Establishment and characterization of NCC-DDLPS5-C1: a novel patient-derived cell line of dedifferentiated liposarcoma

Yooksil Sin1 · Yuki Yoshimatsu1 · Rei Noguchi1 · Ryuto Tsuchiya1 · Takuya Ono1 · Taro Akiyama1 · Shintaro Iwata2 · Jun Sugaya2 · Akihiko Yoshida3 · Akira Kawai2 · Tadashi Kondo1

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Abstract
Dedifferentiated liposarcoma (DDLPS) is a highly aggressive subtype of liposarcoma that is morphologically defined as a transition from a well-differentiated lipomatous component to a non-lipogenic one. Curative therapy for DDLPS is complete resection, and the benefits of current systemic chemotherapy remain marginal. Although DDLPS is molecularly characterized by co-amplification of \( MDM2 \) and \( CDK4 \) (12q14-15) and detailed genomic analyses have been conducted by multiple research groups, the effects of molecular targeted drugs are marginal, and novel therapeutic modalities are required. Although patient-derived cell lines are pivotal for cancer research, no DDLPS cell lines are currently available from public cell repositories. Accordingly, in this study, we established a novel DDLPS cell line, NCC-DDLPS5-C1, using surgically resected tumor tissues from a patient with DDLPS. NCC-DDLPS5-C1 cells exhibited typical gene amplification, overexpression of \( MDM2 \) and \( CDK4 \), and other DNA copy number alterations. The NCC-DDLPS5-C1 cells were capable of rapid cell proliferation, aggressive invasion, and spheroid formation, but not tumor formation in mice. We reported the utility of NCC-DDLPS5-C1 cells for a drug–response assay to detect anticancer drugs that significantly attenuated cell proliferation. Thus, we concluded that the NCC-DDLPS5-C1 cell line could be a useful resource for the study of DDLPS. Considering the diversity of disease in terms of clinical outcomes, continuous efforts are required to develop more patient-derived cancer models with different clinical and pathological backgrounds.

Keywords Dedifferentiated liposarcoma · Sarcoma · Patient-derived cancer model · Drug screening · Patient-derived cell line

Introduction
Dedifferentiated liposarcoma (DDLPS) is a highly aggressive subtype of adipocytic sarcoma. Histologically, DDLPS is characterized by transient features from recurrent atypical lipomatous tumors or well-differentiated liposarcomas to highly cellular regions of high-grade pleomorphic spindle cell components [1]. The incidence of DDLPS is less than 0.1 per million individuals each year [2], and the disease occurs in approximately 10% of cases of intermediate (locally aggressive) well-differentiated liposarcoma [3]. Thus, DDLPS is considered a rare cancer. DDLPS often occurs in patients who are 50–60 years old, with the retroperitoneum and deep extremities being the typical site of origin [1]. DDLPS is particularly refractory to conventional chemotherapy, similar to well-differentiated liposarcomas [4, 5]. Surgical excision is the first-line treatment for DDLPS, and even after complete resection for curative intent, local recurrence is observed in over 40% of cases with DDLPS, whereas distant metastasis is detected in 15–20% of cases. Accordingly, the prognosis of patients with DDLPS remains poor; the 5-year mortality rate is approximately 30%, and the mortality rate is higher after 10–20 years [1, 4, 6, 7].

DDLPS typically harbors complex genomic aberrations without specific chromosomal translocations. Common
genetic aberrations in DDLPS are often observed [8], including recurrent amplification of MDM2 and CDK4 (12q14-15) [9, 10], and several gene amplifications in 1p32 [9], 1q21-23 [11], 5p15 [10], and 6q21-24 [9, 10], as well as loss of 11q23-24 [12], are frequently detected. However, anticancer agents targeting MDM2 and CDK4 have not been shown to improve clinical outcomes [13, 14]. Thus, although novel strategies for systematic therapy are urgently required, genomic approaches have not yielded effective targets for the treatment of DDLPS.

Patient-derived cell lines are pivotal bioresource for translational research and for novel therapies, because they allow the evaluation of novel anticancer drugs. Recently, a considerable amount of genomic and pharmacological data has been obtained and integrated into large-scale cell panels [15–21]. Analysis of these data could help to identify effective anticancer agents and their predictive biomarkers [22, 23]. However, very few sarcoma-derived cell lines were included in these studies. For example, only 28 soft tissue sarcoma-derived cell lines were used in large-scale drug screening studies, accounting for only 2.2% of all 1300 cell lines examined [24]. According to a previous review of cell lines recorded in the cell line database, Cellosaurus [25], multiple cell lines have been reported only for a few types of sarcomas, and no DDLPS-derived cell lines are available from public cell repositories [26]. Thus, this paucity of adequate cell lines has hindered research on sarcomas.

