

Review

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# Overview of liposarcomas and their genomic landscape

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## Abstract

Liposarcoma (LPS) is among the most common soft tissue sarcoma affecting adults. LPS is divided into three biologic subtypes characterized by specific genetic alterations. The most common LPS subtypes, well-differentiated and dedifferentiated LPS, are nearly uniformly characterized by ring chromosomes and giant markers with chromosomal amplification of 12q13-15 and resulting amplification of oncogenes *MDM2*, *CDK4*, and *HMGA2*. Myxoid/round cell LPS commonly exhibits a distinctive (12; 16) translocation resulting in the *FUS-DDIT3* fusion gene. Finally, pleomorphic LPS harbors diverse complex genomic changes and chromosomal rearrangements and frequent mutations in *TP53*, *RB1*, and *NF1* leading to dysregulation of tumor suppressor pathways. In this review, we summarize the currently available knowledge on the genomics and genetics of LPS subtypes as well as recent advances in the multimodality management of LPS.

**Keywords:** Dedifferentiated liposarcoma, liposarcoma, genetics, genomics, myxoid liposarcoma, pleomorphic liposarcoma, round cell liposarcoma, well-differentiated liposarcoma

## INTRODUCTION

Soft tissue sarcomas (STS) encompass over 50 recognized entities according to the World Health Organization (WHO) classification. Liposarcomas (LPS) are among the most common STS histologies, representing 50% of retroperitoneal and 25% of extremity STS<sup>[1]</sup> LPS consist of 3 biologic subgroups encompassing 5 histologic subtypes characterized by specific genetic alterations [Table 1]. These three STS subgroups, their characteristic genetic alterations, and treatment will be reviewed herein.



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## WELL-DIFFERENTIATED AND DEDIFFERENTIATED LPS

Well-differentiated liposarcoma (WDLPS) and dedifferentiated liposarcoma (DDLPS) are the most common histologic subtypes of LPS [Table 1]. Together they represent 60% of all LPS and often coexist, occurring in the retroperitoneum and extremities. WDLPS is a typically indolent histologic subtype that presents as slowly growing masses but can be locally aggressive with minimal to no distant metastatic potential while DDLPS is a higher grade histology with a potential for faster growth and distant metastatic potential<sup>[1,2]</sup>.

### Chromosomal translocations and copy number alterations

Although genetic alterations are more complex in DDLPS than WDLPS, both commonly exhibit ring chromosomes and giant markers with chromosomal amplification of 12q13-15. This segment of chromosome 12q13-15 contains a number of cancer-related genes implicated in tumorigenesis. Included in these are the genes *CDK4*, *MDM2*, and *HMGA2* which are consistently amplified and in the recent TCGA genomic characterization of adult STS they were reported in 100%, 92%, and 76% of LPS cases, respectively<sup>[3]</sup>, as well as *CPM* and *YEATS2*<sup>[4,5]</sup>. *MDM2* is an E3 ubiquitin protein ligase which promotes degradation of p53 to prevent apoptosis and/or cell-cycle arrest and may also have effects independent of p53 (such as through other tumor suppressors such as p21)<sup>[6-10]</sup>. *CDK4* encodes a key regulator of the G1/S cell cycle checkpoint and is coamplified with *MDM2* in over 90% of patients<sup>[4]</sup>. *YEATS4* and *CPM* are genes implicated in dedifferentiation<sup>[11,12]</sup>; the former encodes a putative transcription factor required for physiologic suppression of p53 function while the later encodes a proteolytic enzymes that activates growth factors such as epidermal growth factor.

Development of DDLPS is associated with accumulation of additional chromosomal abnormalities<sup>[4]</sup>. Copy number alterations are common in DDLPS with deletions reported in chromosome 1p, 11q, 13q, 15q and 17p and focal amplifications at chromosomes 1q, 5p, 6q, 8q, 11p, 12q, 14q, and 15q<sup>[3,11,13]</sup>. Recurrent amplifications of 1p32 and 6q23 with resulting overexpression of *JUN* and *ASK1*, respectively, have been implicated in adipocyte dedifferentiation, have been reported only in DDLPS, and are associated with worse prognosis<sup>[3,14-16]</sup>. Chromosomal deletions of tumor suppressor genes including *RUNX3* and *ARID1A* (1p36), *ATM* and *CHEK1* (11q22-24), and *RB1* (13q14.2) have been associated with reduced adipocytic differentiation, genomic instability, and worse patient outcomes<sup>[11,12]</sup>.

