

ORIGINAL ARTICLE

Follicle-stimulating hormone receptors: a new immunohistochemical marker in cancers?

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Summary

Purpose: Follicle-stimulating hormone receptors (FSHR) have been reported in ovarian cancer and prostate cancer cells, but recent studies have highlighted their presence in the endothelium of blood vessels belonging to multiple neoplasias. Current research attempts to determine the role of FSHR in neoplastic proliferation and possible therapeutic or diagnostic implications. This paper aimed to analyze articles that have revealed the presence and/or role of FSHR in various neoplasms in humans.

Methods: After performing an extensive search of MEDLINE/PubMed using MeSH terms "follicle-stimulating hormone receptors" and "cancer", 22 original articles were found relevant for the subject proposed for analysis.

Results: FSHR were found in all neoplasms studied, being present in both tumor cells and endothelial cells of intra- and perineoplastic blood vessels. Although, the presence of these receptors seemed to be ubiquitous, conclusion and the exact role of these receptors could not be stated due to heterogeneous nature of the existing studies.

Conclusions: Although extensive research studies are needed in order to elucidate the exact role of FSHRs and their utility in clinical practice, joint efforts in studying their implication in neoplastic processes can lead to the use of new diagnostic and therapeutic strategies for cancer patients.

Key words: cancer, follicle-stimulating hormone receptor

Introduction

Cancer has become a pathological condition more and more common for clinicians in the current practice of recent decades. Malignancies are one of the leading causes of global morbidity and mortality with over 100 types of cancers and over 8 million deaths in 2012, accounting for about 14% of all deaths worldwide. It is estimated that the number of cancer cases will increase by about 70% over the next 20 years [1]. Thus, cancer as a major impactor on global public health and implicitly on material resources, has become one of the main concerns in the field of screening, prevention, diagnosis, monitoring and treatment in current medicine.

One of the main directions of current medical research is the discovery and study of tumor markers. These are represented by different molecules of the body that may behave differently under the influence of certain neoplastic stimuli. Studying and identifying new tumor markers may lead to the use of new therapeutic and diagnostic strategies for better management of cancer patients.

Studies in the last two decades have highlighted the presence of follicle-stimulating hormone (FSH) and FSHR in some neoplastic processes. Research in the past decade has shown the presence of these receptors in the endothelial cells of the

blood vessels in primary cancers [2,3] or secondary determinations in metastatic cases [4]. Current research attempts to demonstrate and quantify the presence of FSHR in neoplasias and their implications in tumor growth. FSH is produced by the anterior pituitary and is an essential element of human reproduction acting on the ovaries and testes. In women, FSH plays a role in stimulating follicular maturation and oestrogen production [5], and in men it contributes to the maintenance of spermatogenesis [6]. The FSHR is a transmembrane glycosylated protein present in ovarian follicular cells, Sertoli cells [7,8] and in a low level in ovarian endothelial cells [9]. Studying FSHR in neoplasms may lead to the use of new therapeutic and diagnostic strategies for improved management of cancer patients.

The present article analyzed the most important articles that reported the presence of FSHR in tumors. We aimed to summarize and analyze the presence of FSHR reported in different neoplasias and also to highlight some proved or not proved/suggested implications of these receptors in the tumor growth process, which could represent a starting point for future clinical research.

Methods

An extensive search of MEDLINE/PubMed was performed using the following two MeSH terms: "follicle-stimulating hormone receptors" and "cancer". At first, 182 articles were obtained. Filters for language (English) and species (Humans) were added, leading to the final number of 144 articles. Selected were only original articles, excluding editorials, reviews and abstracts.

Results

Selected were 22 articles containing important research on the studied subject, excluding articles not written in English and also those in which FSHR were related to other ovarian diseases and syndromes, not related to the presence and development of cancer.

While reading and analyzing the selected articles we identified some aspects regarding:

- a. FSHR in prostate and ovarian cancer cells;
- b. FSHRs in endothelial cells of intra- and perineoplastic blood vessels;
- c. FSHRs in primary and metastatic cancers;
- d. FSHRs in various benign or malignant tumors;
- e. FSHRs and clinical implications

All the details regarding the 22 studies analyzed and reviewed are summarized in Table 1.

