RESEARCH ARTICLE

Immunohistochemical investigation of metabolic markers fatty acid synthase (FASN) and glucose transporter 1 (GLUT1) in normal endometrium, endometrial hyperplasia, and endometrial malignancy

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Abstract

Background: Cancer cells present higher metabolic needs in comparison to their normal, non-neoplastic counterparts, consuming carbohydrates as a source of energy. Moreover, increased fatty acid biosynthesis is noted in many malignancies. In this regard, we investigated specific metabolic markers, the fatty acid synthase (FASN) which catalyzes fatty acid synthesis and the glucose transporter 1 (GLUT1) which promotes glucose transport through the cellular membrane, in normal endometrium, endometrial hyperplasia, and endometrial malignancy.

Methods: We examined the immunohistochemical expression of GLUT1 and FASN in 43 cases of endometrioid adenocarcinoma, 15 cases of serous endometrial carcinoma, eight cases of clear cell endometrial carcinoma, 11 cases of atypical hyperplasia / endometrial intraepithelial neoplasia, 17 cases of simple hyperplasia, and 20 cases of normal endometrium.

Results: We observed a gradual increase in the expression of both markers, progressing from benign clinical conditions to malignancy. The most notable finding concerned the difference of FASN immunoreactivity between atypical hyperplasia and grade 1 endometrioid adenocarcinoma ($p = 0.01$).

Conclusion: GLUT1 and FASN expression demonstrated a gradual increase when advancing from endometrial hyperplasia to carcinoma. These findings suggest that both GLUT1 and FASN immunohistochemistry might be used as an adjunct in the differentiation between atypical endometrial hyperplasia and endometrial carcinoma in complex cases. HIPPOKRATIA 2017, 21(4): 169-174.

Keywords: Endometrium, metabolism, immunohistochemistry, hyperplasia, malignancy

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Introduction

At the beginning of the 20th century, Otto Warburg introduced the hypothesis that carcinogenesis is related to an imbalance of cellular metabolism[1]. This theory was based on the observation that cancer cells present clear differences in their metabolism in comparison to their normal counterparts. More specifically, he observed that neoplastic cells use glycolysis for their energy consumption, even under high oxygen concentration. On the opposite, non-neoplastic cells use mitochondrial oxidative phosphorylation. This finding was defined as "Warburg phenomenon". Nowadays, aerobic glycolysis is considered as a vital process for cancer cell metabolism.

After the vast scientific discoveries in the field of cancer genetics, the study of the metabolic imbalances of neoplastic cells was somehow abandoned. Nevertheless, many of these findings can explain the increased glucose needs of the tumor cells. Essential elements of the Warburg phenomenon - increased glucose uptake through the cellular membrane, activation of glycolysis, decreased oxidative phosphorylation - are depending on some oncogenes, like *ras*, which activates enzymes of glycolysis, and the *AKT*-kinase gene, which promotes glucose uptake by the synthesis of transmembrane carriers[2].

Apart from aerobic glycolysis, increased lipogenesis is a critical feature in cancer cell growth. Most of the fatty acids in tumor cells originate from *de novo* biosynthesis, regardless of the extracellular concentration of lipids derived from food[3]. Increased lipogenesis is based on the activation of enzymes, which promote synthesis and elongation of fatty acids' chains.

Fatty acid synthase (FASN) is a polyenzymic system, which as its name implies, catalyzes fatty acid synthesis. Recent studies have suggested that a cross-talk between FASN and estrogen receptor (ER) / progesterone receptor (PR) signaling pathways may exist[4] and that FASN inhibition is very important for endometrial cancer therapy[5]. Glucose transporter 1 (GLUT1) is a transmembrane protein, which is responsible for glucose transport through cellular membrane[6]. Therefore, it increases glucose cellu-

lar deposits and enhances energy gain through glycolysis. GLUT1 has been found to be highly expressed in poorly differentiated endometrial cancer in comparison to grade 1 endometrioid adenocarcinoma[7].

