

Proteomic Profiling Identifies LM07 as a Driver of Pulmonary Metastasis in Dermatofibrosarcoma Protuberans

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Abstract

Dermatofibrosarcoma protuberans (DFSP) is a rare sarcoma with low metastatic potential, yet pulmonary metastasis, when it occurs, carries a dismal prognosis. Although imatinib is approved for advanced DFSP, its efficacy in metastatic disease remains limited and resistance inevitably develops. To characterize the proteomic landscape of DFSP pulmonary metastasis and identify functional drivers of metastatic progression, we performed proteomic profiling on 18 tissue specimens from six patients with paired normal, primary, and metastatic tissues. Through integrated differential expression analysis, weighted gene co-expression network analysis, and expression trend analysis, we identified LMO7 as a progressively upregulated protein along the normal–primary–metastasis continuum, a finding validated by immunohistochemistry and quantitative PCR. Functional assays in patient-derived primary DFSP cells demonstrated that LMO7 knockdown significantly inhibited cell proliferation, migration, and invasion. Despite limitations including small sample size and the use of primary cells with limited passages, our findings identify LMO7 as a progressively upregulated protein during DFSP metastatic progression that may contribute to malignant behavior, supporting its potential as a prognostic biomarker and therapeutic target for metastatic DFSP.

Introduction

Dermatofibrosarcoma protuberans (DFSP) is a low-grade soft tissue tumor that typically presents as a painless nodule on the trunk or proximal limbs^[1, 2]. Wide local excision is the primary treatment; however, recurrence rates can reach 30%.^[3] Although metastasis occurs in fewer than 5% of cases, lung metastasis is the most common site of distant spread and carries a dismal prognosis—particularly in the fibrosarcomatous variant, where the rate reaches 14.4%^[4]. Imatinib is approved for metastatic DFSP^[5, 6], but its efficacy is limited and acquired resistance frequently develops^[7]. No established second-line therapies exist^[8], and the molecular mechanisms driving metastasis remain largely unexplored, highlighting the urgent need for novel therapeutic targets and biomarkers.

The pathognomonic COL1A1-PDGFB fusion drives PDGFRB activation in over 90% of DFSP cases, yet this alteration does not fully explain metastatic progression^[1]. Recent evidence implicates aberrant cell adhesion, extracellular matrix remodeling, and cytoskeletal reorganization as potential drivers of tumor invasion and metastasis in soft tissue sarcomas^[9], processes that align closely with the infiltrative growth and eventual distant spread characteristic of DFSP. However, no proteomic study has systematically delineated the protein expression dynamics during DFSP progression from primary tumor to metastasis.

To address this gap, we performed integrative proteomic profiling of paired peritumoral, primary, and metastatic tissues. Through differential expression analysis, weighted gene co-expression network analysis (WGCNA), and expression trend analysis, we identified LMO7 as a progressively upregulated candidate along the peritumoral–primary–metastasis continuum. Emerging evidence supports a pro-

metastatic role for LMO7 across multiple cancer types, including pancreatic cancer^[10], Ewing sarcoma^[11], and colorectal cancer^[12], in which it promotes cell migration, invasion, and cytoskeletal remodeling. However, its role in DFSP has never been explored.

In this study, we validated LMO7 upregulation in patient tissues and demonstrated that LMO7 promotes DFSP cell proliferation, migration, and invasion in patient-derived primary cells. Collectively, our findings establish the first proteomic landscape of DFSP metastasis and identify LMO7 as a potential therapeutic target for metastatic disease.

Results

Proteomic Landscape of DFSP Metastatic Progression

The study workflow is illustrated in **Figure 1A**. A total of 18 clinical specimens were collected from six patients diagnosed with DFSP, including 6 adjacent non-tumor tissues (Normal, N), 6 primary tumors (Primary, P), and 6 lung metastatic tumors (Metastasis, M). To systematically elucidate the molecular alterations underlying the pulmonary metastasis of DFSP, we employed four-dimensional data-independent acquisition mass spectrometry (4D-DIA) to profile global protein abundance across the 18 samples. Histopathological evaluation via hematoxylin and eosin (H&E) staining alongside clinical imaging confirmed the diagnostic features of primary dermal tumor infiltration and matched pulmonary metastatic foci (**Figure 1B**).

Principal component analysis (PCA) based on protein abundance displayed a distinct separation among the Normal, Primary, and Metastasis groups along PC1 (41.2% variance) and PC2 (9.8% variance), indicating substantial proteomic divergence between non-tumor tissues and neoplastic lesions, as well as progressive proteomic shifts during metastatic evolution (**Figure 1C**). Overall, high-throughput proteomic profiling identified 7,044 proteins in normal tissues, 8,202 proteins in primary tumors, and 8,161 proteins in lung metastatic tissues, maintaining consistent protein identification counts across individual matched samples. Furthermore, the dynamic range and distribution of quantified protein intensities were comparable across groups, demonstrating robust coverage and high data reproducibility (**Figure 1D-E**).

Dysregulated Proteomic Features and Functional Pathways in DFSP Progression

To delineate the key proteomic alterations driving DFSP oncogenesis and systemic dissemination, we identified differentially expressed proteins (DEPs) across pairwise comparisons (**Figure 2A**). Primary vs. Normal (PvsN) yielded 1,727 up-regulated and 1,051 down-regulated DEPs, whereas Metastasis vs. Normal (MvsN) revealed 1,322 up-regulated and 796 down-regulated DEPs. Venn analysis identified a core consensus signature consisting of 1,161 shared up-regulated (61.5% overlap) and 724 shared down-regulated proteins (64.5% overlap) (**Figure 2B**). Reactome enrichment analysis demonstrated that the consensus up-regulated proteins were predominantly enriched in RNA processing cascades (e.g., mRNA Splicing - Major Pathway, Processing of Capped Intron-Containing Pre-mRNA), while down-

regulated proteins were clustered in immune and extracellular matrix processes (e.g., Complement cascade, Extracellular matrix organization) (**Figure 2C**). Hierarchical clustering and heatmap analysis further confirmed the consistent elevation of mRNA splicing factors (e.g., *SF3A2*, *U2AF2*, *POLR2F*) and widespread suppression of complement components (e.g., *C1R*, *C1S*, *CFH*, *CFB*) across both primary and metastatic lesions (**Figure 2D**).

