Abstract Mesenchymal stem cells (MSCs), derived from various tissues, are served as a promising source of cells in clinic and regenerative medicine. Umbilical cord-Wharton’s jelly (WJ-MSCs)-derived MSCs exhibit advantages over those from adult tissues, such as no ethical concerns, shorter population doubling time, broad differentiation potential, readily available non-invasive source, prolonged maintenance of stemness properties. The aim of this study was to evaluate the effect of MRI (1.5 T, 10 min) on stemness gene expression patterns (OCT-4, SOX-2, NANOG) of WJ-MSCs. Additionally, we assessed cell viability, growth kinetics and apoptosis of WJ-MSCs after MRI treatment. The quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR) data showed that transcript levels of SOX-2, NANOG in MRI-treated WJ-MSCs were increased 32- and 213-fold, respectively. MTT assay was performed at 24, 48, and 72 h post-treatment and the viability was not significantly different between the two groups. The doubling time of the MRI group was markedly higher than the control group. In addition, the colony formation ability of WJ-MSCs after MRI treatment significantly increased. Furthermore, no change in apoptosis was seen before or after MRI treatment. Our results suggest that the use of MRI can improve the quality of MSCs and enhance the efficacy of mesenchymal stem cell-based therapies.

Keywords MRI · MSCs · Stemness properties · Viability · Clonogenicity · Apoptosis
**Introduction**

Magnetic Resonance Imaging (MRI) as a powerful non-invasive technique is frequently used in the medical diagnostics. It was indicated that MRI is a safe imaging technology compared to diagnostic tools utilizing ionizing radiation and there are no known side effects and problems for individuals upon examination with the MRI machine (Hsieh et al. 2008). However, several studies have demonstrated that strong electromagnetic fields and high static MFs have implications for the occurrence of different types of cancers, such as lung cancers, leukemia, and brain cancers (Barregård et al. 1985; Hsieh et al. 2008). Nonetheless, the safety issue of MRI on human health is still controversial and not well understood.

Mesenchymal stem cells (MSCs) are multipotent cells that have gained significant attention in the field of regenerative medicine and tissue engineering. MSCs can play an influential role in tissue regeneration, repair, and homeostasis via self-renewing capacity with the potential to differentiate into various tissues including bone, muscle, cartilage, fat, and nerve (Han et al. 2019). MSCs can be isolated from various tissues such as bone marrow, adipose tissue, umbilical cord, and placenta (Kang et al. 2016). Umbilical cord-derived MSCs (UC-MSCs) have several advantages compared with MSCs derived from the other origins and are paid increasing attention as a source for cell therapy. These advantages include a noninvasive collection procedure for autologous or allogeneic use, more efficient proliferation, low immunogenicity with a good immunosuppressive ability, and minimal societal, ethical and legal constraints (Nagamura-Inoue and He 2014).

Specific regulatory genes called Oct-4, Sox-2 and Nanog play a critical role in maintaining the pluripotency, self-renewality and undifferentiated state of embryonic stem cells (ESCs) (Tsai et al. 2012). Several studies have demonstrated that these pluripotency genes (Oct-4, Sox-2 and Nanog) are essential for the major properties of MSCs and the genes knockdown reduce the cell proliferation rate and differentiation potential (Malvicini et al. 2019; Matic et al. 2016; Pitrone et al. 2017; Tsai et al. 2012).

The aim of this study was to investigate the expression of stemness genes Oct-4, Sox-2 and Nanog in Wharton’s jelly-derived mesenchymal stem cells (WJ-MSCs) after MRI treatment.