Pathologists often encounter differential diagnostic problems between atypical endometrial hyperplasia and grade 1 endometrioid adenocarcinoma. This study investigates the immunohistochemical expression of the metabolic markers GLUT1 and FASN, in normal, hyperplastic, and carcinomatous endometrium. We aimed to test whether immunohistochemistry could be used as an adjunct in the distinction between atypical endometrial hyperplasia and endometrial carcinoma in problematic cases.

Materials and methods

This retrospective study was approved by the Bioethics Committee of Medical School of the Aristotle University of Thessaloniki. The cases were retrieved from the archives of the Histopathology Department of 'Euromedica Geniki Kliniki of Thessaloniki', obtained from patients subjected to hysterectomy or endometrial curettage between December 2014 and April 2017. A total number of 114 formalin-fixed, paraffin-embedded tissue blocks from endometrial curetting and hysterectomy specimens were examined from 114 consecutive patients. Our material included ten cases of proliferative endometrium, ten cases of secretory endometrium, 17 cases of simple hyperplasia, 11 cases of atypical hyperplasia/endometrial intraepithelial neoplasia, 43 cases of endometrioid adenocarcinoma, 15 cases of serous carcinoma and eight cases of clear cell carcinoma. All carcinoma cases were consecutive in order within the above period. Thirty-three of the endometrioid adenocarcinoma cases were well-differentiated (grade 1), seven moderately differentiated (grade 2) and three poorly differentiated (grade 3).

Immunohistochemical technique

Five microns thick, tissue sections from the paraffin blocks were further processed for immunohistochemistry, using an automated steptavidin-biotin procedure (Nexes, Ventana, USA) and application of the following antibodies: GLUT1 (Rabbit polyclonal antibody, 1:50, Menarini, Florence, Italy) and FASN (Clone H300, 1:50, Santa Cruz Biotechnologies, Santa Cruz, CA, USA). Breast carcinoma tissue was used as positive control for both GLUT1 and FASN[8]. A negative control for immunostaining was carried out by replacing the primary antibody with non-immune rabbit serum.

Immunohistochemical scoring

A combined, semi-quantitative scoring system based on the fraction of the positive neoplastic cells and their staining intensity was used for immunohistochemical evaluation. The staining intensity and the percentage of positive cells were evaluated blindly from the primary author (EA). The staining intensity was scored in a four-tiered scale, according to H-score method, 0: negative, 1: weakly positive, 2: moderately positive, and 3: strongly positive (similar to breast carcinoma positive control tissue). The percentage of the positive cells was multiplied with the intensity score, resulting in values ranging from 0 to 300, according to H-score method (3x percentage of strongly staining nuclei, 2x percentage of moderately staining nuclei, and 1x percentage of weakly staining nuclei). In order to interpret better our results, we regarded our cases as negative (score: 0-30), mildly positive (score: 31-100), moderately positive (score: 101-200), and strongly positive (score: 201-300). The mean value of immunohistochemical expression of each marker per group was finally calculated for further analysis.

Statistical analysis

The R software environment for statistical computing version 3.4.4 was used for conducting the statistical analysis of the collected data. Given the selection of groups and the semi-quantitative way the immunohistochemical scoring was evaluated, it is expected that the variances of each population are not the same. It can be seen indeed from Table 1 that the standard deviations differ significantly; therefore heteroscedasticity was assumed to be the case. Moreover, the sample sizes differ considerably. Therefore, pairwise comparisons with confidence level 95 % between groups using Welch's t-test instead of the Student's t-test due to unequal variances were conducted. The Benjamini & Hochberg method was used to adjust the p-values in order to account for the necessary corrections for multiple testing by controlling the false discovery rate. For testing the association between FAS and GLUT1 within groups, the Spearman's rho rank correla-

Table 1: Fatty acid synthase (FASN) and glucose transporter 1 (GLUT1) immunostaining in normal, hyperplastic and carcinomatous endometrium.