To verify whether our cohort retains the classical molecular etiology of DFSP, we first evaluated PDGFB expression. Boxplot analysis confirmed a marked upregulation of PDGFB in both primary and metastatic tumors ($P < 0.001$), validating the canonical *PDGFB*-driven oncogenic background of our clinical cohort (**Figure 2E**). Correspondingly, single-sample gene set enrichment analysis (ssGSEA) revealed a progressive increase in mRNA splicing scores ($P < 0.01$) accompanied by a prominent drop in complement cascade scores ($P < 0.01$) during tumor progression (**Figure 2E**). Correlation analysis further revealed that PDGFB protein intensity positively correlated with the mRNA splicing score ($R = 0.64$, $P = 0.0041$), but inversely correlated with the complement cascade score ($R = -0.63$, $P = 0.0048$) (**Figure 2F**).

Finally, we cross-validated these functional patterns using an independent proteomic dataset PXD074336 (5 paired DFSP tumor and adjacent non-tumor tissues). GSEA confirmed robust positive enrichment for mRNA Splicing (NES = 2.75, adjusted $P < 0.001$) and marked suppression for the Complement Cascade (NES = -2.57, adjusted $P < 0.001$) in DFSP tumors (**Figure 2G**). Collectively, these findings indicate that canonical *PDGFB* activation intimately coordinates with dysregulated mRNA splicing and complement cascade inhibition to foster DFSP progression.

Extracellular Matrix Remodeling and Pro-Metastasis Proteomic Signatures in DFSP Pulmonary Metastasis

To dissect the molecular underpinnings of DFSP dissemination, we first contrasted the proteomic landscapes of lung metastases against their matched primary tumors (**Figure 3A**). This comparison revealed a striking divergence: proteins gaining abundance in metastases were heavily enriched in pathways governing matrix remodeling, cell-matrix adhesion, and pro-motility signals, including extracellular matrix organization, laminin interactions, and MET-driven signaling cascades. In parallel, proteins depleted in metastases were predominantly linked to DNA replication and keratinocyte differentiation (**Figure 3B**), underscoring a phenotypic switch from proliferative to invasive programs during metastatic transition.

If microenvironmental remodeling is a continuous driver of metastasis, we reasoned that key effector proteins should exhibit gradually escalating expression along the normal-primary-metastasis axis. To test this, we profiled the dynamics of ECM proteoglycan- and integrin-associated factors across disease stages. Indeed, *AGRN*, *ITGAL*, and *TGFB2* each showed a consistent, stepwise elevation from normal tissues to primary tumors, peaking prominently in lung metastases (**Figure 3C**). This progressive pattern implicates *TGFB2*-driven microenvironmental conditioning and integrin-mediated matrix remodeling as cooperative forces that actively shape a permissive niche for pulmonary colonization.

Having established the microenvironmental landscape, we next turned to identify intracellular drivers that may co-evolve with this remodeling process. By projecting PvsN against MvsP log₂ fold-changes onto a nine-quadrant plot (**Figure 3D**), we captured a discrete set of persistently upregulated candidates that traversed both tumor initiation and metastatic progression. Hierarchical clustering further refined this signature, pinpointing a shortlist of genes—PPP1R14A, GAL3ST4, TGFB2, and LM07—that exhibited robust, stepwise expression surges along the disease continuum (**Figure 3E**). Collectively, these data suggest that distant colonization of DFSP arises from a coordinated interplay between microenvironmental conditioning and a dedicated ensemble of intracellular drivers, yielding a prioritized pool of candidate targets for downstream mechanistic and functional interrogation.

Multi-Omics and Co-Expression Network Analysis Prioritize LM07 as a Core Driver of DFSP Progression

To delineate the dynamic expression trajectories governing DFSP evolution, protein patterns across the normal–primary–metastasis continuum were classified using the R package ClusterGVis (version 0.1.4). Among the six identified temporal trends, Cluster 4 (1,168 proteins) exhibited a progressive upregulation along disease progression (**Figure 4A**). Reactome pathway enrichment indicated that Cluster 4 was predominantly enriched in motility-associated cascades, including RHO GTPase, CDC42 GTPase, RHOA GTPase, RAC1 GTPase, and VEGF signaling, underscoring the activation of cell migration networks during metastatic dissemination (**Figure 4A**). Conversely, Cluster 1 (826 proteins) displayed a continuous downward trend, representing a subset negatively linked to malignant progression (**Figure 4A**).

Next, we performed weighted gene co-expression network analysis (WGCNA) to identify consensus protein modules associated with metastatic traits. Setting a soft-thresholding power of $\beta=12$ achieved scale-free topology ($R^2 = 0.8$; **Figure S1A-B**), resolving a total of 19 co-expression modules (**Figure 4B**). Module-trait correlation analysis revealed that the MEpurple module (223 proteins) positively correlated with metastasis ($r = 0.64$, $P = 0.004$; **Figure 4B**), whereas the MEpink module (228 proteins) negatively correlated with tumor progression (**Figure 4B**). Reactome analysis of MEpurple highlighted "Cell junction organization," "Integrin cell surface interactions," and "Extracellular matrix organization" as top enriched pathways (**Figure S1C**), reinforcing its key role in matrix interactions and invasive growth.

To strictly isolate high-confidence drivers, we intersected the pro-metastatic candidate sets derived from Cluster 4, the WGCNA MEpurple module, PvsN upregulated DEPs, and MvsP upregulated DEPs. This multi-layered filtering yielded three top-tier candidates: LM07, PPP1R14A, and GAL3ST4 (**Figure 4C**). Parallel intersection of downregulated clusters and modules identified no progression-suppressive candidates meeting the significance threshold (**Figure 4D**).

