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TLE1 is a robust diagnostic biomarker for synovial sarcomas and correlates with t(X;18): Analysis of 319 cases

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ABSTRACT

Introduction: Genomewide expression profiling has identified a number of genes expressed at higher levels in synovial sarcoma than in other sarcomas. Our objectives in this study were (1) to test whether the differentially expressed gene, Transducin-Like Enhancer of split (TLE1) belonging to the groucho/TLE family, is also distinct on the protein level; (2) to evaluate this biomarker in a series of well-characterised synovial sarcomas on standard, full-sized tissue sections and (3) to correlate the expression of TLE1 with t(X;18) and other established biomarkers.

Methods: Three-hundred and eighty four spindle cell sarcomas from the German consultation and reference centre of soft tissue tumours initially suspected for synovial sarcoma were revisited. Three-hundred and nineteen of these specimens were analysed immunohistochemically using a monoclonal antibody TLE1 and standard, full-sized tissue sections. The nuclear staining was scored semiquantitatively as –, negative; +, weak; ++, moderate and +++, strong positive. Furthermore, 118 specimens among these were further analysed using FISH and/or PCR to detect t(X;18). We correlated the TLE1 expression with the t(X;18) translocation and other established biomarkers (EMA, PanCK, CK7, CD34 and BCL2).

Results: TLE1 expression was observed in 96% of the synovial sarcomas (score $\geqslant$ +, 249/259) and discriminates them from other soft tissue tumours ($p < 0.001$). Multivariate analysis showed that positive TLE1 staining was a statistically independent diagnostic marker. Furthermore molecular analysis showed that t(X;18) was clearly correlated with TLE1 protein expression ($p < 0.001$).

Conclusions: Expression of TLE1 is significantly correlated with t(X;18) and may serve as a new robust diagnostic biomarker in synovial sarcomas and potential therapeutic target.

1. Introduction

Synovial sarcoma is a rare and aggressive soft tissue tumour that accounts for approximately 10% of soft tissue sarcomas and classically occurs in the extremities of young adults, although it may arise at almost any age and anatomic location.[1–4]

According to the WHO classification, there are two major categories of synovial sarcoma: approximately 70% are of the monophasic subtype composed entirely of spindle cells and 30% are biphasic, showing both epithelial and spindle cell components. The poorly differentiated synovial sarcoma appearing as poorly differentiated round cell sarcoma represents a form of tumour progression that can occur in either

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monophasic or biphasic tumours.[5,6] Morphologic variants can also be identified, such as calcifying and fibrous, widening the range of appearances and the differential diagnosis. Demonstration in an appropriate histologic context of t(X;18) by cytogenetics, fluorescence in situ hybridisation (FISH) or reverse-transcriptase polymerase chain reaction is considered the gold standard for the diagnosis of synovial sarcoma; however, several practical issues, including cost and the need for specialised equipment and personnel have limited the use of such diagnostic tests.[7,4] The monophasic subtype consists predominantly or exclusively of spindle cells without glands and therefore closely resembles other sarcomas, notably malignant peripheral nerve sheath tumour (MPNST), fibrosarcoma and solitary fibrous tumour.[8,9] Poorly differentiated synovial sarcomas can resemble several tumour types including Ewing sarcoma.

Immunoreactivity for epithelial markers such as cytokeratin and epithelial membrane antigen (EMA) is frequently used to aid in differentiating synovial sarcoma from other spindle cell neoplasms; however, these markers not only lack specificity but also are limited in sensitivity because such epithelial markers are completely negative in a subset of monophasic cases.[4]

Genomewide expression profiling has identified a number of genes expressed at higher levels in synovial sarcoma than in other sarcomas. Recently TLE1 has gained interest as a potentially useful marker of synovial sarcoma. Our objectives in this study were (1) to test whether the differentially expressed gene, TLE1, is also distinct on the protein level; (2) to evaluate this biomarker in a series of well-characterised synovial sarcomas on standard, full-sized tissue sections and (3) to correlate the overexpression of TLE1 with t(X;18) and other established biomarkers.

