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Tumour Review

A review of retroperitoneal liposarcoma genomics

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ABSTRACT

Retroperitoneal liposarcomas are rare tumours that carry a poorer prognosis than their extremity counterparts. Within their subtypes – well differentiated (WDL), dedifferentiated (DDL), myxoid (MLS) and pleomorphic (PLS) - they exhibit a diverse genomic landscape. With recent advances in next generation sequencing, the number of studies exploring this have greatly increased. The recent literature has deepened our understanding of the hallmark *MDM2/CDK4* amplification in WDL/DDL and addressed concerns about toxicity and resistance when targeting this. The *FUS-DDIT3* fusion gene remains the primary focus of interest in MLS with additional potential targets described. Whole genome sequencing has driven identification of novel genes and pathways implicated in WDL/DDL outside of the classic 12q13-15 amplicon. Due to their rarity; anatomical location and histologic subtype are infrequently mentioned when reporting the results of these studies. Reports can include non-adipogenic or extremity tumours, making it difficult to draw specific retroperitoneal conclusions. This narrative review aims to provide a summary of retroperitoneal liposarcoma genomics and the implications for therapeutic targeting.

Introduction

Retroperitoneal liposarcomas (RPL) are rare tumours that are challenging to manage surgically, and generally respond poorly to chemotherapy. They possess high local recurrence rates and in certain subtypes can metastasise. The retroperitoneum represents the second most common site of origin of these tumours after the extremities. There is general consensus in the sarcoma community that surgery to remove RPL with clear margins is the most beneficial intervention to improve recurrence free survival, and possibly overall survival. Early data from the largest trial of neoadjuvant radiotherapy in retroperitoneal sarcomas has alluded to a potential subgroup benefit in patients with liposarcoma [1]. However, even with successful surgery and appropriately utilised radiotherapy, long-term control rates still require a significant improvement and for this a deeper understanding of the genomic aberrations that underpin the disease are required.

This review explores the current understanding of the genomic landscape in retroperitoneal liposarcoma and the consequences on therapeutic strategy. The anatomical focus on the retroperitoneum, rather than the extremity is undertaken for several reasons. Firstly, a summary of specific retroperitoneal liposarcoma genomics is lacking in the literature. This would be useful to clinicians and scientists alike, dealing with this specific disease in the era of personalised medicine. Secondly, it is well established that variations in the tumour microenvironment can determine response to therapy. Lastly, RPL carries a poorer prognosis than extremity LS, has a distinct natural history and is managed differently.

Methods

Search strategy

A literature search was conducted using the Embase, MEDLINE, PubMed and Cochrane Library databases. The following keywords were used to perform flexible searches within these databases: 'Retroperitoneal' AND 'sarcoma', 'liposarcoma', 'genomics', 'genetics', 'mutation', and 'genomic therapy.' Only papers published in English were included.

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Structure

An overview of the genomic aberrations and genome targeted therapies is presented for the four types of liposarcoma. As well-differentiated (WDL) and dedifferentiated liposarcoma (DDL) account for >90% of retroperitoneal liposarcomas these are the main focus of the article. Some consideration has also been given to the two rarer subtypes, myxoid (MLS) and pleomorphic (PLS) liposarcoma. Efforts are made to report retroperitoneal findings of studies where this data is available. Nevertheless, some data will be from published literature that does not state the anatomical site and some time is given to discussing the genomic differences, if any, between retroperitoneal and extremity liposarcoma. As a consequence of the high-quality outputs of next generation sequencing, genes and related pathways that are consistently found in well conducted research are prioritised above those with minor relevance or in small datasets.

Well differentiated liposarcoma (WDL)

Well differentiated liposarcoma (WDL) is a low-grade tumour, composed of proliferating mature adipocytes and accounts for 40–45% of all liposarcomas [2]. In the retroperitoneum it is termed well-differentiated liposarcoma and accounts for 25% of WDL, the remaining 75% being located in the extremities. In the extremity it is termed atypical lipomatous tumour or ALT. Retroperitoneal tumours are frequently > 30 cms in size at diagnosis. They do not metastasise, but have a high propensity for local recurrence with rates of up to 43% at 8 years when not given radiotherapy [3]. Furthermore, 20% of WDL will dedifferentiate to a higher grade tumour, on average at seven to eight years [4].

The cytogenetic signature of WDL is supernumerary ring chromosomes which contain amplified sequences from the long arm of chromosome 12 (12q13-15). The mutational mechanisms underlying the original amplification are an important area of liposarcoma genomics. Marino-Enriquez et al. believe that an early initiation event – chromothripsis – results in massive fragmentation and rearrangement of the chromosome [5]. An amplification phase follows in which repetitive break-fusion bridge cycles allow incorporation of additional chromosomal regions to the ring neochromosomes and concludes with neochromosome stabilisation. This 'initiation event' could be a fundamentally random event which then becomes fixed through natural selection in a precursor cell [6], or a specific mechanism yet to be discovered.

This amplified region of chromosome 12 harbours multiple important genes, which are also implicated in other cancers. The most compelling evidence to date demonstrates an oncogenic role in WDL for Mouse double minute 2 (*MDM2*), Cyclin-dependent kinase 4 (*CDK4*) and High mobility group protein AT-hook 2 (*HMGA2*). In general amplification of the region results in increased cell proliferation and decreased apoptosis [66]. Outside of this amplicon, additional genes *PPAR-γ* and *RET* are implicated as well as the FGFR pathway.

