Modern Pathology (2014) 27, 1231–1237

STAT6 is amplified in a subset of dedifferentiated liposarcoma

Leona A Doyle, Derrick Tao and Adrián Mariño-Enríquez

Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

A recurrent intrachromosomal rearrangement on chromosome 12q in solitary fibrous tumor leads to the formation of a *NAB2–STAT6* fusion oncogene. As a result, nuclear expression of the cytoplasmic transcription factor STAT6 is found in solitary fibrous tumor and serves as a useful diagnostic marker. *STAT6* is located in 12q13, a region containing well-characterized oncogenes that are commonly amplified in dedifferentiated liposarcoma; we have previously reported that STAT6 is expressed in a subset of dedifferentiated liposarcoma. The aim of this study was to determine the frequency of STAT6 expression in dedifferentiated liposarcoma and the underlying genetic mechanism. STAT6 protein expression was analyzed by immunohistochemistry in a well-characterized series of 35 previously unpublished cases of dedifferentiated liposarcoma, all with nuclear MDM2 and/or CDK4 expression by immunohistochemistry and/or cytogenetic features of dedifferentiated liposarcoma. FISH for *STAT6* was performed in all cases with STAT6 expression, and a subset of control cases without STAT6 expression. In total 4/35 cases (11%) showed STAT6 expression (three with multifocal staining of moderate to strong intensity and one with weak focal staining). FISH demonstrated amplification of *STAT6* in all cases positive for STAT6 by immunohistochemistry; in contrast, FISH performed on four STAT6-negative dedifferentiated liposarcomas demonstrated no *STAT6* amplification ($P = 0.0286$). Of the four *STAT6* amplified cases, three patients were male and one was female, ranging in age from 51 to 76 years. Tumors were located in the mediastinum ($n = 2$), paratesticular soft tissue ($n = 1$), and perirenal soft tissue ($n = 1$). Three patients received pre-operative chemotherapy +/− radiation therapy. In conclusion, *STAT6* is amplified in a subset of dedifferentiated liposarcoma, resulting in STAT6 protein expression that can be detected by immunohistochemistry and may be a potential pitfall in the differential diagnosis of dedifferentiated liposarcoma and solitary fibrous tumor. These findings suggest a role for STAT6-mediated transcriptional activity in some cases of dedifferentiated liposarcoma and highlight the genomic complexity and heterogeneity of dedifferentiated liposarcoma.
Modern Pathology (2014) **27,** 1231–1237; doi:10.1038/modpathol.2013.247; published online 24 January 2014

Keywords: amplification; dedifferentiated liposarcoma; sarcoma; solitary fibrous tumor; STAT6

Liposarcoma is the most common sarcoma in adults. Well-differentiated and dedifferentiated liposarcoma account for 40–45% of all liposarcomas and fall within a biological continuum in which dedifferentiated liposarcoma represents an advanced form of the tumor that has acquired metastatic potential.[1] Clinically, dedifferentiated liposarcoma is an aggressive malignancy that is frequently lethal due to multiple recurrences and late metastases, with no effective therapeutic options other than surgery.[1–3] Morphologically, dedifferentiated liposarcoma is usually a non-lipogenic high-grade sarcoma with a wide range of histological appearances, most commonly with spindle cell and pleomorphic cytomorphology, and infrequently inflammatory, round cell, or meningothelial-like patterns, none of which seem to correlate with the clinical outcome.[1,2]

Cytogenetic and molecular genetic studies over the last two decades have provided insights into the biology of dedifferentiated liposarcoma. The tumor cells of dedifferentiated liposarcoma contain neochromosomes —ring or giant marker chromosomes— composed of repeated interspersed amplicons from distinct non-contiguous chromosomal regions.[4,5] The structure of dedifferentiated liposarcoma neochromosomes is complex and varies between tumors, between time points in the course of disease, and even between individual cells within a single tumor. Despite such genetic heterogeneity, some general features are observed in dedifferentiated liposarcoma neochromosomes: genetic

