Original Article
MicroRNA-613 suppresses proliferation, migration and invasion of osteosarcoma by targeting c-MET

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Abstract: MicroRNA-613 (miR-613) has been reported to play an important role in the pathogenesis of multiple cancers by negatively regulating gene expression at posttranscriptional level. However, the biological role of miR-613 in osteosarcoma (OS) remained unclear. In this study, we aimed to determine the expression and biological roles of miR-613 in OS. We found that miR-613 was significantly downregulated in OS tissues and cell lines, and that decreased miR-613 expression was correlated negatively with advanced TNM stage and lymph node metastasis. Overexpression of miR-613 in OS cells significantly suppressed the proliferation and colony formation by regulating cell arrest at G0/G1 phase, and impaired the migration and invasive abilities of OS cells, followed by suppression of the epithelial mesenchymal transition (EMT). Bioinformatic and luciferase reporter analysis identified cellular-mesenchymal to epithelial transition factor (c-MET, also named as MET) as a direct target of miR-613. Overexpression of miR-613 significantly inhibited the c-MET expression and its downstream PI3k/Akt/mTOR signaling pathway in OS cells. In OS clinical samples, there was a significant inverse correlation between miR-613 and c-MET mRNA expression. Rescue experiments showed that overexpression of c-MET partially prevented miR-613-induced suppression of OS cell proliferation, colony formation, migration and invasion. In conclusion, we provide first evidence for the suppressive activity of miR-613 by repressing c-MET, suggesting that miR-613 might be a potential therapeutic strategy for OS.

Keywords: miR-613, osteosarcoma, c-MET, proliferation, migration, invasion

Introduction

Osteosarcoma (OS) is the most common primary malignant bone tumor in children and adolescents, which accounts for approximately 19% of all malignant bone tumors and approximately 5% of all childhood tumors [1]. Despite the current advances in therapeutic strategies combining chemotherapy, surgery, and sometimes radiotherapy, the prognosis for OS remains poor since this disease has a tendency for local invasion and early metastasis [2, 3]. Therefore, a better understanding of the underlying mechanisms of development and progression of OS is necessary to develop novel alternative therapeutic strategies for improving clinical outcome of OS patients.

The microRNAs (miRNAs) are a family of non-coding, small (18-25 nucleotides in length) RNAs that post-transcriptionally regulate the expression of target genes by binding to specific complimentary recognition sequences in the 3’-untranslated region (UTR) mRNA sequence of target genes [4, 5]. miRNAs has been reported to be involved in many diverse biological and pathological processes, such as cell proliferation, migration, apoptosis [5, 6]. Accumulating evidence indicates that abnormal expressions of miRNAs play critical roles in progression and development of various cancers, and function as oncogenes or tumor suppressors by regulating the expressions of their target genes [6, 7]. Many miRNAs were shown to be associated with OS tumor progression and might serve as an independent prognostic marker or therapy target for osteosarcoma [8, 9]. Thus, investigation of aberrant miRNAs roles in OS might lead to the discovery of novel diagnosis biomarkers or therapy agent.

miR-613, a new discovery tumor-related miRNA, has been reported to suppress the proliferation
miR-613 inhibits OS progression by targeting c-MET

Table 1. Correlation between clinicopathological features and miR-613 expression in OS tissues

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of cases</th>
<th>miR-613 expression</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low (n%)</td>
<td>High (n%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>32</td>
<td>19 (59.4)</td>
<td>13 (40.6)</td>
</tr>
<tr>
<td>≥20</td>
<td>18</td>
<td>11 (61.1)</td>
<td>7 (38.9)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29</td>
<td>17 (58.6)</td>
<td>12 (41.4)</td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>13 (61.9)</td>
<td>8 (38.1)</td>
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<td>TNM stage</td>
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<tr>
<td>I-II</td>
<td>37</td>
<td>19 (51.3)</td>
<td>18 (48.7)</td>
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<tr>
<td>III-IV</td>
<td>13</td>
<td>11 (84.6)</td>
<td>2 (15.4)</td>
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<td>Tumor size</td>
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<td>&lt;5</td>
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<td>20 (58.8)</td>
<td>14 (41.2)</td>
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<tr>
<td>≥5</td>
<td>16</td>
<td>10 (62.5)</td>
<td>6 (37.5)</td>
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<td>20 (52.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>12</td>
<td>12 (100.0)</td>
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</tr>
</tbody>
</table>

