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Histopathogenesis of bone- and soft-tissue tumor spectrum with *USP6* gene rearrangement: multiple partners involved in the tissue repair process

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Summary. Primary aneurysmal bone cyst, nodular fasciitis, myositis ossificans and related lesions as well as fibroma of tendon sheath are benign tumors that share common histological features and a chromosomal rearrangement involving the ubiquitin-specific peptidase 6 (*USP6*) gene. The tumorigenesis of this tumor spectrum has become complex with the identification of an increasing number of new partners involved in *USP6* rearrangements. Because traumatic involvement has long been mentioned in the histogenesis of most lesions in the *USP6* spectrum and they morphologically resemble granulation tissue or callus, we attempted to shed light on the function and role *USP6* partners play in tissue remodelling and the repair process and, to a lesser extent, bone metabolism.

Key words: USP6, Gene fusion, Nodular fasciitis, Primary aneurysmal bone cyst, Myositis ossificans, Fibroma of tendon sheath

Introduction

Aneurysmal bone cyst (ABC), nodular fasciitis (NF), myositis ossificans (MO) and fibroma of tendon sheath (FTS) are benign bone- or soft-tissue tumors that share similar clinicopathological characteristics. All these lesions present gene fusion of *USP6*, encoding a type 6 ubiquitin-specific protease, and one of approximately 50 partners described so far. By fusing with one of these partners, *USP6* is transcriptionally upregulated via a promoter-swapping mechanism. As a result, *USP6* promotes tumorigenesis via multiple pathways, including Wnt, Jak1-signal transducer and activator of transcription 3 (STAT3) and c-Jun.

In this issue, we detail the properties of *USP6*, the clinico-pathological characteristics of USP6-rearranged bone- and soft-tissue neoplasms, the methods available to identify these rearrangements and the biological effects related to these rearrangements. We then focus on the ever-increasing number of partners identified as being involved in the translocation and explore the hypothesis that these different genes could have in common their involvement in the molecular machinery of the tissue repair process.

Identification and structure of USP6: origin, function and isoforms

USP6, also known as Tre-2 and TRE17, is a hominoid-specific gene, located on chromosome 17p13. It likely emerged 21 to 33 million years ago (Paulding et al., 2003) but was only identified as a novel proto-oncogene in 1992 (Nakamura et al., 1992). It encodes a large subfamily of deubiquitination enzymes, the ubiquitin-specific proteases (USPs) (Papa and Hochstrasser, 1993). USP6 proteases are cysteine proteases that cleave ubiquitin from target proteins and other molecules to regulate their degradation via the proteasome. These enzymes are involved in various cellular processes including intracellular trafficking, protein turnover, inflammatory signaling and cell transformation (Amerik and Hochstrasser, 2004; Singhal et al., 2008). There are two splice variants of *USP6* (Nakamura et al., 1992; Paulding et al., 2003), encoding two isoforms, termed USP6 long and USP6 short (Fig. 1). These isoforms are identical through the first 773 amino acids but then diverge. USP6 long encodes the USP domain, which contains cysteine and histidine

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Abbreviations. ABC, aneurysmal bone cyst; FOPD, fibro-osseous pseudotumor of digits; FRPO, florid reactive periostitis ossificans; FTS, fibroma of tendon sheath; NF, nodular fasciitis; MO, myositis ossificans; USP6, ubiquitin-specific peptidase 6.

subdomains required for the catalytic activity (Papa and Hochstrasser, 1993). USP6 short is truncated after the cysteine subdomain of USP and is thus catalytically inactive. Both isoforms contain an N-terminal TBC domain that lacks catalytic activity (Martinu et al., 2004).

The clinico-pathological spectrum of *USP6*-rearranged bone- and soft-tissue neoplasms

The presence of a *USP6* rearrangement in ABC, NF, MO and related lesions as well as FTS provides a strong convincing argument for considering them a spectrum of lesions rather than distinct entities. The demonstration of this *USP6* rearrangement allowed for differentiating the primary from the so-called secondary ABC, ultimately corresponding to non-specific rearrangements within another primary bone lesion. This demonstration also led to including in this spectrum the solid variant of ABC (Sanerkin et al., 1983; Vergel De Dios et al., 1992), the giant cell reparative granuloma of the hands and feet/giant cell lesion of small bones (GCLSBs) (Panoutsakopoulos et al., 1999; Oliveira et al., 2020, 2004; Agaram et al., 2014) and lesions related to MO occurring in the subcutis, fascia or tendons, and fingers, called panniculitis ossificans, fasciitis ossificans, and fibro-osseous pseudotumor of digits (FOPDs) or florid reactive periostitis ossificans, respectively (Oliveira et al, 2020). Regardless of the cellularity of FTS, FTS was recently found to belong to this tumor spectrum (Pižem et al., 2021).

These lesions share many clinicopathological characteristics. They are benign tumors that may occur in all age groups but mainly in young patients, in the first 3 decades of life. They often grow rapidly (Oliveira et al., 2020) and can thus mimic malignancy (De Silva et al., 2003; Oliveira et al., 2020). They may involve any anatomical site. Some, such as FTS, FOPDs and the former "giant cell lesion of small bones" subgroup, typically affect the distal extremities, especially the fingers of the hands, and, to a lesser extent, the toes of the feet (Sciot and Cunha, 2020). Males are more commonly affected by MO and FTS and females by FOPDs (Oliveira et al., 2020); ABC and NF have no sex predilection.

Histologically, the cellularity and stroma components of these lesions vary considerably, both in their respective proportions and composition. They all present a spindle-cell myofibroblastic component, without marked atypia. Mitotic figures are common, sometimes plentiful but not atypical. Most cases feature multinucleated osteoclast-type giant cells, in particular around foci of hemorrhagic suffusions with some extravasated erythrocytes, which may converge to form micro-cavities or pseudo-cystic cavities. Lymphocytic infiltrates are common. Stroma may also contain an abundant myxoid, mucoid or heavily hyalinized matrix with deposition of keloidal collagen bundles (Lu et al., 2015). Many features bone formation. A zonal distribution of fibroblastic proliferation and immature woven bone production is a distinctive pattern in MO and related lesions.

The pathogenesis of these lesions has long been debated. ABC was suggested to be a reactive tumor resulting from a hemodynamic imbalance caused by vascular network dilation as a result of increased venous pressure (Patel et al., 2005). The role played by hemodynamic forces of an osseous and arteriovenous fistula initiated by a primary bone lesion was mentioned (Arora et al., 2014). A traumatic context is described for some lesions. MO occurs after a trauma or repetitive minor injury in up to 60% to 75% of cases (Oliveira et al, 2020). A history of trauma was found in only rare cases of ABC and in 10% to 15% of NF and FTS cases. Identification of a specific chromosomal rearrangement lends unequivocal credence to an oncogenetic pathogenesis and suggests that these lesions are benign neoplasms.

