

## Solid Tumour Section

### Review

# Soft Tissue Tumors: Liposarcoma: Myxoid liposarcoma

Manuel Sánchez-Martín, Ines González-Herrero, Isidro Sánchez-García

Laboratorio 13, Instituto de Biología Molecular y Celular del Cáncer (IBMCC), Centro de Investigación del Cáncer, Campus Unamuno, 37.007-Salamanca, Spain (MSM, IGH, ISG)

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## Identity

### Alias

Myxoid-round cell liposarcoma.

### Note

Sarcomas are relatively rare malignant tumours and comprise less than 10% of all cancers. Classical classifications of sarcomas are based on the site of tumour (bone or soft tissue). Soft tissue sarcoma (STS) is the collective term used for malignancies arising in muscles, fat, vessels, the peripheral nervous system and fibrous tissue.

Histopathologic examination of such tumours has revealed a large number of distinct entities, each

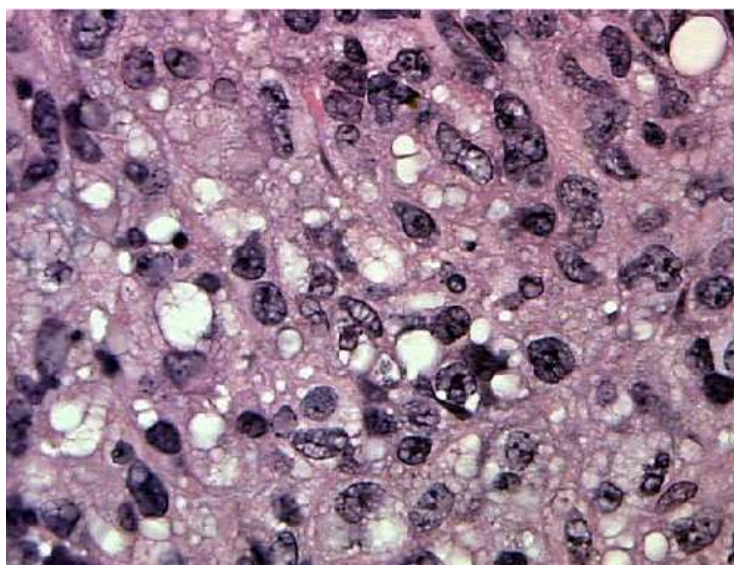
displaying its own morphologic and clinical characteristics.

Cytogenetic and molecular genetic analyses have shown that some of these STS are characterized by specific chromosomal translocations, whereas other STS show complex genetic aberrations.

Liposarcoma is the most common soft tissue malignancy in adults accounting for at least 20% of all sarcomas in this age group. Myxoid-round cell liposarcoma is a subtype of liposarcoma characterized by the presence of the reciprocal chromosomal translocation  $t(12;16)(q13;p11)$ .

This translocation creates the FUS-DDIT3 chimeric gene.

## Clinics and pathology



## Classification

Liposarcoma is a lipogenic tumour subclassified into four main histologic groups, including well-differentiated liposarcoma (lipoma-like and sclerosing types), myxoid-round cell liposarcoma, pleomorphic liposarcoma, and dedifferentiated liposarcoma. The histologic group is predictive of both the clinical course of the disease and the ultimate prognosis.

## Cytogenetics

### *Cytogenetics Morphological*

Cytogenetics analyses have shown that several lipogenic tumours are characterized by specific chromosomal abnormalities, the best known was the reciprocal translocation t(12;16)(q13;p11) of myxoid-round cell liposarcoma, described about twenty years ago. This translocation results in a fusion gene consisting of the 5' part of the FUS (TLS) gene and the complete coding region of the CHOP gene (see fig.1).

## Genes involved and proteins

### **FUS (TLS)**

#### **Location**

16p11

#### **DNA / RNA**

The FUS gene consists of 15 exons located within 11 kb of genomic DNA, and the exon 1 contains a 72-bp untranslated region and the translation initiation codon. The location of the FUS gene was identified as 16p11 by the site of the breakpoint in the translocation. The assignment was further narrowed to 16p11.2 by cytogenetic studies. FUS is rearranged in myxoid liposarcomas in the characteristic chromosomal translocation t(12;16)(q13;p11).

#### **Protein**

The FUS protein, provisionally designated TLS (translocated in liposarcoma), and then called FUS, contains an RNA-recognition motif and is a component of nuclear riboprotein complexes.