and invasion of ovarian cancer cells [10], prostate cancer cells [11], papillary thyroid carcinoma [12], non-small cell lung cancer [13] and hepatocellular carcinoma [14]. However, how did miR-613 regulate the tumorigenesis in OS was still poorly understood. In the present study, we confirmed that miR-613 was downregulated in OS tissues and cell lines, and that decreased miR-613 was significantly correlated with aggressive clinicopathological characteristics in OS. Also, overexpression of miR-613 suppressed OS cell proliferation, colony formation, migration and invasion in vitro. Furthermore, we identified c-MET as a direct and functional target of miR-613 in OS. These findings provide significant clues regarding the role of miR-613 as a tumor suppressor in OS by targeting c-MET.

Materials and methods

Patients and tissue samples

50 pairs of OS tissues and adjacent noncancerous bone tissues (located over 3 cm away from the tumor) were collected from patients at the time of surgical resection at the Second Hospital of Jilin University (Changchun, China) from July 2014 and March 2016. All samples were immediately snap-frozen in liquid nitrogen and then stored in liquid nitrogen until use. None of the patients had received radiotherapy or chemotherapy prior to surgery. The clinical and histological characteristics OS patients enrolled in this study are listed in Table 1. All of the patients (or patients’ parents on behalf of the children) agreed to participate in the study and gave written informed consent. The use of human tissues was approved by the Medical Ethics Committee of Jilin University (Changchun, China).

Cell lines and cell culture

Human osteosarcoma cell lines (HOS, Saos-2, U2OS and MG-63) and normal osteoblast cells (NHOst) were obtained from the Chinese Cell Bank of the Chinese Academy of Sciences (Shanghai, China) and were in Dulbecco's modified Eagle's medium (DMEM; Invitrogen Corp., Carlsbad, CA, USA) supplemented with 10% heat-inactivated 10% fetal bovine serum (FBS; Life Technologies, Beijing, China) and streptomycin (100 mg/mL), penicillin (100 U/mL) at 37°C in a humidified atmosphere containing 5% CO₂.

Plasmid construction and cell transfection

miR-613 mimic and corresponding negative control (miR-NC) were purchased from Ribobio (Guangzhou, Guangdong, China). For luciferase reporter, the wide-type 3'-UTR of c-MET was amplified by from human genomic DNA using PCR and inserted into the pGL3-control vector (Promega, USA) at XbaI/FseI sites. The mutant 3'-UTR of c-MET, which carried the mutated sequence in the complementary site for the seed region of miR-613, was generated by overlap extension PCR based on the pGL3-Met-3'-UTR-WT plasmid. Overexpression c-MET plasmid (pCDNA3.1-c-Met) were kindly provided by Professor Gang Zhang from China Medical University (Shenyang, China). Transfection was performed when cells were grown to 80% confluence, using the Lipofectamine 2000 (Invitrogen) according to the manufacturer’s instructions.

RNA extraction and quantitative PCR

Total RNA including microRNAs was extracted from culture cells or tissues samples using the mirVana miRNA Isolation Kit (Ambion, USA) according to the manufacturer’s instructions,
and the integrity was identified using spectrophotometry and formaldehyde/agarose gel electrophoresis. For detection of miR-613 level, RNA was reversely transcribed; and real-time PCR was performed using TaqMan microRNA assays with specific primers for hsa-miR-613 (Life Technologies, NY, USA) under ABI 7900 Sequence Detection System (Life Technologies). The relative miR-613 expression levels after normalization to U6 was calculated using $2^{-\Delta\Delta Ct}$ method. For detection c-MET mRNA expression level, cDNAs were synthesized with PrimeScript RT reagent Kit (Takara, Dalian, China) according to the manufacturer's instructions. The real-time PCR were performed using Real-time PCR Mixture Reagent (Takara) under ABI 7900 Fast system. The primers for c-MET and GAPDH was used in this study as previously described [15]. The relative expression level of c-MET was normalized to GAPDH using the $2^{-\Delta\Delta Ct}$ method.

