Endokrynologia Polska
DOI: 10.5603/EP.2018.0022
Tom/Volume 69; Numer/Number 2/2018
ISSN 0423–104X

Expression of follicle stimulating hormone receptors in intra-tumoral vasculature and in tumoral cells — the involvement in tumour progression and the perspectives of application in cancer diagnosis and therapy

Marek Pawlikowski

Department of Immunoendocrinology, Chair of Endocrinology, Medical University of Łódź

Abstract
In normal conditions follicle stimulating hormone receptors (FSHR) are expressed in zona granulosa cells of the ovary and Sertoli cells of the testis. However, the ectopic expression of FSHR was recently discovered in intra-tumoral blood vessels endothelia and/or in tumoral cells of many extra-gonadal human tumors (particularly in endocrine tumours). The paper reviews the data concerning the appearance of ectopic FSHR in particular human neoplasms. The possible involvement of FSHR in tumor progression and the use of FSHR examination for diagnostic purposes is also reviewed. Finally, the putative role of FSHR as a new target in oncological therapy is also discussed.
(Endokrynol Pol 2018; 69 (2): 192–195)

Key words: *follicle stimulating hormone receptor, ectopic expression, cancer markers, cancer progression, cancer treatment, follicle stimulating hormone antagonists*

Introduction

Follicle stimulating hormone (FSH, follitropin) is a pituitary glycoprotein hormone known as one of the major regulators of mammalian reproduction. It acts on zona granulosa cells of ovarian follicles and on Sertoli cells of the male testis, stimulating their hormonal function, differentiation, and cell growth. The action of FSH is mediated via specific, membrane FSH receptors (FSHR), present on its targets. The best known mechanism connected with FSHR is adenylate cyclase activation leading to cyclic adenosine-3′, 5′-monophosphate (cAMP) formation, but other pathways are also involved [1]. FSHR are also expressed in tumors evolving from gonads [2]. In the last years many papers reported also on the ectopic expression of FSHR in intra-tumoral blood vessels and/or tumoral cells beyond the gonadal tumors. This review is devoted to these findings and discusses the perspectives of their application in oncological diagnosis and therapy.

FSHR expression in normal tissues beyond the reproductive system

There are few reports on the expression of FSHR in normal tissues beyond the reproductive system. The presence of FSHR was described in monocytes and osteoclasts [3]. This finding is compatible with the observation that FSH releases interleukins from monocytes *in vitro* [4]. FSHR immunopositivity was also found in both adrenal cortex and medulla, and also in the periadrenal sympathetic gangliocytes [5].

FSHR expression in intra-tumoral blood vessels

Radu et al. [6] were the first who discovered the expression of FSHR in endothelia of intra- and peritumoral blood vessels in the large series of solid tumours, including breast, lung prostate, colonic, gastric, pancreatic and kidney cancers. The similar observations were done subsequently in other tumours: adrenocortical benign and malignant neoplasms, pheochromocytomas, pituitary adenomas [5], neuroendocrine tumours [7] and soft tissue sarcomas [8]. In contrast, the endothelia of vessels situated in non-malignant tissues do not express FSHR. It seems reasonable to suppose that FSHR-positive blood vessels represent the vasculature formed through tumoral neo-angiogenesis [9, 10].

Marek Pawlikowski, Chair of Endocrinology, Medical University of Łódź, ul. Dr. Sterlinga 1/3, 91–425 Łódź, tel.: 426644389, e-mail: marek.pawlikowski@umed.lodz.pl

FSHR expression in tumoral cells

The data on FSHR expression in tumoral cells of non-gonadal tumors are rather scarce. As early as in 1998 Dirnhofer et al. [11] reported on the presence of FSH and LH and their receptors in prostate cancer. One year later, Ben Josef et al. [12] reported the expression of FSHR in prostate cancer cell lines PC and DU-145. Further studies confirmed (by means of immunohistochemistry and PCR) the strong expression of FSHR in the samples of prostate cancer [12]. However, a scarce expression was also observed in normal prostate and benign prostatic hyperplasia. Thus, the expression of FSHR cannot be properly considered as ectopic. The same authors confirmed also the expression of FSHR in androgen-refractory prostate cancer cells (PC) but not in androgen-sensitive line LNCaP [13]. Further studies revealed the FSHR expression in the tumoral cells of other, mostly endocrine, tumors, including adrenocortical benign and malignant neoplasms, pheochromocytomas, pituitary adenomas [5], neuroendocrine tumours [7, 14] and thyroid cancers [15].