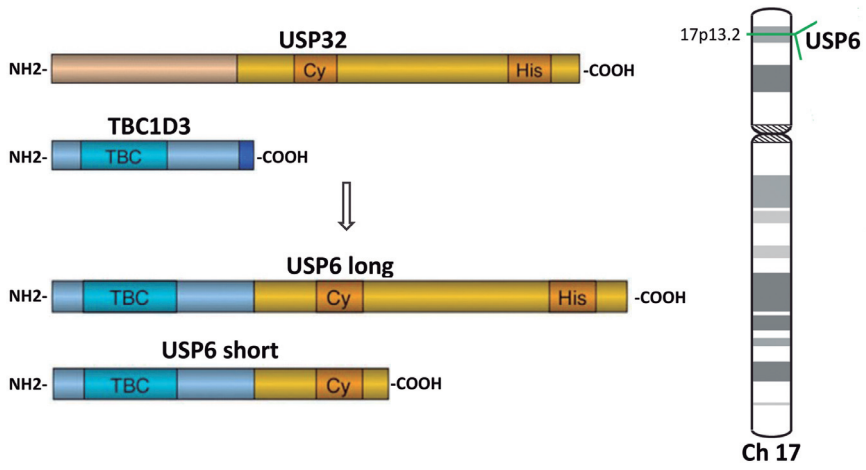

Fig. 1. Long and short isoforms of USP6 resulting from the chimeric fusion of *TBC1D3* and *USP32* genes.

The prognosis of soft-tissue lesions of the spectrum is generally good, with complete excision being curative without local recurrence in most cases (De Silva et al., 2003). Nevertheless, FTS may recur in 5% to 10% of cases. However, in bone, ABC is a potentially locally aggressive and recurrent neoplasm. To date, there does not appear to be a link between the subtype of *USP6* rearrangement and clinical and histological features or recurrence rate.

Identification of *USP6* rearrangements

As described previously, different methods exist to identify chromosome translocations involving *USP6*. They feature varying degrees of sensitivity (Table 1).

Fluorescent *in situ* hybridization (FISH) and RT-PCR are commonly used to detect fusion transcripts involving *USP6*. Because of its high specificity (100%) and sensitivity, FISH is one of the main reference molecular cytogenetics techniques for detecting *USP6* fission. The most commonly used probes are the "split signal" or "break-apart" type. The principle is based on the hybridization of nucleotide probes labelled with a fluorochrome and complementary to a target sequence. FISH and RT-PCR are commonly used to detect fusion transcripts of *USP6*, identifying such fusions in 68% and 49% of ABC cases, respectively, and 86% and 76% of NF cases (Table 1). The sensitivity of FISH is 59% for ABC and 93% for NF, whereas that of RT-PCR is 53% for ABC and 74% for NF (Oliveira et al., 2004; Amary et al., 2013). This difference in sensitivity between ABC and NF may be explained in part by the decalcification processes needed for some ABC cases, which leads to deleterious effects on nucleic acids (Miquelestorena-Standley et al., 2020). FISH is sensitive, low cost and readily available but lacks standardization for the interpretation of results (minimum number of tumor nuclei analyzed, percentage of nuclei rearranged) and does not allow for identifying the *USP6* partners of the fusion. RT-PCR is more expensive, time-consuming, and labour-intensive and requires knowing the different *USP6* partners for identifying *USP6* rearrangements. Both methods are unable to identify fusions with novel partner genes.

Next-generation sequencing (NGS) has become a reference molecular diagnostics method used in daily practice by pathologists. In addition to its great sensitivity, NGS can allow for parallel sequencing of nucleic acids in a single assay and can cover all potential targets, such as fusion transcripts, with as little tissue needed as possible.

Because a gene rearrangement induces an overexpression of the downstream gene in the fusion and thus increases the protein level, detection of this expression by immunohistochemistry may be a useful diagnostic tool for the pathologist. There are very few works on this topic. Sápi et al. recently demonstrated in a series of NF cases, that USP6 overexpression could be demonstrated by immunohistochemistry and that,

Table 1. Number of USP6 rearrangements identified for each neoplasm, based on techniques used in the literature.

Neoplasm/Reference	Technique	Number of patients	Percentage of USP6 rearranged neoplasm
ABC			
Oliveira et al., 2004	FISH *USP6*	8	75%
Oliveira et al., 2004	FISH *CDH11*	8	63%
Oliveira et al., 2004	RT-PCR	8	50%
Oliveira et al., 2004	FISH *USP6*	52	69%
Oliveira et al., 2004	RT-PCR	36	28%
Oliveira et al., 2005	RT-PCR	13	85%
Agaram et al., 2014	FISH *USP6*	22	59%
Guseva et al., 2017	NGS	13	100%
Rehkämper et al.,2018	FISH *USP6*	19	47%
Song et al., 2019	FISH *USP6*	6	33%
Song et al., 2019	NGS	6	50%
Šekoranja et al., 2020	NGS	11	100%
Zhang et al., 2020	FISH *USP6*	7	86%
Zhang et al., 2020	NGS	7	100%
Zhou et al., 2020	FISH *USP6*	17	82%
Wang et al., 2021	FISH *USP6*	6	67%
Legrand et al., 2021	RT-PCR	42	31%
Legrand et al., 2021	NGS	8	100%
Pižem et al., 2021	NGS	8	100%
Jager et al., 2022	FISH *USP6*	4	100%
Lambert et al., 2022	NGS	2	100%
NF			
Erickson-Johnson et al., 2011	FISH *USP6*	48	92%
Erickson-Johnson et al., 2011	FISH *MYH9*	48	65%
Erickson-Johnson et al., 2011	RT-PCR	16	75%
Amary et al., 2013	FISH *USP6*	19	91%
Amary et al., 2013	RT-PCR	19	74%
Chen et al., 2014	FISH *USP6*	29	83%
Chen et al., 2014	RT-PCR	15	73%
Shin et al., 2016	FISH *USP6*	7	86%
Patel et al., 2017	FISH *USP6*	26	77%
Patel et al., 2017	RT-PCR	20	65%
Patel et al., 2017	NGS	8	100%
Salib et al., 2020	FISH *USP6*	3	93%
Paulson et al., 2020	NGS	15	33%
Zhang et al., 2020	FISH *USP6*	7	86%
Legrand et al., 2021	RT-PCR	28	67%
Legrand et al., 2021	NGS	4	75%
Stražar et al., 2021	NGS	7	86%
Wang et al., 2021	FISH *USP6*	35	89%
Cloutier et al., 2021	FISH *USP6*	1	100%
Cloutier et al., 2021	NGS	11	73%
Miyama et al., 2021	RT-PCR	2	100%
FTS			
Carter et al., 2016	FISH *USP6*	9	67%
Mantilla et al.,2021	NGS	11	64%
Wang et al., 2021	FISH *USP6*	11	91%
Pižem et al., 2021	NGS	18	94%
MO			
Sukov et al., 2008	FISH *USP6*	12	17%
Becker et al., 2016	FISH *USP6*	9	89%
Flucke et al., 2018	FISH *COL1A1*	5	80%
Švajdler et al., 2019	NGS	7	71%
Legrand et al., 2021	RT-PCR	7	57%
Legrand et al., 2021	NGS	3	67%
Wang et al., 2021	FISH *USP6*	6	67%
FOPD			
Flucke et al., 2018	FISH *USP6*	5	80%
Švajdler et al., 2019	NGS	5	80%
Wang et al., 2020	FISH *USP6*	2	100%

