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Research Article

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Transformed Follicular Lymphoma (TFL) Predicts Outcome in Advanced Endometrial Cancer

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Abstract

Background: Transformed follicular lymphoma (*TFL, ZC3H12D*) was identified as a candidate tumor suppressor gene that contributes to cell-cycle arrest through regulation of Rb phosphorylation, but the clinical impact of TFL is unknown. The goal of this study was to evaluate the prognostic significance of TFL expression in advanced endometrial cancer.

Methods: Tissue samples were obtained from 103 patients with Federation Internationale des Gynaecologistes et Obstetristes stage III–IV endometrial cancer. Associations between TFL expression and outcomes were evaluated using the Kaplan–Meier method and multivariate Cox proportional hazards regression models.

Results: There were 24 TFL-low cases (23.3%) and the 10-year progression-free survival (PFS) and overall survival (OS) in these cases were lower than those for patients with normal TFL expression in univariate analysis (PFS, $P = 0.003$; OS, $P = 0.106$). In multivariate analysis, TFL status was a significant predictor for PFS [HR = 2.76; 95% confidence interval (CI), 1.45–5.28; $P = 0.002$] and OS (HR = 1.94; 95% CI, 0.91–4.11; $P = 0.085$), adjusted for covariates. The *TFL* gene maps to human chromosome 6q25.1, where estrogen receptor alpha (ERα) gene *ESR1* is also located. Lack of ERα expression is a poor prognostic factor in early endometrial cancer. Among 41 ERα-low patients, 10-year PFS was significantly lower in 15 TFL-low cases (univariate analysis, $P = 0.055$; multivariate analysis, HR = 4.70; 95% CI, 1.68–13.20; $P = 0.003$).

Conclusions: We identified TFL as a strong independent prognostic factor, regardless of ERα status.

Impact: An investigation of the mechanism underlying tumor suppression by TFL may lead to new therapies for patients with advanced endometrial cancer. *Cancer Epidemiol Biomarkers Prev; 27(8); 1–7. ©2018 AACR.*

Introduction

Endometrial cancer is the most common gynecologic malignancy, accounting for 30% of all gynecologic cancer-related deaths (1). Most patients (75%) with the disease are diagnosed at an early stage in Federation Internationale des Gynaecologistes et Obstetristes (FIGO) stages I and II, and the 5-year overall survival (OS) rate is 74% to 91%. However, despite improvements in surgical treatment and adjuvant therapy for patients with advanced endometrial cancer in FIGO stages III and IV, the 5-year OS rates are 57% to 66% and 20% to 26%, respectively (1–3). Prognostic molecular markers for endometrial cancer have been described in several studies, but are not used for treatment decision-making, because most markers correlate with histologic type and are restricted to early-stage disease (3–5). Therefore, therapeutic strategies are determined by the FIGO stage and tumor–node–metastasis classification, combined with pathologic findings, including histologic type, myometrial invasion, peritoneal cytology, cervical stromal invasion, and lymphovascular invasion (3, 6–9).

Advanced endometrial cancer is a systemic disease that is fatal in many cases, but there are survivors for more than 5 years. Outcomes are thought to correlate with biological factors such as chemosensitivity, proliferative ability, and invasive ability (1–3). The current risk stratification has limitations for improvement of therapeutic strategies because it is not based on biology. Treatments including molecular targeted agents are under development, but not all patients benefit from these treatments. Therefore, it is particularly important to define the risk using a molecular approach and to evaluate molecular targets for improving the prognosis of advanced endometrial cancer.

Transformed follicular lymphoma (*TFL, ZC3H12D*) was first identified as a gene at the breakpoint of the t(2;6)(p12;q25) chromosome translocation in a patient with lymphoma in whom disease transformed from follicular lymphoma (10), the common form of indolent lymphoma, to diffuse large B-cell lymphoma, an aggressive type. The *TFL* gene maps to human chromosome 6q25.1, where the estrogen receptor alpha (ERα) gene *ESR1* is also located. ERα expression status is a validated prognostic molecular marker in early-stage endometrial cancer, but this is not clear for the advanced

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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stage (11–14). We evaluated the association between TFL expression and ERα expression in this study.

TFL is a candidate tumor suppressor gene that contributes to cell-cycle arrest and RNA regulation (15). There have only been a few reports on TFL, and its clinical significance is unclear. Here, we establish TFL as a new prognostic marker in advanced endometrial cancer. This is the first study of the clinical significance of TFL in a malignant neoplasm.