Correspondence: Dr A Mariño-Enríquez, MD, Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA.
E-mail: admarino@partners.org
Received 7 November 2013; accepted 4 December 2013; published online 24 January 2014

material from the 12q13-15 chromosomal region is invariably present, usually as small fragments of variable lengths that are amplified at very high levels. Other chromosomes are involved less consistently, such as 1q, 4p, 12q21–22, 13q, and 15q.[5–8] The 12q15 amplicon consistently contains the *MDM2* oncogene, which is considered an essential oncogenic driver in dedifferentiated liposarcoma and the main downregulator of the p53 axis in this tumor type.[1,9] Concomitant amplification of *HMGA2*, *CPM*, *FRS2,* and *YEATS4,* all located at the same chromosomal region, is invariably present along with *MDM2*, even though the pathogenetic relevance of these genes in dedifferentiated liposarcoma is not well established.[5,10–12] In addition, the cyclin-dependent kinase *CDK4* is amplified in about 90% of dedifferentiated liposarcoma. Although *CDK4* is located very close to the main 12q15 amplicon, it belongs to a discontinuous and inconsistent amplicon that includes its locus at 12q14.1 as well as other genes such as *TSPAN31*.[6,10] *CDK4* gene amplification and overexpression very likely have an important role in the tumorigenic process in dedifferentiated liposarcoma, but the contribution of other genes in this amplicon has not been explored.[13,14] In addition to providing greater understanding of the pathogenesis of dedifferentiated liposarcoma, the concurrent amplification and overexpression of *MDM2* and *CDK4* serve as important diagnostic markers that can be detected by immunohistochemistry or FISH.[15] MDM2 and CDK4 also represent attractive potential therapeutic targets—both MDM2 inhibition and CDK4 inhibition have shown promising activity in preclinical models and are being evaluated in clinical trials.[3,16]

STAT6 is a member of the STAT family of cytoplasmic transcription factors, which regulate gene expression by transmitting signals to the nucleus and binding to specific DNA promoter sequences in response to extracellular cytokines. Activation of STAT family members has been implicated in physiological and neoplastic cell growth, and can be therapeutically inhibited.[17] In mesenchymal neoplasia, recent studies have detected a recurrent intrachromosomal rearrangement in solitary fibrous tumor that results in the formation of a *NAB2–STAT6* fusion oncogene.[18,19] The fusion oncoprotein is highly expressed and localizes to the cell nucleus, resulting in a strong nuclear expression of STAT6 that can be detected by immunohistochemistry and serves as a reliable diagnostic marker for solitary fibrous tumor.[20,21] In addition, we have previously reported that a small number of dedifferentiated liposarcomas show STAT6 expression.[20] *STAT6* is located at chromosomal region 12q13, which contains essential oncogenes amplified in dedifferentiated liposarcoma neochromosomes. The aim of this study was to determine the frequency of STAT6 expression in dedifferentiated liposarcoma and the underlying genetic mechanism, in relationship to the known amplification of 12q13-15 in this sarcoma type.

Materials and methods

The study was approved by the Institutional Review Board at Brigham and Women's Hospital. Thirty-five previously unpublished cases of dedifferentiated liposarcoma were retrieved from the surgical pathology files of Brigham and Women's Hospital, Boston, MA, USA. Clinical, histopathological, and immunophenotypical features were reviewed by two surgical pathologists (LAD and AME). All cases showed nuclear expression of MDM2 and CDK4 by immunohistochemistry, and/or cytogenetic features of dedifferentiated liposarcoma—either ring or giant marker chromosomes in the karyotype, *MDM2* amplification by FISH, or both. Two solitary fibrous tumors with STAT6 overexpression were selected as controls.