FSHR research started with studies on their role on ovarian function and ovarian cancer. In

1999, FSHR was first reported by Ben-Josef et al. [10] on a human prostate cancer line cells. Although they haven't found FSHR in normal prostate line cells or colonic cancer cells, 7 years later, one research group conducted by Mariani [11] found that some of the normal prostate (9 out of 13) and benign prostate hyperplasia (8 out of 15) tissue samples analyzed expressed FSHR. They also found FSHR expression in 21 out of 30 prostate adenocarcinoma tissues samples. Also, they reported higher levels of FSHR mRNA and protein in prostate cancer compared to normal and benign hyperplastic prostate glands. FSHR protein was reported to be localized in the glandular epithelium and in some stromal cells of the examined specimens.

In 2008, one study on 188 testicular germ cell tumor specimens obtained from orchiectomised patients showed that FSHR gene haplotypes are a risk factor for testicular cancer [12]. Several studies conducted on ovarian cancer specimens or cell lines showed that FSHR may play a role in ovarian cancer [13-15]. Lenhard et al. [16] in their study on 156 ovarian cancer tissue samples showed that FSHR and luteinising hormone reseptor (LHR) were found in almost 65% of the analyzed samples. Specimens positive only for FSHR had a poor prognosis compared to those positive for FSHR + LHR and also compared to those with sole LHR expression.

Ten years later after Ben-Josef et al. findings, a groundbreaking research on 1336 patients pathologically diagnosed with cancer in various organs (prostate, bladder, kidney, breast, colon, pancreas, liver, lung, stomach, testis, ovary) removed after surgical treatment, the presence of FSHR in peripheral blood vessel endothelium over an approximately 10 mm intra- and extratumoral, excepting renal cell carcinomas 30% of them expressing FSHR in the vessels inside the tumor and 40% only outside the tumor. FSHR were absent in normal tissues and lymphatic vessels. Inflammatory, regenerative and proliferative tissues (rheumatoid arthritis, chronic pancreatitis, Crohn's disease, wound healing) were also reported to lack FSHR. Endothelial cells of the placenta expressed high levels of FSHR [2]. The presence of these receptors in perineoplastic blood vessels was also reported in soft-tissue sarcomas, excepting well-differentiated liposarcomas. Positivity tissue samples for FSHR in endothelial blood vessels ranged from 54 to 92%. Immunohistochemical staining was also positive for tumor cells (ranging from 28 to 68% of the analyzed specimens) but negative for lipomas or normal fat tissue (subcutaneous, pericolic, perirenal) [3]. Further research on breast neoplasms has demonstrated

the presence of FSHR in perineoplastic endothelial cells in breast cancer and vascular remodeling at the periphery of the neoplastic formation, and implicitly the possible clinical implications of a new therapeutic strategy. FSHR were localized on a layer of 2 mm into and 5 mm outside the neoplastic process. The level of expression in the blood vessels was reported as being 100% at the demarcation line between the normal and pathologic tissue. The increased presence of FSHR in breast cancers, without significant differences between the main types of cancer, tumor stage and level of receptor expression, demonstrated their possible usage in therapeutic or diagnostic strategies especially for patients with triple negative breast cancer [17].

In a study on 30 tissue samples with pancreatic neuroendocrine tumors, Sardella et al. [18] demonstrated the presence of FSHR only in neoplastic cells, with almost no positive staining in the endothelium of perineoplastic blood vessels. A recent study by Poniewierska-Baran et al. [19] reported for the first time the presence of FSHR and LHR in human rhabdomyosarcoma cell lines and primary tumor tissue specimens. They've analyzed 58 samples containing rhabdomyosarcoma primary tumor and all tissue specimens and cell lines contained mRNA expression for FSH and LH receptors.