Table 1 – Anatomic location of synovial sarcoma, 300 cases (own data from 1999 to 2009 of the consultation and reference centre of soft tissue tumours, Friedrich-Schiller University, Jena).

Anatomic location	No. of cases
Head & neck	18 (6%)
Neck	8
Pharynx	1
Larynx	1
Other	8
Trunk	63 (21%)
Chest	22
Abdominal wall	9
Mediastinum	3
Lung mass	14
Other	15
Upper extremities	50 (17%)
Forearm-wrist	17
Shoulder	5
Elbow-upper arm	13
Hand	15
Lower extremities	149 (49%)
Thigh-knee	71
Foot	36
Lower leg-ankle	24
Hip-groin	18
Other[a]	20 (7%)
Total	300 (100%)

[a] Anatomic location unknown.

3. Materials and methods

3.1. Tumour samples

Tissue samples of soft tissue tumours were retrieved from the archives of the German consultation and reference centre at the institute of Pathology at Friedrich-Schiller University in Jena. All the specimens ($n = 384$) suspect for synovial sarcoma after an initial evaluation by an outside pathologist were reevaluated. The tumour collective comprised 300 synovial sarcomas, 53 sarcomas (NOS), 18 malignant peripheral nerve sheath tumours (MPNST), 4 fibrosarcomas, 4 carcinosarcomas, 2 melanomas, 1 fibrous histiocytoma, 1 neuroendocrine tumour (NET) and 1 solitary fibrous tumour (SFT). The synovial sarcoma tumour collective and the anatomic location are summarised in Table 1. The age at presentation of the synovial sarcomas ranged from 6 to 85 years (median age 40 y, female $n = 168$, male $n = 132$). Tumour size ranged from 1 to 20 cm with a median size of 5.5 cm. Immunohistochemical analysis was performed according to standard procedures to confirm the diagnosis (EMA, BCL2, PanCK, CK7, CD34, Ki67, S100). In problematic cases ($n = 118$), molecular confirmation was performed by FISH and/or PCR to detect the t(X;18) translocation. From the available slides in the archive ($n = 319$) immunohistochemical analysis of TLE1 was performed. We correlated the TLE1 overexpression with the t(X;18) and other established biomarkers (EMA, PanCK, CK7, CD34, BCL2, S100).

3.2. Immunohistochemistry

Commercially available antibodies against *EMA, BCL2, PanCK, CK7, CD34, Ki67, S100* and *TLE1* were purchased (Table 2). Immunohistochemical staining was performed according to standard procedures. Briefly, slides were pretreated as indicated in Table 2 and then incubated with the TLE1 antibody (1:100; Santa Cruz, CA), followed by antibody detection by a biotinylated antimouse secondary antibody and the multilink biotin-streptavidin-amplified detection system (Biogenex, San Ramon, CA). Staining was visualised using a Fastred chromogen system (DAKO, Hamburg, Germany). The intensity of the TLE1 immunostaining in tumour cells was evaluated independently by two pathologists blinded to the clinicopathological data and scored semiquantitatively as –, negative; +, weak; ++, moderate; and +++, strong positive. Additionally the slides were analysed according to the Remmele score (0–12, intensity × percentage, intensity: 0, negative; 1, weak; 2, moderate; 3, strong × percentage of the stained tumour cells: 0, no staining; 1, <10%; 2, 11–50%; 3, 51–80% and 4, 81–100%).

3.3. Molecular confirmation of synovial sarcoma cases

The presence of the t(X;18) translocation in the synovial sarcoma cases or absence in the nonsynovial sarcoma cases

Table 2 – Antibodies for immunohistochemistry.

Antigen	Product no.	Supplier	Dilution	Pretreatment
TLE1	M101	Santa Cruz Biotech.	1:100	Microwave
PanCK (MNF)	M0821	DAKO	1:200	Prot. enzyme
EMA	M0613	DAKO	1:500	Microwave
CK7	M7018	DAKO	1:750	Microwave
Bcl2	M0887	DAKO	1:300	Microwave
Ki67	M7240	DAKO	1:1000	Microwave
CD34	M7165	DAKO	1:300	Microwave
S100	Z0311	DAKO	1:8000	Prot. enzyme

Table 3 – Summary of TLE1 immunohistochemistry results.