Immunohistochemistry for STAT6 was performed on 4 μm-thick formalin-fixed paraffin-embedded whole-tissue sections following pressure cooker antigen retrieval (0.01 M citrate buffer; pH, 6.0), using a rabbit polyclonal antibody directed against the C-terminus of STAT6 (1:1000; sc-621; Santa Cruz Biotechnology, Santa Cruz, CA, USA). Appropriate positive and negative controls were used throughout. The extent of immunoreactivity was graded according to the percentage of positive tumor cells (0, no staining; 1+, 1–50%; 2+, 51–100%). The intensity of staining was graded as weak, moderate, or strong.

Dual color FISH was performed on 4 μm thick formalin-fixed paraffin-embedded tissue sections for all cases with STAT6 expression, a subset of four dedifferentiated liposarcoma cases without STAT6 expression, and two solitary fibrous tumor controls. Tissue sections were baked overnight at 56 °C, deparaffinized by three consecutive 15 min immersions in xylene, and dehydrated twice in 100% ethanol for 2 min. The slides were then immersed in TRIS–EDTA (100 mM Tris base, 50 mM EDTA, pH 7.0) for 1 h at 95–99 °C and rinsed in PBS for 5 min. Proteolytic digestion of the sections was performed using Digest–All 3 Pepsin solution (Invitrogen, Camarillo, CA, USA) at 37 °C for 10–20 min, twice. The sections were then sequentially dehydrated in alcohol (70, 85, 95, and 100% for 2 min each) and air-dried. The STAT6 probe set consisted of a commercial kit targeting the 12q13 region, which includes a SpectrumOrange probe spanning the *STAT6* locus and a telomeric SpectrumGreen probe that spans the *CDK4* locus (Vysis, Abbott Molecular Inc, Des Plaines, IL, USA) (Figure 1). One-hundred interphase nuclei were scored per case. The presence of five or more orange signals was considered indicative of *STAT6* amplification. Non-neoplastic diploid cells were identified in each case and used as internal controls. The significance of the correlation

between immunohistochemistry and FISH was analyzed using a 2×2 contingency table, and the exact two-tailed *P*-value was calculated according to Fisher's test.

Results

Four of the 35 dedifferentiated liposarcomas (11%) showed STAT6 expression by immunohistochemistry; the clinicopathologic features of these cases are summarized in Table 1. Morphologically, two tumors were high-grade spindle cell and pleomorphic sarcomas (one with focal heterologous smooth muscle differentiation), one was composed of a relatively monotonous population of atypical spindle cells with prominent nuclear palisading, and one was a high-grade spindle-cell sarcoma with hypocellular hyalinized areas characteristic of well-differentiated sclerosing liposarcoma. Three cases showed multifocal (2+) staining of moderate to strong intensity and one (case 4) showed weak focal (1+) staining (Figure 2). STAT6 expression was both cytoplasmic and nuclear in three cases, generally with a stronger nuclear intensity; in case one, although some areas of the tumor predominantly showed nuclear staining, cytoplasmic staining was also present multifocally. STAT6 expression was detected in the dedifferentiated components in all four tumors, and in an area of well-differentiated sclerosing liposarcoma in case four. Interestingly, the tumor with heterologous smooth muscle differentiation (case 2) showed expression of STAT6 only in conventional areas of dedifferentiated liposarcoma; the smooth muscle-like component was negative for STAT6 by immunohistochemistry. Two solitary fibrous tumor control cases showed diffuse strong nuclear STAT6 expression.

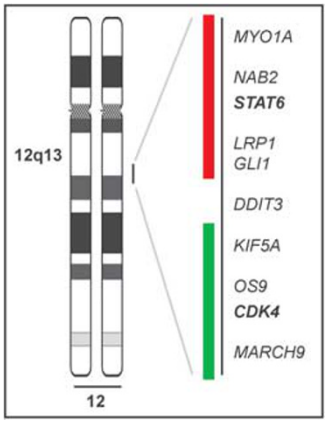

Figure 1 Schematic representation of the *STAT6* FISH probe set.