moreover, this expression was localised in cells carrying the *USP6* rearrangement. In this study, the level of *USP6* was related to the cellularity and age of the NF (Sápi et al., 2021). However, the specificity of this immunostaining should be verified by further studies. To our knowledge, no studies have investigated *USP6* expression by immunohistochemistry in a series of bone- and soft-tissue tumours relevant to the differential diagnosis of *USP6* spectrum lesions.

Biological effects associated with USP6 rearrangements

The biological effects associated with the overexpression of *USP6* after its rearrangement with one of the above partners are summarized in Figure 2.

USP6 is barely expressed in most normal tissues, except for testis and skeletal muscle, where it regulates the turnover of proteins involved in vesicle trafficking and muscle contraction, respectively (Paulding et al., 2003; Vichaiwong et al., 2010). In neoplasm, the chromosomal translocation of *USP6* with one partner results in promoter swapping, with the complete coding sequence of *USP6* placed downstream of the highly active promoter of its fusion partner. This translocation leads to USP6 transcriptional upregulation (Oliveira et al., 2004, 2005) and as a result, protein overexpression. The *USP6* produced is truncated, but its functionality is conserved when the fusion implies the beginning of *USP6* exons 1, 2 or 3 (Oliveira et al., 2005; Švajdler et al., 2019). The overexpression of *USP6* may activate different signaling pathways known to play a crucial role in cell growth, differentiation, migration, genetic stability, apoptosis, self-renewal of stem cells, and maintenance of adult tissue homeostasis. As a result, *USP6* induces both activation of the small GTPase Arf6 through its TBC domain and deubiquitylase (catalytic) activity through its USP domain. This induction may lead to initiation of different pathways involved in tumorigenesis (Martinu et al., 2004). *USP6* can activate the β-catenin–dependent Wnt signaling pathway by inhibiting proteasomal degradation of Frizzleds receptor (Madan et al., 2016; Hu et al., 2018). Through its USP activity, *USP6* can increase c-Jun protein level, the product of a proto-oncogene that belongs to the transcription factor activator protein 1 (AP-1) family. AP-1 sites are present in the promoters of several genes encoding bone-associated proteins such as collagen type I, alkaline phosphatase, osteocalcin, collagenase-3, and parathyroid hormone. Also, c-Jun has a role in bone: its increased expression was found correlated with fully differentiated bone cells in fracture repair (Lewinson et al., 2003; Li et al., 2017).

USP6 is involved in bone remodeling by interfering with normal osteoblastic maturation via inhibiting the expression of bone morphogenetic protein 4 (BMP4), a key regulator of osteogenesis, and simultaneously augmenting Gremlin-1, a BMP antagonist (Lau et al., 2010).

Jak1-STAT3 represent essential mediators of the pathogenic mechanism of *USP6*. *USP6* activates this pathway by de-ubiquitinating and therefore stabilizing Jak1, which leads to STAT3 phosphorylation and then activation and production of autocrine and paracrine factors. The elevated Jak1 level sensitizes *USP6*-expressing cells to these autocrine factors, thus amplifying STAT3 activation in a positive feedback loop (Quick et al., 2016). STAT3 is also a key regulator of cell proliferation, survival, and apoptosis and is constitutively activated in most cancers: it participates in

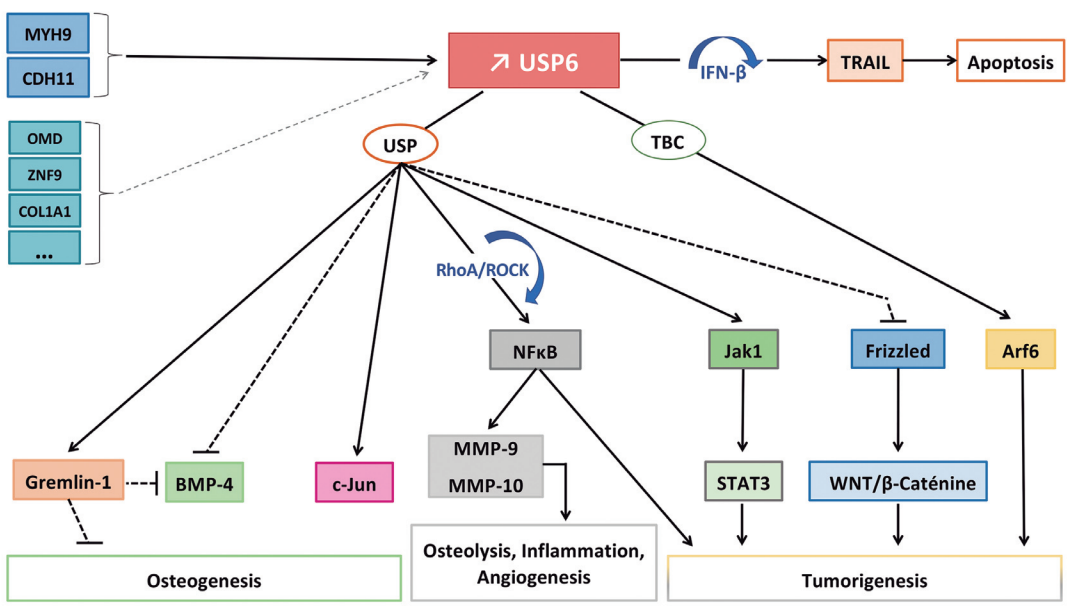

Fig. 2. Cellular pathways and response mechanisms following USP6 gene activation.

cancer progression by promoting the expression of transcription factors related to the epithelial-to-mesenchymal transformation. Activated along with NF-κB, STAT3 can control the communication between inflammatory and cancer cells.