### Mutations

Mutation rates are modest in WDLPS and DDLPS, with few consistently and recurrently mutated genes across case series<sup>[3,11,13,17-19]</sup>. No significant differences have been reported in the mutations between WDLPS and DDLPS to explain the differences in behavior.

### Epigenetics

#### *DNA methylation and histone modifications*

Studies have reported alterations in LPS methylomes leading to changes in expression of differentiation pathway genes. Epigenetic silencing via methylation of *CEBP* - gene was identified in 10 or 42 DDLPS samples (24%) and treatment with demethylating agents induced cellular apoptosis and increased *CEBP* - expression<sup>[18]</sup>. More recently, The Cancer Genome Atlas (TCGA) reported that among DDLPS cases included in the sarcoma analysis, patients whose tumors were hypermethylated compared to hypomethylated had shorter disease-specific survival<sup>[3]</sup>.

Additionally, a small number of other studies describe other epigenetic mechanisms of gene silencing, including altered histone modifications, that are associated with dedifferentiation and/or tumor growth<sup>[20,21]</sup>.

### MicroRNAs

MicroRNAs (miRNAs) are small non-protein coding RNA molecules that exert regulatory functions on gene expression. In the context of the RNA-induced silencing complex (RISC), these 21-25 nucleotide long RNA

**Table 1. Clinical characteristics of liposarcoma histologic subtypes**

Subtype	Genomic alterations	Affected oncogenes	Local recurrence rate	Distant recurrence rate	Chemosensitivity	Radiosensitivity
Well differentiated	12q13-15 amplification	<i>MDM2</i> , <i>CDK4</i>	Moderate	Low/-	None	Moderate
Dedifferentiated	12q13-15 amplification 3p14-21 loss 11q23-24 loss 19q13 loss	<i>MDM2</i> , <i>CDK4</i> Unknown Unknown	High	Low	Low	Moderate
Myxoid	FUS-DDIT3 translocation	Unknown	Low	Moderate	High	High
Round cell	FUS-DDIT3 translocation	Unknown	Moderate	High	High	High
Pleomorphic	Rb/p53 loss	Rb, p53	Moderate	High	High	Moderate

Adapted from Crago and Dickson<sup>[1]</sup>

molecules bind to the 3'-untranslated region of target mRNA and induce the degradation of target mRNA. Dysregulation of miRNAs has been reported in many malignancies and altered miRNA expression can result from deficiencies in their processing pathways, epigenetic modifications, or miRNA gene mutations<sup>[22]</sup>.

There have been a number of miRNA alterations described in LPS. MiR-26a-2 is located near the *MDM2* gene region and is overexpressed in both well-differentiated and dedifferentiated LPS, associated with enhanced cellular proliferation, survival, and invasion<sup>[23,24]</sup>. MiR-155 is a strong oncogene that has been shown to be overexpressed in myxoid/round cell, dedifferentiated, and pleomorphic LPS compared to normal adipose tissue. It promotes cellular growth by targeting casein kinase 1 $\alpha$  that in turn enhances  $\beta$ -catenin signaling and cyclin D1 expression<sup>[25,26]</sup>. MiR-143, miR-193b, and miR-133a exhibit inhibitory effects on cellular proliferation; miR-143 and miR-193b are downregulated in well-differentiated and dedifferentiated LPS compared to normal adipose tissue<sup>[27,28]</sup> while miR-133a is downregulated in dedifferentiated LPS<sup>[29]</sup>.

### MYXOID/ROUND CELL LPS

Myxoid/round cell LPS represents ~30% of LPS [Table 1]<sup>[30]</sup>. Myxoid/round cell LPS typically develop in the proximal extremities. Other sites such as bone, retroperitoneum, serosal surfaces, and contralateral limbs are commonly affected at time of recurrence. Increasing aggressiveness is associated with increasing round cell component with tumors containing > 5% round cell component carrying an unfavorable prognosis<sup>[31-33]</sup> as well as higher histologic grade, multifocality, and p53 overexpression<sup>[4]</sup>. Compared to WDLPS andDDLPS, myxoid/round cell LPS are significantly more sensitive to chemotherapy and radiation therapy<sup>[34]</sup>.

