In cholestatic liver diseases, impaired bile excretion disrupts lipid homeostasis. We investigated changes of lipid metabolism, including mitochondrial \(\beta\)-oxidation, in a rat model of bile duct ligation (BDL) in which chorionic plate-derived mesenchymal stem cells (CP-MSCs) were transplanted. Serum cholesterol level, which was elevated after BDL, was significantly decreased following CP-MSC transplantation. The expression levels of genes involved in intracellular lipid uptake, including long-chain fatty acyl-CoA synthetases and fatty acid transport proteins, were decreased in rats after BDL; however, they were not significantly changed by subsequent CP-MSC transplantation. Carnitine palmitoyltransferase 1A (CPT1A), a rate-limiting enzyme in mitochondrial \(\beta\)-oxidation, was upregulated after BDL and then was downregulated after CP-MSC transplantation. CPT1A expression was changed via microRNA-33—a posttranscriptional regulator of CPT1A—in a peroxisome proliferator-activated receptor \(\alpha\)-independent manner. Cellular adenosine triphosphate production—an indicator of mitochondrial function—was reduced after BDL and was restored by CP-MSC transplantation. Expression levels of heme oxygenases also were significantly affected following BDL and CP-MSC transplantation. Lipid metabolism is altered in response to chronic cholestatic liver injury and can be restored by CP-MSC transplantation. Our study findings support the therapeutic potential of CP-MSCs in cholestatic liver diseases and help in understanding the fundamental mechanisms by which CP-MSCs affect energy metabolism.

1. Introduction

Cholestatic liver injury, which is caused by accumulation of bile acids and lipids, comprises a wide spectrum ranging from acute transient hepatitis to cirrhosis with portal hypertension [1–3]. The liver controls central processes of lipid metabolism including fatty acid synthesis, mitochondrial \(\beta\)-oxidation, and phospholipid transport. Impaired bile excretion, caused by biliary obstruction or liver damage, disrupts cholesterol and phospholipid metabolism [4]. In a rat model of bile duct ligation (BDL), serum levels of very low-density lipoprotein cholesterol and low-density lipoprotein (LDL) cholesterol are drastically elevated, whereas hepatic lipid concentrations are unchanged [5]. However, alterations in mitochondrial function in chronic cholestatic liver diseases have not been elucidated.

Mesenchymal stem cells (MSCs) are multipotent adult stem cells that can differentiate into various cell types of the three germ layers (i.e., the ectoderm, mesoderm, and endoderm) [6]. The human placenta is an abundant source of MSCs. Placenta-derived MSCs (PD-MSCs) which originate from the fetus possess great potential for self-renewal, proliferation, and differentiation [7, 8]. We previously found that full-term placenta harbors several types of PD-MSCs,
including choriionic plate-derived MSCs (CP-MSCs), chorio-

canic placenta samples for research

The sequences of the primers are listed in Table 1. GAPDH

2.3. Histological Analysis. Liver tissue samples were fixed

in 10% formalin, embedded in paraffin, and sectioned at

5 μm thickness. Sections then were stained with hematoxy-
ylin and eosin and observed under light microscopy at

200x magnification (Axioskop2, Carl Zeiss Micro-Imaging,

Oberkochen, Germany).

2.4. Immunofluorescence Staining. To analyze the expression

of carnitine palmitoyltransferase 1A (CPT1A) in liver tissues,

6 μm thick cryostat sections were incubated with protein

blocking solution (Dako, Glostrup, Denmark) for 40 minutes

at room temperature. Then, a mouse anti-CPT1A antibody

(1:100, Abcam, Cambridge, MA, USA) was treated, and

sections were incubated at 4°C overnight. After washing

with phosphate-buffered saline (PBS), samples were incu-
bated with an Alexa 488-conjugated secondary antibody

(1:150, Invitrogen, Carlsbad, CA, USA) for 1 hour at

room temperature. Sections then were stained with 4',6-
diamidino-2-phenylindole (DAPI) for nuclear counter-
staining and were observed under fluorescence microscopy

at 400x magnification (Nikon, Tokyo, Minato, Japan).