USP6 is available independently to induce the activation of STAT3 and NF-κB. NF-κB is a pleiotropic transcription factor involved in inflammation and cellular transformation and thus increases the transcription of matrix metalloprotease 9 (MMP-9) and MMP-10 (Serasanambati and Shanmuga, 2016). Activation of NF-κB depends on the *USP6* USP domain activity, mediated in part by the GTPase RhoA and its effector kinase ROCK (Ye et al., 2010).

A *USP6*-induced negative feedback mechanism, induced by activating the tumor necrosis factor-related apoptosis including ligand (TRAIL) and interferon β, likely results in apoptosis of tumor cells harboring a *USP6* rearrangement (Sápi et al., 2021).

Partners involved in *USP6* chromosomal rearrangements

Currently, more than 50 partners are implicated in chromosomal rearrangements of *USP6*. Their characteristics are summarized in Table 2.

The first cytogenetic abnormalities of *USP6* were reported in 1999 by Panoutsakopoulos et al. (1999), who identified a recurrent chromosomal translocation t(16;17)(q22;p13) in two cases of ABC. This identification provided the first convincing evidence of the clonal neoplastic nature of ABC. Subsequently, two additional cases of solid and extraosseous ABC sharing the same translocation were reported (Dal Cin et al., 2000). In 2004, Oliveira et al. identified the genes involved in the cytogenetic rearrangement. Using 5'RACE-PCR, the authors found that the translocation t(16;17)(q22;p13) arose from the fusion of the promoter region of the osteoblast cadherin 11 gene (*CDH11*) on chromosome 16q22 and USP6 on chromosome 17p13, thus leading to overexpression of the oncogene *USP6* (Oliveira et al., 2004). They showed that this rearrangement was present in only primary ABC but not secondary ABC or giant cell tumors (Oliveira et al., 2004). Additional *USP6* gene partners in ABC were then identified: *ZNF9*, *COL1A1*, *TRAP150* and *OMD* (Oliveira et al., 2005). Since 2017, with the advent of NGS, several alternative partners in ABC have been identified: *E1F1*, *FOSL2*, *STAT3*, *CTNNB1*, *SEC31A*, *PAFAH1B1*, *RUNX2* (Guseva et al., 2017), *SPARC* (Šekoranja et al., 2018), *USP9X* (Blackburn et al., 2019), *ASAP1*, *FAT1*, *SAR1A*, *TNC* (Šekoranja et al., 2020), *ANGPTL2* (Zhang et al., 2020), *LUM* (Panagopoulos et al., 2020) and more recently *RRBP1*, *TPM4*, *DDX17*, *GTF2I*, *KLF3*, *MEF2A* (Legrand et al., 2021) as well as *PTBP1*, *SLC38A2* (Dermawan et al., 2021), *VDR* (Papke et al., 2021) and *RBM5* (Pižem et al., 2021).

Erickson-Johnson et al. were the first to report a rearrangement of *USP6* as a recurrent and specific finding in NF by identifying high mRNA levels of *USP6*. The most common fusion partner in NF was identified as myosin heavy chain 9 (*MYH9*) on chromosome 22q13.1 (Erickson-Johnson et al., 2011). Other fusion partners identified in NF by NGS included *PPP6R3* (Guo et al., 2016), *RRBP1*, *CALU*, *CTNNB1*, *MIR22HG*, *SPARC*, *THBS2*, *COL6A2* (Patel et al., 2017), *COL1A1*, *SEC31A* (Lam et al., 2018), *EIF5A* (Lenz et al., 2020), *PAFAH1B1* (Qiu et al., 2020), *COL1A2* (Wang et al., 2021) and then *PDLIM7*, *MYL12A* (Legrand et al., 2021), *NACA*, *SLFN11*, *LDH6* (Cloutier et al., 2021), *TPM4* (Rodriguez et al., 2022) and *CALD1* (Papke et al., 2021).

USP6 fusions have also been discovered in cellular FTS, which shares similar histological features with NF. Some partners, such as *MYH9* (Mantilla et al., 2021), *COL1A1* (Wang et al., 2020), *PKM*, *RCC1*, *ASPN*, *COL3A1* (Mantilla et al., 2021), *CTNNB1*, *SPARC* and *MIR22HG* (Pižem et al., 2021) are common to both lesions. In addition, *USP6* was found fused with *SERPINH1* and *COL3A1* in cranial fasciitis (Paulson et al., 2020) and *CTNNB1* in intravascular fasciitis (Lu et al., 2020).

In 2008, a *USP6* rearrangement was observed in two cases of *MO* (Sukov et al., 2008), identified later as involving *COL1A1* (Flucke et al., 2018; Bekers et al., 2018; Zhang et al., 2020). This same partner was also described in a subset of FOPDs and in most GCLSBs, which expands the spectrum of *USP6*-induced neoplasms (Agaram et al., 2014).

A particularity of neoplastic cells carrying a *USP6* rearrangement was described as fibroblast-like spindle cells. These neoplastic cells might represent an early phase of osteoblast, fibroblast or myofibroblast differentiation and are not histologically different from cells without translocation, which remains one of the major problems in identifying the cell of origin. This rearrangement is not found in inflammatory, endothelial, osteoblastic or multinucleated osteoblastic giant cells.

To date, no association has been demonstrated between the presence of a *USP6* rearrangement and clinical and histological features or recurrence rate of lesions.

Only four cases of probably malignant nodular fasciitis and one case of unusually aggressive ABC have been reported. These lesions showed fusion of *PPP6R3::USP6* (reported in two cases of NF), *MYH9::USP6*, *RUNX2::USP6* and *CALD1::USP6* genes, respectively (Guo et al., 2016; Warren et al., 2017; Teramura et al., 2019; Sawamura et al., 2021; Papke et al., 2021). Two of these four partners have also been described in one or more cases considered benign (Erickson-Johnson et al., 2011; Guseva et al., 2017). Moreover, the histological features of the lesions are not necessarily predictive of their clinical behavior. Some lesions may present a usual histological appearance and have an aggressive clinical behaviour (Teramura et al, 2019), while others show histological criteria of malignancy and have a favorable evolution (Tomassen et

Table 2. Summary of USP6 fusion partners, classified by their origin, chromosome localization and function.