### Chromosomal translocations and copy number alterations

Myxoid LPS is almost always associated with a chromosomal translocation, most commonly t(12;16)(q13;p11) in over 90% of cases and which leads to the fusion of the *DDIT3* (also known as *CHOP*) and *FUS* (also known as *TLS*) genes resulting in the FUS-DDIT3 fusion protein<sup>[32,33,35,36]</sup>. The *DDIT3* gene encodes for a nuclear protein belonging to the CCAAT/enhancer binding protein (C/EBP) family of transcription factors and is implicated in adipocyte differentiation. The *FUS-DDIT3* fusion protein is implicated to confer tumorigenicity through dysregulated adipocyte differentiation. Although different variants of the FUS-DDIT3 transcript have been reported, no prognostic difference has been described between the variants. Myxoid LPS are also less commonly associated with other translocations, including the t(12;22)(q13;q22) translocation resulting in expression of EWSR1-DDIT3 fusion protein. These resulting fusion proteins are thought to result in malignant transformation by functioning as aberrant transcriptional regulators that interfere with adipocyte terminal differentiation and favor proliferation<sup>[32,37,38]</sup>.

Myxoid LPS have relatively normal karyotypes compared to other STS histologic subtype, includingDDLPS and pleomorphic LPS<sup>[12]</sup>.

## Mutations

In addition to the nearly ubiquitous presence of a chromosomal translocation, a subset of myxoid LPS (15%) are also characterized by mutations or amplifications of *PIK3CA*, which encodes the catalytic subunit of phosphatidylinositol 3-kinase (PI3K)<sup>[12]</sup>. Patients with tumors harboring *PIK3CA* mutations have shorter disease-specific survival compared to those with wild-type *PIK3CA*. Thus, the *PI3K* pathway in patients with myxoid LPS with *PIK3CA* mutations is an attractive therapeutic target. *PTEN* deletion has also been described<sup>[12,39]</sup>. Additionally, myxoid LPS are also characterized by expression of the cancer-testis antigen, NY-ESO-1<sup>[35]</sup>, and patients with myxoid LPS are candidates for various immunotherapy trials targeting NY-ESO-1<sup>[40,41]</sup>.

## Epigenetic alterations

There have been limited studies investigating the epigenetics of myxoid LPS<sup>[11,42-44]</sup>. Epigenetic silencing of *p14ARF*, a p53 target, by promoter methylation has been reported as a common event in both myxoid and pleomorphic LPS.

## MicroRNAs

As in the case for well-differentiated and dedifferentiated LPS, miRs dysregulation has also been demonstrated in myxoid/round cell LPS. miR-155 is a strong oncogene that has been shown to be overexpressed in myxoid/round cell LPS<sup>[26]</sup>. miR-486, which interacts with plasminogen activator inhibitor 1 (PAI-1), a promoter of cellular proliferation and invasion, is downregulated in myxoid LPS<sup>[45,46]</sup>.

## PLEOMORPHIC LPS

Pleomorphic LPS are the rarest histologic subtype of LPS, representing ~5% of cases, and associated with the worst prognosis [Table 1]<sup>[1,47-50]</sup>. Pleomorphic LPs typically arise in the extremities, although less commonly can occur in the trunk or retroperitoneum<sup>[4]</sup>. Up to 50% of patients develop metastatic disease and disease-specific survival is poor<sup>[51]</sup>.

## Chromosomal translocations and copy number alterations

Our current understanding of the molecular pathology of pleomorphic LPS is poor. They characteristically harbor diverse complex genomic changes and chromosomal rearrangements without unifying molecular alterations nor targetable aberrations. Deletion of 13q14.2-5, which contains *RBI*, has been described in up to half of pleomorphic LPS<sup>[12,52]</sup>.

## Mutations

Mutations or loss of *TP53* is frequently seen in pleomorphic LPS, unlike in LPS subtypes where TP53 loss is uncommon. Loss of NF1 is also seen in some patients<sup>[12,47]</sup>.

## Epigenetic alterations

There is not much known about the epigenetics of pleomorphic LPS<sup>[11,42]</sup>. As noted before, promoter methylation resulting in epigenetic silencing of *p14ARF* has been reported as a common event in both myxoid and pleomorphic LPS.

## MicroRNAs

As in the case for well-differentiated and dedifferentiated LPS, miRs dysregulation has also been demonstrated in pleomorphic LPS. miR-155 is a strong oncogene that has been shown to be overexpressed in pleomorphic LPS<sup>[26]</sup>.