Materials and Methods

Patients

All patients in the study were diagnosed with endometrial cancer and treated at Hyogo Cancer Center (Akashi, Japan) between January 1, 1997, and December 31, 2012. Data were collected for 103 patients with cancer of FIGO stages III–IV who satisfied the following inclusion criteria: (i) primary endometrial cancer (except for mesenchymal and malignant mixed Müllerian tumor); (ii) primary surgical treatment and adjuvant treatment; and (iii) no history of malignant neoplasms other than endometrial cancer. An attending pathologist and gynecologic pathologist reviewed the histologic type based on World Health Organization criteria (16) in all cases. Follow-up was performed at the Hyogo Cancer Center with routine transvaginal ultrasonography, vaginal cytology, serum tumor markers, and systematic radiography. Clinicopathologic variants and dates of primary surgery, disease progression, death, or last follow-up were retrieved from hospital records. Written informed consent was obtained from all the subjects, and the Institutional Review Board of the Hyogo Cancer Center approved this investigation (#H25-R-4).

IHC

Representative formalin-fixed, paraffin-embedded surgical specimens were selected from the 103 cases. An anti-TFL mAb was generated by immunizing GST-tagged human recombinant TFL (17, 18). TFL IHC was performed on 5-μm sections using a Leica BOND-MAX autostainer (Leica Microsystems). Tissue sections were treated for heat-induced epitope retrieval using Leica Bond Epitope Retrieval Solution (ER-2, Leica Microsystems) for 20 minutes at 100°C and incubated with a primary anti-TFL antibody for 20 minutes at room temperature. The primary antibody was detected with a Leica Bond Polymer Refine DAB detection system (Leica Microsystems). Sections were counterstained with hematoxylin. Samples of spleen known to yield positive staining for TFL (15, 17, 19) were used as positive controls. TFL expressed in lymphocytes in the splenic marginal zone is shown in Supplementary Fig. S1A. ERα IHC was carried out with a Ventana BenchMark Ultra system using a primary antibody against ERα (CONFIRM anti-Estrogen Receptor, clone SP1) and an iVIEW DAB Universal Kit, and counterstained with Hematoxylin II (all Ventana, Roche Diagnostics), according to the standard Ventana protocols. Substituting the primary antibody with mouse IgG2b (DAKO) for TFL and Rabbit Monoclonal Negative Control Ig (Ventana) for ERα was used as negative control.

Evaluation of staining

All patients were assessed for TFL and ERα expression. Slides were scored individually using standard light microscopy for IHC staining while blinded to patient characteristics and outcomes. TFL expression was evaluated independently by three of the authors (one gynecologic pathologist and two experienced gynecologists), and ERα expression was evaluated by two of the authors (both experienced gynecologists). Scoring for staining was performed in a semiquantitative manner using the H-score to take into account the intensity and heterogeneity of expression. The staining intensity was defined as follows: 0 = no staining, even at high magnification; intensity 1 = staining only at high magnification; 2 = clear staining, but not intense at low magnification; and 3 = intense staining, even at low magnification (TFL, Fig. 1; ERα, Supplementary Fig. S1B). The H-score was

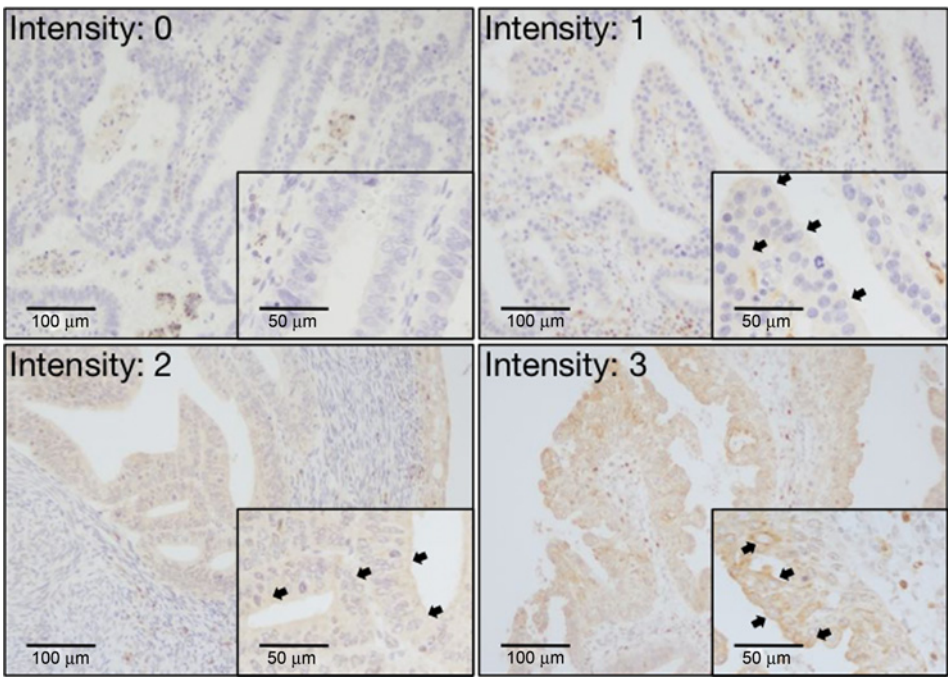

Figure 1.
IHC staining showing intensity of TFL expression in the cytoplasm of endometrial cancer cells. The arrows show representative staining intensity.

