Review Article

Stem Cell INVESTIGATION

Recent translational research into targeted therapy for liposarcoma

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Abstract: Liposarcomas (LPS) are among the most common soft tissue sarcomas, originating from adipocytes. Treatment for LPS typically involves surgical resection and radiation therapy, while the use of conventional cytotoxic chemotherapy for unresectable or metastatic LPS remains controversial. This review summarizes the results of recent translational research and trials of novel therapies targeting various genetic and molecular aberrations in different subtypes of LPS. Genetic aberrations such as the 12q13-15 amplicon, genetic amplification of *MDM2*, *CDK4*, *TOP2A*, *PTK7*, and *CHEK1*, point mutations in *CTNNB1*, *CDH1*, *FBXW7*, and *EPHA1*, as the fusion of *FUS-DDIT3/EWSR1-DDIT3* are involved in the pathogenesis LPS and represent potential therapeutic candidates. Tyrosine kinase inhibitors targeting MET, AXL, IGF1R, EGFR, VEGFR2, PDGFR-β and Aurora kinase are effective in certain types of LPS. Abnormalities in the PI3K/Akt signaling pathway deregulation of *C/EBP-α* and its partner *PPAR-γ*, and the interaction between calreticulin (CRT) and CD47 are also promising therapeutic targets. These promising new approaches may help to supplement existing treatments for LPS.

Keywords: Leiomyosarcoma; target therapy; *MDM2* amplification; *FUS-CHOP* fusion; *FUS-DDIT3/EWSR1-DDIT3* fusion gene; trabectedin; C/EBP-α; calreticulin (CRT)

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Introduction

Liposarcomas (LPS) are malignant tumors originating from mesenchymal cells (1-5). Although LPS can occur in almost anywhere in the body, over half develop in the thigh, and up to one-third involve the abdominal cavity (1-5). According to the WHO Classification of Soft Tissue and of Bone published in 2013, LPS can be divided into four types: well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLSP), myxoid/round cell liposarcoma (MLPS), and pleomorphic liposarcoma (PLPS) (2-8).

The main feature of WDLPS is the excessive proliferation of adipocytes, while DDLPS includes both, a fusiform-cell-rich dedifferentiated portion and an adipocyte-rich well differentiated portion (1,3,5). WDLPS and DDLPS have both shown amplification of *12q13-15*, which includes the *MDM2* gene, but they demostrate different pathological features (9-13). In addition to surgical treatment, the most common types, WDLPS and DDLPS, show obvious resistance to conventional radiotherapy (RT) and cytotoxic chemotherapy (CT) (1,5). MLPS is another common subtype of LPS, with a 5-year overall survival rate of 90%, compared with 50% in patient with round cell LPS (14-17). Most MLPSs show the translocations t(12;22)(q13;q12) and

t(12;16)(q13;p11.2), which lead to fusion of *EWS-CHOP* and *FUS-CHOP* (14,18-20) respectively.

There different histopathological and genetic features mean that LPS variants exhibit different aggressive potentials, reflecting their morphologic diversity. DDLPS, high-grade MLPS, and PLPS have a high propensity to metastasize, while ALT/WDLPS does not metastasize without dedifferentiation, and MLPS exhibits indolent clinical behavior and a lower metastatic potential (*Table 1*) (3,21).

Treatment options of LPS patients involve surgery, CT, and RT. The goal of surgery, as the standard treatment for localized tumors, is to achieve complete tumor resection with negative margins. RT and CT, which can be administered pre- and/or postoperatively as a part of multimodal strategy for the management of localized tumors and they have shown controversial results (22). The standard treatment of metastatic disease is cytotoxic chemotherapy but it shows limited success. LPS sensitivity to CT seems to be correlated with the histologic subtype, and MLPS has a higher sensitivity to cytotoxic CT than other LPS subtypes (3). Histology and the primary site are the independent prognostic factors associated with survival in LPS patients (23). Novel and more effective systemic therapies are needed to meet the needs of LPS patients. Targeted therapy aims to exploit specific biologic features of the tumor in order to eradicate it. However, its rarity and the diverse molecular and genetic characteristics of each subtype are hindering the development of new targeted therapies (3,5,11,15,21). However, there have been several translational studies and trials in different subtypes of LPS (11,16,20,24-27).