Tumour type	*n*	Negative	1+	2+	3+	Any positive (%)	Positive 2+, 3+ (%)
Synovial sarcoma	259	10 (4%)	55	66	128	249 (96%)	194 (75%)
Sarcoma, NOS[a]	38	33 (87%)	3	0	2	5 (13%)	2 (5%)
MPNST[a]	14	10 (71%)	4	0	0	4 (29%)	0 (0%)
Fibrosarcoma	3	3	0	0	0	0	0
Carcinosarcoma	3	2	1	0	0	1	0
Histiocytoma	1	0	1	0	0	1	0
NET	1	1	0	0	0	0	0
Total	319	51 (18%)	64	66	130	260 (82%)	196 (61%)

[a] NOS, not otherwise specified; MPNST, malignant peripheral nerve sheath tumour and NET, neuroendocrine tumour.

was verified by dual colour fluorescence in situ hybridisation (dcFISH) and RT-PCR. For the t(X;18) dcFISH, interphase nuclei were isolated from paraffin-embedded tumour tissue. Nuclei were prepared as described.[10] The dcFISH was performed using the LSI SYT (18q11.2) Dual Colour Break apart Probe (Abbott Molecular Inc., USA) according to the protocol provided by the manufacturer. Fifty nuclei were analysed for chromosomal rearrangements of the SYT gene region located on chromosome 18 using a laser scanning microscope LSM510 (Zeiss, Jena, Germany). DcFISH was assessed positive if at least 10% of the nuclei showed a translocation specific hybridisation pattern.[11]

For SYT/SSX RT-PCR identifying the SYT/SSX1 and SYT/SSX2 fusion gene product total RNA was isolated from paraffin sections using the RNeasy FFPE Kit (Qiagen, Germany). Integrity of mRNA was assessed by β-actin control RT-PCR. Control and SYT/SSX RT-PCR were done using the One-Step RT-PCR Kit (Qiagen, Germany) as described previously.[10] SYT/SSX primers were originally published by Guillou et al.[12] Cases were diagnosed as positive if cdFISH and/or RT-PCR showed positive results.

3.4. *Statistical analysis*

Fisher's exact test was used to determine the strength of association between the investigated parameters. p-Values < 0.05 were considered significant. All calculations were performed on a PC using the statistical software package SPSS (version 15, Munich, Germany). Multivariate analysis was performed with a logistic regression and stepwise conditional forward procedures. For assessing and comparing the variables a significance level of 0.05 was used for inclusion and 0.1 for exclusion of variables.

4. Results

4.1. *Immunohistochemistry*

The summary of all TLE1 immunohistochemistry results is listed in Table 3. Expression of TLE1 was observed in 82% of all evaluated cases (score $\geqslant$ +, 260/319). In synovial sarcomas positive staining was found in 96% (249/259), 75% showed a strong to moderate staining (score +++/++) and 21% showed a weak staining (score +). Examples of the immunohistochemical assessment of TLE1 are shown in Fig. 1. The Remmele score (intensity 0–3 × percentage of staining 0–4) showed a similar result with a high score (5–12) in 59%, moderate (3–4) in 14%, weak (1–2) in 23% and negative (0) in 4%. In general, one-third of the biphasic synovial sarcomas showed a more pronounced staining in the epithelial component than in the spindle cell component compared to an equal staining (Fig. 2). In some monophasic synovial sarcoma cases only a focal (or weak) area with a specific nuclear staining was seen. In these cases the staining was always present at the tumour margin/invasive front. We considered this staining pattern as a positive result. In contrast to synovial sarcoma, TLE1 staining was low to absent in other spindle cell tumours, such as MPNST, fibrosarcoma, fibrous histiocytoma, NET and carcinosarcoma. In not otherwise specified sarcomas (sarcoma, NOS) most of the cases also showed weak or absent expression. Furthermore EMA was positive in 91% (236/260) of the synovial sarcomas, BCL2 in 99.6% (244/245), PanCK in 73% (189/