**Materials and methods**

**Wharton’s jelly MSC isolation**

The study protocol was approved by the Ethics Committee of Rafsanjan University of Medical Sciences, Rafsanjan, Iran (IR.RUMS.REC.1397.231). Informed consent was obtained from each participant. Umbilical cords were collected immediately after birth and placed in DMEM/F12 medium supplemented with 3% penicillin, streptomycin and amphotericin B and transported to the laboratory at room temperature. The cords were rinsed in sterile phosphate buffered saline (PBS) supplemented with 3% penicillin, streptomycin and amphotericin B and cut longitudinally to expose and remove the two umbilical arteries and the umbilical vein. The remaining umbilical cord tissue including the Wharton’s jelly was chopped into 2–5 mm³ explants using single edge razor blades, transferred to 6-well tissue culture plates (Corning Inc., Corning, NY) containing 2 ml of DMEM/F12 (Gibco-Invitrogen Corporation, Carlsbad, CA), 15% fetal bovine serum (Gibco-Invitrogen Corporation, Carlsbad, CA), 1% penicillin/streptomycin; 1% amphotericin B and maintained in a 37 °C incubator with 5% CO₂ atmosphere and saturated humidity. Adherent fibroblast-like cells developed in 3 weeks were isolated by 0.05% trypsin and 0.02% EDTA (Sigma, St. Louis, MO, USA) for further growth and characterization. The isolated MSCs at passages 3–6 were used for the study experiments.

**MSC characterization**

**Mesodermal multilineage differentiation**

The differentiation potential of MSC into mesodermal lineages, adipogenic and osteogenic, was tested. For the adipogenic and osteogenic differentiation, cells were cultured for 21 days in specific media bought from the Bonyakhte Stem Cell Research Center (Tehran, Iran). After 21 days, cells were fixed in 4% paraphormaldeide and stained with Alizarin Red (Sigma) to visualize calcium deposition and Oil Red O (Sigma) to detect the presence of lipid droplets.
Cell surface protein profile

Flow cytometry analysis was used to investigate the cell surface marker profile of MSC. Cells were incubated with the following anti-human monoclonal antibodies conjugated with fluorescein isothiocyanate or phycoerythrin: CD34, CD45, CD73, CD90, CD105 (eBioScience, San Diego, CA), and subjected to flow cytometric analysis using a Beckman Colter flow cytometer and FACScan program (eBioScience).

MRI

For magnetic field treatment, the MSCs in the logarithmic growth phase were examined under a 1.5 Tesla MAGNETOM ESSENZA Siemens MRI scanner (Ali-ebn Abitaleb Hospital, Rafsanjan, Iran). Protocols of MRI can be a little different at different MRI centers, however in this study, MRI protocol included T2—STIR (Short-Tau Inversion-Recovery) and T1—TSE (Turbo Spin Echo) in coronal plane, T2—TSE in the coronal, sagittal and Axial plane, T1—TSE and T1—TSE with spectral Fat Saturation (FS) in Axial plane. These 7 pulse sequences were performed in a total scan time of 10 min for samples. Table 1 shows the sequences and physical parameters in detail.

Effect of MRI on mesenchymal stem cell doubling time

To compare the growth and proliferative characteristics of the cells, the population doubling time was measured. Doubling time was calculated using the formula $DT = \frac{(t2 - t1) \log (2)}{\log (n2 - n1)}$ where $n1$ and $n2$ are initial and final cell numbers and, t2 and t1 are the number of days in culture.

### Table 1 The pelvic MRI sequences and physical parameters

| Sequence                  | T2-SPC-MIR (Coronal) | TI-TSE (Coronal) | T2-TSE (Coronal) | T2-TSE (Sagittal) | TI-TSE (Axial) | T2-TSE (Axial) | TI-TSE-FS (Axial) |
|--------------------------|----------------------|------------------|------------------|------------------|----------------|----------------|------------------|
| Base sequence            | IR*                  | TSH              | TSE              | TSE              | TSE            | 1ST            | ISE              |
| FOV* (mm)                | 350×350              | 350×350          | 350×350          | 280×280          | 350×228        | 350×350        | 350×350          |
| Base Resolution          | 256                  | 320              | 256              | 320              | 256            | 256            | 256              |
| Phase Resolution         | 90%                  | 80%              | 70%              | 75%              | 80%            | 90%            | 70%              |
| Phase oversampling       | 50%                  | 0%               | 0%               | 50%              | 19%            | 0%             | 0%               |
| Slice thickness (mm)     | 4                    | 4                | 4                | 4                | 4              | 4              | 4                |
| Turbo Factor             | 131                  | 2                | 12               | 12               | 3              | 11             | 3                |
| Echo Spacing (ms)        | 3.7                  | 11.3             | 12.4             | 11.1             | 11.5           | 11.1           | 9.06             |
| Parallel Factor          | 3                    | 2                | off              | 2                | off            | off            | off              |
| Fat-Suppression          | None                 | None             | None             | None             | None           | None           | Fat Sat          |
| NEX*                     | 1.5                  | 2                | 2                | 2                | 2              | 1              | 1                |
| FA*                      | –                    | 150              | 150              | 150              | 150            | 150            | 150              |
| Gap                      | –                    | 0%               | 0%               | 55%              | 100%           | 100%           | 100%             |
| Number of slice          | 16                   | 20               | 20               | 15               | 20             | 20             | 20               |
| TR* (ms)                 | 2800                 | 380              | 3220             | 2220             | 478            | 3700           | 637              |
| TE* (ms)                 | 206                  | 11               | 100              | 89               | 12             | 100            | 9.1              |
| TI* (ms)                 | 160                  | –                | –                | –                | –              | –              | –                |
| Scan Time                | 0:52 s               | 1:40 min         | 1:41 mm          | 1:10 s           | 1:59 min       | 1:23 min       | 1:20 mm          |
| Band Width (Hz/Px)       | 651                  | 195              | 160              | 161              | 150            | 160            | 201              |
Effect of MRI on mesenchymal stem cells colony forming potential