2.5. Blood Chemistry. The serum concentrations of total

cholesterol, high-density lipoprotein (HDL) cholesterol,

LDL cholesterol, triglyceride, albumin, total bilirubin, alk-
aline phosphatase (ALP), aspartate transaminase, alanine

transaminase, and C-reactive protein (CRP) were mea-
sured enzymatically by an automated analyzer (Hitachi 747,

Hitachi, Tokyo, Japan).

2.6. Fatty Acyl-CoA Synthetase Activity Assay. Long-chain

fatty acyl-CoA synthetase (ACSL) activity was assessed by

the enzyme-linked immunosorbant assay (ELISA). Liver tis-
sues were homogenized in cold PBS with a glass homogenizer

on ice. ACSL activity was measured using a Rat Fatty

acyl-CoA synthetase ELISA Kit (MyBioSource, San Diego,

CA, USA) in strict accordance with the manufacturer’s

instructions and detected using a microplate reader (BioTek,

Winooski, VT, USA) at 450 nm.

2.7. Quantitative Real-Time Polymerase Chain Reaction. Rat

liver tissues were homogenized and lysed, and total RNA

was isolated with the TRIzol reagent (Invitrogen). Reverse

transcription was performed with 500 ng of total RNA and

Superscript III reverse transcriptase (Invitrogen). Real-time

polymerase chain reaction (PCR) was performed with SYBR

Green PCR Master Mix (Applied Biosystems, Foster City,

CA, USA). The cDNA subsequently was amplified by PCR

using the following thermal conditions: 5 minutes at 95°C,

40 cycles of 95°C for 5 seconds, and 60°C for 30 seconds.

The sequences of the primers are listed in Table 1. GAPDH

or β-actin was used as an internal control for normalization.

2.8. Isolation and Quantification of MicroRNA-33. Total

RNA was isolated with the TRIzol reagent (Invitrogen) and

reverse-transcribed with a Mir-X miRNA First-Strand Syn-
thesis Kit (Clontech, Mountain View, CA). Then, real-time

PCR for microRNA-33 (miR-33) was performed using the

following primer: 5′-GTG CAT TGT AGT TGC ATT

GCA-3′ (forward). The expression of miR-33 was normal-
ized to U6 snRNA expression.

2.9. Western Blot Analysis. Liver tissues were homogenized

and lysed on ice with RIPA buffer containing protease

inhibitor cocktail (Roche, Branchburg, NJ, USA) and a

phosphatase inhibitor (Sigma-Aldrich). Protein lysates

were separated by 8% to 15% sodium dodecyl sulfate poly-

acrylamide gel electrophoresis (SDS-PAGE), transferred to

polyvinylidene difluoride membranes (Bio-Rad Laborato-

ries, Hercules, CA, USA), and then blocked in blocking

buffer (0.1% Tween20 and 8% bovine serum albumin [BSA]

in Tris-buffered saline [TBS]) for 1 hour. Membranes

We therefore used a BDL rat model of chronic cholestatic

liver injury to clarify the alterations in hepatic lipid homeos-
tasis—focusing on mitochondrial dysfunction—and the

impact of CP-MSC transplantation restoring the alterations

in hepatic lipid metabolism.

2. Materials and Methods

2.1. Cell Culture. Collection of placenta samples for research

purposes was approved by the Institutional Review Board of

CHA Gangnam Medical Center, Seoul, Korea (IRB 07-18).

All participants provided written informed consent prior to

collection. Placentas were obtained from women who were

free of any medical, obstetrical, or surgical compli-

cations and who delivered at term (38±2 gestational weeks).

CP-MSCs were isolated as described previously [10] and were

cultured in Dulbecco’s modified Eagle medium/Ham’s F-12

medium (DMEM/F12; Sigma-Aldrich, St. Louis, MO, USA)

supplemented with 10% fetal bovine serum (FBS; Sigma-

Aldrich), 1% penicillin/streptomycin (Sigma-Aldrich), 1 μg/

mL heparin (Sigma-Aldrich), and 25 ng/mL human fibro-

blast growth factor-4 (hFGF-4; Peprotech Inc., Rocky Hill,

NJ, USA) at 37°C in a 5% CO2 incubator containing 20% O2.