Finally, to evaluate the clinical and translational relevance of these three candidates, we interrogated external validation cohorts. In a public bulk RNA-seq dataset^[13], LM07 exhibited significant transcriptomic elevation in DFSP tumors relative to normal controls ($P < 0.01$), whereas PPP1R14A and GAL3ST4 showed no statistical difference (**Figure 4E**). Furthermore, cross-validation in the independent

proteomic dataset PXD074336 confirmed a marked over-expression of LMO7 protein in DFSP tumor tissues compared with paired adjacent controls ($P < 0.0001$) (**Figure 4F**). Collectively, these multi-omics orthogonal validations strongly prioritized LIM domain only 7 (LMO7) as the primary candidate driver for subsequent functional experimentation.

Functional Validation of LMO7 in Promoting DFSP Proliferation, Migration, and Invasion In Vitro

To orthogonally validate the expression pattern of LMO7, we perform immunohistochemistry (IHC) and RT-qPCR on clinical specimens. Both transcript and protein levels of LMO7 displayed a continuous, progressive step-up along the normal–primary–metastasis continuum, peaking in pulmonary metastatic tissues ($P < 0.001$; **Figure 5A**). To explore the functional necessity of LMO7 in driving malignant phenotypes, primary DFSP cells were transfected with LMO7-targeted siRNA (siLMO7). Efficient depletion of LMO7 protein levels was confirmed by Western blot and subsequent densitometric analysis ($P < 0.05$; **Figure 5B**).

Functional assays revealed that LMO7 silencing severely blunted neoplastic cell behaviors. CCK-8 proliferation assays demonstrated that LMO7 knock-down significantly inhibited cell growth at 24 and 48 hours ($P < 0.01$), with a more pronounced antiproliferative effect observed at 72 hours ($P < 0.001$; **Figure 5C**). Wound healing assays indicated a marked delay in scratch closure capacity in siLMO7-treated cells at 24 hours relative to negative controls ($P < 0.001$; **Figure 5D**). Furthermore, Transwell migration and invasion assays revealed that LMO7 depletion drastically diminished both migratory ($P < 0.0001$) and invasive cell counts ($P < 0.0001$; **Figure 5E**). Collectively, these functional evaluations establish LMO7 as a pivotal oncogenic driver that directly fuels DFSP proliferation, motility, and metastatic competence.

Discussion

Dermatofibrosarcoma protuberans (DFSP) is known for its propensity for local recurrence, yet distant pulmonary metastasis, though rare, is highly aggressive and clinically challenging. The molecular events governing this transition from localized growth to distant colonization remain poorly defined. Here, we performed the first 4D-DIA proteomic profiling of matched normal, primary, and metastatic tissues, generating a dynamic proteomic landscape of DFSP progression. Integrative bioinformatics—combining trajectory clustering, co-expression network analysis (WGCNA), and multi-omics cross-validation—nominated LIM domain only 7 (LMO7) as a novel driver of distant dissemination, whose upregulation coincides with extensive extracellular matrix (ECM) remodeling.

Our findings resonate with the classic "Seed and Soil" hypothesis, revealing a dual-faceted mechanism. On one hand, metastasis-upregulated proteins were prominently enriched in microenvironmental pathways, marked by progressive elevation of AGRN, ITGAL, and TGF- β 2. While AGRN and ITGAL are implicated in basement membrane disruption and cell-matrix anchorage, TGF- β 2 functions as a master pro-fibrotic cytokine, orchestrating ECM organization and crosstalk with MET-PTK2 motility cascades. Such microenvironmental conditioning likely constructs a permissive "soil" for circulating tumor cells. On

the other hand, our multi-tiered screening pipeline pinpointed LMO7 as an intrinsic intracellular “seed.” Functional depletion of LMO7 in primary DFSP cells significantly attenuated proliferation, migration, and invasion, directly establishing its functional necessity in fueling metastatic capacity.

Notably, LMO7 expression rose progressively along the metastatic cascade, suggesting a driver mechanism distinct from the canonical COL1A1-PDGFB fusion. Although this fusion drives early tumorigenesis through autocrine PDGFRB activation, its uniform presence in both non-metastatic and metastatic lesions implies that the fusion alone is insufficient to trigger distant spread. Instead, LMO7 upregulation may provide a secondary, PDGFRB-independent “hit.” Structurally, LMO7 is a scaffolding protein with Calponin-homology, PDZ, and LIM domains, known to coordinate actin cytoskeleton dynamics via Rho-GTPase/MRTF signaling^[10] or to modulate epithelial-to-mesenchymal transition (EMT) through TGF- β crosstalk^[12]. The prominent enrichment of RHO GTPase, RAC1, and CDC42 pathways within our pro-metastatic clusters aligns with a cytoskeletal-remodeling model, wherein LMO7 enhances cell motility to facilitate vascular intravasation and tissue colonization.

From a clinical perspective, fibrosarcomatous (FS) transformation is the strongest predictor of DFSP metastasis^[14], yet its molecular underpinnings remain obscure. Whether LMO7 overexpression drives this sarcomatous shift, or represents an independent risk factor, warrants investigation in stratified DFSP-FS cohorts.

Methodologically, our integrated pipeline—overlaying temporal trajectory clustering, WGCNA, and multi-dataset validation—offers a significant advantage over single-timepoint differential expression approaches, effectively filtering out transcriptomic noise and transient alterations. Several limitations should be acknowledged. The discovery cohort was inherently small due to disease rarity, necessitating validation in larger multicenter series. Functional studies relied on patient-derived primary cells with limited passage capacity; future in vivo models would strengthen causal inference. The biochemical interactome and downstream targets of LMO7 in DFSP remain to be fully mapped. Finally, other prioritized candidates such as PPP1R14A and GAL3ST4, while identified in our screen, were not functionally characterized and merit future investigation.