12q13-15 amplicon and genetic amplification

Gene amplification in WD/DDLPS patients with chromosome 12q13-15 amplification may be a key event in the pathogenesis of LPS (28). Such amplified genes can be investigated by molecular biological methods and thus have the potential to act as a biomarker and target (29-31).

The *MDM2* (also known as *HDM2*) gene is located at chromosome 12q15 and is amplified in most WD/DDLPS (*Table 1*) (32-34). Amplification of *MDM2* inhibits the activity of p53, which leads to its loss of function as a tumor suppressor (35-37). Similarly, the cyclin dependent kinase-4 gene (*CDK4*) is also amplified in most WDLPS and DDLPS cases (*Table 1*) (29,32,38). At the molecular level, CDK4 inactivates retinoblastoma (Rb) protein and promotes cell-cycle transition from G1 phase to S phase (39). Similar to *MDM2* and *CDK4*, the *YEATS* domain containing 4 gene (*YEATS4*) is also located on 12q13-q15 (*Table 1*). As a transcription factor participating in p53 regulation, YEATS4 has also shown promising potential in target therapy (17,29,32).

MDM2 inhibitors

Nutlins is the first potent and specific MDM2 inhibitor (40). It replaces p53 from MDM2 with an inhibitory concentration 50 of 100–300 nm. Nutlin-3a has been reported to influence the Rb pathway through activation of the transcription factor E2F1, cause apoptosis in p53-null tumor cells (41). Nutlin-3 thus demonstrates exciting prospects as a therapeutic target. Several other MDM2 inhibitors, such as AT-219 and Ascenta are also currently being developed (42).

Receptor tyrosine kinase inhibitors

A recent study showed that several receptors, including MET, IGFR, AXL, and EGFR were overexpressed in WD/DDLPS (*Table 1*). All these receptors may act as targets, and have already available small-molecule inhibitors (43). For instance, the oral VEGFR2 tyrosine kinase inhibitor apatinib had showed significant effect in advanced round cell LPS (44). The PDGFR beta-mediated pathway also plays a role in the progression of canine LPS, and may thus represent a promising target for adjuvant cancer therapies (45). Aurora kinases have recently been shown to be deregulated in human tumors, making them an attractive target for cancer therapy (46). Aurora kinase A, was also overexpressed in LPS and MLN8237 has proven to a selective and potent inhibitor of Aurora A, in a dose-dependent manner, suggesting that doses effectively and specifically targeted at Aurora A may be effective in tumor growth suppression (46).

FUS-DDIT3/EWSR1-DDIT3 fusion

The characteristics of MLPSs include frequent local recurrence and metastasis (16,47-49). MLPS tumors are also characterized by specific translocations of t(12;16) or t(12;22), resulting in fusion of *FUS-DDIT3* or *EWSR1-DDIT3*, respectively (*Table 1*) (20,49,50). Three EWSR1/DDIT3 and nine FUS/DDIT3 fusion transcripts have been detected to date (1,14,17,19,20,49,50). Regarding the biological role of these fusions in LPS, Aman *et al.* demonstrated that FUS-DDIT3 protein expression was inversely correlated with the expression of cell proliferation-associated

Table 1 The clinical features of different subtype liposarcoma with different genetic features and therapeutic targets