Regarding metastatic tumors, Siraj et al. [4] showed that 79.4% of the analyzed metastatic samples contained FSHR in the blood vessels located at the periphery of the neoplastic process on a layer of approximately 10 mm (ranging from 7 to 15 mm). Also no significant differences were observed between the density of FSHR from metastatic peripheral and intrametastatic blood vessels for secondary lesions from the lung, breast, colon, kidney or leiomyosarcoma. Instead, prostatic-derived metastases showed a three-fold higher density of receptors in peripheral compared to intrametastatic blood vessels. The authors concluded that FSHR are found in the endothelium of blood vessels in almost all metastatic tumors. Using HO8910 human serous ovarian carcinoma cell line and the HEY cell line (a papillary ovarian cystadenocarcinoma cell line), Yang et al. [20] demonstrated that FSHR plays an important role in epithelial ovarian cancer, in the development of epithelial-mesenchymal transition (EMT) induced by FSH, EMT being involved in early phases of the metastatic process.

Current studies of several research groups have attempted to demonstrate the presence of FSHR in neoplasias and their role which is not yet fully elucidated. One of the most active groups of researchers is the one represented by Pawlikowski

et al. In their recent studies they found FSHR in tissue specimens containing thyroid benign and malignant lesions, pituitary adenomas, neuroendocrine tumors, adrenal tumors and hyperplastic adrenal glands [21-25]. According to their results, FSHR staining was positive in some of the endothelial tumor blood vessels and usually in even more specimens in the tumor cells. A small part of the tissue specimens analyzed in their studies were negative for FSHRs.

The largest study on thyroid tissues samples by Liu J et al. [26] analyzed 312 thyroid tissue samples: 73 thyroid adenoma, 73 nodular goitre, 149 thyroid papillary cancer, 12 poorly differentiated thyroid carcinoma and 8 undifferentiated thyroid carcinoma. They authors found FSHR both in normal thyroid tissue and in neoplastic thyroid tissue (in the cytoplasm of thyroid epithelial cells). The percentage of tissue samples positive for FSHR ranged from 0% (undifferentiated thyroid carcinoma) to 41.4% (thyroid adenoma).

According to McLellan et al. [27] FSHR can be found not only in the blood vessels of malignant tumors but also in benign tumors, such as vascular tumors. For the first time FSHR has been reported to be expressed on the endothelium of vascular anomalies (nonmalignant pathologic tissue). After analyzing 82 vascular tumors and malformations (29 infantile haemangiomas: 10 proliferating, 10 involuting and 10 involuted, 4 congenital haemangiomas [noninvoluting], 4 Kaposiform haemangiopericytomas and 4 pyogenic granulomas and 40 vascular malformations (10 capillary, 10 lymphatic, 10 venous and 10 arteriovenous), they concluded that the pathogenesis of infantile haemangiomas and nonmalignant vascular malformations seem to be influenced by FSH receptors.

In terms of clinical implications or useful clinical data, 50 patients with advanced metastatic clear cell renal cell carcinoma (CCRCC) have been the subjects of extensive research regarding the relationship between the presence and density of FSHR in the blood vessels of the primary tumor and their response to sunitinib treatment. Tissue samples were obtained from surgically removed specimens and the response of those patients to sunitinib treatment was recorded. Patients responsive to sunitinib treatment had a density of FSHR in primary tumor blood vessels, 5-fold higher than patients stable to sunitinib treatment, and 8-fold higher than the group of patients non-responsive to sunitinib treatment. The authors concluded that the level of FSHR expression in blood vessels of primary tumor in patients with metastatic CCRCC was correlated with response of metastatic tumors to sunitinib [28].

Table 1. The 22 selected studies from the literature review on FSHRs in neoplasias