2.2. BDL Rat Model and Transplantation of CP-MSCs. Male

7-week-old Sprague-Dawley rats (Orient Bio Inc., Seongnam,

Korea) were maintained in an air-conditioned animal facil-

ity. The common bile duct was ligated under general anesthe-

sia with Avertin (2,2,2-tribromoethanol, Sigma-Aldrich) as

described previously [12, 13]. One week after BDL, CP-

MSCs (2×10^6 cells, 8–10 passages) were injected intrave-

nously via tail vein in the transplanted group. The CP-MSC

number was determined based on the previous dose-
determining experiments [10, 14]. Liver tissues and blood

samples were collected 1, 2, 3, and 5 weeks posttransplanta-

tion in the transplanted group and 1, 2, 3, and 5 weeks

post-BDL in the nontransplanted group. The experimental

protocols were approved by the Institutional Animal Care

and Use Committee of CHA University, Seongnam, Korea

(IACUC-140009).

2.3. Histological Analysis. Liver tissue samples were fixed

in 10% formalin, embedded in paraffin, and sectioned at

5 μm thickness. Sections then were stained with hematoxy-
ylin and eosin and observed under light microscopy at

200x magnification (Nikon, Tokyo, Minato, Japan).

2.4. Immunofluorescence Staining. To analyze the expression

of carnitine palmitoyltransferase 1A (CPT1A) in liver tissues,

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with phosphate-buffered saline (PBS), samples were incu-
bated with an Alexa 488-conjugated secondary antibody

(1:150, Invitrogen, Carlsbad, CA, USA) for 1 hour at

room temperature. Sections then were stained with 4',6-
diamidino-2-phenylindole (DAPI) for nuclear counter-
staining and were observed under fluorescence microscopy

at 400x magnification (Nikon, Tokyo, Minato, Japan).
subsequently were incubated with mouse anti-CPT1A (1:1000, Abcam), rabbit anti-peroxisome proliferator-activated receptor α (PPARα) (1:1000, Abcam), and rabbit anti-GAPDH (1:3000, Santa Cruz Biotechnology, Santa Cruz, CA, USA) antibodies at 4°C overnight. After the reaction, membranes were treated with a horseradish peroxidase-(HRP-) conjugated secondary antibody (anti-rabbit IgG [1:25000, Bio-Rad Laboratories] or anti-mouse IgG antibody [1:25000, Bio-Rad Laboratories]) for 1 hour at room temperature. The bands were detected using an enhanced chemiluminescence reagent (Bio-Rad Laboratories).

2.10. Adenosine Triphosphate Assay. Adenosine triphosphate (ATP) concentrations of homogenized liver tissue samples were measured using an ATP assay kit (Abcam), according to the manufacturer’s instructions, and were assessed using a microplate reader (BioTek) at 570 nm.

2.11. Statistical Analysis. All experiments were conducted in duplicate or triplicate. Data are expressed as mean ± standard deviation. Student’s t-tests were performed for groupwise comparisons, and P < 0.05 was considered statistically significant. Statistical analyses were performed using PASW version 22.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. CP-MSC Transplantation Ameliorates Inflammation in the BDL Rat Liver. To assess the effect of transplantation of CP-MSCs on cholestatic liver injury, BDL rats were divided
into 2 groups: rats in the transplanted group were injected with CP-MSCs, and rats in the nontransplanted group were injected with the culture medium. As shown in Figure 1, we observed the infiltration of inflammatory cells around bile ducts and bile duct proliferation in portal areas in both nontransplanted and transplanted groups 1 week after BDL. Two weeks after BDL, portal areas were expanded as a result of extensive bile duct proliferation and concentric periductal fibrosis, and disorganization of normal lobular structures was observed in the nontransplanted group. Bile duct proliferation was less prominent, and the lobular pattern was preserved in the transplanted group compared to the nontransplanted group (Figure 1). Hepatic steatosis was not observed in the control, nontransplanted, or transplanted groups.