To address these issues, we established sarcoma cell lines using surgically resected tumor tissues [27, 28]. Previously, we reported four DDLPS cell lines [29–32]. However, because of the diversity of disease in terms of clinical outcomes, more cell lines from different patients with DDLPS are needed. Accordingly, in this study, we report the establishment of a novel DDLPS cell line, NCC-DDLPS5-C1, using a surgically resected specimen from a patient with DDLPS. We characterized NCC-DDLPS5-C1 cells and demonstrated their utility for drug screening.

Materials and methods

Patient history

The patient was a 77-year-old man with DDLPS. He reported a growing mass in the left inguinal region. He was diagnosed with inguinal hernia at a previous hospital; however, the mass was found to be a fatty tissue during surgery, and marginal resection was performed to remove the lipoma. Five months after surgery, a mass recurred in the same region, and further inspection was performed. Magnetic resonance imaging revealed a delineated mass (Fig. 1a, b), and the patient was referred to the National Cancer Center Hospital (Tokyo, Japan) based on suspicion of liposarcoma. Needle biopsy indicated DDLPS, and wide resection, including left testiclectomy, was performed without any preoperative chemotherapy or radiotherapy. Microscopic observations revealed that the tumor showed dense proliferation of mitotically active spindle cells (Fig. 1c). The tumor cells were immunohistochemically positive for MDM2 (Fig. 1d). A well-differentiated liposarcoma component was focally observed in the periphery (Fig. 1e), confirming the diagnosis of dedifferentiated liposarcoma. Part of the resected tumor was used to establish the cell line described in this study. The ethical committee of the National Cancer Center approved the use of clinical materials for this study, and written informed consent was obtained from the donor patient.

Histological analysis

For histopathological observations, we prepared paraffin-embedded tumor tissues and sectioned them into 4-μm-thick sections. The sections were then deparaffinized and stained.
with hematoxylin and eosin (H&E) or subjected to immuno histochemical analysis.

**Immunohistochemistry**

We conducted immunohistochemical analyses are described in our previous reports [29–32] using the 4-μm-thick sections prepared as described above. Before the antibody reaction, the sections were exposed to 3% hydrogen peroxide for 15 min and then subjected to heat-induced epitope retrieval. The sections were incubated with primary antibodies against MDM2 (IF2, 1:100; Zymed Laboratories, San Francisco, CA, USA) and labeled with peroxidase (EnVision system; Dako, Santa Clara, CA, USA).

**Cell culture**

The cell line was established from surgically resected tissue, as previously reported [29–32]. The cells were maintained in Dulbecco’s modified Eagle’s medium/F12 (Gibco, Grand Island, NY, USA) supplemented with 5% heat-inactivated fetal bovine serum (Gibco), 100 μg/mL penicillin and streptomycin (Nacalai Tesque, Kyoto, Japan), respectively; 0.4 μg/mL hydrocortisone (Sigma-Aldrich, St. Louis, MO, USA), 5 ng/mL EGF (Sigma-Aldrich), 10 ng/mL bFGF (Sigma-Aldrich), 5 μg/mL insulin (Sigma-Aldrich), and 10 μM Y-27632 (Selleck Chemicals, Houston, TX, USA; Rock inhibitor) at 37 °C in a humidified atmosphere with 5% CO₂. The cells were maintained for more than 5 months under tissue culture conditions and passaged more than 20 times.

**Authentication and quality control of the established cell line**

Authentication was achieved by examining short tandem repeats (STRs) at 10 loci using the GenePrint 10 system (Promega, Madison, WI, USA) according to our previous studies [29–32]. We confirmed the absence of mycoplasma contamination by examining the DNA present in the cells, as previously reported for DDLPS [29–32].