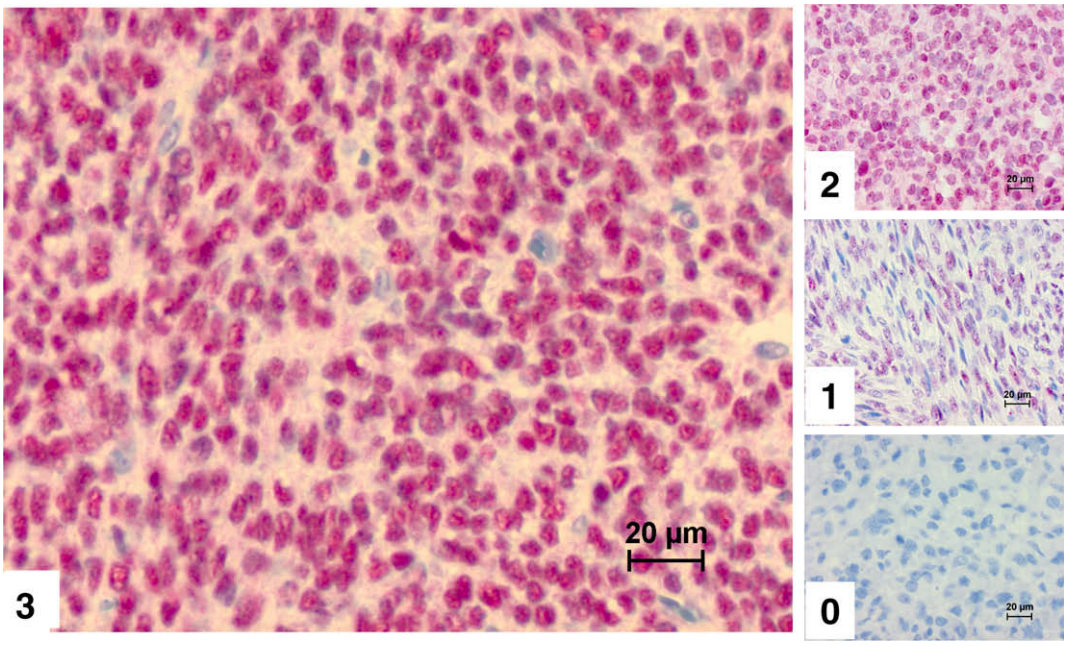

Fig. 1 – Examples of the immunohistochemical assessment of TLE1 staining in synovial sarcomas. Negative staining of tumour cells (0), weakly positive (1), moderately positive (2) and strongly positive (3) (50× magnification).

259), CK7 in 96% (51/53) and CD34 in 3% (7/204). The proliferation index was assessed by Ki67 from 5% to 90% (Table 4).

4.2. *Translocation analysis and TLE1 staining*

We investigated 118 cases for translocation t(X;18). The translocation was found in 51 cases (43%) with a positive result in PCR and/or FISH (all these tumours were classified as synovial sarcoma: 41 monophasic, 4 biphasic and 6 poorly differentiated) and 67 (57%) showed a negative result. Of these, 87 specimens were additionally stained with TLE1. Translocation t(X;18)-positive cases ($n = 40$) showed TLE1 expression in 37 cases (92%, $p < 0.001$). Translocation t(X;18)-negative cases ($n = 47$) showed TLE1 expression in 19 cases. Among these, 5 cases were diagnosed as sarcoma, NOS (three 1+, two 2+), 4 as MPNST (all 1+) and one each as carcinosarcoma and fibrous histiocytoma (each 1+). Eight cases were diagnosed as highly suspicious for synovial sarcoma as all other features (morphologic and clinical presentation, e.g. age and location) and the immunohistochemistry profile favoured this diagnosis (all 2+ or 3+), but we were unable to confirm the diagnosis with translocation analysis due to poor sampling (not enough material after the first FISH and/or PCR, indeterminate molecular result).