	Gene	Name	Chromosome	Protein family	Function	Reference
ABC	CDH11	Cadherin 11	*16q22*	Type II cadherins family	Osteoblastic differentiation and cellular adhesion	Oliveira et al., 2004
	TRAP 150	Thyroid Receptor-Associated Protein 150	*1p34*	Transcriptional factor	Transcription co-activaton	Oliveira et al., 2005
	ZNF9 or CNBP1	Zinc Finger Protein 9	*3q21*	RNA-binding protein	Regulation of sterol metabolism	Oliveira et al., 2005
	OMD	Osteomodulin	*9q92*		Osteoblastic differentiation	Oliveira et al., 2005
	COL1A1	Collagen type 1 Alpha 1 chain	*17q21.33*	Pro-alpha1 chains of type I collagen	Fibril-forming collagen constituting connective tissues, bone, cornea, dermis and tendon	Oliveira et al., 2005
	EIF1	Eukaryotic translation Initiation factor 1	*17q21.2*	Translation factor	Protein translation initiation: mRNA screening, delivery of tRNA, and recognition of start codon	Guseva et al., 2017
	FOSL2	FOS Like Antigen 2	*2p22*	Leucine zipper proteins	Osteoblastic differentiation	Guseva et al., 2017
	PAFAH1B1	Platelet Activating Factor Acetylhydrolase 1b Regulatory Subunit 1	*17p13*	Platelet-activating factor acteylhydrolase	Regulation of Platelet Activating Factor	Guseva et al., 2017
	RUNX2	RUNX Family Transcription Factor 2	*6p21*	Transcription factors	Osteoblastic differentiation and skeletal morphogenesis	Guseva et al., 2017
	CTNNB1	Catenin Beta 1	*3p22*		Cell adhesion, cell signaling and transcription	Guseva et al., 2017
	SEC31A	SEC31 Homolog A, COPII Coat Complex Componen	*4q21*		Budding of the vesicles from the Endoplasmic Reticulum	Guseva et al., 2017
	STAT3	Signal Transducer And Activator Of Transcription 3	*17q21.2*	STAT protein family	Cell proliferation, apoptosis and cell differentiation	Guseva et al., 2017
	SPARC	Secreted Protein Acidic And Cysteine Rich	*5q33*	Cysteine-rich acidic matrix-associated protein	Synthesis of the extracellular matrix, calcification of bone collagen	Šekoranja et al., 2018
	USP9X	Ubiquitin Specific Peptidase 9 X-Linked	*Xp11*	Peptidase C19 family	Oncogene or tumor suppressor gene according to the pathology	Blackburn et al., 2019
	ASAP1	ArfGAP With SH3 Domain, Ankyrin Repeat And PH Domain 1	*8q24.2*	ARF GTPase-activating protein	Cytoskeletal rearrangement, cell motility, adhesion and metastasis	Šekoranja et al., 2020
	SAR1A	Secretion Associated Ras Related GTPase 1A	*10q22.1*		Endoplasmic Reticulum export of proteins	Šekoranja et al., 2020
	FAT1	FAT Atypical Cadherin 1	*4q35.2*	Tumor suppressor	Cell proliferation	Šekoranja et al., 2020
	TNC	Tenascin C	*9q33.1*	Extracellular matrix	Cell motility, survival, differentiation and neurite outgrowth, cell adhesion, migration and proliferation, tissue repair	Šekoranja et al., 2020
	ANGPTL2	Angiopoietin Like 2	*9q33.3*	Vascular endothelial growth factor family	Angiogenic, antiapoptotic and proinflammatory properties	Zhang et al., 2020
	LUM	Lumican	*12q21.33*	Small leucine-rich proteoglycan family	Regulates collagen fibril organization and circumferential growth, corneal transparency, and epithelial cell migration and tissue repair Tumor progression, angiogenesis, and metastasis	Panagopoulos et al., 2020
	DDX17	DEAD-box helicase 17	*22q13.1*	RNA helicases	RNA metabolic pathways, embryogenesis, spermatogenesis, cellular growth and division	Legrand et al., 2021
	GTF2A	General transcription factor III	*7q11.23*	Transcription factor	Growth factor signaling, immune cell signaling, and cell proliferation; Transcription, signal transduction, development of bone and neural tissues	Legrand et al., 2021
	KLF3	Kruppel-like factor 3	*4p14*	Transcription factor	Erythropoiesis, metabolism, cardiac development, adipogenesis, myogenesis, and B lymphopoiesis	Legrand et al., 2021
	MEF2A	Myocyte enhancer factor 2A	*15q26.3*	Transcription factor	Development of heart and all three muscle lineages, neuronal differentiation, Cell growth and apoptosis, DNA damage repair	Legrand et al., 2021
	TPM4	Tropomyosin alpha-4 chain	*9p13.12*	Tropomyosin family	Structure of the non-muscle cells cytoskeleton, contraction of striated and smooth muscles	Legrand et al., 2021
	RRBP1	Ribosome Binding Protein 1	*20p12*	Ribosome-binding protein of the endoplasmic reticulum membrane	Endosplasmic reticulum (ER) proliferation, secretory pathways and secretory cell differentiation, and mediation of ER-microtubule interactions	Legrand et al., 2021
	PTBP1	Polypyrimidine Tract Binding Proteine 1	*19p13.3*	Nuclear ribonucleoproteins (hnRNPs)	Pre-mRNA processing, mRNA metabolism and transport	Dermawan et al., 2021
	SLC38A2	Solute Carrier Family 38 Member 2	*12q13.11*	Sodium-Coupled Neutral Amino Acid Transporter 2 family	Cell survival and metabolism via a neutral amino acid transport system	Dermawan et al., 2021
	VDR	Vitamin D3 Receptor	*12q13.11*	Member of the nuclear hormone receptor superfamily of ligand-inducible transcription factors	Metabolic pathways involved in immune response and cancer	Papke et al., 2021
	RBM5	RNA Binding Motif Protein 5	*3p21.31*		Tumor suppressor gene, cell cycle arrest and apoptosis	Pižem et al., 2022

al, 2021). No other genetic changes have been reported to date in the spectrum of *USP6* rearranged tumors. Matsuda et al did not find, in a series of NF, significant changes in the copy number of the *CDKN2A*, *CDK4* and *MDM2* genes, nor significant mutations in the *TP53*, *RB1* and *CDKN2A* genes (Matsuda et al, 2019). In practice, these rare cases should be identified in an attempt to identify possible *USP6* partners associated with aggressive clinical behaviour, search for possible additional genetic abnormalities and determine whether these cases share common characteristics.