FSHR and tumor progression

FSH, like other pituitary glycoprotein hormones, belongs to a subfamily of proteins similar to growth factors [16, 17]. In its "classical" targets, zona granulosa cells and Sertoli cells FSH exerts the growth–promoting effects [18]. In non-neoplastic ovary FSH also increases vascular endothelial growth factor (VEGF) secretion, leading to enhanced angiogenesis [18]. A similar effect was shown in ovarian cancer cells SK-OV-3 proliferation [19]. FSH also inhibits ovarian cancer cell apoptosis by up-regulating survivin and down regulating programmed cell death gene 6 (PDCD6) and death receptor 5 (DR5) [20]. The localization of FSHR in intra-tumoral microvessels suggests its involvement in cancer neoangiogenesis. Such a suggestion is supported by the observation that the density of FSHR-immunopositive microvessels in the kidney cancer predicts the therapeutic effectiveness of sunitinib, an anti-angiogenic receptor tyrosine kinase inhibitor [21].

FSHR expression: a marker of malignancy?

If FSHR may mediate the effects of FSH on tumor progression, a question arises whether the expression of these receptors is correlated with a higher malignancy grade. The answer seems to be positive. In certain tissues, the FSHR expression is present in malignant, but not in benign tumours. For instance, FSHR immunostaining is detectable in thyroid follicular carcinomas but neither in benign follicular adenomas nor in non-neoplastic thyroid follicles [15]. The FSHR immunopositivity is present in malignant liposarcomas but neither in benign lipomas nor in normal fat [8].

In pituitary adenomas FSHR expression in tumoral cells is prevalent in invasive and proliferating tumours [22]. Thus, the immunostaining of FSHR could play a supplementary role in the histopathological examination. Because one of FSHR isoforms is soluble and detectable in blood serum (FSHR-4), it may possibly also be used as a serum marker. The second potential application of the ectopic expression of FSHR in tumor diagnosis (perhaps even more promising) is a possibility of the *in vivo* detection of the localization of neoplastic foci by means of a radioreceptor assay. Such a method is recently proposed by Xu et al [23]. The quoted authors applied βFSH 33–53 (aminoacid sequency YTRDLVYKDPARPKIQKTCTF), coupled to maleimide — NOTA conjugate labeled with [^{18}F] aluminum fluoride as a radiotracer.

FSHR inhibition or destruction and their possible role in FSHR-expressing cancer treatment

The next question is whether the ectopic expression of FSHR in many human malignances might be a novel target in oncological therapy. Since FSHR is involved in cancer progression (see above), its inhibition or destruction could be supposed to exert a beneficial effect. The list of FSHR antagonists, either peptide or non-peptide, is rather long, because of the search for non-steroid female and male contraceptives [24–30]. One of the known FSHR antagonists is suramin, it was suggested to treat the advanced prostate cancer [31]. The treatment with FSHR antagonists was also proposed in ovarian epithelial cancer [32]. The beneficial effect pf Degarelix, gonadotropin releasing hormone receptor antagonist, in colon cancer is supposed to result from a decrease of FSH level [33]. The next possibility consists of the destruction of tumor or its vasculature using the toxic ligands of FSHR. Possibly, it might be a conjugate of the lytic peptide Hecate with FSH fragments. Hecate is an analogue of the main component of bee venom melittin which preferentially kills the cancer cells. This peptide was already conjugated with β chorionic gonadotropin fragments and tested with promising effects in the case of cancers expressing LH/HCG receptors [34–37]. However, this possibility should be limited by the risk of the stable destruction of non-neoplastic tissues expressing FSHR, like zona granulosa of the ovary in premenopausal women or Sertoli cells in the male testis. The destruction of other non–neoplastic tissues beyond the reproductive system seems also probable (see above). Recently, the sophisticated immunotherapy with human T cells transduced to express anti-FSHR

immunoreceptors was proposed and tested on ovarian cancer cells [38]. Obviously, the clinical trials with FSHR antagonists should be preceded by the resolution of several problems in preclinical studies (functional and molecular characteristics of ectopic FSHR, safety etc.)