In conclusion, this study charts the first proteomic landscape of DFSP metastatic progression and identifies LMO7 as a pivotal driver of pulmonary dissemination, operating in concert with TGF- β 2-mediated microenvironmental remodeling. These findings position LMO7 as a promising prognostic biomarker and therapeutic target for high-risk or metastatic DFSP.

Materials and methods

Patient enrollment and sample collection

This study enrolled DFSP patients who underwent Mohs micrographic surgery at The Third Affiliated Hospital of Sun Yat-sen University between January 2021 and September 2025. Six patients with paired adjacent normal tissues, primary tumors, and lung metastasis were included (**Table S1**). For each

specimen, paired formalin-fixed, paraffin-embedded (FFPE) and frozen tissues were collected. FFPE samples were used for proteomic analysis and immunohistochemistry (IHC), while frozen samples were used for quantitative real-time PCR (qPCR). All specimens were histologically confirmed by one general pathologist and one dermatopathologist. The study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University (approval number: II2026-171-01), and written informed consent was obtained from all participants. All methods were performed in accordance with the relevant guidelines and regulations of the committee and with the ethical standards of the Declaration of Helsinki.

Proteomic Sequencing and Data Processing

FFPE sections were dewaxed with heptane, rehydrated with graded ethanol (100%, 90%, and 75%), and de-crosslinked with 100 mM Tris-base (pH 10). Samples were lysed in buffer containing 6 M urea, 2 M thiourea, 10 mM Tris(2-carboxyethyl)phosphine, and 40 mM iodoacetamide, followed by digestion with trypsin and LysC. Resulting peptides were desalted using C18 cartridges (Thermo, USA), enriched, separated by high-performance liquid chromatography, and analyzed by high-resolution mass spectrometry. Protein identification was performed using DIA-NN software (v1.9.2) against the UniProt human proteome database, with peptide-spectrum match (PSM) and protein false discovery rates (FDR) both set to < 0.01. Proteins detected in <20% of samples were removed, and missing values were imputed with 50% of the minimum intensity per protein. Intensities were normalized by sample median.

Bioinformatics analysis

Differentially expressed proteins(DEPs) between groups were identified using the R limma package (version 3.64.3), with statistical significance determined by $|\log_2FC| > 1$ and adjusted $P < 0.05$.

WGCNA was performed using the WGCNA package in R (v4.5.1) to identify metastasis-associated modules. Pearson correlation matrix was constructed based on peptide abundance, and modules were identified by dynamic tree cutting. Spearman correlation was calculated between module eigengenes and metastatic trait. Expression trend analysis and clustering of protein expression profiles across adjacent normal, primary tumor, and lung metastatic tumor samples were performed using the R package ClusterGVis (v0.1.4). Reactome enrichment for WGCNA modules and trend clusters was performed using clusterProfiler (v4.16.0; $P_{adj} < 0.05$).

RT-qPCR

Total RNA was extracted from DFSP tissue specimens and cells using the RNAsimple Total RNA Kit (DP419, Tiangen). First-strand cDNA was synthesized from 500 ng of total RNA using PrimeScript™ RT Master Mix (RR036A, Takara). Quantitative real-time PCR (qPCR) was performed on a LightCycler® 480 II system (Roche) using TB Green® Premix Ex Taq™ II (RR820A, Takara). Relative gene expression was calculated using the $2^{-\Delta\Delta Ct}$ method, with all reactions performed in triplicate. Primer sequences are provided in **Table S2**.

IHC Staining

FFPE sections were deparaffinized, rehydrated, and subjected to heat-induced antigen retrieval in sodium citrate buffer. After blocking, sections were incubated with anti-LMO7 antibody (29392-1-AP, Proteintech) overnight at 4°C, followed by HRP-conjugated secondary antibody and DAB development. Staining intensity was quantified using ImageJ IHC Toolbox (≥ 5 fields at $\times 200$).

DFSP Cell Isolation, Cultivation, and Transfection

DFSP cells were isolated from surgical specimens. Tissue was minced and digested with 0.2% collagenase type I at 37°C for 4 hours. Cells were cultured in DMEM with 10% FBS at 37°C in 5% CO₂, and passages 2–5 were used for experiments. siRNA targeting LMO7 (sense: 5'-CCUGGUGACAGGAAUAAUUTT-3'; antisense: 5'-AUUUUAUCCUGUCACCAGGTT-3') was transfected using siRNA mate plus reagent (GenePharma). Cells were harvested at 48 hours post-transfection for subsequent analyses.

Functional assays

Cell proliferation was assessed using the CCK-8 assay. Cells were seeded in 96-well plates at 1×10^4 cells per well, and absorbance was measured at 450 nm after 24, 48, and 72 hours of incubation. For wound healing assays, cells were cultured to 80% confluence in 6-well plates, and a scratch was created using a sterile pipette tip. Wound closure was monitored at 0 and 24 hours, and migration rate was calculated as $[(A_0 - A_{24})/A_0] \times 100\%$, where A_0 and A_{24} represent the wound areas at 0 and 24 hours, respectively. Transwell migration and invasion assays were performed using 24-well chambers (Corning). For invasion assays, inserts were pre-coated with Matrigel; migration assays were performed without coating. Cells (5×10^4) were seeded in the upper chamber in serum-free medium, and the lower chamber contained medium with 20% FBS as a chemoattractant. After 24 hours, non-migrated or non-invaded cells were removed, and cells on the lower surface were stained with crystal violet and counted in three random fields per well.

Statistical Analysis

Data are presented as mean $\pm$ SD. Statistical significance was analyzed by t-test. $P < 0.05$ was considered statistically significant.

Declarations

Ethics statement

The study protocol was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University (approval number: II2026-171-01). The patients in this manuscript have given written informed consent to publication of their case details.

Data accessibility

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors state no conflict of interest.