3.2. CP-MSC Transplantation Attenuates BDL-Induced Hypercholesterolemia but Does Not Affect Fatty Acid Uptake. Obstruction of bile excretion induced by BDL results in overflow of biliary phospholipids in the circulation [4]. Therefore, we explored the effect of transplantation of CP-MSCs on cholesterol metabolism by measuring the cholesterol concentrations in serum. Total cholesterol was markedly elevated in the nontransplanted group 2 weeks after BDL compared to the control group, whereas it was significantly reduced in the transplanted group compared to the nontransplanted group \( (P < 0.05; \text{Figure 2(a)}) \). Results similar to those for total cholesterol were found for the concentrations of serum LDL cholesterol and triglyceride (Figure 2(a)). Increases in serum levels of total bilirubin, ALP, and CRP were shown to be attenuated after transplantation of CP-MSCs \( (P < 0.05; \text{Figure S1 in Supplementary Material available online at https://doi.org/10.1155/2017/5180579}) \).

Because hypercholesterolemia is induced by chronic cholestasis, we hypothesized that fatty acid uptake into hepatocytes may be altered in BDL rats. ACSLs and fatty acid transport proteins (FATPs) are thought to be essential for the intracellular uptake and transport of fatty acids [15, 16]. Therefore, we determined the activity of ACSLs and the expression levels of ACSLs and FATPs in rat liver tissues. ACSL activity—measured by ELISA—was increased significantly in the transplanted group compared to the nontransplanted group \( (P < 0.05; \text{Figure 2(b)}) \). The expression levels of ACSL1, which is highly expressed in the normal liver [17], were decreased in BDL rats; however, they were not increased significantly by CP-MSC transplantation (Figure 2(c)). The expression levels of ACSL4 and ACSL5, which are located in rat liver peroxisomes and mitochondria, respectively [18], declined drastically after BDL and were not restored by CP-MSC transplantation (Figure S2). The expression levels of FATP2 and FATP5, which are expressed in hepatocytes [19, 20], were decreased in BDL rats and were not increased significantly by CP-MSC transplantation (Figures 2(c) and S3). Collectively, these findings indicate that cholestasis and hypercholesterolemia induced by BDL are ameliorated by CP-MSC transplantation. However, transplantation of CP-MSCs does not appear to restore processes of fatty acid import into hepatocytes.

3.3. CPT1A Expression Is Changed via MiR-33 in BDL Rats. CPT1A is a rate-limiting enzyme located in the mitochondrial outer membrane that catalyzes \( \beta \)-oxidation of free fatty acid [21]. PPAR\( \alpha \) regulates mitochondrial and peroxisomal fatty acid oxidation by controlling downstream genes, such as CPT1A [22]. We investigated whether the expression of genes associated with fatty acid oxidation is altered in BDL rats and restored by transplantation of CP-MSCs. The mRNA levels of PPAR\( \alpha \) and CPT1A were remarkably decreased after BDL (Figures 3(a) and 3(b)). PPAR\( \alpha \) mRNA levels were similar in the nontransplanted and transplanted groups (Figure 3(a)); however, CPT1A mRNA expression was significantly augmented 2 weeks after CP-MSC transplantation \( (P < 0.05; \text{Figure 3(b)}) \). On the contrary, the increased protein expression levels of CPT1A by BDL were reinstated to near-control levels 3 and 5 weeks after transplantation of CP-MSCs \( (P < 0.05; \text{Figure 3(c)}) \). These results were confirmed by immunofluorescence staining (Figure 3(d)). MiR-33 represses its target genes, which
are involved in free fatty acid oxidation, such as CPT1A [23]. To evaluate whether miR-33 is a posttranscriptional regulator of CPT1A in BDL rat liver, we analyzed the expression levels of miR-33. As expected, we determined that miR-33 expression was reduced in BDL rats and was restored by transplantation of CP-MSCs (Figure 3(e)). Taken together, these results suggest that CPT1A may be regulated posttranscriptionally by miR-33 in a PPARα-independent manner.