Conclusions

FSHR — well known as the receptors mediating the effects of follitropin (FSH) on female and male gonads, are also expressed in gonadal and extra-gonadal tumors. Their appearance was discovered in endothelia of the intra- and peritumoral vessels, but not in the vessels distant from the neoplastic focus (except the intragonadal vascular and umbilical vein). In several tumors, mostly of endocrine origin, FSHR expression was also found in tumoral cells. Since FSHR mediates the action of FSH in gonads, among other, on cell growth and neoangiogenesis, similar effects can be presumed in tumoral tissues. FSHR may be potentially useful in practical medicine as a marker of malignancy. Moreover, because numerous antagonists of FSHR are just known, the attempts of new therapies of cancers are justified.

Acknowledgements

This paper was financially supported by Medical University of Lodz.

References

1. Simoni M, Gromoll J, Nieschlag E. The follicle-stimulating hormone receptor: biochemistry, molecular biology, physiology, and pathophysiology. Endocr Rev. 1997; 18(6): 739–773, doi: 10.1210/edrv.18.6.0320, indexed in Pubmed: 9408742.
2. Huhtaniemi I. Are gonadotrophins tumorigenic — a critical review of clinical and experimental data. Mol Cell Endocrinol. 2010; 329(1–2): 56–61, doi: 10.1016/j.mce.2010.04.028, indexed in Pubmed: 20471448.
3. Robinson LJ, Tourkova I, Wang Y, et al. FSH-receptor isoforms and FSH-dependent gene transcription in human monocytes and osteoclasts. Biochem Biophys Res Commun. 2010; 394(1): 12–17, doi: 10.1016/j.bbrc.2010.02.112, indexed in Pubmed: 20171950.
4. Komorowski J, Pawlikowski M, Stepień H. Pituitary glycoprotein hormones and interleukins secretion. In vitro and in vivo human study. Ann N Y Acad Sci. 1995; 762: 429–431, indexed in Pubmed: 7668548.
5. Pawlikowski M, Pisarek H, Kubiak R, et al. Immunohistochemical detection of FSH receptors in pituitary adenomas and adrenal tumors. Folia Histochem Cytobiol. 2012; 50(3): 325–330, doi: 10.5603/17850, indexed in Pubmed: 23042261.
6. Radu A, Pichon C, Camparo P, et al. Expression of follicle-stimulating hormone receptor in tumor blood vessels. N Engl J Med. 2010; 363(17): 1621–1630, doi: 10.1056/NEJMoa1001283, indexed in Pubmed: 20961245.
7. Pawlikowski M, Winczyk K, Stępień H. Immunohistochemical detection of follicle stimulating hormone receptor (FSHR) in neuroendocrine tumours. Endokrynol Pol. 2013; 64(4): 268–271, indexed in Pubmed: 24002953.
8. Renner M, Goeppert B, Siraj MA, et al. Follicle-stimulating hormone receptor expression in soft tissue sarcomas. Histopathology. 2013; 63(1): 29–35, doi: 10.1111/his.12135, indexed in Pubmed: 23659266.
9. Gartrell BA, Tsao Ck, Galsky MD. The follicle-stimulating hormone receptor: a novel target in genitourinary malignancies. Urol Oncol. 2013; 31(8): 1403–1407, doi: 10.1016/j.urolonc.2012.03.005, indexed in Pubmed: 22513137.
10. Papadimitriou K, Kountourakis P, Kottorou AE, et al. Follicle-Stimulating Hormone Receptor (FSHR): A Promising Tool in Oncology? Mol Diagn Ther. 2016; 20(6): 523–530, doi: 10.1007/s40291-016-0218-z, indexed in Pubmed: 27392476.
11. Dirnhofer S, Berger C, Hermann M, et al. Coexpression of gonadotropic hormones and their corresponding FSH- and LH/CG-receptors in the human prostate. Prostate. 1998; 35(3): 212–220, indexed in Pubmed: 9582090.
12. Ben-Josef E, Yang SY, Ji TH, et al. Hormone-refractory prostate cancer cells express functional follicle-stimulating hormone receptor (FSHR). J Urol. 1999; 161(3): 970–976, indexed in Pubmed: 10022736.
13. Mariani S, Salvatori L, Basciani S, et al. Expression and cellular localization of follicle-stimulating hormone receptor in normal human prostate, benign prostatic hyperplasia and prostate cancer. J Urol. 2006; 175(6): 2072–2077, doi: 10.1016/S0022-5347(06)00273-4, indexed in Pubmed: 16697805.
14. Sardella C, Russo D, Raggi F, et al. Ectopic expression of FSH receptor isoforms in neoplastic but not in endothelial cells from pancreatic neuroendocrine tumors. J Endocrinol Invest. 2013; 36: 174–179.