MDM2

MDM2 is the most studied of all genomic aberrations in WDLS. Its amplification has been considered to represent one of the earliest events in the formation of WDL and DDL [2]. Although, as it potentially requires extrachromosomal material to be formed, it is perhaps not the primary event. *MDM2* encodes a negative regulator of the tumour suppressor p53, blocking it's transcription and targeting p53 for proteasomal degradation [7]. Low levels of p53 cause an abrogation of the tumour suppressive p53 pathway and allow cells to progress through the cell cycle under conditions that could generate or perpetuate DNA damage, thus initiating tumourigenesis [8].

MDM2 amplification is seen in 7% of human cancers and a third of all sarcomas, whereas rates are far higher in WDL and DDL [9]. *MDM2* amplification is observed in both RPL and extremity ALT, but not usually seen in benign adipose tissue. Somaiah et al. performed exome sequencing on 17 patients with retroperitoneal WDL and DDL. *MDM2* and *CDK4* amplification were the only two overlapping gene amplifications universally identified in all the samples [10].

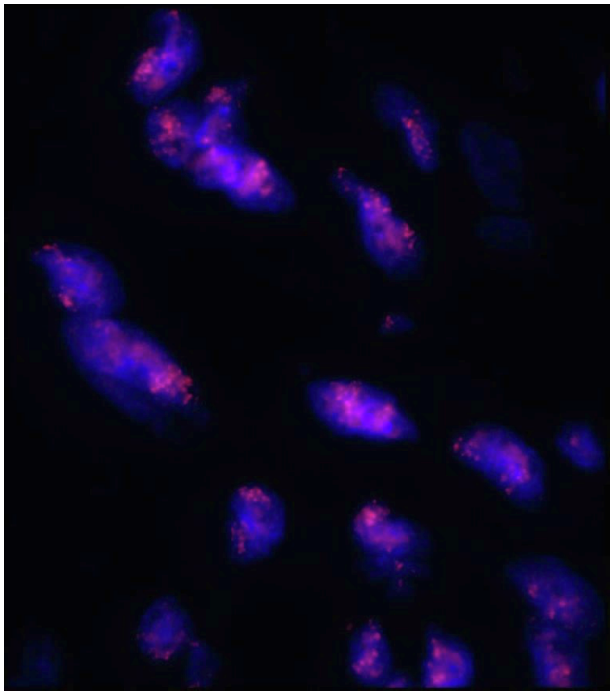

Fig. 1. MDM2 amplification by Fluorescence In Situ Hybridisation (FISH).

There is good evidence from preclinical studies that *p-53* wildtype, *MDM2*-amplified tumours respond to *p53* activation and apoptosis with *MDM2* antagonist treatment [11]. As liposarcomas harbour very few *p53* mutations and are generally *MDM2* amplified, *MDM2* antagonists have been tested in several phase one clinical studies since 2017. (Fig. 1)

Only two studies have specifically reported on *MDM2* antagonists in patients with WDL. Ray-Coquard et al. in a chemotherapy naïve cohort of predominantly RPL, showed no progression in 9/10 WDL, but only one partial response [12]. Wagner et al. in 9 patients with advanced WDL found 4 patients had prolonged stable disease with one prolonged partial response [13] . Both studies reported at least one adverse effect in each patient, with Wagner et al. reporting 1/3 experiencing serious adverse effects.

The putative benefits of *MDM2* inhibition in liposarcoma need balanced against these adverse effects, which are likely exacerbated when combined with standard chemotherapy or other targeted agents. Furthermore, emerging evidence suggests resistance to *MDM2* inhibition occurs through p53 mutation [14]. Therefore, more work is needed to increase drug specificity and avoid early resistance patterns.

CDK4

CDK4 is amplified in over 90% of retroperitoneal WDL/DDL making it the second most commonly amplified gene in liposarcoma [15]. *CDK4* encodes a protein which phosphorylates retinoblastoma protein (pRB), dissociating it from the pRB-E2F complex. Dissociated E2F subsequently binds to DNA, upregulating the transcription of genes required for G1-S transition [16]. In simple terms, amplification of this gene leads to cell cycle progression.

Even though situated very closely on chromosome 12, the rearranged chromosome in liposarcoma is discontinuous, and *CDK4* and *MDM2* are likely from distinct amplicons [17]. Co-amplification of

MDM2 and *CDK4* is thought to be the main driving factor in liposarcomagenesis, leading to p53 inactivation and uncontrolled cell cycle progression.

Lee et al. performed real-time PCR on 48 patients who had undergone compete resection of an intraabdominal liposarcoma (96% retroperitoneal, 31 WDL/17DD) [15]. WDL that developed a local recurrence had significantly higher levels of *CDK4* amplification (P = 0.041). High levels of *CDK4* amplification was associated with poorer RFS compared to low *CDK4* amplification in both univariate and multivariate analysis.

These findings paved the way for pre-clinical research with *CDK4* antagonists. Helias-Rodzewicz et al. treated liposarcoma cell lines with a *CDK4* inhibitor NSC625987 and observed a dramatic increase in adipocytic differentiation in cells with eliminated copies of *CDK4* [18]. Perez et al. induced senescence in both liposarcoma cell lines and mice xenografts using palbociclib, a selective *CDK4*/6 inhibitor [19].

Palbociclib is used to treat ER-positive/*EGFR2*-negative breast cancer and represents the first FDA approved drug in its class [20]. Four trials using CD4 antagonists have reported in retroperitoneal liposarcoma, two using palbociclib, one using ribociclib and the last a pan-*CDK* inhibitor – flavopiridol – in combination with doxorubicin [21–24]. The largest of these to report included 15 patients with retroperitoneal WDL [22]. The 12-week progression-free survival (PFS) rate was 57.2% with one complete response. The most common adverse events were haematological.