FISH demonstrated *STAT6* amplification in all four cases expressing STAT6. The level of amplification was variable between cases, ranging from high-level amplification with innumerable copies of *STAT6* per cell (Figure 3a), to 6–10 *STAT6* copies present in one case. Within each case, there were also different levels of amplification in different cells, with large atypical cells showing more gene copies than less atypical cells. The smooth muscle-like component present in case two, identified by elongated nuclei arranged in fascicles on the DAPI stain, showed high-level amplification. FISH performed on four dedifferentiated liposarcomas negative for STAT6 expression demonstrated no *STAT6* amplification ($P = 0.0286$). All dedifferentiated liposarcomas showed high-level amplification of *CDK4* (Figure 3b). *CDK4* amplification was consistently higher than *STAT6* amplification. Both STAT6-positive solitary fibrous tumors showed just two copies of *STAT6* and *CDK4* per interphase nucleus.

Of the four *STAT6* amplified dedifferentiated liposarcomas, three patients were males and one was female, ranging in age from 51 to 76 years (Table 1). Tumors were located in the mediastinum ($n = 2$), paratesticular soft tissue ($n = 1$), and perirenal soft tissue ($n = 1$). Three patients received pre-operative chemotherapy +/− radiation therapy before resection.

Table 1 Clinicopathological features of four cases of dedifferentiated liposarcoma with *STAT6* amplification and STAT6 protein expression

Patient	*Sex/Age*	*Diagnosis*	*Location*	*Primary/ metastasis*	*Morphology*	*Pre-operative Treatment*	*MDM2/CDK4 Expression*	*STAT6 Expression*	*STAT6 FISH*
1	M/63	Dedifferentiated liposarcoma	Mediastinum	P	Pleomorphic + spindle cell sarcoma	Chemotherapy + radiotherapy	+/+	2+	Amplified
2	M/76	Dedifferentiated liposarcoma	Paratesticular	P	Spindle cell sarcoma with focal heterologous smooth muscle differentiation	Chemotherapy + radiotherapy	+/+	1+	Amplified
3	M/51	Dedifferentiated liposarcoma	Perirenal	P	Spindle cell sarcoma with focally prominent palisading	None	+/+	2+	Amplified
4	F/52	Well-differentiated/ Dedifferentiated liposarcoma	Mediastinum	P	High-grade spindle cell sarcoma with focal sclerosing WDLPS	Chemotherapy + radiotherapy	+/+	2+	Amplified

Abbreviations: F, female; M, male; P, primary.
+, positive; 1+, weak focal staining; 2+, multifocal moderate to strong staining.