**Figure 2**: Changes in serum lipid profiles and expression levels of genes associated with intracellular uptake of fatty acids after BDL and/or CP-MSC transplantation. (a) Serum levels of total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride. (b) Activities of ACSL, as measured by ELISA. (c) mRNA expression levels of ACSL1 (left) and FATP2 (right). β-Actin was used as an internal control for normalization. Data are expressed as a fold change related to the control group. *P < 0.05 (compared to the nontransplanted group). CTL: control group; NTx: nontransplanted group; Tx: transplanted group.
Figure 3: Expression of genes associated with fatty acid oxidation after BDL and/or CP-MSC transplantation. mRNA expression levels of PPARα (a) and CPT1A (b) by real-time PCR. β-Actin was used as an internal control for normalization. Data are expressed as a fold change related to the control group. (c) Protein expression levels of PPARα and CPT1A. GAPDH was used as a loading control, and quantification by densitometry of Western blots was normalized to GAPDH. Data are expressed as a fold change related to the control group. (d) Analysis of CPT1A expression with immunofluorescence staining (scale bar = 200 μm; original magnification, ×400). Liver tissues, which were collected at 3 weeks posttransplantation in the transplanted group and post-BDL in the nontransplanted group, were used in immunofluorescence staining. (e) mRNA expression levels of miR-33. U6 snRNA was used as an internal control for normalization. *P < 0.05 (compared to the nontransplanted group). CTL: control group; NTx: nontransplanted group; Tx: transplanted group.
3.4. CP-MSC Transplantation Restores Cellular ATP Production by Regulating Heme Oxigenases. To demonstrate alterations in cellular energy production after BDL, we measured the ATP levels in BDL rat liver. ATP production was decreased after BDL but was augmented 1 week after CP-MSC transplantation (Figure 4(a)). Heme oxygenases (HOs) are suggested to be involved in regulating mitochondrial function [24]. Therefore, we assessed the expression levels of HOs in liver tissues. We determined that HO-1 expression was increased substantially in a time-dependent manner post-BDL until week 3. However, the augmented expression of HO-1 reverted to near-control levels 2 weeks after transplantation of CP-MSCs (P < 0.05; Figure 4(b)). The HO-2 expression pattern was inversely related to that of HO-1 (Figure 4(c)). These findings implicate that CP-MSC transplantation may ameliorate cellular ATP production via alternative expressions of HO-1 and HO-2.

4. Discussion

In this study, we demonstrated that alterations in lipid metabolism in BDL rats might be ameliorated by transplantation of CP-MSCs. Chronic cholestasis, resulting from BDL, led to massive inflammation, hypercholesterolemia, and a drastic decrease in intracellular fatty acid transport; these changes were partially reverted by CP-MSC transplantation. Regarding mitochondrial β-oxidation, the expression of CPT1A was changed following BDL and CP-MSC transplantation via miR-33, which is known as a posttranscriptional regulator of CPT1A, independent of PPARα. Decreased cellular ATP production after BDL, which reflects mitochondrial dysfunction, was increased by CP-MSC transplantation via regulation of HO-1 and HO-2.

Stem cell therapy with MSCs has been tried for the treatment of various liver diseases, including cirrhosis and hepatic failure, as an alternative to liver transplantation. We previously reported that CP-MSCs had anti-inflammatory, antifibrotic, and proregenerative effects in a chronic liver injury model induced by carbon tetrachloride (CCL4) [10, 11]. Liver fibrosis and increased expression of type I collagen and α-smooth muscle actin in CCL4-treated rats were reduced after CP-MSC transplantation, which suggested that CP-MSCs have antifibrotic effects [10]. Transplantation of CP-MSCs also showed anti-inflammatory effects of attenuating leukocyte infiltration and augmenting anti-inflammatory cytokine interleukin 10 in liver tissues. In addition, CP-MSC transplantation promoted liver regeneration through activating autophagy [11]. In our present study, we demonstrated a novel effect of CP-MSCs as modulators of hepatic lipid metabolism in a BDL rat model. Alterations in serum cholesterol profiles and hepatic fatty acid oxidation, which resulted from BDL, were ameliorated after CP-MSC transplantation.