HMGA2

HMGA2 encodes for a protein that alters chromatin structure and in sarcomas (liposarcomas, uterine leiomyosarcomas and salivary gland pleomorphic adenomas) is found to be rearranged, amplified and overexpressed [25]. Interestingly *HMGA2* is found to be rearranged in up to 70% of benign lipomata, resulting in a truncated protein, and is implicated in their development.

In a series of 38 liposarcomas (7/38 retroperitoneal WDL), Italiano et al used FISH and RT-PCR, to detail the amplification status and expression levels of the 12q13-15 amplicon. *HMGA2* was amplified and rearranged in every sample, at a rate similar to that of *MDM2* [17]. More recently, a separate group used similar techniques showing amplification of the proximal parts of *HMGA2* (5′-untranslated region (UTR) and exons 1–3) was associated with WDL and a good prognosis, whereas *CDK4* and *JUN* amplifications were associated with DDL and a poorer prognosis [26].

Xi et al demonstrated that *HMGA2* is required for *C/EBPβ*-mediated expression of *PPARγ* – the master adipogenesis regulator, promoting adipogenic differentiation. When *HMGA2* was knocked down, it impaired adipocyte growth and when overexpressed promoted the formation of mature adipocytes [27]. Furthermore, Arlotta et al. hypothesised that the *HMGA2* protein specifically promoted the growth of adipocytes. This was confirmed by the very low-fat phenotype of a *HMGA2* knock-out mouse. In transgenic mice with a truncated *HMGA2* there was a high incidence of lipomatosis further linking *HMGA2* to a role in adipogenesis [28].

Narita et al demonstrated that *HMGA2* proteins cooperate with the p16 tumour suppressor to promote cellular senescence, but this antiproliferative activity is negated by co-expression of *MDM2* and *CDK4* [29]. This led others to believe that *HMGA2* alone will only lead to benign lipomata, but in combination with *MDM2/CDK4* amplification, a malignant phenotype would be induced [17].

FRS2

There has been a recent drive to identify other novel genes present on the 12q13-15 amplicon of which Fibroblast growth factor receptor substrate 2 (*FRS2*) is one. *FRS2* codes for a signal transducing protein that links receptor tyrosine kinases (RTKs) to downstream signalling pathways, such as *MAPK/ERK* and *PI3K/AKT/mTOR* [30].

In one study, *FRS2* was amplified in all 57 liposarcomas and mRNA transcriptional upregulation documented in 19 WDL samples, but not in lipomata or normal fat. Jing et al more recently evaluated the frequency of *FRS2* amplification and its relationship with clinical features. In their series 92.1% of WDL were *FRS2* amplified, and retroperitoneal tumours were found to have a higher *FRS2/CEP12* ratio than those in the extremity [31].

Importantly, Zhang et al. have shown that the FGFR selective inhibitor NVP-BGJ-398 inhibited the growth of high grade liposarcoma cell lines with concomitant suppression of FGFR signal transduction [32]. This pathway serves as an additional potential therapeutic target.

There are several other genes studied to varying degrees present on the 12q13-15 amplicon, such as *SAS*, *GLI* and *HOXC* [33]. Others such as *YEATS4* and *TSPAN 31* are more relevant to DDL and will be covered in that section.

Outside of the 12q13-15 amplicon

As sequencing technologies have improved, a deeper interrogation of the genome has become possible. Egan et al. were the first group to perform whole genome sequencing on a WDL, in order to search for therapeutic targets outside of the 12q13-15 amplicon. They found 7 damaging single nucleotide variants, amplification across multiple chromosomes and 11 gene fusions [34]. Of note, they identified a potential gene fusion via whole genome sequencing (WGS) in amplified Discoidin domain-containing receptor 2 (*DDR2*), a gene involved in multiple cellular processes and present on 1q23.3. Importantly, the kinase domain was predicted to remain intact, which is of clinical relevance as *DDR2* activity can be curtailed by kinase inhibitors such as imatinib, nilotinib and dasatanib.

Dedifferentiated liposarcoma (DDL)

DDL is a high grade, more aggressive, typically non-lipogenic sarcoma with the ability to metastasise [35]. It can either arise *de novo*, as a recurrence of WDL or juxtaposed to WDL. Dedifferentiation is the term used to describe this morphological progression. In an inverse relationship to WDL, 75% of DDL are of retroperitoneal origin, with 25% in the extremity [36]. The molecular basis of dedifferentiation is poorly understood but of great interest in sarcoma genomics as this carries a far poorer survival. This section starts with proposed genomic drivers of dedifferentiation, addresses the commonly amplified genes on 12q13-15 and finishes with genomic aberrations unique to DDL.

Genomic drivers of dedifferentiation

The genomic changes associated with progression from WDL to DDL are complex and poorly understood. Both subtypes harbour the neochromosomes and oncogenes previously explored. Nevertheless, DDL tumours must possess additional mechanisms to become high grade, more cellular and aggressive; not resembling their original histological appearance. In general, DDL exhibit more complex chromosomal aberrations [37].

A major element of dedifferentiation is loss or downregulation of adipogenesis. This downregulation results in a non-lipogenic tumour mass which can be difficult to distinguish histologically. Genes involved in adipocyte metabolism such as *LIPE*, *PLIN* and *PLIN2* are amongst those uniquely absent in DDL, suggesting a loss of ability to act like fat in these tumour cells [38,39]. Additionally, DDL tends to have a more rearranged genome, especially the 12q13-15 amplicon which contains genes which control adipocyte differentiation such as *CPM* and *HMGA2*.