Lack of FUS in mice causes lethality into neonatal period, it influences lymphocyte development in a non-cell-intrinsic manner, it has an intrinsic role in the proliferative responses of B cells to specific mitogenic

stimuli, and it is required for the maintenance of genomic stability. The involvement of a nuclear riboprotein in these processes in vivo indicates that FUS is important in genome maintenance.

#### **Somatic mutations**

**Variants:** FUS has been also shown a partner of gene fusions linked in other malignances: fused to ERG in acute myeloid leukaemia with t(16:21)(p11;q22), fused to CREB3L2 in low-grade fibromyxoid sarcoma (LGFMS) by a translocation between chromosome bands 7q33-q34 (CREB3L2) and 16p11 (FUS) or fused to ATF1 in histiocytoma.

### **DDIT3 (CHOP)**

#### **Location**

12q13

#### **DNA / RNA**

The DDIT3 gene was isolated from human cells and has a high level of conservation with previously described hamster gene. Each is composed of 4 exons with intron/exon junctions maintained at identical positions. They showed 91% identity in amino acid sequence and 78% identity in nucleotide sequence. The gene is located on chromosome 12 (12q13.1-q13.2).

#### **Protein**

CHOP (C/EBP-homologous protein) is a nuclear protein which was identified as a dominant-negative inhibitor of the transcription factors C/EBP and LAP.

The protein also was called DDIT3 for DNA damage-inducible transcript 3' and GADD153 for 'growth arrest- and DNA damage-inducible gene.

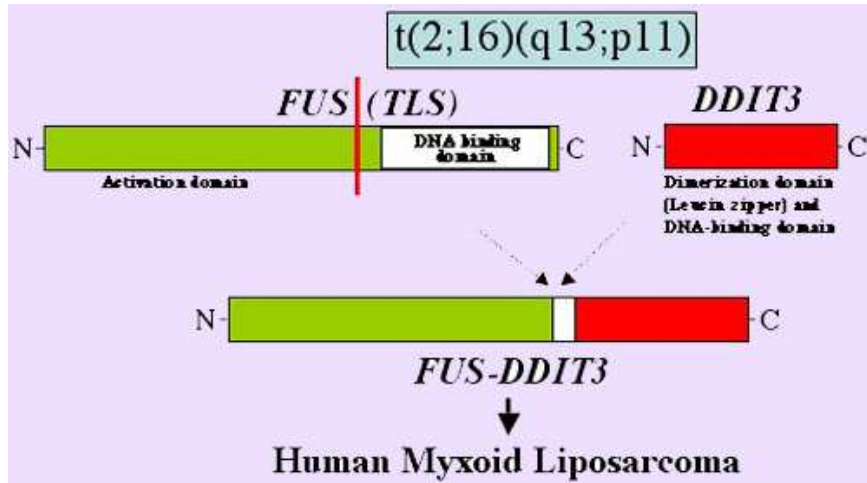
DDIT3 is consistently rearranged in myxoid liposarcomas in the characteristic chromosomal translocation t(12;16)(q13;p11). Its molecular characterization showed that the DDIT3 gene is fused with a gene on chromosome 16 named FUS.

#### **Somatic mutations**

**Variants:** An analysis of peripheral blood samples from 19 patients with myxoid liposarcoma linked to t(12;16) and from 1 patient with myxoid liposarcoma associated to t(12;22;20) chromosomal translocation, resulting in the fusion of the DDIT3 and EWS genes, found FUS-DDIT3 hybrid fragments in 3 patients with t(12;16) and the EWS-DDIT3 hybrid in the patient with the latter translocation.

## Result of the chromosomal anomaly

### Hybrid Gene



The FUS-CHOP fusion genes consist of the 5' promoter region and exons 1-5 or, more rarely, 1-7 or 1-8 of FUS gene fused to the complete coding region, including exons 1-4 or 2-4, of CHOP (DDIT3) gene.

### Fusion Protein

#### Oncogenesis

**Oncogenic properties** Transcriptional control of the fusion gene is dominated by the FUS housekeeping type of regulatory region, leading to stable expression of the fusion protein in tumor cells. The transforming properties of the FUS-DDIT3 fusion protein have been demonstrated in NIH 3T3 cells and fibroblasts. In the FUS-DDIT3 fusion, transcriptional activation is specifically conferred on the chimeric protein by the FUS segment after the translocation event. The portion of FUS that is present in the FUS-DDIT3 and FUS-ERG fusion proteins is similar and this part has been shown to be an autonomous transcriptional activation domain. The protein most likely functions as an abnormal transcription factor acting on a number of downstream target genes.