Because bile acids play a key role in lipid and energy homeostasis, alterations in lipid metabolism are inevitable in cholestatic liver diseases [4, 5, 25]. De Vriese and colleagues reported the results of lipid analysis of BDL rats and identified hypercholesterolemia and changes in the serum phospholipid profile, in proportion to serum levels of total bilirubin and ALP; however, a decrease in liver fat content in BDL rats was also observed [4]. In a more recent study, a high-cholesterol diet was not found to cause hepatic steatosis in BDL mice [25]. Our study findings of hypercholesterolemia without hepatic steatosis in BDL rats are consistent with those of these previous studies. Also, we demonstrated that intracellular fatty acid transport was markedly suppressed after BDL. The absence of hepatic steatosis, despite hypercholesterolemia, might be explained by intestinal lipid malabsorption via bile acids combined with the suppression of fatty acid import into hepatocytes.

Because the previous studies, which reported the changes in lipid metabolism in cholestatic liver diseases, focused on lipid malabsorption and cholesterol profiles, alterations in fatty acid oxidation have not been elucidated so far. Mitochondrial β-oxidation is a catabolic process that yields acetyl-CoA from long-chain acyl-CoA; acetyl-CoA then
serves as a substrate in ATP generation [26]. Fatty acids, in the form of acyl-CoA, enter mitochondria by CPT1A, a rate-limiting enzyme that catalyzes mitochondrial β-oxidation [21]. Moreover, PPARα has been identified as an upstream regulator of CPT1A [22]. We demonstrated that protein expression of CPT1A was upregulated in BDL rats and was downregulated after CP-MSC transplantation, independent of PPARα. In contrast, mRNA expression of CPT1A exhibited an opposite pattern to CPT1A protein expression. Therefore, we explored the possibility of post-transcriptional regulation of CPT1A and verified that CPT1A is changed via alternative expression of miR-33 [23]. Because mitochondrial β-oxidation is a major source of ATP production in the liver [26], we further analyzed ATP production as an estimation of mitochondrial function. We revealed that decreased ATP production in BDL rat liver was restored by transplantation of CP-MSCs. HOs are thought to be mediators by which CP-MSCs correct mitochondrial dysfunction. Although HO-1 has been suggested to play a role in regulating mitochondrial function [24, 27], further studies are warranted to ascertain whether mitochondrial fatty acid oxidation is regulated by HOs. We have failed to demonstrate a consistent therapeutic effect on ATP production over time after CP-MSC transplantation. It may be worthwhile to transplant CP-MSCs repeatedly to overcome these limitations and to augment the therapeutic effect.

5. Conclusions

In our present study, we delineated perturbed lipid homeostasis in a model of chronic cholestatic liver injury. We demonstrated the therapeutic effect of CP-MSC transplantation to ameliorate alterations in lipid metabolism involving mitochondrial fatty acid oxidation. These results provide a novel insight into the mechanisms of stem cell therapy and support the therapeutic potential of CP-MSC transplantation in chronic cholestatic liver diseases.

Abbreviations

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACSL</td>
<td>Long-chain fatty acyl-CoA synthetase</td>
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<td>ALP</td>
<td>Alkaline phosphatase</td>
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<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
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<td>BDL</td>
<td>Bile duct ligation</td>
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<tr>
<td>BSA</td>
<td>Bovine serum albumin</td>
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<td>CHC</td>
<td>Carbon tetrachloride</td>
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<td>CP-MSCs</td>
<td>Chorionic plate-derived MSCs</td>
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<tr>
<td>CPT1A</td>
<td>Carnitine palmitoyltransferase 1A</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<td>DAPI</td>
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<td>Fatty acid transport protein</td>
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<td>Human fibroblast growth factor-4</td>
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<td>Heme oxygenase</td>
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Conflicts of Interest

The authors declare that they have no competing interests.

Authors’ Contributions

Yun Bin Lee and Jong Ho Choi contributed equally to this work.

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