Beird et al. compared the genomic landscape of synchronous WDL and DDL components of 17 tumours (15 retroperitoneal). There were three main findings: firstly, a low somatic mutational burden across both tumour types. Secondly, the presence of shared somatic mutations, albeit in low number. Finally, they identified a significantly larger number of gene fusions and copy number alterations in DDL when compared to WDL [40]. The higher copy number alterations and gene fusions in DDL were attributed to the result of increased break-fusion bridge cycles. The authors also suggested that the low number of similar somatic mutations meant tumours derived from a common ancestral clone but diverged early in their development. They hypothesised that the capacity to dedifferentiate is determined early in the disease.

Horvel et al. compared 29 paired WDL/DDL tumours (21 retroperitoneal) by array-based comparative genomic hybridisation. The analysis segregated all but one pair together, and the genotypic similarities between the components implied that genetic changes preceded phenotypic progression [41]. This further supports the argument that the background genotype of some 'well-differentiated' liposarcomas already possess the capacity to dedifferentiate.

12q13-15 amplicon

Although clearly implicated in WDL pathogenesis, *MDM2* is described as the hallmark of DDL [42]. Creytens et al. performed multiplex ligation-dependent probe amplification on 11 retroperitoneal DDL tumours. They described a significantly higher amplification rate in DDL compared to WDL of *MDM2*, *HMGA2*, *YEATS4* and *TSPAN31*, all present on 12q13-15 (Fig. 2, Table 1)).

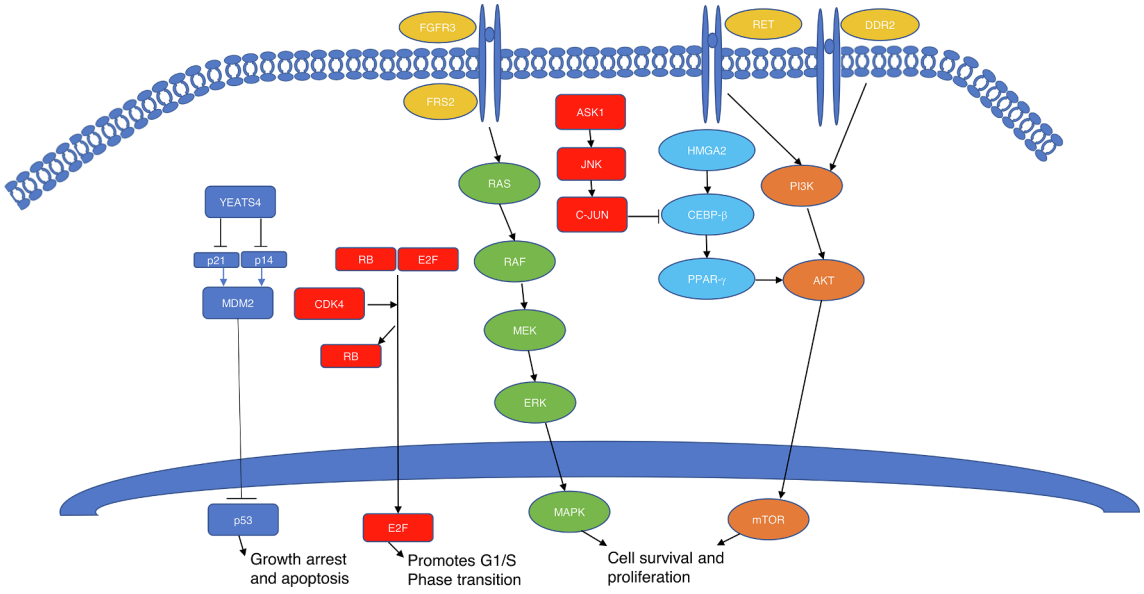

Fig. 2. Pathways active in WD/DDL liposarcoma. MDM2 is overamplified in WDL/DDL and blocks transcription of p53. YEATS4 increases levels of MDM2 by supression of p21 and p14. CDK4 is commonly found to be co-amplified with MDM2, and phosphorylates Rb, dissociating it from the pRb-E2F complex, allowing E2F to drive G1/S transition. HMGA2 is amplified in both WDL and DDL and drives CEBP-β mediated expression of PPAR-γ promoting adipogenic differentiation. In DDL co-amplification of ASK1 and c-JUN blocks CEPB-β driven adipocytic differentiation. The MAPK/ERK pathway is activated in WDL and DDL by FRS2 and FGFR3 amplification respectively. The PI3K pathway is also active; in WDL increased levels of RET drive it, whilst DDR2 amplification in DDL achieves the same. Both pathways drive cell survival, proliferation and angiogenesis.

Table 1
Evidence summary of genomic drivers of retroperitoneal histological subtypes and related clinical trials.