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Author contributions

YH and TL contributed to conceptualization, investigation, methodology, formal analysis, and writing – original draft. YJ contributed to methodology, resources, and writing – review & editing. ZL, XT, JC, and YX contributed to resources and data curation. LL contributed to conceptualization, supervision, and writing – review & editing. MW and YX contributed to conceptualization, supervision, funding acquisition, and writing – review & editing. All authors approved the final version and agree to be accountable for all aspects of the work.

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Figures

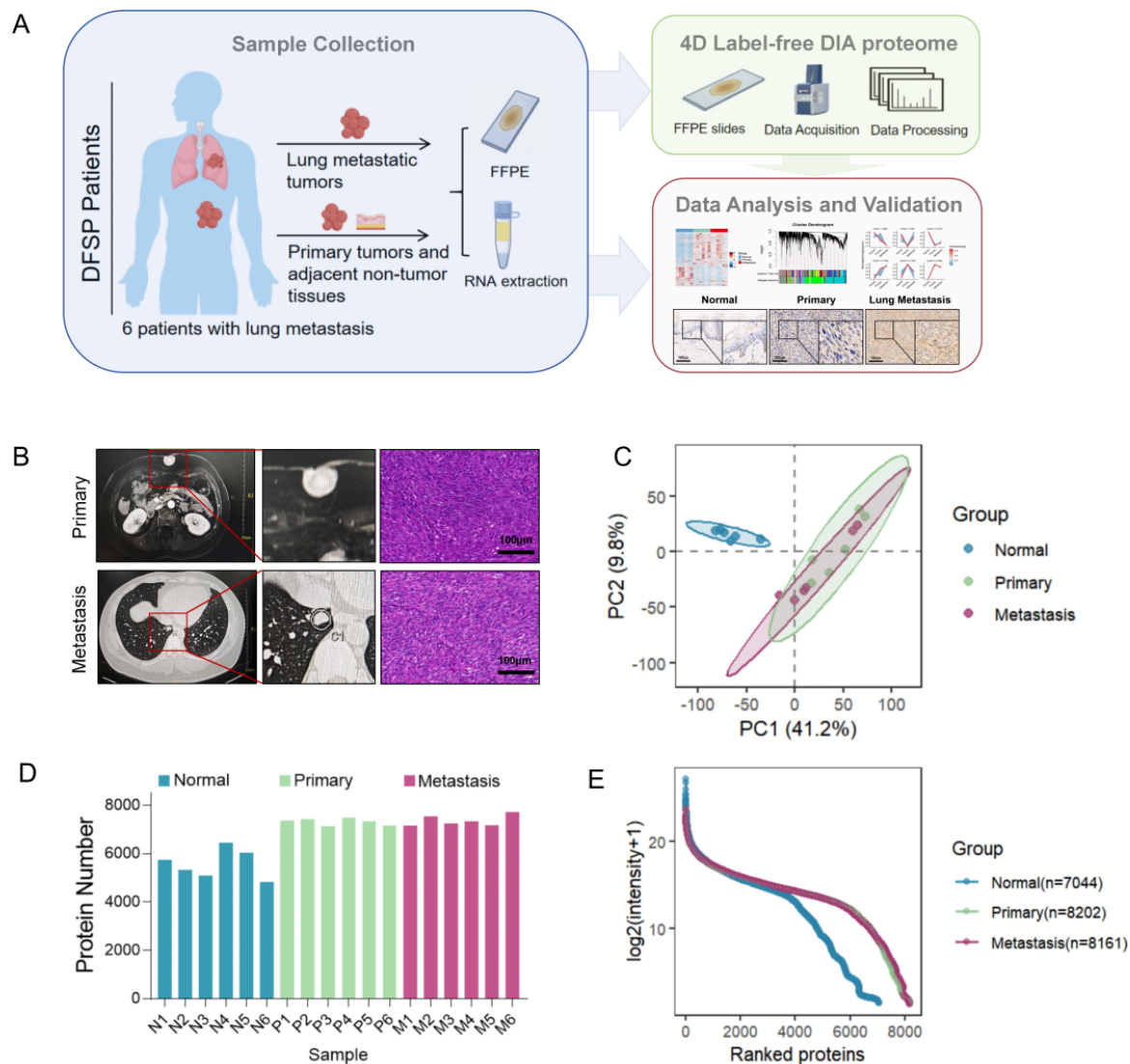


Figure 1. Proteome profiling of patients with DFSP.

(A). Schematic overview of the study design and workflow.

(B). Validation by HE and Imaging examination to confirm the type of DFSP samples.

(C). Principal component analysis (PCA) of a total of 18 DFSP samples, including 6 adjacent non-tumor tissues (Normal,N), 6 primary tumors (Primary,P), 6 lung metastatic tumors (Metastasis,M).

(D). The bar chart showing numbers of protein identified in DFSP samples.

(E). Rank of quantified proteins' distributions in different DFSP groups.