Cell proliferation and colony formation assays

To assess cell proliferation, MTT assay was performed. Briefly, U2OS cells were seeded at a concentration of $10^4$ cells/well in a 96-well plate. miR-613 mimic, miR-NC, or c-MET overexpression plasmid (pCDNA3.1-c-MET) were transfected into the cells using Lipofectamine 2000 the following day in accordance with the manufacturer's instructions, respectively. At indicated time points (24, 48 and 72 h), the culture medium was removed and replaced with medium containing 10 μl of sterile MTT dye (5 mg/ml). After cultured for 4 h, 150 μl dimethyl sulfoxide (DMSO, Sigma-Aldrich) was added into each well. Absorbance was measured at 490 nm in a microtiter plate reader (Molecular Devices, Menlo Park, CA).

For colony formation assay, the transfected cells were harvested and seeded at a density of 1000 cells/well in 6-well plates at 37°C and 5% CO$_2$ in a humidified incubator. Two weeks later, the colonies were fixed with 10% formaldehyde for 5 min and stained with 1.0% crystal violet for 1 min. The colony number in each well was counted in light microscope (Olympus, Tokyo, Japan).

Cell cycle analysis

Transfected cells were harvested and plated in six-well plates and cultured for 48 h. The cells then were incubated with 50 μg/mL propidium iodide (PI; BD Biosciences San Jose, CA, USA) for 30 min in the dark. The percentage of cells in G0/G1, S and G2/M phases of the cell cycle was determined using a flow cytometer (FACS Calibur, BD Biosciences, San Jose, CA, USA) after propidium iodide (PI) staining.

Cell migration and invasion assays

Wound healing was performed to determine the capacity of cell migration. Briefly, the wound was generated when the cells reached 90-95% confluent in a 6-well plate by scratching the surface of the plates with a 200 μl pipette tip. The wound closure was photographed 24 h later under a light microscope (Olympus). The distance between the wound edges of the scratch area was determined with Adobe Photoshop 7.0 software.

The invasive potential of cells was measured in transwell insert with 8.0 μm pore polycarbonate membrane (Corning) coated with Matrigel (BD, Franklin Lakes, NJ, USA). Briefly, transfected cells were trypsinized and seeded onto the upper chambers of the trans-well (1 × 10$^5$ cells/well) coated with Matrigel in serum-free medium. The lower chambers of the transwell were filled with DMEM medium containing 10% FBS. After incubated at 37°C and 5% CO$_2$ for 48 h, cells on the upper surface of the filter were removed using a cotton swab, whereas cells invasive through the filter to the lower surface were fixed with 4% paraformaldehyde for 10 min and stained with 0.1% crystal violet for 5 min. Cells were observed and counted at five selected randomly fields using a light microscope (Olympus).

Luciferase assay

U2OS cells were seeded in 24-well plates at density of $2 \times 10^5$ cells/well and incubated for 24 h before transfection. U2OS cells were cotransfected with WT-MET-3’UTR or Mut-MET-3’UTR plasmid, phRL-SV40 control vector (Promega, Beijing, China), and miR-613 or miR-NC using Lipofectamine 2000 (Invitrogen, Beijing, China). The renilla and firefly luciferase activities were determined with a dual luciferase assay (Promega, Beijing, China) 48 h after transfection. Renilla-luciferase was used for normalization.
miR-613 inhibits OS progression by targeting c-MET