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calculated as the product of the staining intensity and the percentage of tumor cells stained, which gives a score ranging from 0 to 300.

Statistical analysis

The primary aim of the study was to evaluate the prognostic impact of TFL expression. Therefore, progression-free survival (PFS) was defined as the primary endpoint and overall survival (OS) as a secondary endpoint. PFS was defined as the time from the date of primary surgery to that of disease progression, death, or censored at last follow-up. OS was defined as the time from the date of primary surgical resection to that of death for any reason or censored at last follow-up. Prognostic impact of TFL expression and other covariates were evaluated using the Kaplan–Meier method with a log-rank test. Multivariate Cox proportional hazards regression models were used to evaluate TFL expression, with covariates of age, FIGO stage, histologic type, myometrial invasion, and peritoneal cytology. HRs with 95% confidence intervals (95% CI) were calculated. Effects of clinicopathologic variables on TFL expression were evaluated by Mann–Whitney *U* test. Statistical analyses were conducted using GraphPad Prism 5.0d (GraphPad Software Inc.) or R for Mac OS X (R 3.1.0 GUI 1.64 Mavericks build), with a two-sided $P < 0.05$ considered to indicate statistical significance.

Results

Characteristics of patients

Clinicopathologic characteristics of the 103 patients with FIGO stage III–IV endometrial cancer are shown in Table 1. No patients had received preoperative chemotherapy or radiotherapy. All underwent total hysterectomy and bilateral salpingo-oophorectomy with or without omentectomy, accompanied by lymphadenectomy or lymph node sampling in 89 cases. Patients were classified as FIGO stages IIIA (19.4%), IIIB (1.9%), IIIC1 (38.8%), IIIC2 (16.5%), and IVB (23.3%). No cases were in stage IVA with extension of the disease to the rectum or bladder. After surgery, 101 patients received adjuvant platinum-based chemotherapy, and two received platinum-based chemoradiotherapy. During a median follow-up period of 71 months (range, 5–199 months), there were 43 relapses and 35 deaths.

Table 1. Clinical characteristics of 103 patients with advanced endometrial cancer

Variable	Number of patients
Age (range, 34–78 y)	
<57 y	51
≥57 y	52
FIGO stage	
IIIA–IIIC2	79
IV	24
Histologic type I	63
Endometrioid grade 1	29
Endometrioid grade 2	34
Histologic type II	40
Endometrioid grade 3	15
Serous	20
Clear	1
Undifferentiated	4
Myometrial invasion	
<50%	45
≥50%	58
Peritoneal cytology	
Negative	59
Positive	44
Cervical stromal invasion	
Negative	73
Positive	30
Lymphovascular invasion	
Negative	23
Positive	80
Primary treatment surgery	
Lymphadenectomy	79
Lymph-node sampling	10
No lymphadenectomy	14
Primary treatment adjuvant chemotherapy	
TC or DC	70
AP	10
CAP	16
CAP or TC plus irradiation	5
Chemoradiotherapy	2

Abbreviations: AP, doxorubicin + cisplatin; CAP, cyclophosphamide + doxorubicin + cisplatin; DC, docetaxel + carboplatin; TC, paclitaxel + carboplatin.

TFL expression levels in control endometrium and endometrial cancer

Evaluation of TFL H-scores by scatter plot analysis was used to compare TFL expression between control endometrium and endometrial cancer. Control endometrium samples were collected from surgical specimens in 41 cases of benign gynecologic disease (23 pre- and 18 postmenopausal cases). A gynecologic pathologist reviewed all slides to confirm the absence of neoplasms, hyperplasia, and other gynecologic diseases in the endometrium. The median TFL H-score was significantly higher in endometrial cancer compared with that in control endometrium samples (70 vs. 100, $P = 0.001$; Fig. 2). Differences in TFL H-scores were more prominent in premenopausal cases ($P = 0.003$) than in postmenopausal cases ($P = 0.061$).

Prognostic impact of clinicopathologic variables and relationship with TFL expression

The risk of recurrence and mortality were evaluated based on univariate and multivariate analyses of clinicopathologic variables (Supplementary Table S1). In univariate analysis, age, FIGO stage, histologic type, myometrial invasion, and peritoneal cytology were associated with 10-year PFS or OS. Cervical stromal invasion (negative vs. positive: 10-year PFS, 62% vs. 43%, $P = 0.025$; 10-y OS, 73% vs. 48%, $P = 0.025$) and lymphovascular invasion (negative vs. positive: 10-year PFS, 68% vs. 53%, $P = 0.129$; 10-year OS, 75% vs. 64%, $P = 0.212$) tended to be associated with prognosis and were excluded as confounders in multivariate analysis because of multicollinearity with myometrial invasion status. Therefore, age, FIGO stage, histologic type, myometrial invasion, and peritoneal cytology were defined as confounders in multivariate analysis. Scatter plot analyses showed that TFL expression was not correlated with these variables (Supplementary Fig. S2).