Figure 1

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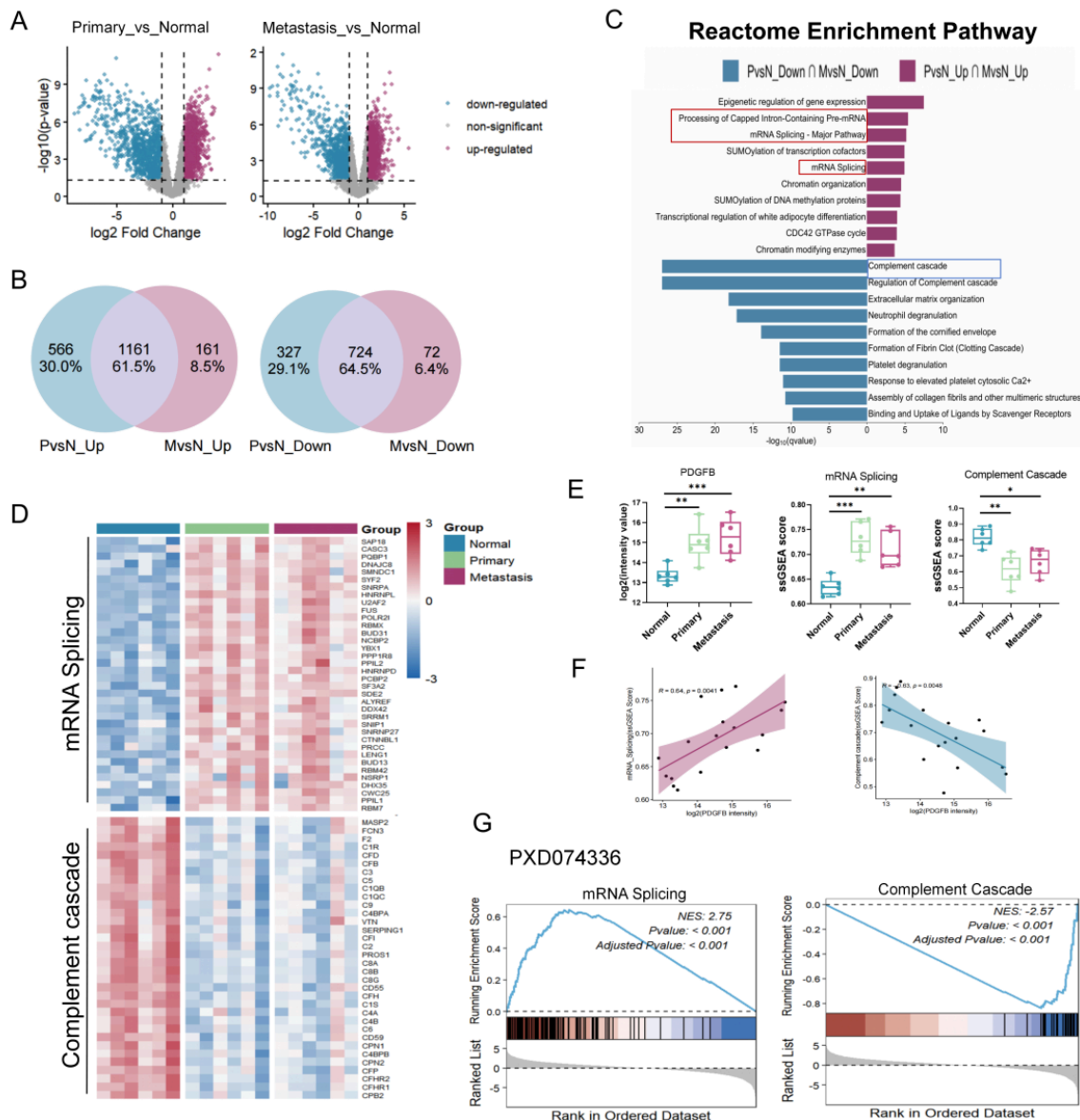


Figure 2. Proteomic Features and Functional Pathways in Primary and Lung Metastatic DFSP Tumors.

(A). Volcano plots displaying differentially expressed proteins (DEPs) for PvsN and MvsN, respectively.

(B). Venn diagrams showing overlapping DEPs between PvsN and MvsN.

(C). Bar chart showing the Reactome pathways for overlapping DEPs between PvsN and MvsN.

(D). Heatmap plot depicting dysregulated proteins of enriched pathways shown in panel C.

(E). Boxplots showing log2-transformed PDGFB intensity, along with ssGSEA scores for mRNA splicing and the complement cascade in DFSP samples (n=18).

(F). Pearson correlation analysis between log2-transformed PDGFB intensity and ssGSEA scores for mRNA splicing (left) and the complement cascade (right) in DFSP samples (n=18).

(G). GSEA validation of mRNA splicing and complement cascade pathways in an independent external proteomic dataset (PXD074336)

Figure 2

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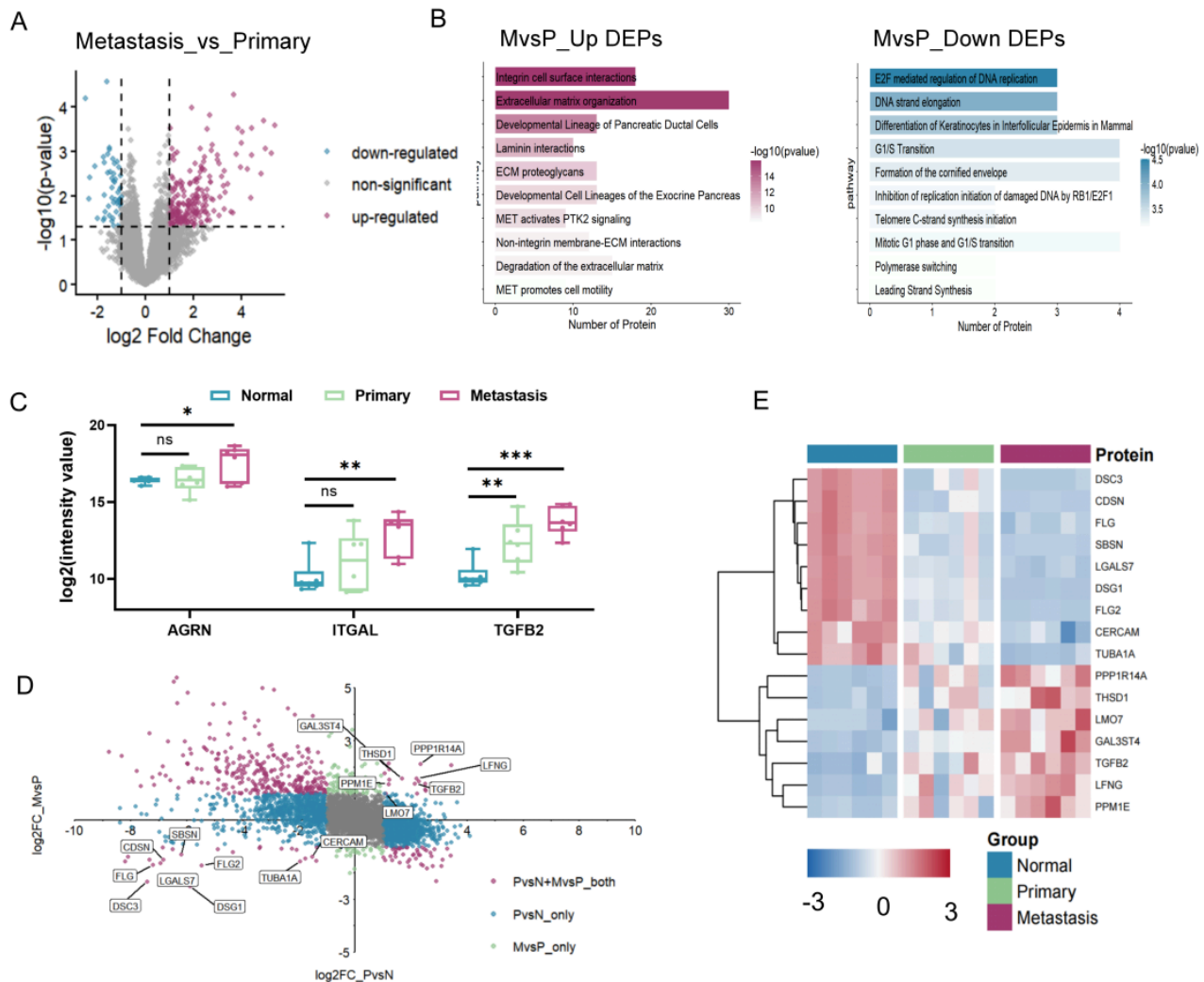