4.3. *Statistical analysis*

Expression of TLE1 (96%) discriminates synovial sarcomas from other soft tissue tumours ($p < 0.001$). Multivariate analysis with the dependent variable "synovial sarcoma" was conducted for 184 cases clinically suspected for synovial sarcoma (152 proven synovial sarcoma, 32 other tumours) in which information about the five biomarkers BCL2, PanCK, CD34, EMA and TLE1 was available. Positive TLE1 staining is the most powerful statistically independent diagnostic marker together with positive staining for EMA and negative staining for CD34 (Table 5).

Furthermore, molecular analysis showed that t(X;18) was clearly correlated with strong expression of the gene TLE1 ($p < 0.001$, score 2+/3+ versus 0/1+). The positive predictive value (PPV) of the TLE1 expression (2+, 3+) for the diagnosis synovial sarcoma was 98% (194/196), the value of sensitivity (194/259) and specificity (58/60) was 75% and 96%, respectively.

5. Discussion

Distinguishing monophasic synovial sarcoma from other monomorphous spindle cell sarcomas is a diagnostic challenge. Reliable biomarkers to confirm the diagnosis are needed. Genomewide expression profiling has identified a number of genes expressed at higher levels in synovial sarcoma than in other sarcomas. Our objectives in this study were (1) to test whether the differentially expressed gene, Transducin-Like Enhancer of split (TLE1) belonging to the groucho/TLE family, is also distinct on the protein level; (2) to evaluate this biomarker in a series of well-characterised synovial sarcomas on standard tissue sections and (3) to correlate the overexpression of TLE1 with t(X;18) and other established biomarkers.

This is the largest analysis of TLE1 staining in synovial sarcomas in standard, full-sized tissue sections. Revisiting 384 spindle cell sarcomas of the German consultation and reference centre of soft tissue tumours initially suspected for synovial sarcomas, we were able to analyse 319 cases immunohistochemically using the antibody TLE1 and validate the expression patterns with other established biomarkers such as EMA, PanCK, CD34, CK7, BCL2, S100 and Ki67. Furthermore, 118 cases were analysed using FISH and/or PCR to detect t(X;18) in diagnostic problematic cases. The fact that we

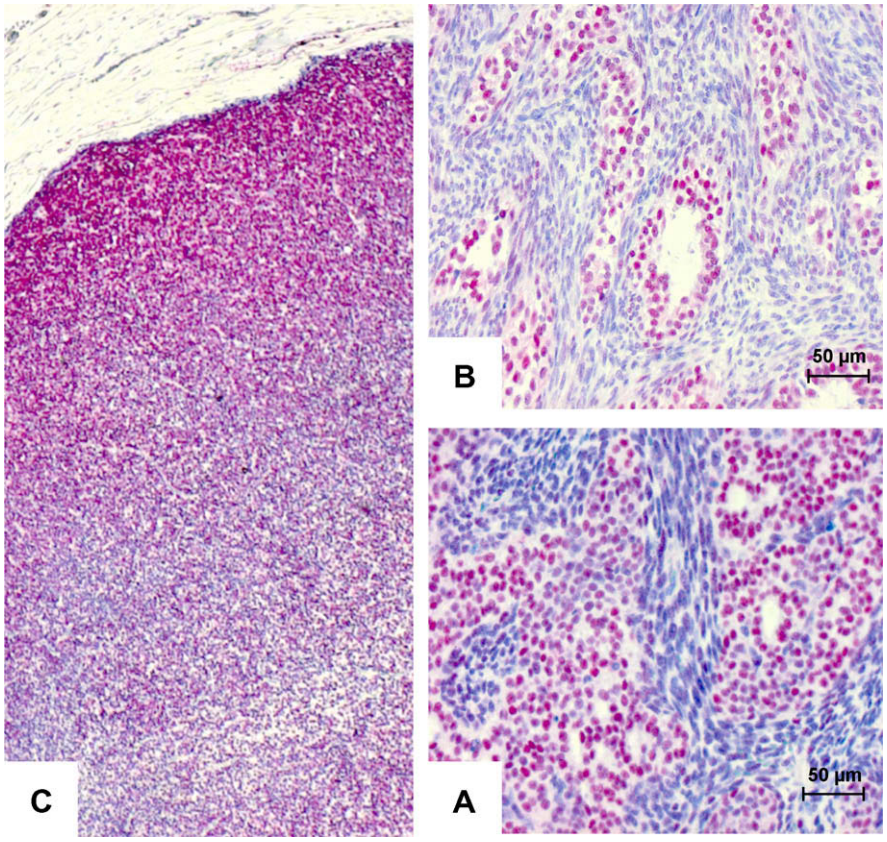

Fig. 2 – Biphasic synovial sarcoma with pronounced TLE1 staining in the epithelial department (A), (B) and (C): pronounced TLE1 staining at the invasive front of a synovial sarcoma similar to the nuclear staining of beta catenin in colorectal cancer.

