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Association of STAT3 with Cx26 and Cx43 in human uterine endometrioid adenocarcinoma

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Abstract. Signal transducer and activator of transcription-3 (STAT3) drives endometrial carcinogenesis, while signaling via gap junctions gets weakened during cancer progression. Connexin 26 (Cx26), Cx43 and STAT3 were immunohistochemically evaluated in 78 endometrioid adenocarcinomas: Nuclear expression of STAT3 positively correlated with cytoplasmic immunoreactivity to Cx43 (P=0.004, r=0.318) and Cx26 (P=0.006, r=0.309). STAT3 correlated with Cx43 (P=0.022, r=0.411) and Cx26 (P=0.008 r=0.466) in G1 tumors. A statistically significant linkage remained in G2 cancers between STAT3 and Cx43 (P=0.061, r=0.262) and Cx26 (P=0.016, r=0.331); however, no correlations were observed in G3 tumors. STAT3 was significantly associated with Cx 43 (p=0.003, r=0.684) and Cx26 (p=0.049, r=0.500) in estrogen receptor (ER) negative adenocarcinomas. STAT3 did not correlate with Cx43 in ER positive adenocarcinomas; however, STAT3 expression remained correlated with Cx26 expression (P=0.035, r=0.268). In progesterone receptor negative tumors STAT3 was significantly associated with Cx43 (P=0.035, r=0.451) and Cx26 (P<0.0001, r=0.707). However, in PgR positive adenocarcinomas STAT3 correlated with Cx43 (P=0.03, r=0.290) but not with Cx26. Thus, it appears that hormone dependent acceleration of cancer growth breaks the association between STAT3 and Cx expression. These associations become weaker as the tumors dedifferentiate from G1 to G3 endometrioid adenocarcinomas. The present study provides evidence that the loss of correlation between STAT3 and selected Cx proteins occurs in tumors with more aggressive behavior.

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Introduction

It has previously been demonstrated that connexin 26 (Cx26), Cx32 and Cx43 are aberrantly distributed (in the cytoplasm instead of membranous locations) and that their expression levels are reduced in human endometrial hyperplasia and endometrial cancer (1). In addition, suppression of gap junctional intercellular signaling (GJIC) has been shown to be mediated via 5'-CpG island methylation in the promoter region of E-cadherin gene in endometrial cancer cell lines (2).

As well as a reduction in E-cadherin expression, stimulation of Src also results in inhibition of GJIC (3). Signal transducer and activator of transcription-3 (STAT3) is a downstream molecule of Src that if activated via phosporyltion acts as an oncogene (3). By contrast, connexins (Cx) are considered as suppressors of cancer metastasis (4). For example, Cx32 expression reduced anchorage independency and the invasion capacity of a human metastatic renal cell carcinoma cell line (Caki-1 cell) (4). A previous study used RNA interference to demonstrate that Cx32 expression inhibited Src via down-regulation of vascular epithelial growth factor (VEGF) and a reduction in STAT3 phosporylation (4). Cx proteins build gap junctions channels for intercellular communication, and Src-mediated phosphorylation of Cx43 hinders such a communication (5). Unlike the Src effector Cas, phosphorylation of another Src effector, STAT3, does not influence Src-mediated GJIC suppression but is still required for preservation of gap junctional communication in cells with high levels of GJIC (5). The potential relationship between STAT3 and GJIC was investigated by comparing the quantity of tyr705-phosphorylation of STAT3 with the speed and intensity of fluorescent dye Lucifer yellow migration in electrophorated non small cell lung cancer (NSCLC) cell lines, with additional detection of tyr418-phosphorylation of Src (6). The study showed that gap junctions require the activation of STAT3 in order to maintain intracellular communication in non neoplastic and neoplastic lung cell lines. Cell proliferation is generally associated with a reduction in GJIC (7). Coexistent activation of src and its effector molecule STAT3 is also observed in NSCLC cell lines. STAT3 deactivation results in a reduction in gap junctional communication exclusively in normal cells or in lines with low Src activity and high levels of gap junction communication (7). Similarly, STAT3 blockage abrogated junctional permeability