Lack of TFL expression as a risk factor for PFS and OS

Multivariate analysis indicated that TFL expression was significantly associated with OS and PFS when performed in a stepwise manner with cutoff values for TFL H-score adjusted for age, FIGO stage, histologic type, myometrial invasion, and peritoneal cytology (Supplementary Fig. S3A). The frequency distribution of the TFL H-score showed a bimodal pattern with a dip at 60 and peaks at 20 and 100 (Supplementary Fig. S3B).

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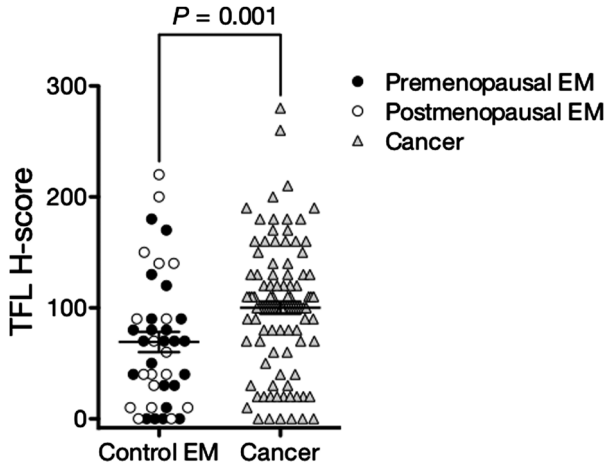

Figure 2.
TFL expression in control endometrium (Control EM) compared with endometrial cancer (Cancer). Each bar is the mean TFL H-score ± SE.

From this result, a TFL H-score ≤60 was defined as indicating low TFL expression status.

Of the 103 patients, 24 (23.3%) were classified as TFL-low. In univariate analysis, OS and PFS were significantly associated with TFL expression status (Fig. 3). In multivariate analysis adjusted for age, FIGO stage, histologic type, myometrial invasion, and peritoneal cytology, lack of TFL expression remained as an independent predictor of a poor prognosis (Table 2). The outcome in each subgroup of clinicopathologic variables was visualized using forest plots of HRs and 95% CIs from multivariate analysis (Supplementary Fig. S4). For PFS, this analysis showed that lack of TFL expression was a risk for recurrence, regardless of clinicopathologic variables, except myometrial invasion <50%. A similar result was obtained for OS, with association with TFL expression more prominent in subgroups with age ≥57, myometrial invasion ≥50%, and positive peritoneal cytology.

Association of TFL expression with ERα expression

The association between TFL expression and ERα expression was evaluated because *TFL* maps to human chromosome 6q25.1, where the ERα gene, *ESR1*, is also located. In previous studies (11–14), ERα cutoff values have been based on staining intensity and staining area. For these reasons and due to the frequency distribution (Supplementary Fig. S3C), we also defined an ERα H-score ≤30 as the cutoff point for low ERα expression status. In univariate analysis, lack of ERα expression was associated with a poor prognosis in our patients, but in multivariate analysis, ERα expression was not independent of clinicopathologic variables (Supplementary Table S2). Scatter plot analyses showed that TFL H-scores were significantly correlated with ERα expression status (Fig. 4A). In the ERα-low group, the scatter plot was clearly divided into cases with high and low TFL expression, but this did not occur in the ERα-high group. A Kaplan–Meier plot of PFS clearly showed that TFL was a definitive prognostic marker, regardless of ERα status (Fig. 4B). The effect of TFL was more prominent in the ERα-low group (Supplementary Table S3; Supplementary Fig. S5). OS showed a similar trend to PFS (58% vs. 44%, $P = 0.635$; adjusted HR = 2.86; 95% CI, 0.88–9.34; $P = 0.081$). In the ERα-high group, PFS and OS were not associated with TFL expression status (PFS: 67% vs. 56%, $P = 0.295$, adjusted HR = 1.78; 95% CI, 0.49–6.47; $P = 0.381$; OS: 77% vs. 67%, $P = 0.358$, adjusted HR = 1.78; 95% CI, 0.38–8.35; $P = 0.468$).

Discussion

The results of this study provide important insights into lack of TFL expression as a poor prognostic marker in advanced endometrial cancer. Most molecular markers for endometrial cancer are restricted to early-stage disease and correlate with pathologic findings. In contrast, there is no definitive marker for advanced endometrial cancer (3–5). For this reason, risk stratifications of clinical staging combined with pathologic findings are used in clinical decisions in endometrial cancer (3, 6–9). Survival of patients with advanced endometrial cancer may be improved by a reliable prognostic marker and innovative treatment strategies. Our results show that lack of TFL expression is an independent prognostic factor for this disease. Also, TFL may serve as a target in new treatment strategies for endometrial cancer.