Table 4 – Summary of all immunohistochemistry results of the synovial sarcomas.

Antibody	*n*	Positive	Negative
TLE1	259	249 (96%)	10 (4%)
PanCK	259	189 (73%)	70 (27%)
EMA	260	236 (91%)	24 (9%)
BCL2	245	244 (99.6%)	1 (0.4%)
CD34	204	7 (3%)	197 (97%)
CK7	53	51 (96%)	2 (4%)

confirmed several expression patterns that have been previously reported using other tumour collectives of these rare neoplasia supports the validity of our findings.[4]

Using standard, full-sized tissue sections is an appropriate study design to validate and establish a new biomarker especially when the marker was initially only assessed on tissue microarrays (TMAs). Advantages of the relatively little labour intensive TMA technique are the comparatively small amounts of tissue and reagents required for investigating specific biomarkers.[13] However, after applying this screening method, the evaluation and validation on standard tissue sections are indispensable. Full-sized sections have the advantage of providing an overview of a larger tumour area, thus enabling the evaluation of the presence and extent of heterogeneity in protein expression within a malignant neoplasia.[14,15] In this study we scored the intensity and the percentage of the staining of TLE1 and converted the data into the Remmele score (0–12). Importantly, using the Remmele score (0–12) and an intensity score (0–3), we were able to reproduce approximately the percentage of positive results previously published on TMA sections of synovial sarcomas.[4] Terry and colleagues used two antibodies and found slightly less intense staining for the M101 TLE1 antibody, but they also

Table 5 – Multivariate analysis.

	p	Exp(ß)	Limits of 95.0% confidence interval, exp(ß)	
			Lower	Upper
TLE1	0.000	355.524	60.359	2.094083
EMA	0.017	9.940	1.512	65.360
CD34[a]	0.006	20.377	2.360	175.944

[a] CD34 as a negative marker & TLE1 and EMA as positive markers

scored the cases positive if the second antibody Pan TLE showed a positive staining. This might be the explanation for their slightly higher percentage of positive tumour cases although they used TMA sections. Nevertheless, the staining of TLE1 seems to be a robust biomarker for synovial sarcomas in two independent tumour collectives of synovial sarcomas.

Recently Kosemehmetoglu and colleagues[16] detected TLE1 expression in other soft tissue tumours including rhabdomyosarcoma, schwannoma, liposarcoma and MPNSTs.[16] However, not all of their investigated tumours were included in the differential diagnosis of synovial sarcomas and some of them can be ruled out by other biomarkers. In this study we analysed the expression of TLE1 in a diagnostic setting, in which an experienced pathologist had considered synovial sarcoma in the differential diagnosis (all cases were referred as consultation cases). In diagnostically uncertain cases, we recommend paying attention only to a strong nuclear staining, which showed the best positive predictive value in our statistical analysis (PPV 98%). However, our tumour collective is enriched for cases expected to be true positives, markedly reducing the proportion of false positives and the PPV should thus be interpreted cautiously. Molecular analysis should still be the gold standard in problematic cases. However, TLE1 staining can guide the diagnosis in the setting of confusing, indeterminate or unavailable molecular results. Due to the latter investigation, we expanded our study to 14 MPNSTs, but could not find a moderate or strong nuclear expression. The differences might be explained by the interpretation of the staining. Expression profiling studies of several independent groups did not show an upregulation of TLE1 in MPNSTs (unpublished data). Nevertheless the authors also found a moderate to strong staining in 85% of the synovial sarcomas ($n = 20$) and confirmed our results in standard sections. Very recently Jagdis and colleagues published a study reporting a positive predictive value of 92% and a negative predictive value of 100% supporting our results for the robustness of TLE1 as biomarker in synovial sarcomas.[17]