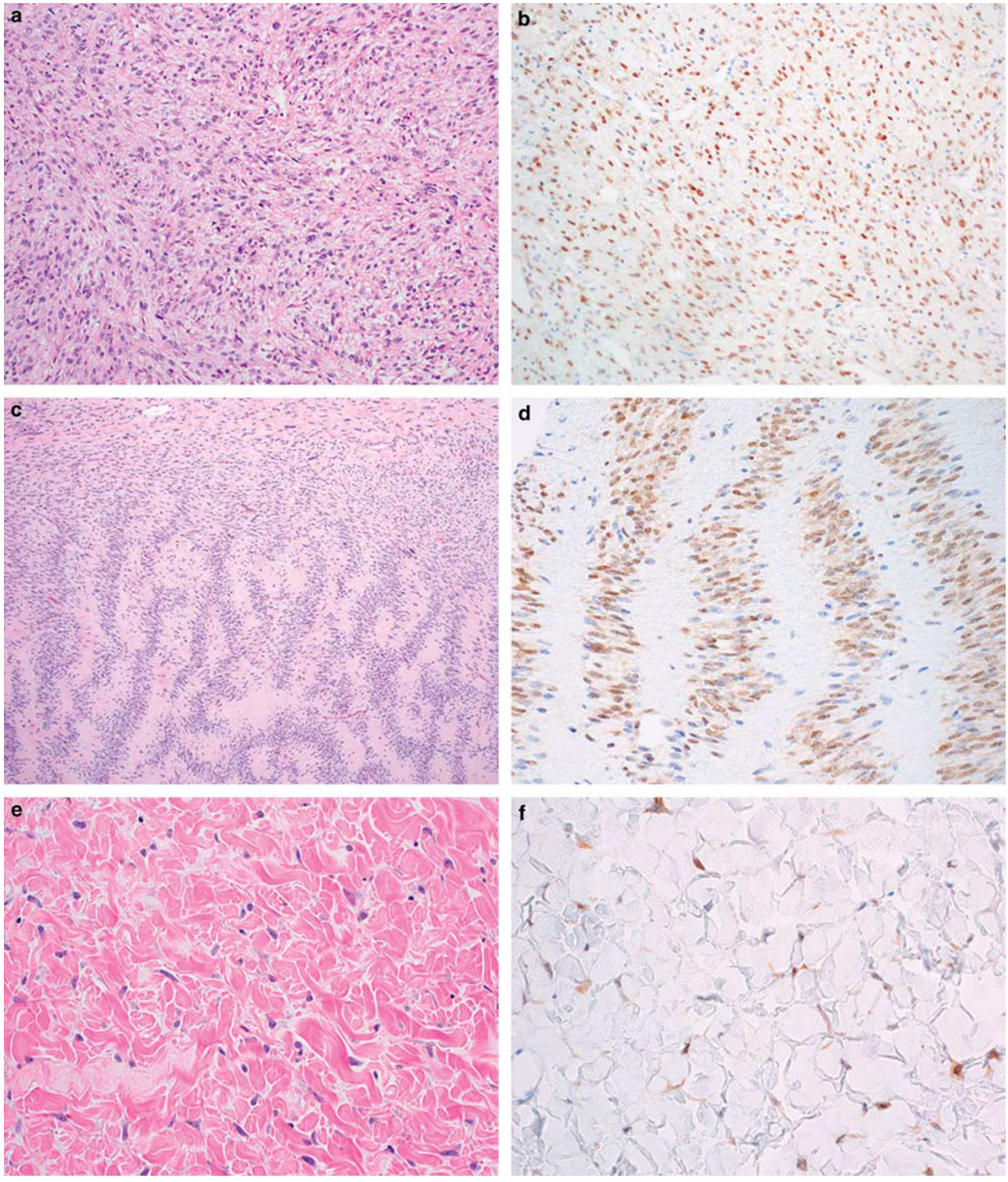

Figure 2 High-grade dedifferentiated liposarcoma with pleomorphic and spindle-cell morphology (case 1) (**a**) showing diffuse expression of STAT6 (**b**). Dedifferentiated liposarcoma with predominantly spindle cell morphology and prominent nuclear palisading (case 3) (**c**). The tumor cells showed diffuse nuclear expression and weak cytoplasmic expression of STAT6 (**d**). Hypocellular hyalinized areas of well-differentiated sclerosing liposarcoma (case 4) (**e**) showed weak focal expression of STAT6 (**f**).