First author [Ref]	Year	Number of patients/tissue samples	Type of neoplasia / Localization	Conclusions
Ben-Josef E et al. [10]	1999	-	PC3 and DU145 human prostate cancer cells	1 st time report of human prostate cancer cells express FSH and FSHR
Mariani S et al. [11]	2006	13 normal 15 BPH 30 Pca	DLD-1 human colon cancer cells prostate	No positive staining in normal prostate glands or colon cancer FSHR expressed in some normal human prostate, benign prostatic hyperplastic (BPH) tissue, prostate adenocarcinoma (Pca) FSHR mRNA and protein levels higher expressed in Pca tissue compared to normal human prostate and BPH tissue
Ferlin A et al. [12]	2008	188 TGCT 152 controls	testicular	FSHR gene haplotypes are a risk factor for testicular germ cell tumor (TGCT), particularly non-seminoma
Heubner M et al. [13]	2009	115 EOC 115 controls	ovarian	FSHR Ala307-Ser680 haplotype not confirmed as a risk factor for epithelial ovarian cancer (EOC)
Ludwig AH et al. [14]	2009	215 cancer 352 controls	ovarian	Supports the androgen and gonadotropin hypotheses of ovarian cancer development
Zhang Z et al. [15]	2009	-	MCV152 benign OET cell SKOV-3 malignant EOC cell	Overexpression of FSHR may play a role in ovarian epithelial tumors (OET) development
Radu A et al. [2]	2010	1336	prostate, breast, colon, pancreas, urinary bladder, kidney, lung, liver, stomach, testis, ovary	FSH receptor in prostate tumors located in the endothelial cells at the periphery of the tumors, in shells that had a thickness of approximately 10 mm (range, 7 to 15) inside and outside the tumor Same distribution of FSH receptor was observed in all 11 tumor types examined, except renal-cell carcinomas having a different pattern
Lenhard M et al. [16]	2011	156	ovarian	FSHR and LH-R are both expressed in ovarian cancer
Pawlikowski M et al. [21]	2012	28 37 1	pituitary adenomas adrenal tumors hyperplastic adrenal gland	More than half of the tissue samples showed FSHR in the endothelium of blood vessels located intra- and/or peritumorally. FSHR can also be found in neoplastic cells in some cases
Siraj MA et al. [28]	2012	50	clear cell renal cell carcinoma	Level of endothelial FSHR expression correlated with the efficacy of treatment with sunitinib
Sardella C et al. [18]	2013	30	pancreatic neuroendocrine tumors	Expression of FSHR only in neoplastic cells
Renner M et al. [3]	2013	335	soft tissue sarcomas (STS)	FSHR present in endothelial cells of the tumor blood vessels for all 11 subtypes of STS + tumor cells, except well-differentiated sarcoma
Pawlikowski M et al. [22]	2013	14	neuroendocrine tumors	FSHR staining in the majority of tumor cells and also in endothelium of tumor blood vessels in 50% of tissue samples
Siraj A et al. [4]	2013	209	Metastases of lung, breast, prostate, colon, kidney, uterine corpus leiomyosarcoma in liver, lymph node, bone, pleura, lung, and brain	FSHR staining present in blood tumor vessels of metastases with different levels of expression
Yang Y et al. [20]	2014	-	HO8910 cell line, a human serous ovarian carcinoma HEY cell line	FSHR plays an important role in the development of epithelial-mesenchymal transition induced by FSH in epithelial ovarian cancer
Liu J et al. [26]	2014	312	thyroid adenoma, nodular goitre, thyroid papillary cancer, poorly differentiated thyroid carcinoma, undifferentiated thyroid carcinoma	LHR and FSHR both in normal thyroid tissue and neoplastic thyroid tissue (present in the cytoplasm of thyroid epithelial cells), excepting undifferentiated thyroid carcinoma
McLellan R et al. [27]	2014	82	infantile haemangioma, congenital haemangioma, kaposiform haemangiopericytoma, pyogenic granuloma, vascular malformations	FSHR may play a role in infantile haemangioma and vascular malformations