in normal liver cells with high GJIC (3). Recruitment of Src and GJIC were inversely associated with each other but deactivation of STAT3 did not restore GJIC despite activation of Src (6). By contrast, reduction of STAT3 activity abolished GJIC in immortalized lung epithelial cells and in the NSCLC lines with high levels of GJIC. In the light of these findings, STAT3 appears to be indispensible for gap junctional communication in the mentioned cell lines (6). STAT3 function is multidirectional and could affect a number of cellular signaling pathways. Cx proteins are one of numerous families of proteins that may cooperate with STAT3. In cardiac tissues taken from Cx43 knockout mice, STAT3 remained active in the cell (8). Namely, normoxemia did not alter levels of phosphorylation of STAT3, but repeated ischemia and reperfusion increased phosphorylation of STAT3 in cells without functional Cx43 (8). Cx43 is switched on during embryonic stem cell-mediated cardiomyogenesis in a leukemia inhibitory factor (LIF) and bone-morphogenic protein-2 (BMP-2)-induced mouse ES cell (mES-D3 line) with engagement of STAT3 and MAP kinase (ERK1/2) (9). Apart from the association between STAT3 and Cx, it should be emphasized that STAT3 is a versatile driver of endometrial carcinogenesis, while signaling via gap junction channel proteins with involvement of Cx26 and Cx43 is considered to be weakened in progression of carcinogenesis (1,10). The present study aimed to compare the expression levels of STAT3, Cx43 and Cx26 in 78 endometrioid adenocarcinoma samples using immunohistochemical analysis.

Materials and methods

Patient samples. Tumor specimens of human uterine endometrioid adenocarcinomas were obtained from postoperative material of 78 total hysterectomies with bilateral adnexectomies. The study was in accordance with the 2004 revision of the Declaration of Helsinki (11), and was approved by the Bioethical Committee for Studies on Humans of the Medical University of Bialystok (Waszyngtona, Poland). Written informed consent was obtained from all patients included in this study. The tumor samples were categorized into 3 groups according to grade of histopathological differentiation: 15 were well differentiated G1 neoplasms, 52 were moderately differentiated G2 neoplasms and 11 were poorly differentiated G3 neoplasms. Cancers were staged as International Federation of Gynecology and Obstetrics (FIGO) IA tumors (depth of tumor infiltration: tumor invades less than half of myometrium). Tumors that invaded >50% of myometrium (FIGO IB) or spread to the endocervix (FIGO II) comprised a common group for statistical evaluation (2009 FIGO classification of endometrial cancer) (9). Node-negative and node-positive patients were not included in the statistical evaluation, due to scarcity of node-positive endometrioid adenocarcinomas in the present study. The tumors were also divided into subgroups with lack or presence progesterone receptor (PR) and estrogen receptor (ER) positivity. Postoperative material was fixed in 10% buffered formalin for 48 h prior to sampling and embedding in paraffin blocks at 56.8˚C. Tissue sections (3-5 μm thick) were sliced from paraffin blocks and then mounted on 3-aminopropyltriethoxysilane-coated slides, dewaxed and rehydrated. Such processed slides were stained with hematoxylin and eosin (Dako, Glostrup, Denmark) for standard diagnosis given by two pathologists.