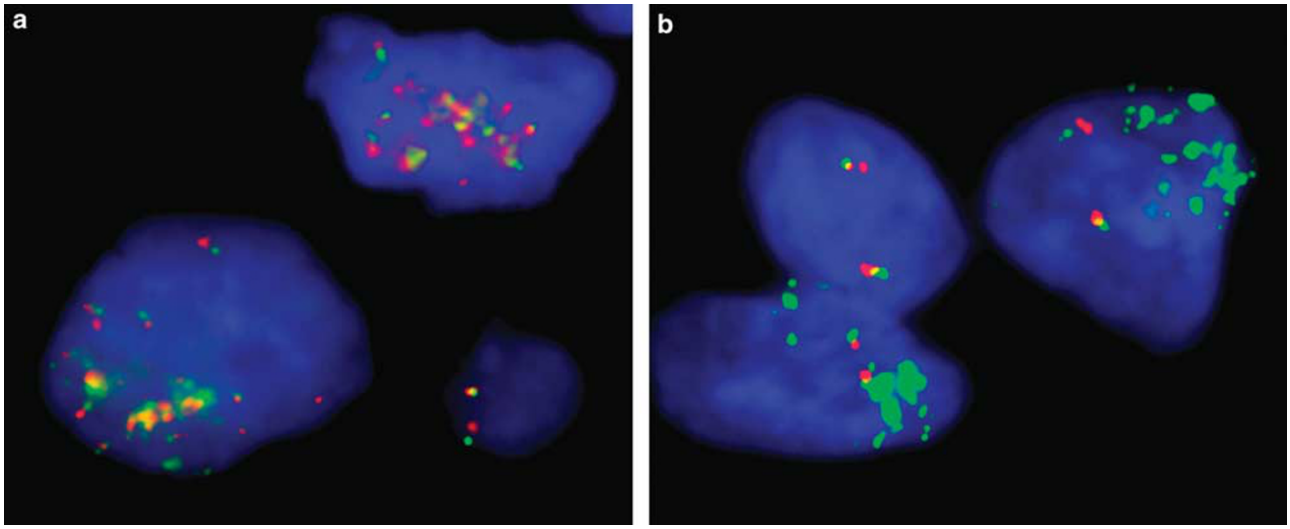

Figure 3 *STAT6* amplification detected in dedifferentiated liposarcoma interphase nuclei by FISH. A non-neoplastic cell is shown in each field as an internal control. (**a**) High-level amplification of *STAT6* demonstrated by the presence of multiple red signals, isolated, or overlapping with green signals. *CDK4* is highly amplified, as represented by innumerable green signals (case 1). (**b**) No amplification of *STAT6* despite high-level amplification of *CDK4* in a dedifferentiated liposarcoma control case, negative for STAT6 by immunohistochemistry.

Discussion

The significance of *STAT6* amplification and overexpression in a subset of dedifferentiated liposarcoma must be considered from both a diagnostic and a biological perspective, with potential therapeutic implications. Diagnostically, the specificity of STAT6 immunodetection for the diagnosis of solitary fibrous tumor in the appropriate morphological context is very high.[20,21] Dedifferentiated liposarcoma, however, can resemble solitary fibrous tumor morphologically, and STAT6 expression in a subset of dedifferentiated liposarcoma could complicate this differential diagnosis. The degree of STAT6 expression in solitary fibrous tumor is generally more diffuse and of a stronger intensity than in dedifferentiated liposarcoma, although the range of expression is variable, limiting the value of this observation for the evaluation of individual cases. The predominantly nuclear aberrant localization of STAT6 in solitary fibrous tumor, in contrast to the cytoplasmic and nuclear expression seen in dedifferentiated liposarcoma, may be a helpful discriminatory feature. Nevertheless, expression of STAT6 in dedifferentiated liposarcoma is a potential diagnostic pitfall that must be taken into consideration when evaluating a STAT6-positive spindle cell neoplasm, particularly in small needle biopsies of retroperitoneal or deep lesions. The presence of areas with varied morphologies, including areas of well-differentiated liposarcoma, and the demonstration of MDM2 and CDK4 expression by immunohistochemistry, or amplification by FISH, should allow for a diagnosis of dedifferentiated liposarcoma in the vast majority of cases.[11,15] However, the mere presence of fat formation within the tumor should not prompt a diagnosis of dedifferentiated liposarcoma, given the existence of a well-recognized subgroup of fat-forming solitary fibrous tumor, both benign and malignant.[22,23]