## THERAPEUTIC OPPORTUNITIES AND CONSIDERATIONS

Despite our increasing understanding of the genomic alterations across LPS subtypes, their implications for LPS management and translation into novel therapeutics in the clinic has, to date, remained limited.

Here we review the current state of multimodality treatment of LPS and highlight opportunities for future advancements in LPS management.

### **Local therapies - surgical resection and radiation therapy**

For patients with primary localized LPS, surgery with complete gross tumor resection (R0/R1 margins) remains the definitive management and only potential curative treatment. However, local recurrence rates are high (> 80%)<sup>[53,54]</sup>. Radiation therapy (RT) and/or chemotherapy can be used as adjuncts to reduce local and distant recurrence risk for those with dedifferentiated, myxoid/round cell, or pleomorphic LPS.

### **Systemic therapies**

#### *Cytotoxic therapies*

WDLPS andDDLPS are relatively chemoresistant<sup>[1,2,55]</sup>, with response rates in the literature reported as low as  $\leq 12\%$ <sup>[56]</sup> and as high as  $21\%$ <sup>[53]</sup> [Table 1]. Thus, in the primary or recurrent resectable setting, systemic therapy has not been frequently used and there is no consensus regarding their use in the neoadjuvant or adjuvant setting. For those with unresectable or metastatic LPS, cytotoxic chemotherapy is the standard of care<sup>[4,57]</sup>. Myxoid/round cell LPS is considered to be relatively chemosensitive and thus chemotherapy may be considered for those patients with resectable disease in the neoadjuvant or adjuvant as well as in the unresectable or metastatic settings<sup>[58]</sup>. The role of systemic therapy for pleomorphic LPS is less well defined although a number of retrospective studies suggest a degree of chemosensitivity in the metastatic setting<sup>[58]</sup>.

Despite the differences in chemosensitivity, in the first line, anthracycline (typically doxorubicin), often in combination with ifosfamide, is the standard systemic therapy. Second-line systemic therapy options that are used frequently include trabectedin<sup>[59-61]</sup>, eribulin<sup>[60,62-64]</sup> and gemcitabine/docetaxel<sup>[65]</sup>. Other regimens with activity in soft tissue sarcomas are used infrequently, include gemcitabine, and dacarbazine monotherapies as well as combination of gemcitabine/dacarbazine<sup>[58]</sup>. Though trabectedin and eribulin are both approved for the treatment of all liposarcomas, trabectedin has much higher response in MRCLS and eribulin leads to longer progression free survival benefit in pleomorphic LPS.

#### *Investigational therapies - targeted therapies*

For patients who have failed standard of care systemic therapies, there are a number of investigational therapies that may be considered including targeted agents<sup>[66]</sup> and immunotherapies alone or in combination with other therapies<sup>[41,67,68]</sup>. Amplification of the *CDK4* oncogene as well as *MDM2* are seen in > 90% of WDLPS/DDLPS. Small molecule inhibitors targeting *CDK4/6* (palbociclib) and *MDM2*, are being evaluated in ongoing studies, either alone or in combination with chemotherapy. These trials are enrolling patients with WDLPS/DDLPS<sup>[58,69]</sup>.

Pazopanib, a tyrosine kinase inhibitor approved for use in second/third-line and beyond in non-adipocytic soft tissue sarcoma, has limited activity in LPS subtypes<sup>[68,69]</sup>. Olaratumab is a recombinant human immunoglobulin G (IgG) monoclonal antibody that binds PDGFR $\alpha$  and blocks receptor activation and has shown improved overall survival in a randomized phase Ib/II study for all soft tissue sarcoma subtypes, when given in combination with doxorubicin compared to doxorubicin alone<sup>[58]</sup>, but the recently released phase III data did not validate these results. Selenixor (XPO-1 inhibitor) and PPAR $\gamma$  agonists are also under investigation for advanced LPS.

#### *Investigational therapies - immunotherapy*

In recent decades, major advances have been made in cancer therapy through the use of immune checkpoint blockade - with the FDA approval of therapies targeting the CTLA-4 and PD-1 across multiple cancer types and cancer care continuum in the metastatic and adjuvant settings<sup>[70]</sup>. Current FDA approvals for immune checkpoint blockade therapies are limited to cancer types characterized by high mutational burden such

as melanoma, non-small cell lung carcinomas, urothelial cancers, and microsatellite instability-high or mismatch repair-deficient solid tumors. Interestingly, immunotherapy was first reported as a potential therapeutic strategy for sarcomas by William Coley<sup>[71]</sup> in 1891, when he noted spontaneous regression of a recurrent malignant sarcoma in a patient after a serious bout of infection.