**Mouse models** In vivo, mice expressing FUS-DDIT3 develop liposarcomas. Overexpression of FUS-DDIT3 transgene driven by the elongation factor 1alpha (EF1alpha) promoter to all tissues, results in most of the symptoms of human liposarcomas, including the presence of lipoblasts with round nuclei, accumulation of intracellular lipid, induction of adipocyte-specific genes and a concordant block in the differentiation program (see figure 2). No tumours of other tissues were found in these transgenic mice despite widespread activity of the EF1alpha promoter. This establishes FUS-DDIT3 overexpression as a key determinant of human liposarcomas and provided the first in vivo evidence for a link between a fusion gene created by a chromosomal translocation and a solid tumour. In contrast, transgenic mice expressing high levels of DDIT3, which lacks the FUS domain, do not develop any tumour but consistently show the accumulation of a

glycoprotein material within the terminally differentiated adipocytes, a characteristic figure of liposarcomas associated with FUS-DDIT3. However, transgenic mice expressing the altered form of DDIT3-FUS (created by the in frame fusion of the FUS domain to the carboxy end of DDIT3) developed liposarcomas. The characteristics of the liposarcomas arising in the DDIT3-FUS mice were very similar to those previously observed in the FUS-DDIT3 transgenic mice indicating that the FUS domain is required not only for transformation but also influences the phenotype of the tumor cells. These results provide evidence that the FUS domain of FUS-DDIT3 plays a specific and critical role in the pathogenesis of liposarcoma. In this sense, when mice expressing the FUS domain are crossed with DDIT3-transgenic mice to generate the double-transgenic FUSxDDIT3, these animals develop liposarcoma. These results provide genetic evidence that FUS and DDIT3 domains function in trans for the mutual restoration of liposarcoma, and identify a new mechanism of tumour-associated fusion genes which might have impact beyond myxoid liposarcoma.

## References

- Thelin-Järnum S, Lassen C, Panagopoulos I, Mandahl N, Aman P. Identification of genes differentially expressed in TLS-CHOP carrying myxoid liposarcomas. *Int J Cancer*. 1999 Sep 24;83(1):30-3
- Hicks GG, Singh N, Nashabi A, Mai S, Bozek G, Klewes L, Arapovic D, White EK, Koury MJ, Oltz EM, Van Kaer L, Ruley HE. Fus deficiency in mice results in defective B-lymphocyte development and activation, high levels of chromosomal instability and perinatal death. *Nat Genet*. 2000 Feb;24(2):175-9
- Pérez-Losada J, Pintado B, Gutiérrez-Adán A, Flores T, Bañares-González B, del Campo JC, Martín-Martín JF,

