central depression of gonadotrophin release by the dopaminergic system as a cause is ruled out, due to the fact that thyroid stimulating hormone (TSH) or prolactin remains unaffected, as shown by a previous study. Biologically active dimeric inhibin A may reduce FSH concentration. However, in serous epithelial ovarian cancer, which is the most common ovarian malignancy, inhibin A was not found to be high (20,21). Expression of FSHR in OSE and EOC and lowering of FSH in postmenopausal EOC may have some common cause and these may have a more important role to play than LH/LHR.

FSHR mutation

FSHR may precipitate malignancy in OSE if its amount in those cells are sufficiently high or if it probably crosses a threshold. It may also cause cancer if it is mutated or at least if there is single neucleotide polymorphism (SNP). While nerve growth factor (22) could be responsible for such aberrant expression of FSHR and lowering of serum FSH, there could be concomitant SNP involved in FSHR gene as well. This eventually could precipitate cancer and may also be responsible for low FSH level. Hence, it is worth to take a look in FSHR gene and its mutations in such tumor.

Materials and Methods

A systematic review of reports from Medline/Pubmed was performed from May 2005 to May 2006 on the mutation of FSHR gene, their significance in OSE and ovarian cancer. Many reports were collected from journal and additional reports were perused from the reference lists of retrieved articles.

Results

Mutations affecting gonadotropin genes are extremely rare, but recent genetic studies have revealed that the pathogenesis of subfertility or infertility can be due to mutations in the FSH receptor (FSHR) gene. While mutations affecting FSHR are sporadic, polymorphism of the FSHR gene seems to be a common phenomenon. To date, six inactivating and only one activating mutation have been detected in the FSHR gene (23). Mutations in the FSHR gene could severely affect gametogenesis and result in infertility. Therefore screening programs have been initiated, in which patients with disturbed fertility were searched for mutations in the FSHR gene. Several Finnish families were identified displaying an inherited pattern of ovarian dysgenesis, a disease leading to streaky underdeveloped ovaries and primary amenorrhea. By genetic linkage the locus of the genetic defect was confined to chromosome 2p21. Analysis of the FSHR gene resulted in the identification of a mutation (Ala189Val) homozygous in all affected females. Functional studies revealed that the mutation affects the proper protein folding and thereby inactivates the receptor. In a male patient hypophysectomized because of a pituitary tumor, who despite undetectable serum gonadotropins had normal semen parameters, scientists hypothesized an activating mutation of the FSHR. Screening of exon ten of the FSHR gene resulted in the identification of an Asp567Gly transition in the third intracytoplasmatic loop. Functional studies resulted in a 1.5-fold increase in basal cAMP production compared to wild type FSHR, indicating that the heterozygous mutation leads to a ligand-independent constitutive activation of the FSHR. This patient provides an exceptional model of nature defining the role of FSH in human spermatogenesis (24,25). Mutations of the FSHR might have differential effects in each gender. For example activating mutations have not been described in women; therefore it is not clear whether the constitutive activity of the receptor could disturb normal follicular development resulting in certain infertility.

Ichikawa et al. (26) examined point mutations in these genes in various types of ovarian tumors. Although the results suggest that somatic mutational activation may not be crucial for ovarian tumorigenesis, this analysis was performed on only a limited number of tumors and cell lines, and on limited gene loci. Kotlar et al. (27) hypothesized that mutations in the FSH receptor (FSHR) might occur in sex cord-stromal tumors originating from steroid-producing cells of the ovary found with high prevalence of the F591S mutation in the FSHR. Activating mutations of the FSH receptor observed in male fertility and in certain ovarian tumours result in hypersecretion of oestrogens (23) (Beck-Peccoz et al. 1998). Fuller et al. (28) failed to identify activating mutations of the FSH receptor in 15 granulosa cell tumors and argued against a role for the FSH receptor in tumorigenesis. But after Ichikawa this experiment has not been repeated on postmenopausal epithelial cancer patients.

Overall, the FSHR gene encodes 695 amino acids. The transmembrane domain of FSHR has 70% similarity in sequence homology with thyroid stimulating hormone receptor (TSHR) and LHR (29). A core promoter spanning 225 bp, which represents a TATA-less promoter with no evident regulatory elements beside an E-box (30), as its prime mover. The C-terminal part of the extracellular domain, the transmembrane domain, and intracellular domain are encoded by exon 10 whereas exons 1 to 9 encode the extracellular domain (31). The SNP in core promoter region at position -29 results in a G toA exchange in a potential GGAA binding domain for an E-twenty-six specific transcription factor and occurs in about 30% of the subjects (32). Other two SNPs are found in exon 10 at nucleotide positions 919 and 2039 (numbered according to the translation start codon with ATG as ''1'') corresponding to amino acid positions 307 and 680 of the mature protein (33). Polymorphisms within exon 10 cause two major, almost equally common allelic variants in the Caucasian population: Thr307-Asn680 and Ala307-Ser680 (32,33). Some studies in normal and infertile men and women revealed no difference (33-35), whereas other investigations found significant differences in the distribution of allelic variants between patients and controls (36,37), suggesting that ethnic differences could be involved. The FSHR polymorphism at position 680 in exon 10 influences serum FSH levels and the sensitivity of the FSHR to FSH stimulation *in vivo*. In women with normal ovarian function undergoing controlled ovarian hyperstimulation for *in vitro* fertilization/intracytoplasmic sperm injection, researchers showed that basal FSH levels and the amount of FSH for ovarian stimulation depended on FSHR genotype. Women homozygous for Ser at position 680 had higher FSH levels and needed more FSH compared to women with homozygous Asn680 (38,39). This suggests that the FSH receptor genotype can influence the ovarian response to FSH stimulation. It is shown that 680 variant occurs significantly more often in women that develop iatrogenic ovarian hyperstimulation syndrome (OHSS) but that the Asn680 variant is associated with the severity of OHSS. Hence, it seemed probable that 307Ala and 680Ser could some how be related to epithelial ovarian cancer.

In fact, there is already one experiment relating SNP with ovarian cancer. While 307Ala and 680Ser carriers were associated with significantly increased risk of developing serous and mucinous types of ovarian cancers but not endometrioid and clear cell types, the two SNPs were found to be in modest linkage disequilibrium for the cancer and control groups respectively (40,41). The major haplotype of 307Ala-680Ser was also associated with higher cancer risk, especially for the serous and mucinous carcinomas.

However, the FSHR polymorphism at position 680 showed no effect on serum FSH levels and other clinical parameters in men (32,42). This discrepancy between the two genders remains unexplained.

Discussion

To this date, no attempt has been made to detect SNP in promoter region or in exon 10 of FSHR gene in women with postmenopausal epithelial ovarian cancer except a team of pathologist from Hong Kong University. They have seen somatic mutation in archival tissue and have not seen germline mutation from blood. They were able to detect significantly more somatic SNP in those ovarian cancer tissues. But they opined that such understanding may be important in selecting patients for ovulation induction therapy. However, this may have enormous implication in determining neoplastic pathways in such cancers and may pave the way to find a remedy and a method of intervention with such cancers. Hence, more work is warranted on the subject.

At this stage it is not clear how FSHR is expressed by the OSE, but the search for SNP in germline may clarify the role and significance of FSHR in relation to epithelial ovarian cancer and may even explain significant lowering of serum FSH level in such cases.

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