**Genetic analysis**

To observe DNA copy number alterations, we conducted single nucleotide polymorphism (SNP) array genotyping using the Infinium OmniExpressExome-8 v1.4 BeadChip (Illumina, San Diego, CA, USA) following the manufacturer’s instructions and the procedure described in our previous studies [29–32]. The SNP array data were analyzed using R version 4.0.3 (R Foundation for Statistical Computing, http://www.R-project.org) and DNAcopy package version 1.64.0 (Bioconductor, https://bioconductor.org/). When the chromosome regions had copy numbers greater than 3 or less than 1, they were considered amplifications and losses, respectively. Genes with copy number alterations were annotated using the biomaRt package version 2.46.0 (Bioconductor) and “Cancer Gene Census” in the Catalogue Of Somatic Mutations In Cancer database (GRCh 37 v91), as previously reported [29–32].

**Western blot analysis**

Western blotting was performed as previously reported [29–32]. Antibodies against MDM2 (1:100; Calbiochem, San Diego, CA, USA), CDK4 (1:1000; Santa Cruz Biotechnology, Dallas, TX, USA), and β-actin (1:5000; Abcam, Cambridge, UK) were used for western blotting. NCC-DDLPS3-C1 cell line [29–32] was used as a positive control and normal human foreskin fibroblast (HFF) cell line that kindly provided by Dr. T. Kiyono was used as a negative control. The relative expression level of each protein was normalized to that of β-actin. The molecular weight marker (Precision Plus Protein 2 Color Standard, #1610374) was purchased from Bio-Rad (Hercules, CA).

**Cell proliferation assay**

An xCELLigence RTCA-DP device (Agilent, Santa Clara, CA, USA) was employed to monitor cell proliferation in real time. Electronic microtiter plates were seeded with 5.0 × 10⁵ cells (E-Plate; Agilent), and proliferation was measured for 170 h using the xCELLigence system according to the manufacturer’s instructions. Cell density measurements were performed in quadruplicate with programmed signal detection every 20 min. Data acquisition and analyses were performed using RTCA software (version 1.2, OLS).

**Spheroid formation assay**

Spheroid formation was assessed as described previously for DDLPS [29–32]. Briefly, the cells (1 × 10⁵) were placed on round-bottom ultra-low-attachment 96-well plates (96-well Black Round-Bottom Ultra Low Attachment Microplate; Corning, Inc., Corning, NY, USA) and kept in a humidified atmosphere of 5% CO₂ at 37 °C for 3 days. Paraffin-embedded spheroids were created using iPell (Genostaff, Tokyo, Japan) and 10% formalin neutral buffer solution. Four-micrometer-thick paraffin sections were prepared for H&E staining and immunohistochemical studies.

**Invasion assay using a real-time cell analyzer**

Invasion potential was evaluated using a real-time cell analyzer (xCELLigence; Agilent, Santa Clara, CA, USA) according to the manufacturer’s instructions and the
procedure described in our previous studies [29–32]. Briefly, the established cells and MG63 osteosarcoma cells [24] (JCRB; Ibaraki Osaka, Japan) were seeded into upper chambers coated with Matrigel at a density of $4 \times 10^4$ cells/chamber. The tissue culture medium, which was used to maintain the cells, was poured to the lower chamber. Thereafter, the cells on the Matrigel-coated membrane migrated to the bottom chamber and adhered to the electronic sensors on the underside of the membrane. The attached cells influenced the electrical impedance of the electronic sensors, and the invasion capability of the cells was estimated based on the positive correlation between the impedance and the number of cells. Impedance was monitored and plotted as a function of time after seeding.

Assessment of tumorigenicity in nude mice

Animal experiments were performed in compliance with the guidelines of the Institute for Laboratory Animal Research, National Cancer Center Research Institute. Female BALB/c nude mice from CLEA Japan, Inc. (Tokyo, Japan) were housed under specific pathogen-free conditions, with food and water available ad libitum under a 12-h light/dark cycle. We mixed 100 μL cells with Matrigel (BD Biosciences) and subcutaneously injected the mixture into mice ($1 \times 10^6$ cells). Subsequently, tumor size was measured weekly using digital calipers, and tumor volume was calculated using the following formula: volume = (length × width$^2$)/2. After 2 weeks, the tumors were resected and stained with H&E.

Screening for the antiproliferative effects of anticancer reagents

The inhibitory effects of anticancer agents on cells proliferation were monitored as previously reported [29–32]. A list of anticancer agents is provided in Supplementary Table 1. We performed concentration–response experiments to validate the available hits in the pilot screening and determined the sample concentration required to inhibit cell growth by 50% in comparison with the growth of control cells (IC$_{50}$) from concentration–response curves.