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First author [Ref]	Year	Number of patients/tissue samples	Type of neoplasia / Localization	Conclusions
Pawlikowski M et al. [23]	2015	44	thyroid (undifferentiated cancers, papillary cancer, follicular cancer and adenomas)	FSHR not present in non-neoplastic thyroid follicles and most of follicular adenomas FSHR present in almost all tumor cells FSHR present in the endothelium of blood vessels belonging to neoplastic tumors and follicular adenomas
Pawlikowski M et al. [24]	2015	36	thyroid (benign lesions, papillary cancer, follicular cancer, 1 anaplastic cancer)	FSHR present in all (except one papillary cancer) tumor cells FSHR immunostaining observed in the endothelium of thyroid blood vessels (particularly endothelium) in 40% of samples
Pawlikowski M et al. [25]	2015	42	pituitary adenomas	FSHR expressed in intratumor cells (68% of samples) and blood vessels (78% of samples) FSHR immunostaining significantly higher in invasive tumors compared to non-invasive tumors
Planeix F et al. [17]	2015	83	breast cancer	FSHR expressed in blood vessels at the periphery of breast neoplasia (2 mm intratumoral to 5 mm extratumoral)
Poniewierska-Baran A et al. [19]	2016	58	primary rhabdomyosarcoma (26 PAX3-FOXO1-positive, 7 PAX7-FOXO1-positive and 25 fusion-negative) fusion-positive (RH28, RH30 and RH41) and fusion-negative (JR, RD, RH18, RH36 and SMS-CTR) cell lines	FSHR and luteinizing hormone receptors (LHR) reported for the first time in all human rhabdomyosarcoma cell lines and primary tumor tissue specimens

Discussion

Research in the past decade studying the role of various tumor markers in neoplasias, and particularly their role in angiogenesis [2,29], has led to new dilemmas and possibly new answers for both researchers and clinicians. Recent reviews regarding the role of FSHR in genitourinary malignancies have shown, at that moment, that an important progress has been made regarding prostate adenocarcinomas and current attempts tried and still try to explore and find the role of degarelix, suramin and other possible drugs involved in FSHR signaling. There is hope and enthusiasm but a lot of effort and work remains to be done until we can fully understand and exploit the role of FSHR in the carcinogenesis of prostate adenocarcinomas, not to mention other types of neoplasias [30]. In their most recent review a group led by Papadimitriou et al. [31] has analysed FSHR isoforms and aspects regarding their mutations and also the heterogeneous methods of identification used by various groups of researchers. Although there are current reviews summarizing the FSHR role from different viewpoints, the current study attempted to show the evolution of FSHR research from the beginning to the present

day, highlighting not only the most important studies but also all studies containing information that could relate with clinical implications, what has been made and what remains to be done in various types of malignancies.

FSHR plays an essential key role in human reproduction acting on the ovaries and testes. In women, FSH stimulates follicular maturation and oestrogen production [5]. FSHR exist in 4 isoforms: FSHR1, FSHR2, FSHR3 and FSHR4. From these, only FSHR1 and FSHR3 are known to have biological functions. Initial studies showed that high levels of FSHR may be responsible for aggressive cell proliferation and neoplastic development [32]. Later studies improved the initial theories by stating that FSHR3 seems to play an important role in epithelial ovarian cancer development and even being a predictor for poor prognosis [33,34]. Besides the studies about the role of FSHR, there are many research groups trying to discover or to elucidate the role of various newly discovered tumor markers in the development of ovarian cancer [35].

Several authors analyzed various neoplasias trying to prove the presence of FSHR in endothelial cells of peritumoral blood vessels. In fact, only the groups led by Radu [2-4] and Ghinea [17,28] ubiquitarily succeeded to do this, using their highly spe-

cific monoclonal antibody FSHR323. The results of their studies showed immunohistochemical staining only in the endothelium of peritumoral blood vessels in various neoplasias and benign prostate hyperplasia. Control samples consisting of normal or inflammatory tissue were negative. This led to the hypothesis of FSHR being involved in tumor angiogenesis. On the other hand, one study carried out by Urbanska et al. [36] stated that “we were unable to detect FSHR protein in the blood vessels of human or mouse cancers by immunohistochemical analysis using commercially available antibodies”. Even so, there is one recent study by Maclellan et al. [27], which reported similar results with those of Radu et al., using a commercially available polyclonal FSHR antibody. They’ve obtained similar results, having FSHR staining only in the endothelium of peritumoral blood vessels, but their study was made on non-malignant pathologic tissue and compared rates of FSHR density between various types of pathologic tissue samples and positive controls of the ovary, testis, placenta and different types of adenocarcinoma (colon, gastric, pancreatic and renal). No positive FSHR staining was reported for normal tissue samples or lymphatic vessels.