TFL is a member of the Zc3h12 family (Zc3h12a, 12b, 12c, and 12d) of single CCCH-type zinc finger motifs; hence, it is named Zc3h12d (20). There is a close relationship between the immune system and Zc3h12 proteins (18, 19, 21, 22), and the importance of Zc3h12 proteins in cancer has recently been shown. For example, MCPIP (Zc3h12a) has a regulatory role in the c-Maf/IL4 axis via Dicer function in processing of small RNAs such as miR-155, and there is an inverse correlation between MCPIP expression and survival in lung cancer. Thus, these data suggest that MCPIP expression and Dicer function may decrease survival in lung cancer (23).

TFL was first reported as tumor suppressor gene *p34*, based on loss of heterozygosity in human chromosomal fragment 6q25.1 in sporadic lung cancer tissues (24). In previous studies, we showed that TFL is localized in discrete granules in the cytoplasm

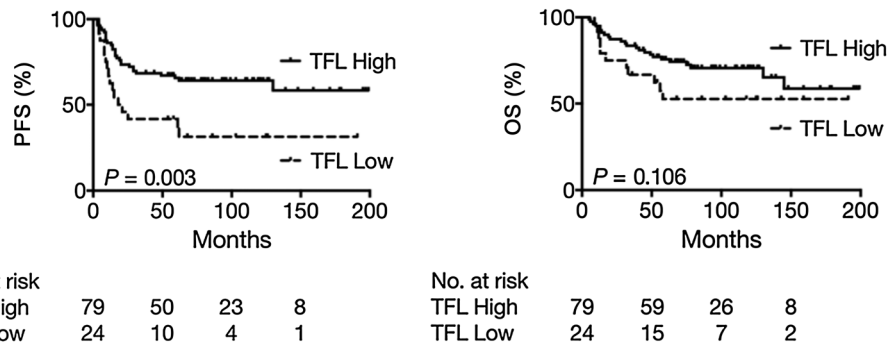

Figure 3.
Kaplan–Meier curves for PFS and OS based on TFL expression status.

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Table 2. Univariate and multivariate analysis of estimated progression-free survival and overall survival based on TFL expression status

		Univariate analysis				Multivariate analysis	
Survival	**TFL status**	**Number of patients**	**5 years (95% CI)**	**10 years (95% CI)**	***P***	**HR (95% CI)**	***P***
Progression free	High	79	66% (56–77)	64% (54–76)	0.003	1.00 (reference)	0.002
	Low	24	42% (26–67)	31% (17–58)		2.76 (1.45–5.28)	
Overall	High	79	76% (67–86)	71% (61–82)	0.106	1.00 (reference)	0.085
	Low	24	53% (36–78)	53% (36–78)		1.94 (0.91–4.11)	

NOTE: HRs are adjusted for age, FIGO stage, histologic type, myometrial invasion, and peritoneal cytology.

and contributes to cell-cycle arrest in G_1 to S phases through regulation of Rb phosphorylation in the mouse pro-B cell line Ba/F3 and Jurkat human leukemia cells (15, 19). This essential role in cell-cycle regulation suggests that TFL might participate in the development and progression of endometrial cancer.

TFL expression in endometrial cancer was significantly higher than in control endometrial tissue. These data are opposite to results for most tumor suppressor genes, but TFL expression may be induced by oncogenic transformation of uterine epithelial cells, such as ARF (25). Another possibility, based on recent reports of other Zc3h12 family members such as MCPIP, is that the cause of the correlation between TFL expression and prognosis is not due to tumor suppressor function, but to posttranscriptional regulation. Localization of TFL in cytoplasmic granules (15, 19) may indicate that TFL regulates cancer cell proliferation, migration, invasion, metastasis, and treatment resistance via posttranscriptional modulation, similarly to MCPIP. Understanding of the role of TFL may be useful in development of therapy for prevention of tumor progression.

Given that *TFL* is located at 6q25.1, 2cM upstream from *ESR1*, it is of note that most TFL-low cases were also ERα-low (Fig. 4A) and that TFL was an independent prognostic factor (Supplementary Table S3). In breast cancer, ERα status is a reliable prognostic factor that is currently used in clinical treatment planning (26–28). In endometrial cancer, the prognostic significance of ERα status has been shown in many studies (11–14), but few have examined the regulatory mechanism of ERα loss and the cause of a poor prognosis in ERα-low patients (14, 29–32). One interpretation of our result is that the clinical impact of ERα loss may represent that of TFL loss. The close synteny raises the possibility that genetic changes in TFL might contribute to lack of ERα expression.