Histotypes	% of incidence in LPS	Diagnosis	Prognosis	Genetic aberrations	Drugs/inhibitors	Mechanism of action
ALT: adipocytic, sclerosing, and inflammatory	40–45	FISH analysis of *MDM2*/*CDK4*	Locally aggressive; recurrence is likely to occur if excision is not complete; progression from ALT to DDLPS is reported in 25–40% of patients	*MDM2* amplification; *CDK4* amplification; *YEATS4* amplification; TKIs	MDM2 inhibitors: cis-imidazoline analogs (Nutlin-3)/ spirooxindoles/AT-219/ Ascenta; E2F1 activator: Nutlin-3a; pazopanib/ sorafenib	Strong binding to MDM2 and irreversibly disrupts the MDM2/ p53 protein complex; apoptosis Induction in Null-p53 cancer cells; negative P53 regulation; target RAF, VEGFR1-3, PDGFRB, c-kit and flt-3
DDLPS			Strong propensity for distant lung metastases (10–15%) and recurrence			
MLPS	30	FISH analysis of aberrant fusion Gene FUS–CHOP/ DDIT3	Frequent recurrence; 10–20% of patients develop distant metastases	T(12;16) or t(12;22): *FUS-DDIT3/EWSR1-DDIT3*/TLS-CHOP fusion; PTEN mutations (loss of function mutations); PI3K mutations (p110 alpha mutations)	PTEN/AKT inhibitors: nelfinavir	Localize to the nucleus and the cytoplasm, bind RN, and are also involved in nucleo-cytoplasmic shuttling involved in the induction of transcription; PI3k/AKT pathway dysregulation
PLS	5	Histologic analysis	The rarest and most aggressive LPS subtype; highly resistant to all current treatment options with a very poor clinical outcome; local recurrence in 30–35% of patients; lung is a frequent site of relapse; cutaneous and subcutaneous PLS exhibit a better outcome than that of deep soft tissue, with 17% incidence of local recurrence and rare cases of distant metastases	Complex karyotype with chromosome arrangements including gains and losses	$p14^{ARF}$ methylation	$p14^{ARF}$ methylation in the origin and growth of PLS

molecules (20). Suggesting that FUS-DDIT3 is the regulatory site involved in the development of MLPSs at the transcription and expression levels, these fusion oncogenes might be potentially powerful therapeutic targets, and detailed investigations are needed to develop them as novel treatment methods for LPS. Another specific TLS-CHOP fusion, caused by the translocation of t(12;16), presents in almost all the myxoid LPS (14). The TLS-CHOP fusion protein has three common types: type I (also known as type 7-2), type II (type 5-2), and type III (type 8-2) and p53 status has been reported to show an association with type II fusion in MLPS (14).

PI3K/Akt signaling pathway

PI3K-Akt pathway is a signal transduction pathway, which can promote the growth and survival of extracellular signals. This signaling pathway is highly regulated through a variety of mechanisms, and often interacts with other signaling pathways (24). Disruption of the PI3K-Akt pathway regulation can result in an increased signaling activity, which is linked to a range of diseases, such as type II diabetes and cancer (24).

In MLPSs, p110α catalytic subunit mutations of *PI3K* gene have been frequently detected and are associated with a poor prognosis (51). Other frequently mutated genes include *PIK3CA* (18% of MLPSs), *TP53* (17% of PLPS), and *NF1* (8% of PLPS) (51). *PIK3CA* mutations are also associated with a poor clinical prognosis and Akt activation in MLPSs (51). These results indicate that Akt pathway plays a potential role in MLPS, supporting the need for further studies of this histologic subtype, including the effects of PI3K inhibitors (*Table 1*) (24,51).

Demicco *et al.* also studied the PI3K-Akt pathway in 44 cases of round cell and myxoid LPS (26). Compared with purely mucinous tumors, tumors with round cell alterations, frequently have higher levels of IGF1R or PIK3CA activation. Moreover, PI3K-Akt pathway activation in round cell LPS is verified by the increase in p4EBP1 than that of myxoid LPS, because the p4EBP1 increase is closely related to activating events, such as *PTEN* loss, IGF1R expression, or mutation of *PIK3CA*. In conclusion, these data support an important role for the PI3K-Akt pathway in MLPSs (*Table 1*) (19,26).

CCAAT/enhancer binding protein (C/EBP-α)

The C/EBP-α is a transcription factor involved in blood cell differentiation. C/EBP-α mutation can reduce CCATT/enhancer binding protein alpha activity, leading to transition of myeloid antecedents. C/EBP-α can interact with CDK4 and CDK2 (25). In normal adipogenesis, C/EBP-α and its partner PPAR-gamma can promote each other's expression and maintain high levels of mRNAs and differentiation (25). C/EBP-α and PPAR-γ are reported to be down-regulated in DD/WDLPS. It has also been reported that, grown in differentiating conditions, the DD cell lines lacked the induction of C/EBP-α expression, despite partial induction of PPAR-γ (25). Furthermore, PPAR-γ levels increased appropriately with the increase of C/EBP-α in the medium without PPAR-γ ligand (25). These results suggested that restoring or increasing C/EBP-α might be a promising therapeutic approach for DDLPS (25).