- Battaner E, Sánchez-García I. The chimeric FUS/TLS-CHOP fusion protein specifically induces liposarcomas in transgenic mice. *Oncogene*. 2000 May 11;19(20):2413-22
- Waters BL, Panagopoulos I, Allen EF. Genetic characterization of angiomatoid fibrous histiocytoma identifies fusion of the FUS and ATF-1 genes induced by a chromosomal translocation involving bands 12q13 and 16p11. *Cancer Genet Cytogenet*. 2000 Sep;121(2):109-16
- Pérez-Losada J, Sánchez-Martín M, Rodríguez-García MA, Pérez-Mancera PA, Pintado B, Flores T, Battaner E, Sánchez-García I. Liposarcoma initiated by FUS/TLS-CHOP: the FUS/TLS domain plays a critical role in the pathogenesis of liposarcoma. *Oncogene*. 2000 Dec 7;19(52):6015-22
- Pérez-Mancera PA, Pérez-Losada J, Sánchez-Martín M, Rodríguez-García MA, Flores T, Battaner E, Gutiérrez-Adán A, Pintado B, Sánchez-García I. Expression of the FUS domain restores liposarcoma development in CHOP transgenic mice. *Oncogene*. 2002 Mar 7;21(11):1679-84
- Aman P, Ron D, Mandahl N, Fioretos T, Heim S, Arheden K, Willén H, Rydholm A, Mitelman F. Rearrangement of the transcription factor gene CHOP in myxoid liposarcomas with t(12;16)(q13;p11). *Genes Chromosomes Cancer*. 1992 Nov;5(4):278-85
- Storlazzi CT, Mertens F, Nascimento A, Isaksson M, Wejde J, Brosjo O, Mandahl N, Panagopoulos I. Fusion of the FUS and BFBF2H7 genes in low grade fibromyxoid sarcoma. *Hum Mol Genet*. 2003 Sep 15;12(18):2349-58
- Park JS, Luethy JD, Wang MG, Fargnoli J, Fornace AJ Jr, McBride OW, Holbrook NJ. Isolation, characterization and chromosomal localization of the human GADD153 gene. *Gene*. 1992 Jul 15;116(2):259-67
- Daugaard S. Current soft-tissue sarcoma classifications. *Eur J Cancer*. 2004 Mar;40(4):543-8
- Ron D, Habener JF. CHOP, a novel developmentally regulated nuclear protein that dimerizes with transcription factors C/EBP and LAP and functions as a dominant-negative inhibitor of gene transcription. *Genes Dev*. 1992 Mar;6(3):439-53
- Eneroth M, Mandahl N, Heim S, Willén H, Rydholm A, Alberts KA, Mitelman F. Localization of the chromosomal breakpoints of the t(12;16) in liposarcoma to subbands 12q13.3 and 16p11.2. *Cancer Genet Cytogenet*. 1990 Aug 1;48(1):101-7
- Turc-Carel C, Limon J, Dal Cin P, Rao U, Karakousis C, Sandberg AA. Cytogenetic studies of adipose tissue tumors. II. Recurrent reciprocal translocation t(12;16)(q13;p11) in myxoid liposarcomas. *Cancer Genet Cytogenet*. 1986 Dec;23(4):291-9
- Kuroda M, Ishida T, Horiuchi H, Kida N, Uozaki H, Takeuchi H, Tsuji K, Imamura T, Mori S, Machinami R. Chimeric TLS/FUS-CHOP gene expression and the heterogeneity of its junction in human myxoid and round cell liposarcoma. *Am J Pathol*. 1995 Nov;147(5):1221-7
- Rabbitts TH, Forster A, Larson R, Nathan P. Fusion of the dominant negative transcription regulator CHOP with a novel gene FUS by translocation t(12;16) in malignant liposarcoma. *Nat Genet*. 1993 Jun;4(2):175-80
- Panagopoulos I, Aman P, Fioretos T, Höglund M, Johansson B, Mandahl N, Heim S, Behrendtz M, Mitelman F. Fusion of the FUS gene with ERG in acute myeloid leukemia with t(16;21)(p11;q22). *Genes Chromosomes Cancer*. 1994 Dec;11(4):256-62
- Panagopoulos I, Mandahl N, Mitelman F, Aman P. Two distinct FUS breakpoint clusters in myxoid liposarcoma and acute myeloid leukemia with the translocations t(12;16) and t(16;21). *Oncogene*. 1995 Sep 21;11(6):1133-7
- Zinszner H, Albalat R, Ron D. A novel effector domain from the RNA-binding protein TLS or EWS is required for oncogenic transformation by CHOP. *Genes Dev*. 1994 Nov 1;8(21):2513-26
- Panagopoulos I, Mandahl N, Ron D, Höglund M, Nilbert M, Mertens F, Mitelman F, Aman P. Characterization of the CHOP breakpoints and fusion transcripts in myxoid liposarcomas with the 12;16 translocation. *Cancer Res*. 1994 Dec 15;54(24):6500-3
- Sánchez-García I, Rabbitts TH. Transcriptional activation by TAL1 and FUS-CHOP proteins expressed in acute malignancies as a result of chromosomal abnormalities. *Proc Natl Acad Sci U S A*. 1994 Aug 16;91(17):7869-73
- Ichikawa H, Shimizu K, Hayashi Y, Ohki M. An RNA-binding protein gene, TLS/FUS, is fused to ERG in human myeloid leukemia with t(16;21) chromosomal translocation. *Cancer Res*. 1994 Jun 1;54(11):2865-8
- Crozat A, Aman P, Mandahl N, Ron D. Fusion of CHOP to a novel RNA-binding protein in human myxoid liposarcoma. *Nature*. 1993 Jun 17;363(6430):640-4
- Panagopoulos I, Aman P, Mertens F, Mandahl N, Rydholm A, Bauer HF, Mitelman F. Genomic PCR detects tumor cells in peripheral blood from patients with myxoid liposarcoma. *Genes Chromosomes Cancer*. 1996 Oct;17(2):102-7
- Aman P, Panagopoulos I, Lassen C, Fioretos T, Mencinger M, Toresson H, Höglund M, Forster A, Rabbitts TH, Ron D, Mandahl N, Mitelman F. Expression patterns of the human sarcoma-associated genes FUS and EWS and the genomic structure of FUS. *Genomics*. 1996 Oct 1;37(1):1-8

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