The capacity of the cells for self-renewal can be evaluated by a colony forming assay. The MSCs were seeded at a density of 1.6–2 cells/cm² culture flask for colony development. After 14 days, the colonies were stained with 0.5% crystal violet (Sigma-Aldrich, St. Louis, MO, USA) for 5 min at room temperature. The colonies on the plates were photographed and counted for comparison of plating efficiency (PE) and surviving fraction (SF) (Clonogenic Assay: Adherent Cells):

PE (The ratio of the number of colonies to the number of cells) was calculated using the following formula: PE = number of colonies counted/number of cells plated. The SF parameter as the number of colonies that arise after treatment of cells is calculated using the formula: SF = number of colonies counted/number of cells plated × PE.

Cytotoxicity (Viability) assay

Spectrophotometric 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was used to determine the possible toxic effect of MRI on MSC viability. After incubation of MRI-treated and untreated MSCs for 24 h and 48 h at 37 °C, cells were incubated with MTT solution for 4 h and then the medium was substituted by DMSO followed by measuring optical density at 570 nm using an ELISA reader (BioTek ELX800, Winooski, Vermont, USA).

Apoptosis assay

To assess the cell death of MRI-treated and untreated MSCs by Annexin V/PI double staining methodology, 1 × 10⁶ cells/mL were labeled with Annexin V-FITC and PI, and then cells were analyzed using a flow cytometer (Becton–Dickinson, San Jose, CA). FloMax software was used to determine the fraction of cells in each quadrant.

Real time -PCR for gene expression

Total RNA from MRI-treated and untreated MSCs was extracted using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) and converted to cDNA using the SuperScript TMII enzyme (Inc., CA, USA) according to the manufacturer’s instructions, and cDNA was amplified with gene-specific primers. qRT-PCR was performed using Fast SYBR Green Master Mix (Applied Biosystems, Foster City, CA) applying the primers detailed in Table 2. As an internal control, levels of GAPDH were quantified in parallel with target genes. For each group three samples were analyzed at each time point.

Cryopreservation-induced cell death (CICD)

MRI -treated and -untreated MSCs were cryopreserved for at least 4 months before further evaluation. To evaluate MSCs after thawing, cryovials were retrieved from liquid nitrogen storage and rapidly thawed in a 37 °C water bath.

Statistical analysis

The experiments were performed at least three times and all the values are expressed as mean ± standard deviation. Statistical analysis was performed using SPSS 18 (SPSS, Munich, Germany). Differences between the treatment group and control were determined using independent sample Student t-test.

Table 2 A list of primer sequences used in this study

| Gene  | Forward primer (5’→3’) | Reverse primer (5’→3’) | Product size (bp) |
|-------|------------------------|------------------------|-------------------|
| SOX2  | CAGCATGTCTCTACTCGCAG   | GAGGAAGAGGTAACCACAGG   |                   |
| NANOG | GCAACACAGACCCAGAACATC  | GGAAAGATTCCAGCCAGTGT  |                   |
| OCT4  | TGTCAGGGGCTTGGTTCAC    | ACTCTCCCAAGCTTGCAATT  |                   |
| BCL2  | TCGCTCTGTGAGTAGACTG    | CAGAGTCTTCAGACAGGCCAG |                   |
| BAX   | GACGAACCTGGACGTAACATG  | AAAGTAGAAAAGGGCGACAACC |                   |
A *p*-value less than 0.05 was considered statistically significant.