Results

Authentication of the established cell line

A cell line was established from the tumor tissue of a patient with DDLPS; the cell line was designated NCC-DDLPS5-C1. The STRs of the cells and their original tumors were analyzed. We found that the STR allele pattern of NCC-DDLPS5-C1 cells did not match that of any cell line in the public cell banks. Thus, we concluded that NCC-DDLPS5-C1 was a novel DDLPS cell line. We did not detect the DNA sequence unique to mycoplasma in the tissue culture medium of NCC-DDLPS5-C1 cells (data not shown).

Characterization of the cell line

We performed SNP array analysis of multiple allelic duplications in NCC-DDLPS5-C1 cells (Fig. 2, Supplementary Table 2, 3 and 4). Characteristic amplification of the 12q13-15 region, which included $MDM2$ and $CDK4$, was observed in this study. Western blot analysis confirmed the overexpression of $MDM2$ and $CDK4$ in NCC-DDLPS5-C1 cells (Fig. 3a–c). The original images are displayed in Supplementary Fig. 2. These findings demonstrated that the NCC-DDLPS5-C1 cell line maintained the characteristics of DDLPS.

We microscopically observed that NCC-DDLPS5-C1 cells exhibited a pleomorphic spindle appearance under two-dimensional culture conditions (Fig. 4a, b). Moreover, NCC-DDLPS5-C1 cells proliferated constantly, with a population doubling time of 47 h (Fig. 4c). NCC-DDLPS5-C1 cells also formed spheroids on low-attachment microplates with atypical oval cells with a pleomorphic appearance (Fig. 4d). NCC-DDLPS5-C1 cells exhibited more aggressive invasion ability than MG63 cells, which are often used as control cells in sarcoma research (Fig. 4e) [15, 19, 33–36].

Tumorigenesis in nude mice

NCC-DDLPS5-C1 cells inoculated into BALB/c nude mice did not form tumors.
Sensitivity to anticancer drugs

The inhibitory effects of 214 anticancer agents on NCC-DDLPS5-C1 cell proliferation were examined at a fixed concentration of 10 µM (Supplementary Table 5). The anticancer agents showing marked inhibitory effects on proliferation were further examined, and their IC50 values were calculated (Table 2). Growth curves for two anticancer drugs, bortezomib and romidepsin, are shown in Fig. 5.

Discussion

DDLPS is a highly aggressive type of liposarcoma that is refractory to conventional chemotherapy and radiotherapy. Recurrence and metastasis are often observed, even after complete surgical resection with curative intent, and the prognosis remains poor. Therefore, novel therapeutic strategies are required to treat DDLPS. Advancements in modern technology have enabled large-scale genomic studies combined with drug screening using a number of cell lines, and molecular targeted drugs, such as MDM2 inhibitors, have been developed in recent years. To facilitate the development of novel therapies, we established a patient-derived cancer model in DDLPS.

NCC-DDLPS5-C1 cells showed typical amplification of MDM2 and CDK4, and their overexpression was also confirmed at the protein level. Therefore, NCC-DDLPS5-C1 cells could be suitable for investigating molecular mechanism of tumorigenesis. Because NCC-DDLPS5-C1 cells showed rapid proliferation and aggressive invasion ability,
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Anticancer drugs that suppress tumor growth and invasion can be assessed using these cell lines. However, NCC-DDLPS5-C1 cells did not form tumors when they were inoculated into mice. The invasiveness of DDLPS cell lines varied among the cell lines, probably reflecting the clinical and pathological diversity of disease. The integration of all cell line data will lead the comprehensive understanding of phenotypes of DDLPS cell lines. Further studies are needed to elucidate the molecular mechanisms mediating tumor formation by patient-derived cancer cells in animal models.

We found that NCC-DDLPS5-C1 cells were markedly sensitive to two anticancer drugs, bortezomib and romidepsin. We previously established four DDLPS cell lines, i.e., NCC-DDLPS1-C1, NCC-DDLPS2-C1, NCC-DDLPS3-C1, and NCC-DDLPS4-C1, which also exhibited sensitivity to romidepsin [29–32]. The drugs which showed the sensitivity to DDLPS cell lines are summarized in Supplementary Table 6, suggesting that the cell lines exhibited the similar but distinct response to drug treatments. The overall features of drug response should be integrated with the genetic and proteomic alterations, and such studies should be performed using numerous numbers of cell lines from DDLPS with different clinical and pathological backgrounds. The growth-suppressive effects of romidepsin in DDLPS have not been examined in clinical trials; therefore, its clinical utility in the treatment of DDLPS should be established in the future studies.