Western blot assays

Transfected cells were plated into six-well culture plates and cultured for 24 h. Cell were washed in PBS (PH=7.2) and suspended in 100 μl of RIPA buffer (Pierce, Dallas, TX, USA) on ice for 30 min. Concentrations of supernatant protein were determined using the BCA protein assay kit (Pierce). Supernatant samples containing 30 μg total proteins were separated by 8%-12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) depending on the molecular weights of the target proteins, and were transferred to nitrocellulose membrane (Millipore, Billerica, MA, USA) by electroblooting. After blocking with 5% fat-free milk, the membrane was probed with anti-E-cadherin antibody (Cat# sc-21791, Santa Cruz Biotechnology, Santa Cruz, CA, USA), anti-N-cadherin antibody (Cat# sc-53488, Santa Cruz Biotechnology), anti-Vimentin antibody (Cat# gtx100-619, GeneTex, Irvine, CA, USA), anti-phosphoSer473-Akt antibody (Cat# 4051, Cell Signaling Technology, Danvers, MA,USA), anti-Akt total antibody (Cat# 4691, Cell Signaling Technology), anti-pTyr458-PI3K antibody (Cat# 4228, Cell Signaling Technology), anti-PI3K antibody (Cat# 4249, Cell Signaling Technology), Anti-mTOR antibody (Cat# 2972, Cell Signaling Technology), anti-pSer2481-mTOR antibody (Cat# 2974, Cell Signaling Technology), anti-c-Met antibody (Cat# 3148, Cell Signaling Technology), anti-GAPDH antibody (Cat# 5174, Cell Signaling Technology) overnight at 4°C. Membranes were incubated with corresponding horseradish peroxidase-conjugated secondary antibodies (Santa Cruz Biotechnology) for 1 h at room temperature. Protein bands were observed on X-ray film using an enhanced chemiluminescence detection system (ECL; Beyotime, Shanghai, China).

Statistical analysis

All statistical analyses were performed using SPSS 19.0 (SPSS, Chicago, IL, USA) and GraphPad Prism 5 software (GraphPad Software, Inc., city, state). Data were expressed as mean ± SD from at least three separate experiments. The statistical difference of data between groups was analyzed by one-way analysis of variance (ANOVA) and Student’s t test. Correlation analysis was performed using the Pearson’s correlation assay. Differences were considered to be statistically significant at P<0.05.

Results

miR-613 is downregulated in osteosarcoma tissues and cell lines

Expression of miR-613 was measured in all 50 OS samples and adjacent noncancerous bone tissues (ANT) using qRT-PCR. Data show that miR-613 was significantly downregulated in OS tissues compared to matched noncancerous bone tissues (Figure 1A). In accordance with clinical data, the expression level of miR-613 was significantly reduced in all the OS cell lines relative to normal human osteoblast cell line NHOst (Figure 1B). Clinopathological records of these OS tissues demonstrated that the decreased miR-613 expression was significant.
miR-613 inhibits OS progression by targeting c-MET

ly associated with lymph node metastasis and the TNM malignancy staging, but not with age, gender and tumor size (Table 1). These data imply that miR-613 might play crucial roles in OS progression and development.

miR-613 inhibits OS cell growth in vitro

To investigate the potential functions of miR-613 in OS cells, U2OS cells, with lowest expression in four cell lines (Figure 1B), were transfected with the miR-613 mimic or miR-NC to enhance miR-613 expression. The result of qRT-PCR demonstrated that miR-613 expression level became higher in U2OS cells transfected with the miR-613 mimic than the cells transfected with miR-NC (Figure 2A). MTT assay showed that the cell proliferation was significantly inhibited in miR-613-mimic-transfected U2OS cells compared with miR-NC-transfected U2OS cells (Figure 2B). Consistent with this result, overexpression of miR-613 in U2OS cells by transfection of miR-613 mimic

Figure 2. miR-613 inhibits OS cell proliferation, colony formation, and induced cell cycle at G0/G1 stage. A. Expression of miR-613 was measured in U2OS cells after transfected with miR-613 mimic or miR-NC. B-D. Cell proliferation, colony formation and cell cycle were determined in U2OS cells after transfected with miR-613 mimic or miR-NC. P<0.05, **P<0.01.
miR-613 inhibits OS progression by targeting c-MET

significantly inhibited the colony formation (Figure 2C). Since cell cycle closely links with cell proliferation, cell arrest was determined in U2OS cells transfected with miR-613 or miR-NC. Fluorescence-activated-cell-sorting (FACS) analysis showed the prolonged G0/G1-phase and the shortened S-phase in U2OS cells transfected with miR-613 compared to cells transfected with miR-NC (Figure 2D). These results might imply that miR-613 inhibit OS cell growth by regulating cell cycle.