Immunohistochemistry. Standard immunohistochemical procedure for STAT3, Cx43, Cx26 ER and PgR was performed in endometrioid adenocarcimonas according to previously described protocols (10, 12-13). Briefly, endogenous peroxidase activity was blocked with 60 sec treatment of slides 3% hydrogen peroxide (Santa Cruz Biotechnology, Inc. Santa Cruz, CA, USA, and then the slides were exposed to 1.5% normal blocking serum (Dako) for 90 min to inhibit unspecific binding reaction. Anti-STAT3 rabbit polyclonal antibodies (sc-7179) (and goat polyclonal antibodies to Cx26 (sc-7261) and Cx43 (sc-6560) were diluted (1:500 for STAT3 and 1:100 for Cx26 and Cx43) and incubated with specimens in PBS for 24 h. The secondary antibodies used were goat anti-rabbit IgG-B (sc-2040) and rabbit anti-goat IgG-B (sc-2774) (dilution, 1:100 for both). Immunohistochemistry was performed as previously described (14). All primary and secondary antibodies were purchased from Santa Cruz Biotechnology, Inc.. EnVision method (Dako) was used for visual detection of complexes of antibodies with STAT3 antigens with 10 min long incubation with diaminobenzidine as a chromogen (DAB). Other proteins were visualized with streptavidin-biotin-peroxidase complex method (LSAB kit; Dako). Slides were counterstained with hematoxylin. Normal endometrium and breast glandular tissue served as weak positive control for STAT3 Cx43, Cx26, ER and PR. The normal non-neoplastic endometrium was obtained from uterine corpses surgically removed from premenopausal women with uterine leiomyomas, whereas the normal, non-neoplastic breast glandular tissue samples were obtained from the tissue margins adjacent to benign fibroadenomas that were surgically removed with margin of uninvolved tissue. For negative controls, the primary antibodies were omitted.

Scoring system and statistical evaluation. Immunoreactions were scored under light microscopy (Nikon Eclipse Ni-U; Nikon Corporation, Tokyo, Japan) in 10 different fields under magnification of x200 to record the mean percentage of immunoreactive malignant cells. The cut-off was 10% malignant positive cells for separation between positive and negative results. A three-grade scale was applied: 0, (negative cancers) <10% positive malignant cells; 1+, with immunoreactivity between 10-50% positive malignant cells (moderate positivity); 2+, with >50% positive tumor cells (strong positivity). Spearman's correlation rank test served for the comparison between pairs of proteins in different groups. The statistical software Statistica 12 64-Bit (StatSoft Polska Sp. z o.o., Cracow, Poland) was used for the statistical analysis.$P<0.05$ was considered to indicate a statistically significant difference.

Results

The cytoplasm was a site of cellular accumulation of Cx26 and Cx43 in endometrioid adenocarcinomas, instead of its functional membranous presence in normal endometrium (Fig. 1A and B). Nuclear expression of STAT3 positively correlated with Cx43 ($P=0.004$, $r=0.318$) and Cx26 ($P=0.006$, $r=0.309$) in the examined samples (Fig. 1C and D). STAT3 expression correlated with Cx43 ($P=0.022$, $r=0.411$) and Cx26 ($P=0.008$ $r=0.466$) in well-differentiated tumors. A statistically significant linkage remained in moderately

Table I. Association between STAT3 and connexin expression levels in uterine endometrioid adenocarcinoma samples.

	STAT3-Cx43		STAT3-Cx26	
Patients' group	P-value	r	P-value	r
All patients; n=78	**0.004**	**0.318**	**0.006**	**0.309**
Age <60 years; n=33	0.167	0.246	0.439	0.139
Age >60 years; n=45	**0.011**	**0.375**	**0.003**	**0.438**
IA; n=40	**0.002**	**0.478**	0.097	0.266
IB+II; n=38	0.341	0.159	**0.034**	**0.344**
G1; n=15	**0.022**	**0.411**	**0.008**	**0.466**
G2; n=52	0.061	0.262	**0.016**	**0.331**
G3; n=11	0.415	0.274	0.200	0.418
ERα (-); n=16	**0.003**	**0.684**	**0.049**	**0.500**
ERα (+); n=62	0.074	0.229	**0.035**	**0.268**
PR (-); n=22	**0.035**	**0.451**	**<0.0001**	**0.707**
PR (+); n=56	**0.030**	**0.290**	0.166	0.188

Statistically significant values are highlighted in bold. IA, malignant infiltration spread less than half thickness through the myometrium; IB+II, malignant infiltration spread more than halfway through the myometrium and/or involving cervix; G1, well-differentiated adenocarcinoma; G2, moderately differentiated ones; G3, poorly differentiated tumors; ERα (-), estrogen receptor alpha negative tumors; ERα (+), estrogen receptor alpha positive tumors; PR (-), progesterone receptor negative tumors; PR (+), progesterone receptor positive tumors.