Properties of *USP6* partner genes

We focused on the potential role that the identified *USP6* partner genes play in the tissue repair process by referring to the suggested pathogenesis of lesions belonging to the *USP6* spectrum. Indeed, NF and MO can occur after trauma in 15% and 60% to 75% of cases, respectively, whereas ABC is potentially related to

Table 2. Continued

FN	MYH9	Myosin Heavy Chain 9	*22q21*	Conventional non-muscle myosin	Cytogenesis, cell motility, actin filaments disassembly	Erickson-Johnson et al., 2011
	PP6R3	Protein Phosphatase 6 Regulatory Subunit 3	*11q13*		Regulation of the catalytic subunit of protein phosphatase 6	Guo et al., 2016
	RRBP1	Ribosome Binding Protein 1	*20p12*	Ribosome-binding protein of the endoplasmic reticulum membrane	Endosplasmic reticulum (ER) proliferation, secretory pathways and secretory cell differentiation, and mediation of ER-microtubule interactions	Patel et al., 2017
	CALU	Calumenin	*7q32*	Calcium-binding protein	Calcium binding protein involved in endosplasmic reticulum functions	Patel et al., 2017
	THBS2	Thrombospondin 2	*6q27*	Thrombospondin family	Inhibitor of tumor growth and angiogenesis	Patel et al., 2017
	MIR22HG	MIR22 Host Gene	*17p13*	lncRNA class	Host gene of miR-22, a tumor suppressor gene	Patel et al., 2017
	COL6A2	Collagen Type VI Alpha 2 Chain	*21q22*	Alpha chains of type VI collagen	Organization matrix components	Patel et al., 2017
	SPARC	Secreted Protein Acidic And Cysteine Rich	*5q33*	Cysteine-rich acidic matrix-associated protein	Synthesis of the extracellular matrix, calcification of bone collagen	Patel et al., 2017
	CTNNB1	Catenin Beta 1	*3p22*		Cell adhesion, cell signaling and transcription	Patel et al., 2017
	COL1A1	Collagen type 1 Alpha 1 chain	*17q21.33*	Pro-alpha1 chains of type I collagen	Fibril-forming collagen constituting connective tissues, bone, cornea, dermis and tendon	Lam et al., 2018
	SEC31A	SEC31 Homolog A, COPII Coat Complex Component	*4q21*	Sec31 protein	Budding of the vesicles from the Endoplasmic Reticulum	Lam et al., 2018
	SERPINH1	Serpin Family H Member 1	*11q13.5*	Serine proteinase inhibitors	Encodes the collagen chaperon HSP47	Paulson et al., 2020
	COL3A1	Collagen Type III Alpha 1 Chain	*2q32.2*	Pro-alpha1 chains of type III collagen	Constitutes extensible connective tissues	Paulson et al., 2020
	EIF5A	Eukaryotic Translation Initiation Factor 5A	*17p13.1*		Cell cycle progression, skeletal muscle stem cell differentiation	Lenz et al., 2020
	PAFAH1B1	Platelet Activating Factor Acetylhydrolase 1b Regulatory Subunit 1	*17p13*	Platelet-activating factor acteylhydrolase	Regulation of Platelet Activating Factor	Qiu et al., 2020
	COL1A2	Collagen Type I Alpha 2 Chain	*7q21.3*	Pro-alpha2 chain of type I collagen	Fibril-forming collagen constituting connective tissues, bone, cornea, dermis and tendon	Wang et al., 2021
	MYL12A	Myosin light chain 12A	*18p11.31*		Cytokinesis, receptor capping, and cell locomotion; Regulation of smooth muscle and non-muscle cell contractile activity; DNA damage repair	Legrand et al., 2021
	PDLIM17	PDZ and LIM domain 7	*5q35.3*	PDZ and LIM domains	Osteogenic differentiation and mineralization	Legrand et al., 2021
	NACA	Nascent-Polypeptide-Associated Complex Alpha Polypetide	*12q23-q24.1*		Controls protein translocation to the ER	Cloutier et al., 2021
	SLFN11	Schlafe Family Member 11	*17q12*		Inhibits DNA replication in response to DNA damage	Cloutier et al., 2021
	LDHA	Lactate Dehydrogenase A	*11p15.1*	Lactate Dehydrogenase family	Catalyses the conversion of pyruvate to lactate under anaerobic conditions	Cloutier et al., 2021
	TPM4	Tropomyosin alpha-4 chain	*9p13.12*	Tropomyosin family	Cytoskeletal structure of non-muscle cells, contraction of striated and smooth muscle	Rodriguez et al., 2022
	CALD1	Caldesmon 1	*7q33*		Regulation of smooth and non-muscular muscle contraction	Papke et al., 2021

injury or reactive vascular malformation, contexts that can lead to tissue repair phenomena, and MOs share many histological features with a reparative callus in the context of bone fracture. Several *USP6* partner genes encode transcription factors or regulatory proteins involved in various cellular functions after tissue trauma, such as haemostasis, immune response, fibrovascular proliferation, bone formation and tissue remodeling.

On consolidating these findings, we propose a unifying concept concerning the pathogenesis of this spectrum of lesions by showing, in light of data from the literature, that these genes could have in common their involvement in the molecular machinery of the tissue repair process of these lesions. The results are summarized in Fig. 3.

After a trauma, inflammation factors as well as vascular cells, fibroblasts and myofibroblasts are recruited to induce the healing of injury, which leads to wound healing for the skin or bone callus formation as part of bone repair (Bahney et al., 2019). The first step in both processes is the hemostasis phase, which results in a fibrin-rich blood clot. This formation requires contraction, adhesion and secretion for platelet aggregation (Bahney et al., 2019). *MYL12A* takes part in the process because the protein encoded, a myosin regulatory light chain, is implicated in regulating platelet contractile activity via its phosphorylation (Getz et al., 2010). *PAFAH1B1* promotes the expression of angiogenesis-associated proteins and maintains the angiogenic function of endothelial cells (Josipovic et al., 2016). Several genes that might also play an angiogenic role include *LUM* (Karamanou et al., 2018); *ANGPTL2* (Zhang et al., 2020), a member of that vascular endothelial growth factor family, known for its angiogenic and antiapoptotic properties and also proinflammatory properties; and *STAT3* (Zhou et al., 2013), activated in collagen-stimulated platelets. Thrombocytes express thrombospondin-1 and *CALU*, which are released upon thrombin stimulation and may affect the synthesis of certain coagulation factors (Hansen et al., 2009). Also, by interacting with vascular endothelial growth factor, SPARC and THSB2 may