Advances in genetic understanding of endometrial cancer have led to interest in molecular targeted agents, including inhibitors of EGFR, HER2, and PI3K/AKT/mTOR, which act on cell-cycle arrest (3, 33–35). Given the clinical importance of our findings, it will be of interest to study the mechanisms underlying regulation of cancer development by TFL, as a future molecular target.

Given its retrospective nature, this study has several limitations. First, potential selection bias could have occurred because of the focus on analysis of FIGO stage III–IV cases treated at a single institution over a long period. To find a significant influence of TFL expression on outcome, we excluded FIGO stage I–II cases because their numbers are large and there is relatively little difference in outcome. Future studies on all stages of endometrial cancer in a large cohort will be necessary to ascertain the role of TFL in outcome. Second, adjuvant treatment was highly variable because this treatment changed over the relatively long study period (36–44). In addition, the extent of lymph node dissection was defined individually on the basis of clinical features and intraoperative findings. The optimal surgical treatment for FIGO III–IV endometrial cancer is still uncertain, and standard optimal treatment concepts changed over the period of the study (3, 37, 43, 45–49). The 5-year OS rates of 82% for stage III and 33% for

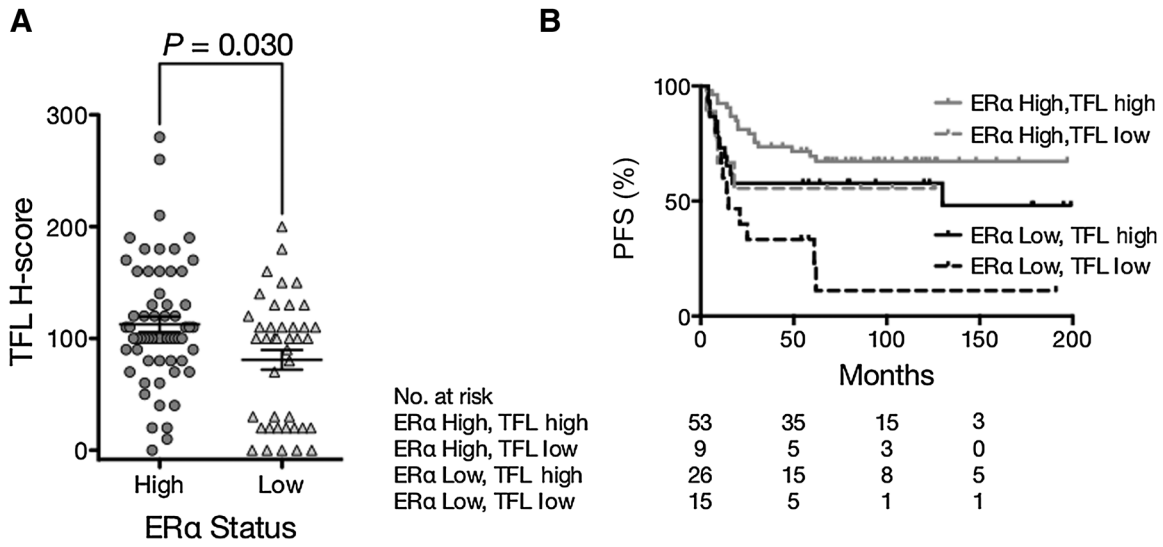

Figure 4.

A, Scatter plot showing the range of TFL H-scores in ERα-high and low cases. Each bar is the mean TFL H-score ± SE. **B,** Kaplan–Meier curves for PFS based on TFL and ERα status.

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stage IV cases are better than those in previous reports (1–3). Third, potential confounders such as age, FIGO stage, and histologic type were considered in multivariate analyses, but residual confounders such as chemosensitivity and performance status cannot be ruled out. For all of these reasons, it will be important to replicate our findings in a large prospective cohort.

In summary, the current study is the first to show that lack of TFL expression is a significant independent predictor of poor prognosis for a malignant neoplasm. There is currently no definitive prognostic marker for advanced endometrial cancer. Our findings suggest that TFL may be such a marker and a target for potential new treatment for this disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S. Wakahashi, K. Wakahashi, K. Minagawa, K. Matsuo, T. Sudo

Development of methodology: S. Wakahashi, K. Matsuo, T. Matsui, T. Sudo

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Wakahashi, F. Kawakami, K. Matsuo

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Wakahashi, F. Kawakami, K. Wakahashi, K. Minagawa, K. Matsuo, Y. Katayama

Writing, review, and/or revision of the manuscript: S. Wakahashi, F. Kawakami, K. Matsuo, Y. Katayama, H. Yamada

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. Wakahashi, K. Minagawa, K. Matsuo, T. Matsui