Considering the diversity of disease in terms of patient outcomes, additional cell lines from patients with different backgrounds should be established. However, it is unclear how many cell lines are required for the development of treatments for DDLPS. Phenotypic variations will be observed when additional cell lines are established and characterized, and we will need to have more cell lines until when the variations do not increase. In general, several dozens of patients should be included in clinical trials, and a similar number of cell lines may be required to obtain conclusive results.
This study has five limitations that should be mentioned. First, we established a cell line from a single patient with DDLPS, and we need to obtain more cell lines so that we can obtain the data with more conclusive. Second, we did not clone the cells, and multiple different types of tumor cells should be included in NCC-DDLPS5-C1. Although NCC-DDLPS5-C1 may maintain the heterogeneity of tumor cells, which is observed in the original tumor tissues, the characters will be changed after the long passaging. Third, the NCC-DDLPS5-C1 cells did not form tumor when they were inoculated in the mice. As DDLPS is a highly aggressive sarcoma, NCC-DDLPS5-C1 may have a potential to survive and proliferate in the mice. We may need to challenge the different types of immune-deficient mice to promote the formation of tumor of NCC-DDLPS5-C1 in the mice. Fourth, it is not clear from which portion of tumor tissue the NCC-DDLPS5-C1 was established. DDLPS is defined as a transition from a well-differentiated lipomatous component to a non-lipogenic one, which included morphologically different types of tumor cells. The identification of precious histological origin of established cell lines is generally difficult, and to integrate the genomic and proteomic data with the characters of cell lines, it is crucial to identify the origin of cell line. Lastly, different in vitro models, such as organoids, should be developed, and complimentary used, so that we will have more reliable patient-derived cancer models.

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**Declarations**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethics approval** The ethical committee of the National Cancer Center approved the use of clinical materials for this study (approval number 2004-050).

**Informed consent** Written informed consent for publication was provided by the patient.

| CAS#           | Name of drugs   | IC50 (µM) |
|----------------|-----------------|-----------|
| 179324-69-7    | Bortezomib (PS-341) | 0.002767  |
| 380843-75-4    | Bosutinib (SKI-606) | 3.398     |
| 288383-20-0    | Cediranib (AZD2171) | 7.071     |
| 1032900-25-6   | Ceritinib (LDK378) | 6.265     |
| 877399-52-5    | Crizotinib (PF-02341066) | 6.876     |
| 302962-49-8    | Dasatinib        | 5.197     |
| 1108743-60-7   | Enretticin (RXDX-101) | 4.267     |
| 441045-17-6    | Erizulin         | 11.01     |
| 84217-64-7     | Foretinib (GSK1363089) | 2.921     |
| 901119-35-5    | Fostamatinib (R788) | 9.455     |
| 26833-87-4     | Homoharringtonine | 0.1312    |
| 57852-57-0     | Iraducbicin HCl  | 0.3966    |
| 50-07-7        | Mitomycin C      | 1.778     |
| 1421373-65-0   | Osimertinib (AZD9291) | 2.672     |
| 65702-64-6     | Pazopanib HCl (GW78034) | 2.271     |
| 943199-70-8    | Ponatinib (AP24534) | 1.163     |
| 1092364-38-9   | Pozitinin (HM781-36B) | 13.08     |
| 939981-39-2    | RG-7112          | 2.418     |
| 128517-07-7    | Romidepsin (FK228, Depsipeptide) | 0.003721  |
| 284461-73-0    | Sorafenib        | 2.887     |
| 341031-54-7    | Sunitinib Malate | 7.26      |
| 104987-11-3    | Tacrolimus (FK506) | 44.25     |
| 905854-02-6    | Tivantinib (ARQ 197) | 2.369     |
| 475108-18-0    | Tivozanib (AV-951) | 1.994     |

**Fig. 5** Growth curves were used to determine the IC50 values of the investigated anticancer agents. A, B Viability was examined following treatment with anticancer agents at different concentrations. The names of the examined anticancer agents are given under the graph. The passage number of NCC-DDLPS5-C1 was 22 in this experiment.
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