Endometrial type	number	FASN	GLUT1
Proliferative endometrium	10	5 ± 2.02	21 ± 8.93
Secretory endometrium	10	17 ± 7.08	29 ± 12.09
Simple endometrial hyperplasia without atypia	17	68.23 ± 28.03	44.11 ± 18.68
Atypical hyperplasia /endometrial intraepithelial neoplasia	11	71.81 ± 24.42	76.36 ± 47.81
Endometrioid adenocarcinoma	43	114 ± 42	114.65 ± 57.13
Endometrioid adenocarcinoma grade 1	33	96.96 ± 29.74	98.18 ± 52.05
Endometrioid adenocarcinoma grade 2 and 3	10	172 ± 22	169 ± 36.35
Serous carcinoma	15	142.66 ± 78.6	156.66 ± 66.83
Clear cell carcinoma	8	151.25 ± 102.6	177.5 ± 55.74

FASN: fatty acid synthase, GLUT1: glucose transporter 1, values are given in means ± standard deviation.

tion coefficients along with their p-values at a confidence level 95 % were calculated.

Results

Histologic re-evaluation of the hematoxylin and eosin stained tissue sections confirmed the original diagnosis of each case included in this study. The results for FASN and GLUT1 immunostaining of all the groups are summarized in Table 1.

FASN immunoreactivity

FASN immunostaining was negative in proliferative and secretory endometrium. On the contrary, this marker was expressed in the cytoplasm of all the other groups of the current study. The immunostaining in simple endometrial hyperplasia without atypia and atypical hyperplasia/endometrial intraepithelial neoplasia was approximately equal, but immunohistochemical positivity gradually increased towards the high-grade endometrial carcinomas. More specifically, the difference between the simple hyperplasia group and grade 1 endometrioid adenocarcinoma group was statistically significant ($p = 0.002$). FASN expression was also significantly lower in the simple hyperplasia group in comparison to grade 2-3 endometrioid adenocarcinoma group. ($p < 0.001$). Expression of FASN in the simple hyperplasia group was significantly lower from the endometrioid adenocarcinoma group (all grades, $p < 0.001$), as well as from the serous carcinoma group ($p = 0.01$). Atypical hyperplasia group showed moderate immunoreactivity to FASN, which was significantly weaker from the grade 1 endometrioid adenocarcinoma group ($p = 0.01$). Within the endometrioid adenocarcinoma group, FASN expression was strong in grade 2-3 subgroup (Figure 1) and significantly higher in comparison to grade 1 cases ($p < 0.001$). Finally, there was no significant difference between the endometrioid adenocarcinoma (grade 2-3), clear cell, and serous carcinoma groups.

GLUT1 immunoreactivity

Positivity for GLUT1 was defined as distinct, linear membranous staining, with or without cytoplasmic reactivity. The numerous red blood cells in endometrial curettage specimens served as positive internal control. The lowest immunoreactivity scores were recorded in normal endometrium, where GLUT1 expression was negative. Immunohistochemical positivity progressively raised from non-atypical endometrial hyperplasia towards endometrial carcinoma. Positivity in the endometrioid adenocarcinoma was a constant feature (Figure 2). A noteworthy, interesting and consistent finding was the expression pattern of GLUT1, which was much stronger in the more superficial neoplastic cells (Figure 3). A statistically significant difference between normal endometrium on the one hand and all the types of endometrial hyperplasia and endometrial carcinoma, on the other hand, was also found ($p < 0.001$). The expression in atypical hyperplasia was significantly higher from the simple, non-atypical hyperplasia ($p = 0.04$). There was not found

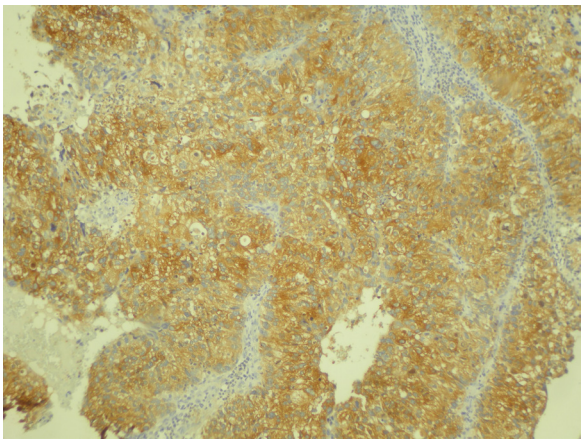

Figure 1: Grade 2 endometrioid adenocarcinoma with strong immunohistochemical expression for fatty acid synthase (streptavidin-biotin-peroxidase method, original magnification x100).