**Results**

**Characterization of MSCs**

Umbilical cord derived-MSCs were isolated and expanded based on their plastic adherence. Phenotypic characterization showed that isolated MSCs were positive for the MSC-specific markers CD90 and CD105, but negative for the CD34 and CD45 (hematopoietic markers). Multi-lineage differentiation potential of MSCs cultured in adipogenic and osteogenic differentiation media showed positive staining with Oil Red O and Alizarin Red, respectively (Fig. 1).

**Toxicity assay**

A viability assay showed that MRI is safe at that dose (1.5 T). The analysis of changes in cell viability after MRI treatment was performed using the MTT assay. An increase in cell viability was shown in the MRI-treated group compared with the untreated-control group at 24 h, 48 h and 72 h, but the differences were not statistically significant (Fig. 2).

**Doubling time**

The proliferation potential of MSCs in the MRI-treated group and control group was assessed by calculating the population doubling time. The DT of MRI-treated MSCs was significantly higher than that of untreated control MSCs. The data indicated that MSCs in the MRI group had slower growth than MSCs in the control group (Fig. 3).

**Colony forming assay**

The colony forming assay was applied to examine the self-renewal potential of the cells. This study showed that MRI led to a dramatic increase in the clonogenicity of mesenchymal stem cells with PE of $3.03 \pm 0.743$ and SF of $28.9 \pm 13.6$ compared to MSCs without treating (Fig. 4 and Table 3).

**Apoptosis assay**

To quantify and analyze the percentage of apoptotic cells after MRI treatment, MSCs were stained with Annexin-V FITC/PI and analyzed by flow cytometry. Living, apoptotic, and necrotic cells were defined as Annexin-V⁻/PI⁻, Annexin-V⁺/ PI⁻, and Annexin-V⁻/PI⁺, respectively. The apoptosis of mesenchymal stem cells after the MRI treatment showed no differences between the MRI group compared with the untreated-control group (Fig. 5).

**Gene expression analysis by real-time PCR**

**Bax and Bcl-2**

Results showed that the mRNA level of Bax, as a proapoptotic marker, significantly increased, whereas the mRNA level of Bcl-2, as an antiapoptotic marker, was not significantly changed in the MRI-treated MSCs (Fig. 6).

**Stemness markers (Oct-4, Sox-2 and Nanog)**

To investigate the effect of MRI on MSCs, the mRNA expression levels of three major stemness markers, Oct-4, Sox-2 and Nanog, were assessed. The quantitative results revealed that the expression of Sox-2 and Nanog in the MRI group was significantly higher than that in the control group (213- and 32-fold increase, respectively, for Nanog and Sox-2) (Fig. 7), but there was no significant difference in Oct-4 mRNA level.

**Cryopreservation-induced cell death assessment**

To identify and characterize the influence of cryopreservation on cell viability and apoptosis of MSCs, cells were cryopreserved with DMSO and analyzed after thawing. Results showed that there was no regrowth of MRI-treated MSCs after thawing (Fig. 7).

**Discussion**

MSC-based cell therapy is a promising therapeutic strategy used in various clinical fields, including tissue regeneration and immunomodulatory therapy. MSCs are considered relatively safe in terms of genomic instability compared with induced...
Fig. 1 Isolation, characterization and differentiation capacity of umbilical cord mesenchymal stem cells. A Morphology of the adherent-mesenchymal stem cells (magnifications: ×100). B Immunophenotype of MSCs. The immunophenotype of MSCs analyzed by flowcytometry. Positive markers (CD90, and CD105) were expressed whereas negative markers (CD34 and CD45) were not. C Representative images of osteogenic (C1, ×100) and adipogenic (C2, ×100) differentiation of MSC in vitro. Scale bar indicates 50 μm.
pluripotential stem (Mittendorf et al. 2014) cells and embryonic stem (ES) cells (Kim et al. 2017). In the advancement of stem cell therapy, attempts are being made to develop an efficient production system to produce sufficient clinically relevant numbers of MSCs in a timely manner (Han et al. 2014).