Recent evidence suggests that immune checkpoint inhibitors may have activity in particular subtypes of soft tissue sarcomas<sup>[72,73]</sup> and in histologic subtypes such as undifferentiated pleomorphic sarcoma (UPS) and DDLPS that have mutational and copy number heterogeneity<sup>[11]</sup>. Two multicenter phase II clinical trials examining the efficacy of anti-PD-1 therapy in advanced metastatic sarcoma included patients with DDLPS have been reported in recent years<sup>[72,73]</sup>. The first study, SARC028, enrolled 86 patients with advanced STS and bone sarcomas to receive pembrolizumab (anti-PD-1)<sup>[72]</sup>. Of the 80 patients evaluable for response, 10 had DDLPS with 2 of these patients (20%) achieving disease control (stable disease or partial response) after only 8 weeks of treatment with pembrolizumab. The second study, Alliance A091401, enrolled and randomized 85 patients with locally advanced, unresectable, or metastatic sarcoma to receive nivolumab (anti-PD-1) monotherapy or nivolumab plus ipilimumab (anti-CTLA-4)<sup>[73]</sup>. No responses were observed in the 5 patients with LPS, although patients with both WDLPS and DDLPS were enrolled in this study. Both SARC028 and A091401 have been expanded to include additional patients with UPS and LPS; results from these expansion cohorts are eagerly anticipated.

Although immune checkpoint therapy offered significant and durable responses for some patients with DDLPS in the SARC028 study, most failed to respond to immunotherapy or had short-lived responses. At baseline, both the tumor immune microenvironment and the poor antigenicity of these tumors may facilitate escape of immune recognition. There are considerable ongoing efforts in other malignancies to identify predictors of response to immune checkpoint blockade and elucidate mechanisms of resistance to immunotherapy. In STS, ongoing studies include those combining immunotherapies with other systemic therapies (cytotoxic) or local treatment modalities (RT, injectables) in advanced disease or applying immunotherapy for earlier stage sarcoma, such as in the neoadjuvant setting<sup>[65,66,72]</sup>.

Patients with myxoid LPS often overexpress the cancer testis antigen, NY-ESO-1, which is being targeted by investigational immunotherapies including adoptive cell therapies and peptide vaccines<sup>[4]</sup>. The adoptive transfer of T-cells genetically modified to express a T-cell receptor recognizing NY-ESO-1, has shown promising responses in a heavily pre-treated MRCLS patients in a pilot study<sup>[74]</sup>.

## CONCLUSION

LPS is classified into 3 biologic groups encompassing 5 histologic subtypes characterized by specific genomic and genetic alterations and variable clinical behavior and prognosis. Both WDLPS and DDLPS are characterized by the presence of chromosomal amplification of 12q13-15 with associated amplification of oncogenes MDM2, CDK4, and HMGA2. DDLPS is notable for having additional and more complete genetic alterations compared to WDLPS. Myxoid/round cell LPS are nearly uniformly characterized by the presence of a chromosomal translocation, most commonly t(12;16)(q13;p11) resulting in the fusion protein FUS-DDIT3, with mutations in *PIK3CA* more common in high grade tumors. Lastly, pleomorphic LPS is notable for diverse complex genomic changes and chromosomal rearrangements without unifying molecular alterations nor targetable aberrations. To date, achieving a comprehensive understanding of LPS biology has been challenging, in part due to the rarity of these tumors and relative dearth of *in vitro* and *in vivo* experimental model systems. Many of the ongoing clinical trials are testing novel therapeutic targets, with correlative analyses of associated biospecimens, which should help shed light on molecular mechanisms behind response and resistance to these novel therapies, and lead to future advancements in the multimodality treatment for patients with LPS.



## DECLARATIONS

### Authors' contributions

Design: Keung EZ, Somaiah N

Literature research: Keung EZ, Somaiah N

Manuscript writing: Keung EZ, Somaiah N

Manuscript editing: Keung EZ, Somaiah N

Manuscript revision: Keung EZ, Somaiah N

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Not applicable.

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### Conflicts of interest

Both authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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