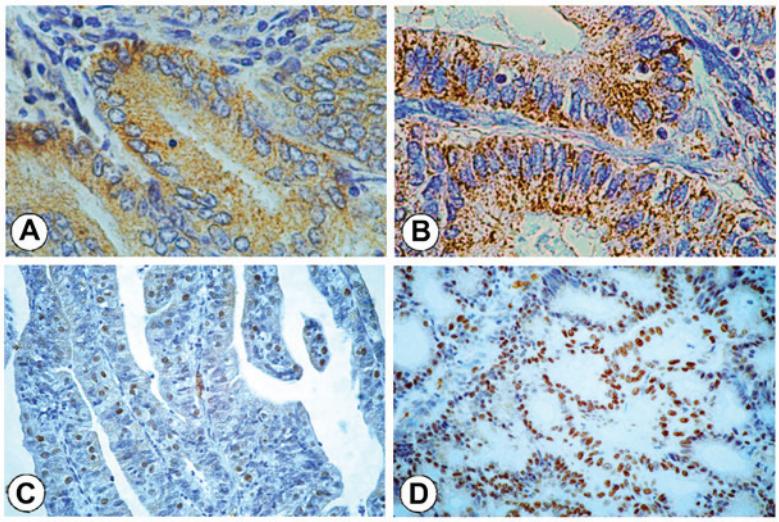

Figure 1. (A) Finely granular staining to Cx26 in cytoplasm of endometrial cancer cells (original magnification, x400). (B) Coarsely granular immunoreactivity to Cx43 in cytoplasm of malignant cells (original magnification, x400). (C) Weak nuclear reactivity for STAT3 and (D) strong nuclear reactivity for STAT3 with certain secretory features in endometrioid adenocarcinoma (original magnification x200).

differentiated G2 cancers with STAT3 correlating with Cx43 (P=0.061, r=0.262) and with Cx26 (P=0.016, r=0.331). In G3 tumors, however, no correlation was observed between STAT3 and Cx43 (P=0.415, r=0.274) and Cx26 (P=0.200, r=0.418). ER negativity was associated with sustained statistically significant relationships between STAT3 and Cx43 (P=0.003, r=0.684) and Cx26 (P=0.049, r=0.500). ER positivity coexisted with loss of significance in STAT3 and Cx43 coexpression (P=0.074, r=0.229), while STAT3 remained correlated with Cx26 (P=0.035, r=0.268). A similar trend was observed in PR negative tumors where statistical correlations remained for STAT3 and Cx43 (P=0.035, r=0.451) or STAT3 and Cx26 (P<0.0001, r=0.707). In PR positive adenocarcinomas statistical significance persisted in relation to STAT3 and Cx43 (P=0.03, r=0.290) but was completely lost between STAT3 and Cx26 (P=0.166, r=0.188) (Table I).

Discussion

It has previously been demonstrated in IK-ER1 overexpressing ER-alpha endometrial carcinoma cells that estradiol suppressed formation of gap channels via Cx26 and Cx32 (15). In the present study using human endometrial cancer tissues, sex hormone receptor positivity contributes to loss of statistically significant

linkage between STAT3 and Cx43 in the case of ER positive cancers as well as loss of association between STAT3 and Cx26 in PR-positive cancers. The findings reflect impaired function of aberrantly expressed Cx proteins and complete lack of association between STAT3 and Cx43 expression in PR-positive and ER-positive endometrial cancer. It should be remembered that the compared proteins have opposite functions. Namely, STAT3 as a driver of endometrial carcinogenesis and connexins as suppressors of endometrial growth (2,3,10,13,16), but such a role is mediated only by nuclear STAT3 and membranous Cx proteins. It should not be remarkable that nuclear expression of STAT3 positively correlated with expression of Cx proteins, however, the expression of Cx43 and Cx26 was observed to be cytoplasmic indicating loss of their growth suppressing properties that require a membranous location. In spite of their opposite functions, expression of these proteins could be switched on together. For instance, heterodimer ciliary neurotrophic factor expression increased Cx43 mRNA and protein expression and caused nuclear localization of phosphorylated STAT3 in astrocytes (17).