Study supervision: K. Minagawa, K. Matsuo, T. Sudo

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.
2. Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, et al. Carcinoma of the corpus uteri. FIGO 26th annual report on the results of treatment in gynecological cancer. Int J Gynaecol Obstet 2006;95:S105–43.
3. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet 2016;387:1094–108.
4. Salvesen HB, Haldorsen IS, Trovik J. Markers for individualised therapy in endometrial carcinoma. Lancet Oncol 2012;13:e353–e61.
5. Werner H, Salvesen H. Current status of molecular biomarkers in endometrial cancer. Curr Oncol Rep 2014;16:1–12.
6. Bendifallah S, Canlorbe G, Raimond E, Hudry D, Coutant C, Graesslin O, et al. A clue towards improving the European Society of Medical Oncology risk group classification in apparent early stage endometrial cancer? Impact of lymphovascular space invasion. Br J Cancer 2014;110:2640–6.
7. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. Lancet North Am Ed 2000;355:1404–11.
8. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92:744–51.
9. Murali R, Soslow RA, Weigelt B. Classification of endometrial carcinoma: more than two types. Lancet Oncol 2014;15:e268–e78.
10. Minagawa K, Yamamoto K, Nishikawa S, Ito M, Sada A, Yakushijin K, et al. Deregulation of a possible tumour suppressor gene, ZC3H12D, by translocation of IGK@ in transformed follicular lymphoma with t(2;6)(p12;q25). Br J Haematol 2007;139:161–3.
11. Creasman WT. Prognostic significance of hormone receptors in endometrial cancer. Cancer 1993;71:1467–70.
12. Engelsen IB, Stefansson IM, Akslen LA, Salvesen HB. GATA3 expression in estrogen receptor alpha-negative endometrial carcinomas identifies aggressive tumors with high proliferation and poor patient survival. Am J Obstet Gynecol 2008;199:543.
13. Kauppila AJ, Isotalo HE, Kivinen ST, Vihko RK. Prediction of clinical outcome with estrogen and progestin receptor concentrations and their relationships to clinical and histopathological variables in endometrial cancer. Cancer Res 1986;46:5380–4.
14. Wik E, Raeder MB, Krakstad C, Trovik J, Birkeland E, Hoivik EA, et al. Lack of estrogen receptor-alpha is associated with epithelial-mesenchymal transition and PI3K alterations in endometrial carcinoma. Clin Cancer Res 2013;19:1094–105.
15. Minagawa K, Katayama Y, Nishikawa S, Yamamoto K, Sada A, Okamura A, et al. Inhibition of G1 to S phase progression by a novel zinc finger protein p58TFL at P-bodies. Mol Cancer Res 2009;7:880–9.
16. Kurman RJ, International Agency for Research on Cancer, World Health Organization. WHO classification of tumours of female reproductive organs. 4th ed. Lyon, France: International Agency for Research on Cancer; 2014.
17. Huang S, Qi D, Liang J, Miao R, Minagawa K, Quinn T, et al. The putative tumor suppressor Zc3h12d modulates toll-like receptor signaling in macrophages. Cell Signal 2012;24:569–76.
18. Minagawa K, Wakahashi K, Kawano H, Nishikawa S, Fukui C, Kawano Y, et al. Posttranscriptional modulation of cytokine production in T cells for the regulation of excessive inflammation by TFL. J Immunol 2014;192:1512–24.
19. Minagawa K, Katayama Y, Matsui T. TFL, a hidden post-transcriptional modulator behind inflammation. Inflammation and cell signaling 2014;1:e244.
20. Liang J, Song W, Tromp G, Kolattukudy PE, Fu M. Genome-wide survey and expression profiling of CCCH-zinc finger family reveals a functional module in macrophage activation. PLoS One 2008;3:e2880.
21. Matsushita K, Takeuchi O, Standley DM, Kumagai Y, Kawagoe T, Miyake T, et al. Zc3h12a is an RNase essential for controlling immune responses by regulating mRNA decay. Nature 2009;458:1185–90.
22. Uehata T, Akira S. mRNA degradation by the endoribonuclease Regnase-1/ZC3H12a/MCPIP-1. Biochim Biophys Acta 2013;1829:708–13.
23. Suzuki HI, Arase M, Matsuyama H, Choi YL, Ueno T, Mano H, et al. MCPIP1 ribonuclease antagonizes dicer and terminates MicroRNA biogenesis through precursor MicroRNA degradation. Mol Cell 2011;44:424–36.
24. Wang M, Vikis HG, Wang Y, Jia D, Wang D, Bierut LJ, et al. Identification of a novel tumor suppressor gene p34 on human chromosome 6q25.1. Cancer Res 2007;67:93–9.
25. Zindy F, Williams RT, Baudino TA, Rehg JE, Skapek SX, Cleveland JL, et al. Arf tumor suppressor promoter monitors latent oncogenic signals *in vivo*. Proc Natl Acad Sci USA 2003;100:15930–5.
26. Cleator S, Heller W, Coombes RC. Triple-negative breast cancer: therapeutic options. Lancet Oncol 2007;8:235–44.
27. Harbeck N, Gnant M. Breast cancer. Lancet 2017;389:1134–50.