Other studies reported heterogeneous results stating the presence of FSHR staining both in tumor cells and the endothelium of tumor blood vessels in some, but not all, tumor tissue samples [21-25]. Others reported the FSHR presence only in neoplastic cells [18]. Different results between different groups of researchers can be explained by different methods of detecting FSHR, different commercially available antibodies [23,24,26] or in some cases different types of tumors [18]. Better or more homogeneous results seem to be obtained using cell lines for research [19,20].

As far as clinical and therapeutically aimed studies, Radu et al. [2] used in their research a mouse model to see if newly discovered FSHR can be accessed intravenously by coupling their monoclonal antibody with colloidal gold and injecting it in mice. As a result, they proved that this newly discovered target can be accessible for intravenously injected drugs. Furthermore, Urbanska et al. [36] succeeded to build a T-cell-based immunotherapy targeting the FSHR present on tumor cells of ovarian cancer using for detection the mRNA expressed by FSHR. Their group has not succeeded in performing immunohistochemical staining with the commercially available antibodies for FSHR. After *in vitro* and *in vivo* (using mice) experiments, they proved that their anti-FSHR 33-53 β -28z and anti-FSHR agonist A-28z immunoreceptors T-cells succeeded in suppressing the growth of tumor cells expressing FSHR.

Recently Ghiringhelli et al. [37] reported that in one patient with metastatic colon cancer they added degarelix (gonadotropin-releasing hormone receptor antagonist) to biweekly regimen of fluorouracil and leucovorin (LV5FU2) + bevacizumab, as a last resort after available chemotherapy options failed to stop tumor progression. A 12-month tumor stabilization was obtained according to imaging studies and carcinoembryonic antigen estimations. Furthermore, tumor blood vessels reduced dramatically after adding degarelix. This could be the first clinical argument in favor of the hypothesis that FSHR are involved in tumor angiogenesis, but further clinical trials and studies are required.

On the other hand, despite little clinical evidence and implications reported until now, a group of researchers lead by Xu et al. [38] and Zhu et al. [39] performed some experimental research regarding the targeting of FSHR for tumor imaging purposes in prostate adenocarcinomas. They succeeded in obtaining two promising candidates in their preclinical studies. The radiotracers used (^{18}F -Al-NOTA-MAL-FSH1 and ^{18}F -Al-NOTA-MAL-FSH2) for *in vitro* and *in vivo* experimental studies showed a potential use of these radiotracers with positron emission tomography (PET) imaging in detecting tumors positive for FSHR. Another group led by Hong et al. [40] tried another approach by using the concept of immunoPET using radiolabeled monoclonal antibodies (mAbs). *In vivo* experiments on mice showed specific uptakes of ^{64}Cu -NOTA-FSHR-mAb in various FSHR positive tumors, making it a future candidate radiotracer used for therapeutic purposes.

Conclusions

The presence of FSHR in the endothelium of blood vessels surrounding malignant tumors using a highly specific FSHR mAb, raised the hypothesis of possible implications of these receptors in carcinogenesis, particularly in tumor angiogenesis. The results obtained by only two small group of researchers led by Rady and Ghinea seem to be slowly confirmed step by step by other studies using less specific antibodies. Results of all recent studies on cell lines, tissue samples (human or animal), case reports and experimental radiotracers bring us closer to demonstrate that FSHR probably play a key role in angiogenesis of most malignant tumors, as recently was hypothesized by Radu et al.

In conclusion, FSHR detection remains a real challenge as long as standard protocols and specific antibodies will not be available for all research

groups. Despite extensive research, heterogeneous results cannot provide solid conclusions and further work is needed in order to elucidate the exact role of FSHR in tumor development. We can be optimistic regarding the future use of FSHR for diagnostic or therapeutic purposes, but there are a lot of questions without answer and many unsolved dilemmas before we can actually quantify the real benefit of this novel therapeutic target for cancer patients.

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Conflict of interests

The authors declare no conflict of interests.

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