Histology	Genes	Associated Pathways	Genomic Aberration	Targeted Drug	Trials
WDL/DDL	MDM2		Amplified 20/20 (100%)	MDM2 Antagonist RG7112	EudraCT 2009-015522-10
	CDK4		Amplified 20/20 (100%)	CDK4/6 Inhibitor - Palbociclib	NCT01209598
	HMGA2		Amplified and rearranged 38/38 (100%)	HMGA2 Inhibitor – Netroposin	Not in RPL
	FRS2	MAPK/ERK + PI3K/AKT/mTOR	Amplified 98/101 (97%)	FGFR selective inhibitor NVP-BGJ-398	Not in RPL
	DDR2	PI3K/AKT/mTOR	Amplified 6/56 (11%), fused in 1 sample	Kinase inhibitors – Imatinib/Nilotinib	Not in RPL
	PPAR-γ		Expressed in 44/54 (81.5%)	PPARγ ligand – Pioglitazone	NCT00004180
	YEATS 4	P14/P21/MDM2	Amplified 30/40 (75%)	NA	NA
DDL	FGFR3	PI3K/AKT/mTOR + RAS	Amplified in 2/56 (4%)	Pan-FGFR Inhibitors	Not in RPL
	RB		Loss of Heterozygosity 16/27 (60%)	NA	NA
	CEBPA		24% methylation	Demethylating agent – Decitabine	Not in RPL
MLS	RET	PI3K/AKT/mTOR	Overexpressed compared to fat 3/4 (75%)	PI3K Inhibitors	Not in RPL
	FUS-DDIT3	ATM + CEPB-β	Gene fusion t(12;16)(q13:p11) in 95% of cases	Trabectedin - blocks targets of FUS-DDIT3	NCT00579501 NCT00060944
	YAP-1	Hippo/ FUS-DDIT3	Positive 77/85 (90.6%)	Verteporfin	Not in RPL
PLS	P53		Mutated 19/31 (60%)	NA	NA
	VEGF		Overexpressed 27/40 (68%)	VEGF Inhibitor – Pazopanib/ Regorafenib	NCT01692496 NCT02048371

In the largest study of its kind Bill et al. correlated the degree of *MDM2* amplification with clinical and biological outcomes. Elevated *MDM2*, as measured by genomic amplification and mRNA expression was associated with a shortened time to recurrence [43]. Other studies have confirmed a higher *MDM2* copy number is associated with poorer outcomes, poorer response to cytotoxic therapy and interestingly a higher propensity for a retroperitoneal location [44,45]. There are limited validated prognostic markers in DDL. As generating *MDM2* copy number ratios becomes increasingly easy, this should be given serious consideration as a prognostic biomarker.

As mentioned previously, *MDM2* has been targeted in various phase one and two studies. In a phase 1 study of SAR405838 (a novel MDM2 antagonist), 15/21 patients with DDL had stable disease, but none displayed an objective response [11]. Importantly, all baseline tumour biopsies were *TP53* wild type. During treatment, Jung et al. with liquid biopsies demonstrated *TP53* mutations appearing in circulating cell-free DNA, with the mutation burden increasing over time and correlating with a change in tumour size [14]. This was the first clinical demonstration of a *TP53* mutation in response to an MDM2 antagonist, representing an escape mechanism for *MDM2* amplified cells. A CRISPR screen in LPS lines exposed to a MDM2 inhibitor to look for synthetic lethality would be the next step based on these findings, and could have implications for the future of this class of targeted therapy.

Similar to *MDM2*, *CDK4* plays a pivotal role in DDL. An arrayed loss of function shRNA screen performed on three DDL cell lines to determine which genes were required for cell proliferation and survival generated *CDK4* as the main hit from the 12q13-15 amplicon [6]. Kim et al performed co-overexpression of *CDK4* and *MDM2* in bone marrow stem cells. Increased cell growth, migration and inhibited adipogenic differentiating potential was demonstrated when both oncogenes were overexpressed. In a mouse model, co-overexpression of both genes resulted in a sarcoma with a DDLS-like pathology [46].

It would seem obvious to derive from this data that *MDM2* and *CDK4* work synergistically, or at least both are needed to promote tumour proliferation. When DDL cells were exposed to RG7388 (*MDM2* antagonist) and palbociclib, together they exerted a greater antitumour effect than either drug alone. Furthermore, there was an increased PFS noted in mice [47]. However, recently Sriraman et al. have disputed this synergistic concept after finding that *MDM2* and *CDK4* inhibitors can antagonise each other in their cytotoxicity. They found nutlin treated liposarcoma cells survived longer when co-treated with palbocicib concluding that *CDK4* is required for p53 induced-gene expression [48].

In the aforementioned Creytens study examining the 12q amplicon, *YEATS4* also came out as having a significantly higher amplification ratio and was also overexpressed. *YEATS4* is a component of the NuA4 histone acetyltransferase (HAT) complex [49]. This complex plays a potential role in the activation of transcriptional programs associated with oncogene mediated growth induction and supressing the p53 tumour suppressor pathway. It is also a recognised oncogene in non-small cell lung cancer. Interestingly, in a large scale genomic-screening study of DDL cell lines, *YEATS4* knockdown was more powerful at reducing tumour proliferation than loss of *MDM2* expression. In the context of adverse side effects and *MDM2* resistance to therapeutic antagonists, *YEATS4* and genes outside of this amplicon should be studied in more detail, in hope of seeing a translational benefit [50].

Peroxisome proliferator-activated receptor gamma (*PPAR*-y) is a nuclear hormone receptor that plays a critical role in the terminal differentiation of adipocytes. *PPAR*-y mRNA has been found in various liposarcoma subtypes and human liposarcoma cells can be induced to undergo terminal differentiation by treatment with the *PPAR*-y ligand pioglitazone [51]. Despite this, reported results from a phase 2 trial of rosiglitazone in 12 patients with DDL were disappointing with no clinical response observed [52].