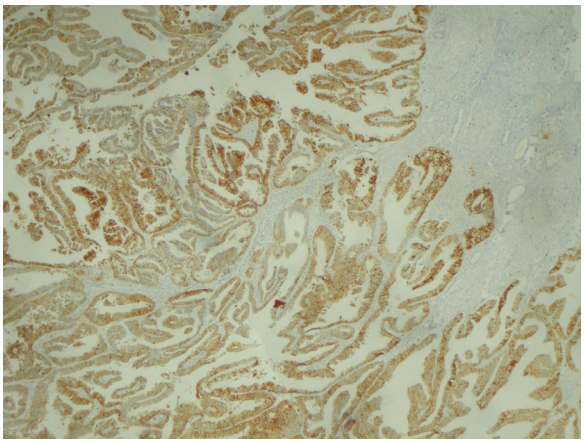

Figure 2: Glucose transporter 1 (GLUT1) staining of grade 1 endometrioid adenocarcinoma (streptavidin-biotin-peroxidase method, original magnification x50).

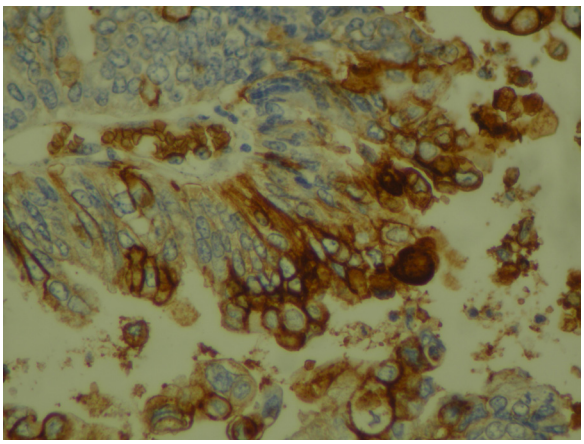

Figure 3: High-power view demonstrating strong membranous and cytoplasmic positivity of more superficial grade 1 endometrioid adenocarcinoma cells for glucose transporter 1 (GLUT1) (streptavidin-biotin-peroxidase method, original magnification x400).

a statistically significant difference between the grade 1 endometrioid adenocarcinoma and the atypical hyperplasia; however, the difference between the latter group and all grades of the endometrioid adenocarcinoma was statistically significant (p =0.04). The highest immunoreactivity score was noted in high grade (2-3) endometrioid adenocarcinoma, which differed significantly from grade 1 endometrioid adenocarcinoma (p <0.001), but not from the serous or clear cell carcinoma. GLUT1 immunoreactivity in the latter two high-grade types of carcinoma was also strong and significantly higher from grade 1 endometrioid adenocarcinoma (p =0.007 for serous carcinoma and p =0.004 for clear cell carcinoma), as well as from the total number of cases of endometrioid adenocarcinoma. Endometrioid adenocarcinoma as a group (including all three grades) differed significantly both from the serous carcinoma (p =0.04) and the clear cell carcinoma (p =0.02).

We would add that the association between FASN and GLUT1 measured using the Spearman's rho rank correlation coefficients within all the study groups was always positive, between 0.13 and 0.46. The highest value was calculated in the serous carcinoma group, where also statistical significance was reached (p =0.002).

Discussion

Fatty acid synthase (FASN) is a polyenzymic system, which as its name implies, plays a crucial role in fatty acid synthesis. It catalyzes the formation of saturated fatty acids with long chains, which are essential structural parts of macromolecules such as acetyl coenzyme A, Malonyl coenzyme A, and nicotinamide adenine dinucleotide phosphate (NADPH)[9]. These circulating lipids are used by tissues, which undergo a proliferative process for the synthesis of cellular membranes.