Figure 3. Proteomics Features in Primary Tumors Compared with Lung metastatic Tumors.
 (A) Volcano plot displaying differentially expressed proteins (DEPs) between lung metastatic lesions and primary DFSP tumors (MvsP).
 (B) Reactome pathway enrichment analysis showing top biological cascades for upregulated (left) and downregulated (right) DEPs in MvsP.
 (C). Boxplots displaying the progressive upregulation of core ECM and cell-adhesion regulators (AGRN, ITGAL, and TGFB2) across Normal (n=6), Primary (n=6), and Metastasis (n=6) groups.
 (D). Nine-quadrant plot displaying protein expression changes between PvsN(x-axis) and MvsP(y-axis).
 (E). Heatmap depicting the hierarchical clustering and expression profiles of candidate metastasis-associated proteins across DFSP progression stages.

Figure 3

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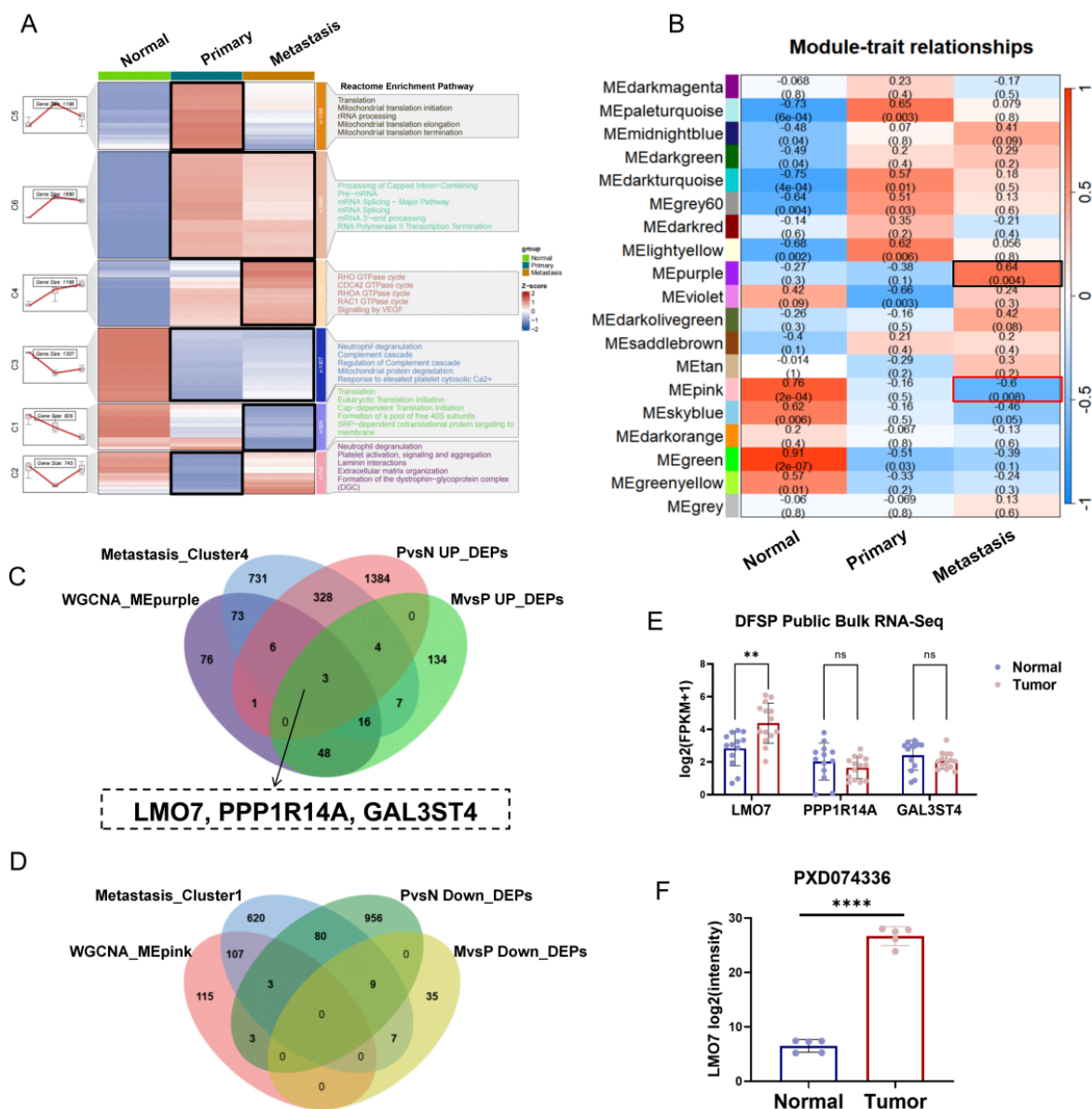