The aim of this study was to investigate of MRI effects on stemness genes (Oct-4, Sox-2 and Nanog) expressions on MSCs.

Our results are consistent with previous studies showing that ectopic expression of stemness genes, such as Oct-4, Nanog, and Sox-2, promotes the proliferation potential of NIH 3T3 fibroblasts and MSCs while maintaining the lineage differentiation capacity (Go et al. 2008; Zhang et al. 2005).

Lengner and colleagues showed that oct-4 plays no role in the self-renewal of somatic stem cells (Lengner et al. 2007). A recent study revealed that Nanog maintains self-renewal capability of MSCs by delaying cellular senescence, increases the endogenous expression of Oct-4 and Sox-2, and preserves stemness (Park et al. 2019). Many studies have shown that both Oct-4 and Sox-2 bind the Nanog promoter and induce Nanog expression (Park et al. 2019). Park et al. reported that secretome from Nanog-overexpressing MSCs accelerated the telogen-to-anagen transition in hair follicles and could be an excellent candidate as a powerful anagen inducer and hair growth stimulator for treating alopecia (Park et al. 2019).

Fig. 2 Effects of MRI on cell viability. There was no significant difference in MSC viability in two treatment groups after 24 h, 48 h and 72 h.

Fig. 3 The doubling time of MRI-treated mesenchymal stem cells compared with untreated mesenchymal stem cells was significantly increased. *p < 0.05 versus control group.

Fig. 4 MRI enhanced colony formation ability of mesenchymal stem cells. A colony formation assay was performed on MRI-treated MSCs for 14 days. A Macroscopic and B microscopic appearance of MSCs in different groups. C Colony number of MSCs in two treatment groups. **p < 0.01 versus control group.
In this study, we also showed that the long-term effect of exposure to 1.5 T MRI for 10 min enhanced colony formation capacity (approximately 25 folds) of WJ-MSCs and increased the number of active stem cells. In addition, the findings of the flow cytometry revealed that MRI treatment does not influence the percentages of WJ-MSCs in apoptosis. Result showed that short-term exposure to a magnetic field did not induce apoptosis after 24 and 48 h.

In the current investigation, we evaluated the cytotoxic effects of MRI treatment on WJ-MSCs using the MTT assay. MTT assay determines cell viability by quantitative assessment of a metabolic product and indicates the activity of mitochondria in living cells, which has a direct relationship with cell proliferation and longevity (Tabatabaei et al. 2015). The results indicated that MRI does not significantly impact the metabolic activity, mitochondrial function and viability of WJ-MSCs.

In addition, we used a doubling time assay to investigate the average duration of cell growth and division. The findings reported that MRI can decrease the average division time of WJ-MSC in a short time, however, colony formation assay showed that this change was not permanent and reversed after a short time.

The result of the MRI effect on regrowth of the cryopreserved MSCs suggests that the cell death of all MRI-treated MSCs is due to increased sensitivity of these cells to the physical and chemical stress caused by the freezing process. There is growing evidence that the increase in ROS content is the most common event for various types of cells after cryopreservation (Savitskaya and Onishchenko 2016).

It has been shown that cryopreservation procedures can induce both apoptosis and necrosis (Savitskaya and Onishchenko 2016). It was previously shown that during thawing in mesenchymal stem cells, apoptosis was induced by the activation of apoptosis-related proteins, including Ca^{2+}-dependent protease calpain, caspase-8, -9, and -3 (Bissioly and Pramanik 2014).

Previous investigations have demonstrated that extended exposure to magnetic field decreased the viability percentage and/or proliferation rate of stem cells and terminally differentiated somatic cells (Javani Jouni et al. 2013; Marędziak et al. 2014; Raylman et al. 1996; Rosen and Chastney 2009).