Calreticulin (CRT)

CRT is also known as calregulin, CaBP3, CRP55, ERp60 and calsequestrin-like protein, and is encoded by the *CALR* gene. It is expressed in many cancer cells and plays an important role in promoting macrophages to engulf hazardous cancerous cells (52). Most cells are undamaged because of the presence of another molecular signal that blocks CD47-CRT. Hence, blocking CD47 with antibodies may have a positive effect on the treatment of cancer. Anti-CD47 did not affect the function of normal cells while removing cancer cell in mouse models of non-Hodgkin's lymphoma and myeloid leukemias.

A recent study showed that several genes located at 19p13.1-13.2 were highly expressed in DDLPS, including genes encoding, CRT, which can inhibit the differentiation of adipocytes. The expression of CRT was detected in 45 patients with LPS, including 15 patients with DDLPS. CRT knockdown by siRNA resulted in adipogenesis and reduced cell proliferation in DD cells (52). CRT and CD47 might thus be effective therapeutic utilities in LPS, especially DDLPS (*Table 1*).

Minor-groove DNA binders

Trabectedin (Ecteinascidin-743, ET743) is an alkylating agent isolated from *Ecteinascidia turbinate*, which affects cancer cells by damaging DNA (53). Gronchi *et al.* reported on a multi-center phase II trial of neoadjuvant trabectedin in MLPS patients, initiated by the National Cancer Institute (54). Three of 23 patients showed a pathological complete responseindicating that a 24-h

intravenous infusion of 1.5 mg/m^2 trabectedin every 3 weeks might be a good treatment for MLPS (54).

PNU-166196 (brostallicin) can also bind to the DNA minor groove and regulate the transcription of the FUS-DDIT3 gene (55). A recent phase II study of brostallicin in advanced soft tissue sarcomas performed by the EORTC suggested that brostallicin resulted in rare tumor response (56). More investigations are therefore needed to explore the role of DNA minor groove binders in LPS-targeted therapy.

Other potential targets

TOP2A, PTK7, and CHEK1 were overexpressed in 140 cases of LPS, including all subtypes and in LPS cell lines (27). In LPS cell lines resulted in increased cell proliferation and reduced invasiveness (27). Furthermore, point mutations in *CTNNB1*, *CDH1*, *FBXW7*and *EPHA1* also represent potential oncogenic events in LPS cells (51). The *C-MET* amplification rate detected by ISH is 4.8% (3/62) in LPS. 7.1% (1/14) in myxoid LPS, 28.6% (2/7) in PLPS, and zero in other types of LPS (57). *EGFR* amplification ratio is 17.5% (14/80) in LPS. Nearly 3.6% (1/28) in DDLPS, 41.7% (5/12) in WDLPS, 62.5% (5/8) in PLPS and 17.6% (3/17) in other/unknown types of LPS) (57). At the same time, increased expression of C-KIT, EGFR, PD-L1, and PD-1+TILs has been validated in these LPS by immunohistochemistry, indicating the potential for target therapy and immunotherapy (57,58). Further, investigation of these genetic aberrations might help in the development of more therapeutic methods for LPS patients.

Conclusions

Genetic aberrations, such as the *12q13-15* amplicon, genetic amplification of *MDM2*, *CDK4*, *TOP2A*, *PTK7*, and *CHEK1*, point mutations in *CTNNB1*, *CDH1*, *FBXW7*, and *EPHA1*, and the fusion of *FUS-DDIT3/EWSR1-DDIT3* contribute to the pathogenesis of LPS and might also represent good therapeutic candidates. Tyrosine kinase inhibitors targeting MET, AXL, IGFR, EGFR, *VEGFR2*, PDGFR-β and Aurora kinase signaling may also be effective in certain types of LPS. Disruption of the PI3K/Akt signaling pathway and deregulation of *C/EBP-α* with its partner *PPAR-γ*, also represent promising therapeutic methods for LPS trials. Furthermore, targeting interaction between calreticulin and CD47 may also lead to useful novel cancer treatments. All these potential new targeted approaches and promising immunotherapies may provide useful supplements to existing treatments for LPS.

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Footnote

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