**miR-613 inhibits OS cell migration, invasion and epithelial mesenchymal transition (EMT) in vitro**

Wound healing assay and transwell invasion assay were used to analyze the potential role of miR-613 in U2OS cell migration and invasion. Compared to miR-NC transfection group, ectopic expression of miR-613 significantly inhibited migration and invasion of U2OS (Figure 3A and 3B; P<0.01). To further investigate the mechanism of how miR-613 regulates the migration and invasion of OS cells, Western blot analyses were performed to detect epithelial mesenchymal transition (EMT) marker expression since EMT play crucial role in cell metastasis. As shown in Figure 3C, the expression of E-cadherin protein, an epithelial cell marker, was increased, whereas the mesenchymal markers N-cadherin and Vimentin were decreased in U2OS cells transfected with miR-613 compared to cells transfected with miR-NC, suggesting that miR-613 suppressed OS cell migration and regulation by regulating EMT.
miR-613 inhibits OS progression by targeting c-MET

We used two different online database searches TargetScan (http://www.targetscan.org/) and miRanda (http://www.microrna.org/microrna/home.do) to predict target gene of miR-613. Both bioinformatic tools predicted that there were two miR-613 binding sites in the 3′-UTRs of c-MET (located at the 499-505 and 814-820) mRNA (Figure 4A). To determine whether c-MET was negatively regulated by miR-613, the 3′-UTR of c-MET containing wild-type (WT) or mutant-type (Mut) miR-613 target sequences was cloned into the pGL3 vector. Cotransfection with these reporters plasmid and miR-613 or miR-NC into U2OS cells, then luciferase activities were performed 48 h after transfection. The result showed that transfection with miR-613 mimic repressed wild-type 3′UTR-c-MET reporter activity (P<0.01), while had no inhibition effect on the mutant 3′UTR-c-MET reporter activity (Figure 4B). In addition, we also found that overexpression of miR-613 significantly inhibited the c-MET expression on mRNA level (Figure 4C) and protein level (Figure 4D) and its downstream PI3K/Akt/mTOR signaling pathway (Figure 4D) in OS cells. These data suggested that c-MET is a direct target of miR-613 in OS cells.
miR-613 inhibits OS progression by targeting c-MET

As above results shows that c-MET is a direct target of miR-613, we next detected c-MET expression in OS tissues and the corresponding adjacent noncancerous bone tissues. qRT-PCR assay showed that c-MET mRNA expression level was significantly higher in OS tissues than those of adjacent noncancerous tissues (Figure 5A). Moreover, Pearson’s correlation assay showed that c-MET mRNA expression level was inverse correlated with miR-613 expression in OS tissues ($r=-0.601$, $P<0.0001$, Figure 5B).

Restoration of c-MET rescues tumor suppression role in OS cells by miR-613

To investigate whether the suppressive effect of miR-613 on the proliferation, migration and invasion of OS cells was mediated by c-MET repression, we rescued c-MET expression in miR-613-overexpressing U2OS cells (Figure 6A). In addition, restoration of c-MET expression could partially reverse effect on proliferation, cycle, migration and invasion of OS cells induced by miR-613 overexpression (Figure 6B-F).