15. Pawlikowski M, Fuss-Chmielewska J, Jaranowska M, et al. Expression of follicle stimulating hormone receptors (FSHR) in thyroid tumours - a marker of malignancy? Thyroid Res. 2015; 8(1): 1–4, doi: 10.1186/s13044-015-0014-6, indexed in Pubmed: 25685198.
16. Vitt UA, Hsu SY, Hsueh AJ. Evolution and classification of cystine knot-containing hormones and related extracellular signaling molecules. Mol Endocrinol. 2001; 15(5): 681–694, doi: 10.1210/mend.15.5.0639, indexed in Pubmed: 11328851.
17. Govindaraj V, Arya SV, Rao AJ. Differential action of glycoprotein hormones: significance in cancer progression. Horm Cancer. 2014; 5(1): 1–10, doi: 10.1007/s12672-013-0164-8, indexed in Pubmed: 24129797.
18. Kuo SW, Ke FC, Chang GD, et al. Potential role of follicle-stimulating hormone (FSH) and transforming growth factor (TGF 1) in the regulation of ovarian angiogenesis. J Cell Physiol. 2011; 226(6): 1608–1619, doi: 10.1002/jcp.22491, indexed in Pubmed: 20945379.
19. Park YH, Kim SuJ, Jeong BH, et al. Follicular stimulating hormone enhances Notch 1 expression in SK-OV-3 ovarian cancer cells. J Gynecol Oncol. 2010; 21(2): 119–124, doi: 10.3802/jgo.2010.21.2.119, indexed in Pubmed: 20613903.
20. Huang Y, Jin H, Liu Y, et al. FSH inhibits ovarian cancer cell apoptosis by up-regulating survivin and down-regulating PDCD6 and DR5. Endocr Relat Cancer. 2011; 18(1): 13–26, doi: 10.1677/ERC-09-0308, indexed in Pubmed: 20943720.
21. Siraj MA, Pichon C, Radu A, et al. Endothelial follicle stimulating hormone receptor in primary kidney cancer correlates with subsequent response to sunitinib. J Cell Mol Med. 2012; 16(9): 2010–2016, doi: 10.1111/j.1582-4934.2011.01495.x, indexed in Pubmed: 22129368.
22. Pawlikowski M, Radek M, Jaranowska M, et al. Expression of follicle stimulating hormone receptors in pituitary adenomas - a marker of tumour aggressiveness? Endokrynol Pol. 2014; 65(6): 469–471, doi: 10.5603/EP.2014.0065, indexed in Pubmed: 25554615.
23. Xu Y, Pan D, Zhu C, et al. Pilot study of a novel (18)F-labeled FSHR probe for tumor imaging. Mol Imaging Biol. 2014; 16(4): 578–585, doi: 10.1007/s11307-013-0712-1, indexed in Pubmed: 24389931.
24. Santa Coloma TA, Dattatreyamurty B, Reichert LE. A synthetic peptide corresponding to human FSH beta-subunit 33-53 binds to FSH receptor, stimulates basal estradiol biosynthesis, and is a partial antagonist of FSH. Biochemistry. 1990; 29(5): 1194–1200, indexed in Pubmed: 2108722.
25. Santa-Coloma TA, Crabb JW, Reichert LE. Serine analogues of hFSH-beta-(33-53) and hFSH-beta-(81-95) inhibit hFSH binding to receptor. Biochem Biophys Res Commun. 1992; 184(3): 1273–1279, indexed in Pubmed: 1590789.
26. Arey BJ, Deecher DC, Shen ES, et al. Identification and characterization of a selective, nonpeptide follicle-stimulating hormone receptor antagonist. Endocrinology. 2002; 143(10): 3822–3829, doi: 10.1210/en.2002-220372, indexed in Pubmed: 12239093.
27. van Straten NCR, van Berkel THJ, Demont DR, et al. Identification of substituted 6-amino-4-phenyltetrahydroquinoline derivatives: potent antagonists for the follicle-stimulating hormone receptor. J Med Chem. 2005; 48(6): 1697–1700, doi: 10.1021/jm049676l, indexed in Pubmed: 15771412.
28. Bonger KM, Hoogendoorn S, van Koppen CJ, et al. Synthesis and pharmacological evaluation of dimeric follicle-stimulating hormone receptor antagonists. ChemMedChem. 2009; 4(12): 2098–2102, doi: 10.1002/cmdc.200900344, indexed in Pubmed: 19902448.
29. Nataraja S, Yu H, Palmer S. Discovery and Development of Small Molecule Allosteric Modulators of Glycoprotein Hormone Receptors. Frontiers in Endocrinology. 2015; 6: 142, doi: 10.3389/fendo.2015.00142.
30. Chitnis SS, Selvaakumar C, Jagtap DD, et al. Interaction of follicle-stimulating hormone (FSH) receptor binding inhibitor-8: a novel FSH-binding inhibitor, with FSH and its receptor. Chem Biol Drug Des. 2009; 73(6): 637–643, doi: 10.1111/j.1747-0285.2009.00810.x, indexed in Pubmed: 19635055.
31. Daugherty RL, Cockett AT, Schoen SR, et al. Suramin inhibits gonadotropin action in rat testis: implications for treatment of advanced prostate cancer. J Urol. 1992; 147(3): 727–732, indexed in Pubmed: 1538472.