Seven-day exposure to 0.5 T static magnetic fields (SMF) inhibited viability, proliferation, cytokine secretion, surface antigen expression, and adipogenic and osteogenic differentiation of adipose-derived stem cells (ASCs) (Wang et al. 2016). Several studies have demonstrated that different intensities of the magnetic field and durations of exposure did not cause DNA damage in cells, such as ASCs (Wang et al. 2016), THP1 (Amara et al. 2007), peripheral blood mononuclear cells (Reddig et al. 2015) and

| Group | Cell plated | Plating efficiency (PE) | Surviving fraction (SF) |
|-------|-------------|-------------------------|------------------------|
| Control | 100 | 0.12 ± 0.06 | 1 |
| MRI | 100 | 3.03 ± 0.743 | 28.9 ± 13.6 |

![Fig. 5](representative dot plot of untreated MSCs (A) and MRI-treated MSCs (B). Flow cytometry data indicated that apoptosis was not significantly different between the two groups)
leukocytes (Kubinyi et al. 2010). Jalali et al. also used contrast enhanced abdominopelvic MRI using 3 Tesla scanner to assess its effect on expression and methylation level of ATM and AKT genes (involved in the repair pathways of genome) in human peripheral blood lymphocytes and they found no negative effect at 1.5 T magnetic field strengths (Jalali et al. 2021).

Gruchlik et al. demonstrated that exposure to an SMF (300 mT) for 24 h inhibited the IL-6 secretion in normal human colon myofibroblasts (Gruchlik et al. 2012). Vergallo et al. reported that SMF exposure (1.4 T, 24 h) significantly inhibited the release of IL-6, IL-8, and INF-α from macrophages (Vergallo et al. 2013). In another study, exposure to a strong SMF (4.75 T) for 24–48 h significantly decreased the production of IL-2 in human peripheral blood mononuclear cells (Aldinucci et al. 2003). Recent study has shown that low-frequency electromagnetic field can affect cell morphology and behaviors such as cell proliferation, differentiation and apoptosis (Barati et al. 2021; Nezamtaheri et al. 2022).

According to previous studies, it seems that the exposure to magnetic fields is associated with epigenetic changes but not with genetic changes (mutations or DNA damage).

A review of the current literature suggests that Wharton’s jelly-derived mesenchymal stem cells (WJ-MSCs) have the best potential to differentiate into adipocytes, chondrocytes, osteocytes, muscle cells, neurons, cardiomyocytes, and hepatocytes (Beeravolu et al. 2017).

WJ-MSCs have been widely explored for cell-based therapy for immune-mediated, inflammatory, and degenerative diseases, due to their remarkable anti-inflammatory, immunosuppressive, immunomodulatory and regenerative potential (Liau et al. 2020; Noronha et al. 2019).

Overall, our findings suggest that MRI treatment may be a useful approach for producing high-quality MSCs by improving their stemness properties but further study is needed to determine safety, possible toxicity and also efficacy.

This strategy has great potential for developing pluripotency in WJ-MSCs to become more versatile in clinical applications. To the best of our knowledge, no other study has investigated the MRI effects on the stemness genes expression of MSCs.

However, it is worth noting that cancer stem cells, as a key driver of tumor formation and metastasis, express deregulated stemness-associated genes, such as OCT-4, Nanog, Sox-2 (Müller et al. 2016). Additionally, the personal exposure to MRI has the potential for deregulation of stemness-related genes in normal stem cells. Therefore, it seems that precautions should be taken to reduce the possible risks of MRI exposure. Further studies are needed to determine MRI-treated MSCs have no adverse or unwanted effects following cell therapy. Our findings suggest that MRI treatment may be a useful strategy
for gaining high-quality MSCs in clinical studies of MSC-based therapies.

Finally, preclinical and clinical studies should be designed to identify whether MRI treatment can be an effective approach to improve the therapeutic function of MSCs.

In conclusion

MSCs exposed to MRI promoted the colony-forming potential and induce stemness genes (Oct-4, Sox-2 and Nanog) expression. Therefore, it suggests that MRI may enhance the efficacy of mesenchymal stem cell-based cell therapy.

Authors’ contributions MT designed the experiments, supervise the project, wrote the manuscript; FA performed the experiments, data analysis; F-SK performed the experiments; AM contributed to sample preparation; AH-C designed and performed the experiments, data analysis, wrote the manuscript, supervised the project.

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Data availability The data that support the findings of this study are available on request to the corresponding author.

Declarations

Ethics approval and consent to participate This work was approved by the local ethical review board.

Consent for publication All authors gave consent for the publication.

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