Features unique to DDL

Co-amplification of 1p32 and 6q23 are mutually exclusive, present in DDL and never seen in WDL. Genes housed in these regions are implicated in the dedifferentiation process [38]. 1p32 is home to *JUN*, a downstream target of the JNK pathway. *ASK1*, a protein kinase, is present on 6q23 and activates the JNK pathway leading to *JUN* activation. Snyder et al. defined the role of *JUN* in 81 liposarcoma samples, from both the retroperitoneum and extremities, by performing immunohistochemistry and FISH on *JUN* and its activating kinases. *JUN* was found to be expressed in the majority of DDL (32/35) and their WD components, but only in the minority of pure WDL (6/22). They also noted that when *JUN* was amplified, it was interspersed with amplified *MDM2*, concluding that it was amplified at a similar time in the evolution of these tumours [53].

Mariani et al took this a stage further, analysing the expression levels of key genes in adipogenesis in 16 liposarcomas, of which 14 were retroperitoneal. By comparing the expression levels through qPCR in tumours that overexpressed *JUN* with those that didn't, – they found that the *C/EBPβ* transcriptional network (key to adipogenesis), was impaired in the group that overexpressed *JUN* [53]. They concluded that dedifferentiated tumours are committed to differentiate into adipocytes. Their failure to differentiate was driven by *JUN* overexpression, which would be in keeping with the non-adipogenic nature of DDL. High amplification levels of *JUN* (>16 copies) have also been correlated with decreased DFS, corroborating the oncogenic role of *JUN* in this disease [44].

Asano et al. examined 104 genes in 37 DDL (29 retroperitoneal.) Other than the *MDM2* and *CDK4* genes, the most remarkable category of amplified genes were those encoding RTKs which were amplified in 11/37 samples. Amplified genes included *DDR2, ERBB3, NTRK1, FGFR3, ROS1* and *IGF1R. NTRK1* fusions have recently been succesfully targeted in other soft tissue sarcomas by larotrectenib – a selective small-molecule inhibitor of all three TRK proteins – in a tumour 'agnostic' fashion [54]. In retroperitoneal DDL, downstream of these RTKs, point mutations have been documented in the *H-Ras* gene [55]. The activation of RTKs and their downstream signalling pathways therefore provides another avenue for drug targeting and development in DDL.

ZIC-1 is implicated in liposarcoma development. In 51 DDL samples, when compared with normal fat, *ZIC-1* was found to be overexpressed. When knocked down, there was reduced proliferation, invasion and higher levels of apoptosis in the DDL lines. The role of the *ZIC1* has only recently been established. It codes for a transcriptional activator in the differentiation of white and brown fat, and is involved in neuronal maturation [56]. It is a potential selective therapeutic target due to the low or absent *ZIC1* expression in adult tissues outside of the CNS [57].

One of the best characterised tumour suppressor genes *RB1* has been implicated in liposarcoma. 27 DDL (20 retroperitoneal) underwent mutational analysis. 60% of DDL showed loss of heterozygosity and 66% expressed an abnormal RB protein. This was compared to 12.5% and 33% in WDL [58]. A two-hit mechanism was suggested by the authors as a mechanism to initiate tumour development.

Many sarcomas possess epigenetic faults. Epigenetic mechanisms modify gene expression without causing any change in cellular DNA. Taylor et al reported concurrent sequencing of tumour genomes, exomes and transcriptomes to delineate the molecular landscape of primary and recurrent retroperitoneal DDL. 24% of DDLS methylomes

revealed alterations in the differentiation pathway gene *CEBPA* and treatment with demethylating agents restored *CEBPA* expression, was anti-proliferative and pro-apoptotic in vitro and reduced tumour growth in vivo [59]. This was the first illustration of a potential role for demethylating agents in liposarcoma.

Additional genes exclusively amplified in DDL include *GLI1, MAP3K12, CDK2*, *ALX 1* and *TBX5*. None of these genes have been found to be amplified in WDLS [37].

Comparison of genomic aberrations between retroperitoneal and extremity liposarcoma

It is widely accepted that retroperitoneal WDL/DDL and extremity ALT/DDL differ clinically in regard to recurrence rates, dedifferentiation and survival. Extremity liposarcomas have a lower local recurrence rate, dedifferentiate less frequently and have an improved disease specific survival compared to their retroperitoneal counterparts [60,61]. The superior outcomes of extremity liposarcoma are likely due in part to anatomical location, the suitability for radiotherapy and the fact that clear surgical margins are easier to achieve. What is not understood is whether underlying genomic differences contribute to this disparity in outcomes.

There are several reasons why there is a poor understanding of the genomic differences between the two anatomical subtypes. Firstly, as with all sarcomas, these are rare tumours and when collected for analysis tend to be compared on histological subtype, rather than anatomical location to increase the power of the datasets. When anatomical location is analysed, the comparison tends to be made between 'central versus peripheral.' Central can include retroperitoneal, abdominal, pelvic and mediastinal; which should be treated as separate entities. Lastly, when comparisons are made, they are done with very low numbers and rarely validated elsewhere in the literature.

As expected, there is no data comparing primary myxoid and pleomorphic liposarcomas by anatomical location due to their rarity. Nevertheless, Italiano et al. compared amplification profiles of MDM2 + /CDK4 + ALT/WDL and DDL with MDM2 + /CDK4-ve ALT/WDL and DDL[17]. Interestingly they found MDM2/CDK4 − ve tumours more frequently occurred in the extremity (71% v 47%, p = 0.0045). 35% of MDM2 + ve/CDK4 + ve tumours were retroperitoneal, compared to only 7% of MDM2 + ve/CDK4 − ve (p = 0.0002). This was further explored by Bouzid et al. who correlated amplification status with outcomes in 116 liposarcomas. They found CDK4 amplification to be associated with an axial location (66% v 39%, p = < 0.05) and shorter recurrence free survival [26].