32. Bose CK. Follicle stimulating hormone receptor (FSHR) antagonist and epithelial ovarian cancer (EOC). J Exp Ther Oncol. 2007; 6(3): 201–204, indexed in Pubmed: 17552360.
33. Ghiringhelli F, Isambert N, Ladoire S. Degarelix as a new antiangiogenic agent for metastatic colon cancer? World J Gastroenterol. 2013; 19(5): 769–772, doi: 10.3748/wjg.v19.i5.769, indexed in Pubmed: 23431078.
34. Bodek G, Rahman NA, Zaleska M, et al. A novel approach of targeted ablation of mammary carcinoma cells through luteinizing hormone receptors using Hecate-CGbeta conjugate. Breast Cancer Res Treat. 2003; 79(1): 1–10, indexed in Pubmed: 12779076.
35. Leuschner C, Hansel W. Targeting breast and prostate cancers through their hormone receptors. Biology of Reproduction. 2005; 73(5): 860–865, doi: 10.1095/biolreprod.105.043471.
36. Rivero-Müller A, Vuorenoja S, Tuominen M, et al. Use of hecate-chorionic gonadotropin beta conjugate in therapy of lutenizing hormone receptor expressing gonadal somatic cell tumors. Mol Cell Endocrinol. 2007; 269(1-2): 17–25, doi: 10.1016/j.mce.2006.11.016, indexed in Pubmed: 17363137.
37. Hansel W, Enright F, Leuschner C. Destruction of breast cancers and their metastases by lytic peptide conjugates in vitro and in vivo. Mol Cell Endocrinol. 2007; 260-262: 183–189, doi: 10.1016/j.mce.2005.12.056, indexed in Pubmed: 17101210.
38. Urbanska K, Stashwick C, Poussin M, et al. Follicle-stimulating hormone receptor as a target in the redirected T-cell therapy for cancer. Cancer Immunol Res. 2015; 3(10): 1130–1137, doi: 10.1158/2326-6066.CIR-15-0047, indexed in Pubmed: 26112923.