Table 2. Continued

FTS	COL1A1	Collagen type 1 Alpha 1 chain	*17q21.33*	Pro-alpha1 chains of type I collagen	Fibril-forming collagen constituting connective tissues, bone, cornea, dermis and tendon	Wang et al., 2021
	MYH9	Myosin Heavy Chain 9	*22q21*	Conventional non-muscle myosin	Cytogenesis, cell motility, actin filaments disassembly	Mantilla et al., 2021
	ASPN	Asporin	*9q22.31*	Small leucine-rich proteoglycan family	Regulates chondrogenesis, binds collagen and calcium and induce collagen mineralization	Mantilla et al., 2021
	COL3A1	Collagen Type III Alpha 1 Chain	*2q32.2*	Pro-alpha1 chains of type III collagen	Constitutes extensible connective tissues	Mantilla et al., 2021
	PKM	Pyruvate Kinase M1/2	*15q23*	Pyruvate kinase	Role in embryogenesis, regeneration and multiple types of cancer	Mantilla et al., 2021
	RCC1	Regulator Of Chromosome Condensation 1	*1p35.3*		Functions in chromatin and mitotic spindle assembly	Mantilla et al., 2021
	MIR22HG	MIR22 Host Gene	*17p13*	lncRNA class	Host gene of miR-22, a tumor suppressor gene	Pižem et al., 2021
	CTNNB1	Catenin Beta 1	*3p22*		Cell adhesion, cell signaling and transcription	Pižem et al., 2021
	SPARC	Secreted Protein Acidic And Cysteine Rich	*5q33*	Cysteine-rich acidic matrix-associated protein	Synthesis of the extracellular matrix, calcification of bone collagen	Pižem et al., 2021
	CAP1	Cyclase Associated Actin Cytoskeleton Regulatory Protein 1	*1p34.2*		Regulates actin filament dynamics, cell polarity	Pižem et al., 2021
	EMP1	Epithelial Membrane Protein 1	*12p13.1*		Regulates cell proliferation and metastatic capacity of many cancers	Pižem et al., 2021
	LINC00152 or CYTOR	Cytoskeleton Regulator RNA	*2p11.2*	MicroRNA precursor family	Promotes cell proliferation and epithelial-mesenchymal transition via a long non-coding RNA	Pižem et al., 2021
	NR1D1	Nuclear Receptor Subfamily 1 Group D Member 1	*17q21.1*	Member of the nuclear receptor subfamily 1	Regulates circadian rhythm, metabolic, inflammatory and cardiovascular processes	Pižem et al., 2021
	RAB1A	RAB1A, Member RAS Oncogene Family		Ras superfamily of GTPases	Controls vesicular trafficking from the endoplasmic reticulum to the Golgi apparatus	Pižem et al., 2021
	TNC	Tenascin C	*9q33.1*	Extracellular matrix	Cell motility, survival, differentiation and neurite outgrowth, cell adhesion, migration and proliferation, tissue repair	Eisenberg et al., 2022
MO	COL1A1	Collagen type 1 Alpha 1 chain	*17q21.33*	Pro-alpha1 chains of type I collagen	Fibril-forming collagen constituting connective tissues, bone, cornea, dermis and tendon	Flucke et al., 2018
FOPD	COL1A1	Collagen type 1 Alpha 1 chain	*17q21.33*	Pro-alpha1 chains of type I collagen	Fibril-forming collagen constituting connective tissues, bone, cornea, dermis and tendon	Švajdler et al., 2019

regulate vascular sprouting (Bornstein et al., 2000; Puolakkainen et al., 2003).

During platelet degranulation, cytokines are released for recruiting inflammatory cells including lymphocytes, macrophages, eosinophils and neutrophils (Bahney et al., 2019). Several genes that rearrange with *USP6* can play a role in this phase. One example is *TNC*, coding for tenascin-C, which is overexpressed during wound healing. Tenascin-C may also modulate cellular movement and cell adhesion to other matrix components and control lymphocyte influx and leucocyte maturation (Marzeda et al., 2018). Similarly, *LUM* is involved in the extravasation of inflammatory cells during wound healing (Karamanou et al., 2018). *KLF3* can also participate in this process because it ensures normal B-cell development in bone marrow, besides being involved in myeloid differentiation (Vu et al., 2011). By modulating the NF-κB signalling pathway, *ANGPTL2* upregulates the expression of inflammation-related factor genes (Li et al., 2018).

After resolution of the inflamatory phase, the next step in the repair process is a proliferative phase, characterized by the formation of granulation tissue. This phase needs the involvement of fibroplasia and both vasculogenesis and neoangiogenesis for vascular remodelling (Bahney et al., 2019). By involving Wnt signalling, tenascin-C may promote the angiogenic switch and the formation of blood vessels (Marzeda et al., 2018). *MYH9* may also play a critical role in modulating the angiogenics by interacting with the cell-surface nucleolin, which is essential for the migration and tubule formation of endothelial cells (Huang et al., 2006).

Additionally, mesenchymal stem cells are recruited, which will differentiate into fibroblasts and myofibroblasts. For example, lactate dehydrogenase A, by catalysing the conversion of pyruvate into lactate, allows for the recruitment of many fibroblasts (Martínez-Ordoñez et al., 2021). Regenerating myoblasts and myofibroblasts initiate a gene program that is characterized by the early expression of *TPM4*, *MEF2A*, and more anecdotally, *KLF3* (Liu et al., 2004; Himeda et al., 2010; Abdul-Hussein et al., 2013). In NF, the involvement of *USP6* partner genes in myofibroblast differentiation is lower than in other tumors, with only four partner genes: *MYH9*, *EIF5A*, *MYL12A* and *CALD1* (Huang et al., 2006; Luchessi et al., 2009; Jarkovska et al., 2014).

During the last phase of healing, the granulation tissue is gradually remodeled, which leads to an increase in collagen fibers. *COL1A1*, *COL1A2*, *COL3A1*, *COL6A2*, and also *SERPINH1* are implicated in this pathway (Marzeda et al., 2018; Christiansen et al., 2010). THBS2 protein can modify the structure of collagen fibrils (Bornstein et al., 2000). Similarly, by potentiating AP-1-dependent transcription, *NACA* affects osteocalcin and type I collagen (Hariri et al., 2020).