28. Lindström LS, Karlsson E, Wilking UM, Johansson U, Hartman J, Lidbrink EK, et al. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. J Clin Oncol 2012;30:2601–8.
29. Dhasarathy A, Kajita M, Wade PA. The transcription factor snail mediates epithelial to mesenchymal transitions by repression of estrogen receptor-α. Mol Endocrinol 2007;21:2907–18.
30. Fujino T, Risinger JI, Collins NK, Liu F-s, Nishii H, Takahashi H, et al. Allelotype of endometrial carcinoma. Cancer Res 1994;54:4294–8.
31. Tibiletti M, Bernasconi B, Taborelli M, Furlan D, Fabbri A, Franchi M, et al. Involvement of chromosome 6 in endometrial cancer. Br J Cancer 1997; 75:1831.
32. Velasco A, Pallares J, Santacana M, Yeramian A, Dolcet X, Eritja N, et al. Loss of heterozygosity in endometrial carcinoma. Int J Gynecol Pathol 2008;27:305–17.
33. Bjornsti MA, Houghton PJ. The TOR pathway: a target for cancer therapy. Nat Rev Cancer 2004;4:335–48.
34. Slomovitz BM, Coleman RL. The PI3K/AKT/mTOR pathway as a therapeutic target in endometrial cancer. Clin Cancer Res 2012;18:5856–64.
35. Teplinsky E, Muggia F. Targeting HER2 in ovarian and uterine cancers: challenges and future directions. Gynecol Oncol 2014;135:364–70.
36. Akram T, Maseelall P, Fanning J. Carboplatin and paclitaxel for the treatment of advanced or recurrent endometrial cancer. Am J Obstet Gynecol 2005;192:1365–7.
37. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet 2005;366:491–505.
38. Hoskins PJ, Swenerton KD, Pike JA, Wong F, Lim P, Acquino-Parsons C, et al. Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: a phase II study. J Clin Oncol 2001;19:4048–53.
39. Kuoppala T, Maenpaa J, Tomas E, Puistola U, Salmi T, Grenman S, et al. Surgically staged high-risk endometrial cancer: randomized study of adjuvant radiotherapy alone vs. sequential chemo-radiotherapy. Gynecol Oncol 2008;110:190–5.
40. Maggi R, Lissoni A, Spina F, Melpignano M, Zola P, Favalli G, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. Br J Cancer 2006;95:266–71.
41. McMeekin DS, Filiaci VL, Thigpen JT, Gallion HH, Fleming GF, Rodgers WH, et al. The relationship between histology and outcome in advanced and recurrent endometrial cancer patients participating in first-line chemotherapy trials: a Gynecologic Oncology Group study. Gynecol Oncol 2007;106:16–22.
42. Nomura H, Aoki D, Takahashi F, Katsumata N, Watanabe Y, Konishi I, et al. Randomized phase II study comparing docetaxel plus cisplatin, docetaxel plus carboplatin, and paclitaxel plus carboplatin in patients with advanced or recurrent endometrial carcinoma: a Japanese Gynecologic Oncology Group study (JGOG2041). Ann Oncol 2011;22: 636–42.
43. Rose PG. Endometrial carcinoma. N Engl J Med 1996;335:640–9.
44. Susumu N, Sagae S, Udagawa Y, Niwa K, Kuramoto H, Satoh S, et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. Gynecol Oncol 2008;108:226–33.
45. Eto T, Saito T, Kasamatsu T, Nakanishi T, Yokota H, Satoh T, et al. Clinicopathological prognostic factors and the role of cytoreduction in surgical stage IVb endometrial cancer: a retrospective multi-institutional analysis of 248 patients in Japan. Gynecol Oncol 2012;127: 338–44.
46. Fujimoto T, Nanjyo H, Nakamura A, Yokoyama Y, Takano T, Shoji T, et al. Para-aortic lymphadenectomy may improve disease-related survival in patients with multipositive pelvic lymph node stage IIIc endometrial cancer. Gynecol Oncol 2007;107:253–9.
47. Giede C, Le T, Power P, Le T, Bentley J, Farrell S, et al. The role of surgery in endometrial cancer. J Obstet Gynaecol Can 2013;35:370–4.
48. Landrum LM, Moore KN, Myers TK, Lanneau GS Jr, McMeekin DS, Walker JL, et al. Stage IVB endometrial cancer: does applying an ovarian cancer treatment paradigm result in similar outcomes? A case-control analysis. Gynecol Oncol 2009;112:337–41.
49. Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet North Am Ed 2010;375: 1165–72.

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