Discussion

Dysregulation of miRNAs has been reported to play crucial roles in tumorigenesis and progression by regulating target molecule in various types of cancer including OS [8, 9]. For example, Qu et al reported that restoration of miR-150 expression in OS cells could inhibit cell proliferation, migration and invasion, and induced apoptosis in vitro, as well as suppressed tumor growth of OS in vivo by repressing IGF2 mRNA-binding protein 1 (IGF2BP1) [16]. Dong et al demonstrated that overexpression of miR-874 in OS cells remarkably inhibit proliferation, migration, and invasion and induce cell apoptosis by targeting E2F transcription factor 3 (E2F3) [17]. Zhou et al found that miR-154 significantly inhibited cell proliferation, colony formation, migration and invasion, as well as induced cell cycle arrest at the G1 stage in OS cells by targeting Wnt5a [18]. In this study, we found that miR-613 was frequently downregulated in OS specimens and cell lines, and decreased miR-613 was associated with lymph node metastasis and advanced TNM stage. Functional analyses showed that overexpression of miR-613 suppressed OS cell proliferation, colony formation, migration and invasion, as well as induced cell arrest at G1/G0 phase. c-MET was identified as a direct target of miR-613. Overexpression of c-MET reversed the suppressive effects of miR-613 on proliferation and invasion of OS cells. Taken together, our work suggests that miR-613 exerts its suppressive effect on growth and metastasis of OS by targeting c-MET.
miR-613 inhibits OS progression by targeting c-MET

MiR-613 has been reported to be downregulated in several types of cancer including prostate cancer, non-small cell lung cancer, thyroid cancer, hepatocellular carcinoma, ovarian cancer, esophageal squamous cell carcinoma and breast cancer [9-14, 19, 20], suggesting miR-613 is a new tumor suppressor. However, to date, the biological function and molecular mechanism of miR-613 in OS remain unclear. Therefore, we selected miR-613 for further investigation in this study. Here, we first confirmed that miR-613 was downregulated in OS tissues and cell lines. To better understand the function of miR-613 in OS, the effect of miR-613 on OS cell proliferation, colony formation, cycle, migration and invasion was examined in vitro using MTT and colony formation, flow cytometry, wound healing and transwell invasion assays. Our results showed that overexpression of miR-613 significantly inhibited OS cell proliferation, colony formation, migration and invasion, and induced cell arrest at G1/G0 stage. These results suggested that miR-613 might serve as tumor suppressor in OS.

It is a necessary step to identify of miRNA-regulated gene targets for understanding miRNA biological functions [4, 5]. To clarify molecular basis of miR-613 biological function in OS growth and invasion, we further searched for the downstream target genes regulated by miR-613. Based on target prediction programs, we found that c-MET is a tentative target of miR-613. Cellular-mesenchymal to epithelial transition factor (c-MET, also named as MET), a receptor for hepatocyte growth factor (HGF) [21, 22], could cause cellular activation through aberrant HGF stimulation, which contribute to tumor growth, invasiveness, and metastasis [23, 24]. The c-MET signaling has been reported to promote the tumorigenicity in a variety of manners including the highly oncogenic PI3K/AKT pathway [25-28]. In OS, c-MET has been showed to be upergulated and function as oncogene [29-32]. In the present study, we initially demonstrated that miR-613 binds to the 3'-UTR of c-MET, dramatically decreasing c-MET expression and its downstream PI3K/AKT/mTOR pathway. The following experiments showed an inverse relationship between miR-613 and c-MET in OS tissues samples. The functional experiments indicated that overexpression of c-MET could reverse effect on cell proliferation, colony formation, cycle, migration and invasion in OS cells mediated by miR-613 overexpression. All these data support the notion that miR-613 function as tumor suppressor in OS by negatively regulating c-MET.
miR-613 inhibits OS progression by targeting c-MET

In conclusion, we show, for the first time, that miR-613 is down-regulated in OS tissues and cell lines, and that decreased miR-613 significantly was associated with lymph node metastasis and advanced TNM stage. We also identified a likely novel mechanism of miR-613 to suppress OS growth and invasion by inhibiting c-MET. Thus, miR-613 functions as a tumor suppressor in OS by targeting c-MET. These findings might contribute to improve understanding the potential molecular mechanisms of OS progression.

Disclosure of conflict of interest

None.

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