Figure 4. Novel biomarkers associated with DFSP progression.
 (A). Different expression patterns of proteins during DFSP progression identified using the ClusterGVis package.
 (B). Heatmap of the correlation network between module eigengenes and DFSP traits, as identified by WGCNA.
 (C). Venn diagram showing the candidates from the intersection of four protein sets positively associated with DFSP metastasis.
 (D). Venn diagram showing the candidates from the intersection of four protein sets negatively associated with DFSP metastasis.
 (E). The expression levels of LMO7, PPP1R14A and GAL3ST4 in a public DFSP bulk RNA-Seq dataset[13].
 (F). The expression levels of LMO7 in PXD074336.

Figure 4

See image above for figure legend.

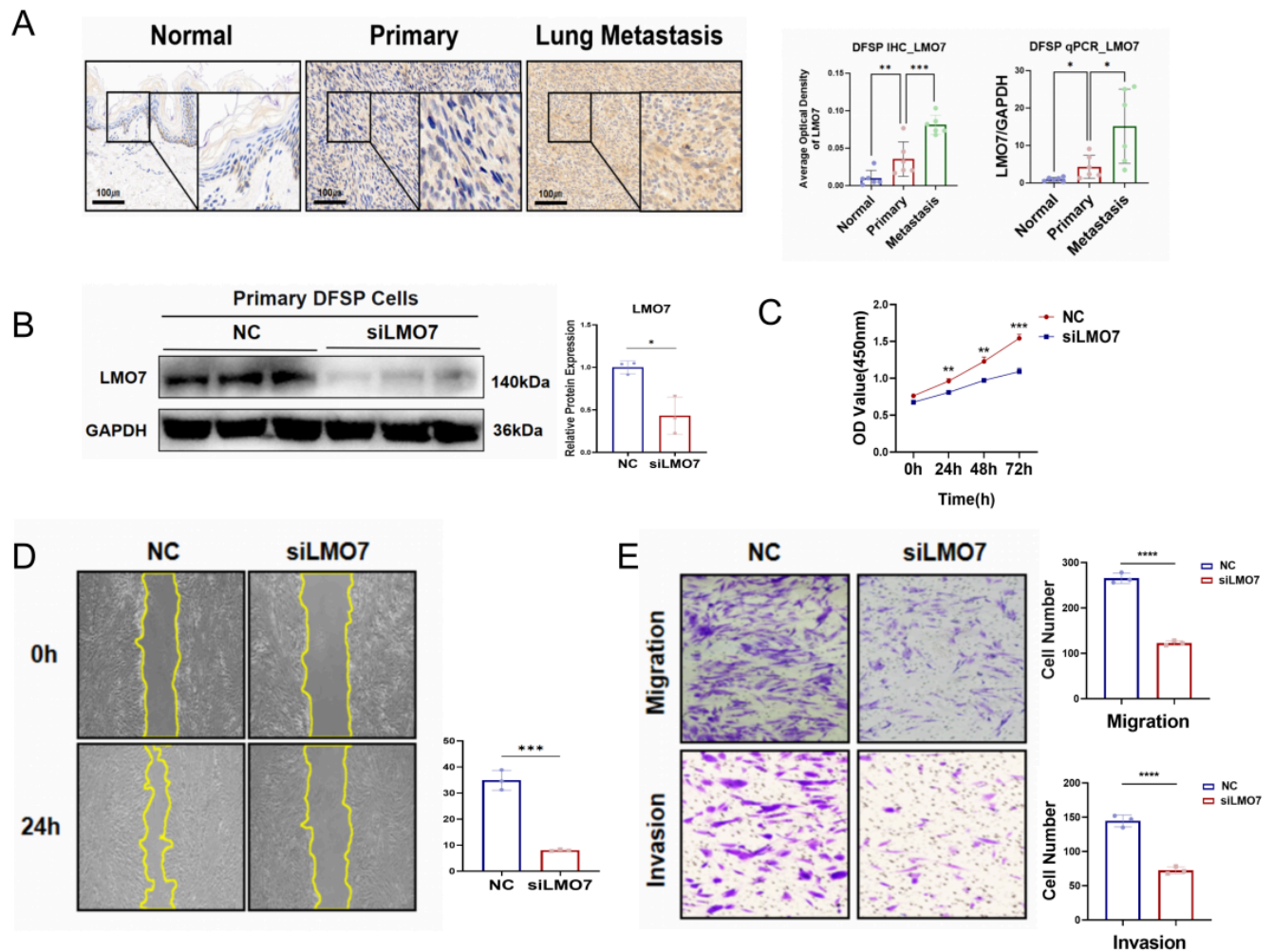


Figure 5. Identification and validation of LMO7 as a potential driver of lung metastasis in DFSP.

(A). Protein expression levels of LMO7 among adjacent non-tumor tissues, primary and lung metastatic DFSP tissues in proteomic analysis.

(B). Western blot analysis and grayscale quantification of LMO7 expression.

(C). CCK-8 assay demonstrating decreased proliferation in siLMO7-treated DFSP cells.

(D-E). Wound healing, Transwell migration, and invasion assays showing reduced capabilities in siLMO7-treated DFSP cells. (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$)

Figure 5

See image above for figure legend.

Supplementary Files

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