Riccioti et al. performed a microarray analysis of 47 cases of DDL. There was a trend towards higher levels of CDK4 amplification (p = 0.0715) and significantly higher levels of MDM2 amplification (p = 0.0016) in retroperitoneal DDL compared to other sites. Higher amplification levels of MDM2 showed a trend towards decreased disease-free survival [44]. The authors concluded that for a given amplification of one gene, each additional copy of the other increased the effect on the disease-free survival. The biological rationale being that progressive loss of both pathways may have a synergistic effect of cell cycle dysregulation.

Work comparing genomic drivers of retroperitoneal and extremity liposarcoma outside of MDM2 and CDK4 is lacking. The authors believe that differences between the two anatomical subtypes are due in part to the genomic aberrations that drive them, but there is currently insufficient data to confidently summarise this. Improvements in next generation sequencing and increased collaboration will bring us a step closer to answering this question, and potentially narrow the gap in clinical outcomes.

Myxoid liposarcoma

Myxoid liposarcoma (MLS) accounts for up to 20% of liposarcomas, predominantly affecting the soft tissues of the extremity. These tumours can be pure myxoid, classed as a low-grade tumour or contain areas with greater cellularity, known as round cell dedifferentiation which is associated with a poorer prognosis [62].

Primary retroperitoneal myxoid liposarcomas are rare. Due to their rarity in the retroperitoneum, the following summary utilises data which comes from all anatomical sites. The largest series of myxoid liposarcomas found only 5 of 213 (2.3%) to arise from the retroperitoneum as a primary tumour [45].

FUS-DDIT3

MLS exhibits a paucity of genomic imbalances and in particular lacks high levels of amplification observed in its retroperitoneal counterparts. They are genetically characterized (> 95%) by the presence of *FUS-DDIT3* (t(12;16(q13;p11) fusion gene [63] creating a fusion transcript, of which three are commonly described. There is no accepted mechanism for how the *FUS-DDIT3* fusion gene drives MLS development. However there is strong evidence to support the notion that this is the primary oncogenic event in these tumours which are otherwise karyotypically normal [64]. These two genes have been extensively studied in isolation, and several theories exist as to how their interaction promotes sarcomagenesis.

Firstly, *FUS* which is a downstream target of DNA repair regulator ATM is implicated in DNA damage repair. *DDIT3* is able to inhibit adipocyte differentiation by binding to the *CEBP-β* family of proteins – the master adipogenesis regulator. Through this fusion, Conyers et al. believe that *FUS-DDIT3* is able to inhibit adipogenesis whilst maintaining a population of immature adipocytes in a cycle of proliferation without differentiation [65].

More recently, Trautman et al. have concentrated on the Hippo pathway as another mechanism of sarcomagenesis in MLS. Trautman et al. showed that *FUS-DDIT3* expressing mesenchymal stem cells are dependent on *YAP1*, a transcriptional co-activator in the Hippo pathway, linked to tissue growth and tumourigenesis. They used Verteporfin to inhibit *YAP1* which supressed the viability and proliferation of all three MLS cell lines analysed in a dose-dependent manner [63]. *YAP1* represents genuine progress in understanding MLS development and offers a novel signalling target.

PI3K

The PI3K signalling cascade is implicated in MLS. RET which activates PI3K is overexpressed in MLS compared to normal fat, and high expression levels are a poor prognostic feature [66]. PI3K activates the protein AKT which causes downstream activation, cell cycle entry and subsequently survival. The catalytic subunit of PI3K – encoded by *PIK3CA* was recently shown to have point mutations in 18% of MLS patients, associated with a shortened disease specific survival and more likely to be present in round cell tumours than myxoid[50,67]. These findings are important as a subset of MLS may respond to treatment with PI3K inhibitors (Fig. 3).