Regulation of FASN synthesis is not fully understood. PI3K/Akt pathway is considered to be responsible for the regulation of FASN gene expression in breast carcinoma[10]. In addition, a positive correlation between pAkt and FASN expression in ovarian carcinoma has been reported, using an immunohistochemical method[11].

Utilization of lipids seems to serve as an alternative pathway for the energy gain of cancer cells. Hypoxia seems to be the primary signal for fatty acid synthesis[12]. The effect of fatty acid synthesis in the development of malignancy makes it obvious that FASN inhibition may have a crucial role in antineoplastic therapy. In endometrial cancer, for example, orlistat, which is a weight loss medication, inhibits neoplastic cell growth by blocking FASN synthesis[7,13]. Recently, it has been suggested, that inhibited FASN suppresses the malignant biological behavior of colorectal carcinoma cells, by down-regulating mTOR signaling pathway and energy metabolism[14]. Patuletin, which is another FASN inhibitor, enhances apoptosis in human breast cancer cell line SK-BR3[15]. In addition, FASN expression is increased in hepatocellular carcinoma. Therefore, its inhibition may be a promising target for the therapeutic approach of this malignancy[16].

The number of previous studies on FASN immunohistochemical expression in normal and neoplastic endometrium is quite limited[17-19]. During the menstrual cycle, FASN expression in hormone-dependent endometrial cells has been associated with the mitotic index, Ki-67, estrogen receptor (ER), and progesterone receptor (PR) expression. It is assumed that this linkage to proliferation is maintained in hormone-independent endometrial carcinoma cells[17]. Indeed, it has been shown that FASN is overexpressed in endometrial carcinomas. This overexpression is associated with worse prognosis. It has been also recognized as an independent predictor of recurrence and a significant marker of clinically aggressive endometrial carcinomas[18]. Moreover, FASN expression in endometrial cancer has not only been associated with the development of malignancy, but with obesity as well[20].

The present study showed a gradual increase of FASN expression in the endometrium that paralleled the gradual progression to neoplasia. Normal (proliferative and secretory) endometrium cases were FASN-negative, while simple, non-atypical hyperplastic endometrium was mildly positive. FASN immunoreactivity did not differ significantly between endometrial hyperplasia without atypia and atypical hyperplasia/endometrial intraepithelial neoplasia, but both of the latter groups differed significantly in this regard from endometrioid adenocarcinoma. Furthermore, in grade 1 endometrioid adenocarcinoma cases, FASN positivity was significantly higher compared to atypical hyperplasia. This potentially important differential diagnostic finding has not been reported in the previous studies on FASN immunohistochemistry in the endometrium. Increased FASN expression was also noted going from grade 1 to grade 2 and grade 3 of endometrioid adenocarcinoma. Since type 1 endometrial carcinoma is highly linked to obesity, and FASN is highly important for adipose tissue accumulation, this molecule may have an additional significance for endometrioid adenocarcinoma development[19]. In our study, FASN expression did not differ significantly between the endometrioid adenocarcinomas (grade 2 and 3) and type 2 endometrial tumors, i.e. serous carcinoma and clear cell carcinoma.

The growth of neoplastic cells is a phenomenon which is highly depending on energy consumption, achieved by glycolysis. Increased glucose uptake is obtained by membrane glucose carriers, such as GLUT1. In a variety of malignancies, including colorectal and hepatocellular cancer, an increase of GLUT1 synthesis has been identified[21-22]. On the contrary, GLUT1 expression in non-melanoma skin carcinomas is downregulated in comparison to healthy skin, due to its consumption by neoplastic cells[23]. In general, hypoxic and ischemic conditions in normal cells, induce increased GLUT1 expression[24] and conversion to an oncogene. This also occurs for the neoplastic cells, which exhibit greater immunostaining intensity for GLUT1, even when they grow far from a vascular supply. This fact has not been yet elucidated. A possible explanation is that the tumor cells, as they try to overcome the decreased oxygenation from blood, they produce GLUT1

as a compensatory mechanism for energy consumption through glycolysis.