In our multivariate analysis TLE1 staining was an independent parameter including PanCK, CK7, EMA and BCL2 as positive biomarkers and CD34 as a negative biomarker of synovial sarcomas indicating a high value of sensitivity and specificity which was confirmed in univariate analysis. Additionally, TLE1 expression was significantly correlated with the translocation t(X;18) which may be of interest to laboratories that do not have the experience, manpower or equipment to do molecular translocation analysis on a routine basis.

TLE1 is one of 4 Transducin-Like Enhancer of split (TLE) genes that encode human transcriptional repressors homologous to the Drosophila corepressor Groucho.[4,18] The TLE family proteins are required for many developmental processes, including lateral inhibition, segmentation, sex determination, dorsal/ventral pattern formation, terminal pattern formation and eye development.[19] As corepressors, Gro/TLE family proteins do not bind to DNA directly, but are rather recruited to the template by DNA-bound repressor proteins. The repressive effect of Groucho and TLE1 is dependent on phosphorylation status and involves histone deacetylase (HDAC) activity.[4,19,20] The HDAC inhibitor FK228 has recently been shown to inhibit proliferation of synovial sarcoma, supporting the idea that TLE1 overexpression may play an important role in synovial sarcoma pathobiology and identifying TLE1 as a potential therapeutic target.[21] The Groucho/TLE family proteins are also linked to the Wnt pathway.[21] Interestingly, when heterogeneity occurred in our synovial sarcoma cases, the nuclear staining was more pronounced at the tumour margin in analogy with invasive colorectal carcinomas where the nuclear beta catenin is more pronounced at the invasive front indicating a gene expression pattern that favours tumour invasion associated with the Wnt pathway.[22,23]

In conclusion strong nuclear TLE1 expression is a robust immunohistochemical biomarker for synovial sarcoma, particularly in those cases that do not exhibit biphasic histology, distinguishing this tumour entity from other spindle cell tumours. The data presented here define a set of immunohistochemical markers, and in particular TLE1, as a useful tool to diagnose synovial sarcoma. TLE1 staining should be used as a screening method prior to molecular cytogenetic and/or molecular genetic translocation analysis. Immunohistochemistry is much faster and, at present, more cost effective than translocation analysis. The biomarker TLE1 will significantly aid in the pathologic diagnosis of this tumour, and may have implications for understanding its biology and for developing new anticancer-targeted therapies.

Conflict of interest statement

None declared.

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REFERENCES

1. Amary MF, Berisha F, Bernardi Fdel C, et al. Detection of SS18-SSX fusion transcripts in formalin-fixed paraffin-embedded neoplasms: analysis of conventional RT-PCR, qRT-PCR and dual color FISH as diagnostic tools for synovial sarcoma. *Mod Pathol* 2007;**20**(4):482–96.
2. Antonescu CR, Busam KJ, Iversen K, et al. MAGE antigen expression in monophasic and biphasic synovial sarcoma. *Human Pathol* 2002;**33**(2):225–9.
3. Ladanyi M, Antonescu CR, Leung DH, et al. Impact of SYT-SSX fusion type on the clinical behavior of synovial sarcoma: a multi-institutional retrospective study of 243 patients. *Cancer Res* 2002;**62**(1):135–40.
4. Terry J, Saito T, Subramanian S, et al. TLE1 as a diagnostic immunohistochemical marker for synovial sarcoma emerging from gene expression profiling studies. *Am J Surg Pathol* 2007;**31**(2):240–6.
5. Fletcher CD, Krishnan Unni K, Mertens F, editors. *World Health Organisation classification of tumours. Pathology and genetics of tumours of soft tissue and bone*. Lyon: IARC Press; 2002.
6. Weiss SW, Goldblum JR. *Enzinger and Weiss's soft tissue tumors*. St. Louis: Mosby; 2008.