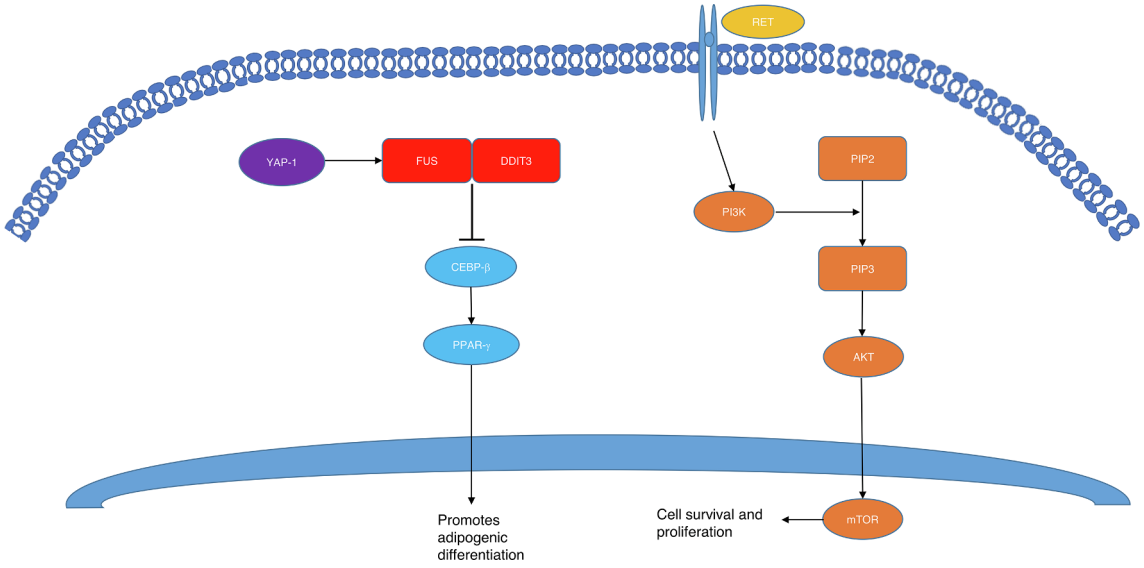

Fig. 3. Pathways active in MLS. As part of the FUS-DDIT3 fusion protein, DDIT3 is able to bind to CEBP-B and prevent adipocytic differentiation. FUS-DDIT3 expressing cells have been shown to be dependent on YAP-1, a transcriptional co-activator. Recurrent promoter mutations in TERT have been documented, and TERT mutations are associated with telomere lengthening, malignant transformation and progression. The PI3K signalling pathway is highly active in MLS. PIK3CA has been shown to have point mutations, contributing to the overactivation of the PI3K/AKT pathway.

Trabectedin

MLS differs from other liposarcomas by possessing a relative degree of chemosensitivity. The most promising drug – trabectedin - works in multiple ways. It binds to the DNA minor groove dissociating the aberrant *FUS-CHOP* transcription factor from promoters of its target genes and also induces lethal DNA strand breaks [57,68].

It has been shown in a large, phase three multicentre randomised control trial to improve PFS compared to those treated with dacarbazine (PFS 4.2 m vs 1.5 m) [69]. There are however limited treatment options for trabectedin resistant MLS patients. Bello et al. have sought to tackle this by working on a patient-derived xenograft with acquired resistance to trabectedin. The authors hypothesise a defective excision repair in the resistant tumour is the result of a mutation in a DNA repair gene UVSSA [70]. UVSSA is likely a DNA repair gene, which could be prophylactically drugged, in order to overcome resistance.

Pleomorphic liposarcoma

Primary retroperitoneal pleomorphic liposarcoma is very rare and in keeping with this, molecular studies are limited. The largest review of PLS documented 32 cases out of 667 liposarcomas (4.8%), and of these only 4 were retroperitoneal [71]. The published literature agrees that these tumours have significantly lower recurrence free and overall survival compared to other liposarcomas, predominantly effect the extremities and are remarkably chemoresistant.

PLS differs from other LS by containing no consistent cytogenetic abnormality. Compared to other LS subtypes, PLS has the most chromosomal imbalances with large numbers of gains and deletions. Conyers et al summarised these as gains in 1p, 1q21-q32, 2q, 3p, 3q, 5p12-p15, 5q, 6p21, 7p, 7q22 with losses of 1q, 2q, 3p, 4q, 10q, 11q, 12p13, 13q14, 13q21-q, 13q23-24 [65]. Ghadimi et al showed overexpression of *VEGF* which is housed on one of these gains (6p21.1), and raises the possibility of *VEGF* inhibition in PLS.

The largest study of PLS genomics performed microarray analysis and *P53* gene sequencing on 53 samples. *P53* was mutated in 60% of samples, with varying expression levels. *P53* mutations are not commonly found in other liposarcomas, and are may contribute to chemoresistance. Retinoblastoma protein (*Rb*), was found to be even more poorly expressed, with 77% of samples failing to express it. This was in concordance with work by Taylor et al.who described a 60% deletion rate in 24 samples of 13q14.2-q14.3 – a region that houses *Rb* [6].

It is suggested that the higher frequency of imbalances explains the aggressive biological nature of the tumour [72]. In terms of therapeutics, it is likely that successful treatment will involve targeting multiple pathways rather than a single dominant one, reflecting the complex tumour biology.

Conclusion

Since the advent of next generation sequencing, the number of studies exploring the molecular landscape of retroperitoneal liposarcoma has increased, albeit at a slower rate than epithelial counterparts. These studies have identified and implicated several targets outside of the hallmark *MDM2/CDK4* in WDL/DDL and *FUS-DDIT3* in MLS. As toxicity and resistance have hampered the progress of *MDM2* inhibitors, researchers have looked to other genes inside the 12q13-15 amplicon such as *FRS2* in WDL and outside this in DDL with greater interest in the RTK pathways. A new signalling target of *YAP-1* in MLS represents progress in this morbid cancer, and the outcomes of PI3K inhibitor trials are eagerly awaited.

Outside of cancer genomics, a slow but steady increase in research into sarcoma epigenetics and immunology is developing. Stimulation of host immunity or inhibiting a dysregulated epigenome may provide breakthroughs in these difficult to treat cancers. New techniques such as CRISPR, nanopore and single cell sequencing are anticipated to generate new targets, quickly, and give a much deeper understanding of the sarcoma genome.

To prevent sarcomas lagging behind epithelial cancers over the next decade and benefit from these technologies, several crucial steps must be taken. Greater collaboration between centres is strongly encouraged to share rare tissue samples and clinical outcome data. In the UK the results from the 100 K genomes project should be carefully and robustly explored as this represents a wealth of genomic data where sarcomas are well represented. Whole geome sequencing of sarcomas should be introduced as a standard of care where economically feasible, as will be the case in the authors' institution in 2021. Those treating sarcomas will need to closely monitor their evolving biology and therapeutic strategies in this era of personalised medicine, with the ultimate goal of improving patient outcomes in this complex and morbid disease.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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