Mechanistically, amplification of *STAT6* in dedifferentiated liposarcoma is in keeping with the chromosomal location of this gene at 12q13 and the genetic makeup of dedifferentiated liposarcoma. Consistent *MDM2* amplification and frequent *CDK4* coamplification highlight the relevance of 12q13-15 amplicons in dedifferentiated liposarcoma,[4,10,24] but the remarkable heterogeneity of these and other amplicons in dedifferentiated liposarcoma is still poorly understood. Ring and giant marker chromosomes in dedifferentiated liposarcoma are topologically complex structures and are thought to result from multiple rounds of sequential breakage, fusion and bridging of donor chromosomes.[25] The resulting neochromosomes show a notable degree of plasticity, as demonstrated by the genetic variability between cases, and within each case.[4] Some structural considerations have been proposed to explain the composition of certain dedifferentiated liposarcoma amplicons; for example, a fragile site located immediately centromeric to the 5′ end of *DDIT3* at 12q14.1 has been proposed to define the centromeric boundary of the *CDK4* amplicon, so that chromosomal breakage at this site would have a role in the formation of the non-contiguous amplicons from 12q13-15.[6] Nevertheless, several genes centromeric to this breakpoint are coamplified in around 15% of dedifferentiated liposarcoma (including *GLI1*, *DCTN2*,[6,14] and as demonstrated in this report, *STAT6*), indicating that some cases of

dedifferentiated liposarcoma contain either larger amplicons extending over this site, or additional discontinuous amplicons from 12q13.

The relevance of *STAT6* amplification in the pathogenesis of dedifferentiated liposarcoma remains to be defined. The relatively low frequency of *STAT6* amplification in dedifferentiated liposarcoma indicates that it is most likely a passenger genomic event. Nevertheless, STAT6 may contribute substantially to the biology of dedifferentiated liposarcoma. Evidence in support of this interpretation originates from the only study that systematically analyzed the functional relevance of amplified genes in dedifferentiated liposarcoma: shRNA-mediated *STAT6* knockdown in three dedifferentiated liposarcoma cell lines significantly reduced cell proliferation, with lethal effects comparable to or greater than those resulting from *CDK4* knockdown.[14] Despite recent advances in the characterization of dedifferentiated liposarcoma neochromosomes, the functional contribution of each of the genes amplified within dedifferentiated liposarcoma amplicons is still unclear. Although *MDM2* is the best studied target of the 12q15 amplicon,[11,16] the consistent presence within the same amplicon of *YEATS4* and *FRS2* amplification, combined with *HMGA2* rearrangement, have also been demonstrated to be biologically essential.[6,12] Abundant experimental evidence also supports the functional relevance of *CDK4* in dedifferentiated liposarcoma.[13,14] Less common genomic events have been variably associated with particular biological features, for example, amplification of *JUN* and dedifferentiation.[8] The presence of *STAT6* amplification demonstrated in this report, combined with the functional evidence of STAT6 dependency in dedifferentiated liposarcoma,[14] highlights the biological and potentially therapeutic relevance of STAT6 in at least a subset of dedifferentiated liposarcoma and provides a basis to explore STAT6-targeting agents[17] as a rational therapeutic strategy in dedifferentiated liposarcoma.

In summary, *STAT6* amplification occurs in a subset of dedifferentiated liposarcoma, which results in expression of STAT6 that can be detected by immunohistochemistry and may be a potential pitfall in the differential diagnosis of dedifferentiated liposarcoma and solitary fibrous tumor. *STAT6* amplification in dedifferentiated liposarcoma further highlights the genomic complexity and heterogeneity of ring and giant marker chromosomes of this tumor type, particularly concerning amplicons originating from the chromosomal region 12q13-15. STAT6 transcriptional activity may be biologically relevant in some cases of dedifferentiated liposarcoma and may provide a therapeutic opportunity.

Acknowledgments

We are very grateful to Dr Jonathan A Fletcher for insightful discussions and valuable feedback about this study. AME is supported by a Career Development Award from the Sarcoma Alliance for Research through Collaboration (SARC).

Disclosure/conflict of interest

The authors declare no conflict of interest.

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