After a fibrovascular phase, which is characterized

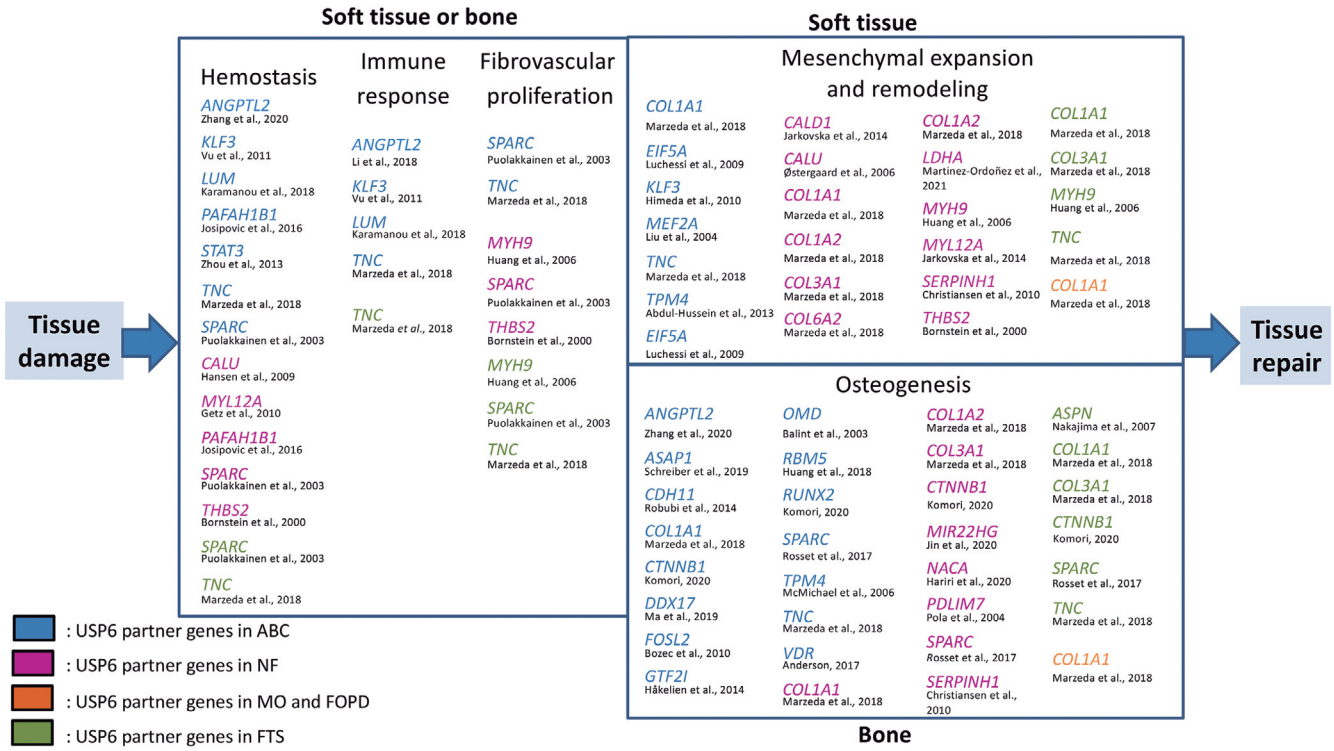

Fig. 3. Implication of USP6 partners in different phases of bone- and soft- tissue repair.

by vascular remodelling, repair of bone tissue requires the recruitment of mesenchymal progenitor cells that will ultimately differentiate into chondrocytes and osteoblasts to regenerate bone (Bahney et al., 2019). Indeed, most *USP6* partner genes are implicated in osteoblastic differentiation and mineralization, and these include *CDH11*, *OMD*, *FOSL2*, *RUNX2*, *CTNNB1*, *SPARC*, *ASAP1*, *GTF2I* and *VDR* (Balint et al., 2003; Bozec et al., 2010; Robudi et al., 2014; Håkelien et al., 2014; Anderson, 2017; Rosset et al., 2017; Schreiber et al., 2019; Komori, 2020). *PDLIM7*, also known as LIM mineralization protein-1 (*LMP-1*), induces the expression of some BMPs (i.e., osteogenic molecules essential for bone formation) (Pola et al., 2004; Pan et al., 2015). A downstream target of BMP signaling is *RUNX2*, whose transcriptional activity is regulated by *CTNNB1* or *DDX17* as well as *RBM5* (Huang et al., 2006). *RUNX2* is implicated in osteoblastogenesis via the Wnt/ß-catenin signalling pathway (Gaur et al., 2005; Ma et al., 2019; Komori, 2020). By downregulating PTEN, *MIR22HG* activates AKT signalling and also promotes osteogenic differentiation (Jin et al., 2020). Also, by phosphorylating NF-κB signalling, ANGPTL2 contributes to osteoclast differentiation (Li et al., 2018). *TPM4* plays a critical role in regulating osteoclast attachment structures and thus is involved in osteoclast function (McMichael et al., 2006).

TNC is also a component of softer regenerative matrices because it induces or blocks proliferation of fibroblasts, bone and cartilage development (Marzeda et al., 2018). In FTS, *ASPN* negatively regulates chondrogenesis by blocking transforming growth factor β (TGF-β)–receptor interaction and inhibiting canonical TGF-β/Smad signaling (Nakajima et al., 2007).

CALU, with its diverse cellular distribution, its calcium-binding ability, and its interaction with proteins involved in calcium signalling, has a role during processes in which the cytoskeleton is rearranged or cell proliferation is affected, such as wound healing (Kyriakides and Bornstein, 2003; Østergaard et al., 2006).

Conclusions

A spectrum of fibrous and/or ossifying lesions of bone and soft tissue feature USP6 rearrangements. The number of partner genes involved in these *USP6* rearrangements is large and will probably continue to grow with the advent of new molecular biology techniques. We propose a unifying concept concerning the pathogenesis of this spectrum of lesions by showing, in light of literature data, that these genes could have in common their involvement in the molecular machinery of the tissue repair process. To date, no link has been demonstrated between the partners involved in *USP6* rearrangement and the clinical and histological characteristics of the lesions or their recurrence. Exceptional cases of malignant NF and unusually aggressive ABC need to be collected to identify possible *USP6* partners or additional genetic abnormalities associated with aggressive clinical behavior and to determine whether these cases share common characteristics.

Conflict of interest. The authors have no relevant financial or non-financial interests to disclose. The authors have no conflicts of interest to declare that are relevant to the content of this article. All authors certify that they have no affiliation to or involvement with any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. The authors have no financial or proprietary interests in any material discussed in this article.

Author contributions. All authors contributed to the study conception and design.

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