7. Coindre JM, Pelmus M, Hostein I, et al. Should molecular testing be required for diagnosing synovial sarcoma? A prospective study of 204 cases. *Cancer* 2003;**98**:2700–7.
8. He R, Patel RM, Alkan S, Hammadeh R, et al. Immunostaining for SYT protein discriminates synovial sarcoma from other soft tissue tumors: analysis of 146 cases. *Mod Pathol* 2007;**20**(5):522–8.
9. Knösel T, Schulz B, Katenkamp K, Katenkamp D, Petersen I. Solitary fibrous tumor and haemangiopericytoma: What is new? *Pathologe*, in press. PMID: 20013263 [Epub ahead of print].
10. Katenkamp K, Richter P, Slatosch T, Katenkamp D, Berndt A. Simultaneous analysis of t(X;18) by FISH- und SYT/SSX-RT-PCR in synovial sarcoma. *Pathologe* 2005;**26**(2):111–6.
11. Lu YJ, Birdsall S, Summersgill B, et al. Dual colour fluorescence in situ hybridization to paraffin-embedded samples to deduce the presence of the der(X)t(X;18)(p11.2;q11.2) and involvement of either the SSX1 or SSX2 gene: a diagnostic and prognostic aid for synovial sarcoma. *J Pathol* 1999;**187**:490–6.
12. Guillou L, Coindre J, Gallagher G, et al. Detection of the synovial sarcoma translocation t(X;18) (SYT;SSX) in paraffin-embedded tissues using reverse transcriptase-polymerase chain reaction: a reliable and powerful diagnostic tool for pathologists. A molecular analysis of 221 mesenchymal tumors fixed in different fixatives. *Human Pathol* 2001;**1**:105–12.
13. Knösel T, Emde A, Schlüns K, et al. Immunoprofiles of 11 biomarkers using tissue microarrays identify prognostic subgroups in colorectal cancer. *Neoplasia* 2005;**7**(8):741–7.
14. Knösel T, Emde V, Schlüns K, et al. Cytokeratin profiles identify diagnostic signatures in colorectal cancer using multiplex analysis of tissue microarrays. *Cell Oncol* 2006;**28**(4):167–75.
15. Knösel T, Yu Y, Stein U, et al. Overexpression of cyclooxygenase-2 correlates with chromosomal gain at the cyclooxygenase-2 locus and decreased patient survival in advanced colorectal carcinomas. *Dis Colon Rectum* 2004;**47**(1):70–7.
16. Kosemehmetoglu K, Vrana JA, Folpe AL. TLE1 expression is not specific for synovial sarcoma: a whole section study of 163 soft tissue and bone neoplasms. *Mod Pathol* 2009;**22**(7):872–8.
17. Jagdis A, Rubin BP, Tubbs RR, Pacheco M, Nielsen TO. Prospective evaluation of TLE1 as a diagnostic immunohistochemical marker in synovial sarcoma. *Am J Surg Pathol* 2009;**33**(12):1743–51.
18. Stifani S, Blaumueller CM, Redhead NJ, et al. Human homologs of a Drosophila Enhancer of split gene product define a novel family of nuclear proteins. *Nat Genet* 1992;**2**:119–27.
19. Chen G, Courey AJ. Groucho/TLE family proteins and transcriptional repression. *Gene* 2000;**249**(1–2):1–16 [Review].
20. Yochum GS, Ayer DE. Pf1, a novel PHD zinc finger protein that links the TLE corepressor to the mSin3A-histone deacetylase complex. *Mol Cell Biol* 2001;**21**:4110–8.
21. Ito T, Ouchida M, Morimoto Y, et al. Significant growth suppression of synovial sarcomas by the histone deacetylase inhibitor FK228 in vitro and in vivo. *Cancer Lett* 2005;**224**:311–9.
22. Knösel T, Petersen S, Schwabe H, et al. Incidence of chromosomal imbalances in advanced colorectal carcinomas and their metastases. *Virchows Arch* 2002;**440**(2):187–94.
23. Schmalhofer O, Brabletz S, Brabletz T. E-cadherin, beta-catenin, and ZEB1 in malignant progression of cancer. *Cancer Metastasis Rev* 2009;January 20.