Regulation of GLUT1 gene expression is a complicated and not well-understood process. In the past, it has been observed that GLUT1 synthesis is induced by activation of oncogenes, such as *ras* and *src*[25]. Src blockade reduced glucose metabolism due to inhibition in ERK1/2-MNK1-eIF4E-mediated cap-dependent translation of *c-Myc* and transcription of the glucose transporter GLUT1[26]. GLUT1 is also responding to other stimuli, such as hypoxia in neurons and by oncogenic activation in lung adenocarcinoma[27]. According to recent studies, GLUT1 expression is promoted by diacylglycerol (DAG) or protein kinase C (PKC) induction, via an ERK-mediated pathway[28]. Also, insulin seems to increase GLUT1 function in human osteosarcoma cell lines, not by affecting GLUT1 expression, but by inducing its translocation to the plasma membrane[29].

Previous studies have also shown that GLUT1 is overexpressed in endometrial endometrioid adenocarcinomas[5,30-32] and serous endometrial carcinoma[33]. The present study also showed a positive correlation between GLUT1 expression and endometrial neoplasia development. Normal proliferative and secretory endometrium were negative, while hyperplastic endometrium (with or without atypia) was mildly positive. Immunohistochemical expression raised in endometrioid adenocarcinoma and it was significantly higher in grade 2 and 3, compared to grade 1. Serous and clear cell carcinoma also demonstrated strong positivity for GLUT1, which did not differ significantly from grade 2 and 3 endometrioid adenocarcinoma group. However, in contrast to previous studies[34], a significant difference in expression between non-atypical and atypical hyperplasia was not found. On the other hand, GLUT1 expression in atypical hyperplasia/endometrial intraepithelial neoplasia differed significantly from endometrioid adenocarcinoma as a group (all grades), and from high-grade adenocarcinomas, but not from grade 1 endometrioid adenocarcinoma. In addition, GLUT1 positivity was found to be stronger in more superficial neoplastic cells in our study. This interesting observation was noted in all our carcinoma cases, and it has been also reported in one of the previous studies[34]. It may be interpreted as a compensatory reaction of cells far from the blood supply, in accordance with the relation as mentioned earlier of GLUT1 expression to hypoxia.

The correlation of high immunohistochemical reactivity to GLUT1 and worse prognosis in human neoplasia has been presented in various studies[35,36]. GLUT1 expression is also a late event in malignant progression of intestinal metaplasia of Barrett esophagus[37]. The high impact of GLUT1 in tumorigenicity constitutes it as a candidate for therapeutic targeting modalities. A recent study shows that GLUT1 overexpression seems to promote the metastatic potential of melanoma cells, and this marker could be used as a prognostic indicator and therapeutic target for melanoma[38]. In addition, other studies show that inhibition of GLUT1 could partially restore the antineoplastic effects of adriamycin in breast carcinoma[39], while oncogene miR-148b inhibits glycolysis in gastric cancer through GLUT1 targeting[40].

In conclusion, the present study investigated the immunohistochemical expression of two important metabolic markers, in normal, hyperplastic and neoplastic endometrium. These two markers were negative in the normal endometrium. FASN expression was significantly lower in simple endometrial hyperplasia, in comparison to endometrioid adenocarcinoma and serous carcinoma. Atypical hyperplasia of the endometrium demonstrated a lower positivity to FASN than grade 1 endometrioid adenocarcinoma, while grade 2 and 3 endometrioid carcinoma group showed significantly higher expression of this marker than the well-differentiated endometrioid adenocarcinoma. Grade 1 endometrioid adenocarcinoma presented significantly lower reactivity for GLUT1 than grade 2 and 3 endometrioid adenocarcinoma, and serous and clear cell carcinoma as well. In this study, we also observed a gradually increased expression of both FASN and GLUT1 going from endometrial hyperplasia to carcinoma, evidence that these molecules are implicated in the process of carcinogenesis of the endometrium. In practical terms, both GLUT1 and FASN immunohistochemistry may be used as an adjunct for the histological distinction between atypical endometrial hyperplasia and endometrial carcinoma in problematic cases.

Conflict of interest

Authors declare no conflict of interest.

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