Characteristically, in our previous study, there was no linkage between Cx26 expression and patients' age, histological type of cancer and histological grade except for a positive correlation between Cx26 expression and tumor size (18). GJA1/Cx43 and GJA6/Cx30 have emerged as prognostic factors in breast cancer, which similarly to endometrial cancer is regarded as an estrogen dependent malignancy (19). In addition diminished Cx26 expression was associated with improved overall survival rates for breast cancer patients following chemotherapy, while Cx46 expression was a marker of significantly improved survival of selected groups of breast cancer patients in pre-chemotherapy and post-chemotherapy periods (20). In this perspective of prognostic significance of Cx, the present findings connect Cx expression with the carcinogenesis driver STAT3 in another estrogen dependent neoplasm, endometrial cancer.

The association between STAT3 and Cx43 expression is also gradually lost in the process of dedifferentiation from G1 to G3 endometrioid adenocarcinomas in the current study. Generally weakening of STAT3 expression was not observed within grading in our previous studies (10,13) however expression of Cx43 was reduced with tumor grade in endometrial cancer samples in a study by Schlemmer *et al* (21).

In the context of associations between STAT3 and Cx43 and Cx26, therapeutic perspectives have emerged that aim to downregulate STAT3 expression (particularly reducing STAT3 nuclear accumulation where it acts as an activator of transcription) and upregulation of expression of Cx proteins (particularly encouraging a membranous location of Cx where they act as cell growth suppressors). For instance, kaempferol regulates STAT3 and Cx, inducing differentiation in colon cancer cells expressing low levels of Cx43 (keratin-negative cells) (22). Kaempferol resulted in differentiation that was accompanied with increased quantity of Cx43 and its phosporylation, an increase in GJIC and a decrease in activation of STAT3 and ERK. In cancer cells that, even weakly, expressed Cx43, kaempferol recruited STAT3 and triggered resultant overexpression and phosporylation of this connexin, which led to the restoration of GJIC (22). Kaempferol mediated restoration of GJIC via STAT3-dependent overexpression and phosporylation of Cx43, if only cancer cells expressed this connexin at least at low level (22). In addition, gap junctional communication was not restored if STAT3 was inhibited in lung cell lines with a high stimulated Src level (7); similarly, gap junctional communication was not restored in rat liver epithelial cells habouring activated Src when trichloronitritodiammineplatinum(IV), STAT3 inhibitor or a retroviral vector (expressing a STAT3-specific shRNA) decreased expression of STAT3 (3). This evidence indicates a pleiotropic significance of STAT3: That it enables permeability of gap junctions and contributes to maintenance of gap junction communication (3,7). It should be emphasized that, besides Cx expression, STAT3 is an extraordinarily versatile mediator and it interacts with a number of molecules, including leptin and its receptor OB-R, IL-11 or oncostatin M that affect the invasive properties of malignant cells via their impact on cellular adhesion, motility and survival in gynecological cancers (10,23-27). Thus, there may be multiple and complex associations between STAT3 and other cellular mediators, and therefore any statistically significant coexpression of engaged proteins should be carefully evaluated. Nevertheless, further studies are required to elucidate the role of STAT3 signaling in endometrial cancer.

In conclusion, ER and PR-positivity defines endometrioid adenocarcinomas as sex steroid hormone dependent neoplastic growth and is associated with deregulation of the link between STAT3 and Cx expression. By contrast, lack of immunoreactivity for the presence of mentioned receptors is associated with the preservation of the statistically significant relationship between STAT3 and the studied Cx. These findings provide evidence that hormone dependent acceleration of cancer growth breaks the association between STAT3 and Cx expression. Such associations are gradually lost in the progression of dedifferentiation from G1 to G3 endometrioid adenocarcinomas. In conclusion, it appears that loss of correlation between STAT3 and selected Cx proteins occurs in ER and PR-positive tumors and also in tumors with more aggressive behavior.

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