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IL-17A Inhibits Osteogenic Differentiation of Bone Mesenchymal Stem Cells via Wnt Signaling Pathway

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Interleukin-17A (IL-17A) is not only an important modulator of inflammatory reactions, but also affects bone metabolism, which is involved in osteogenic differentiation of stem cells. However, the role and mechanism of IL-17A in osteogenic differentiation of bone mesenchymal stem cells (BMSCs) are not fully understood. In this study, we investigated the role and mechanism of IL-17A in osteogenic differentiation of BMSCs.

Material/Methods: The osteogenic differentiation of BMSCs was induced by osteoblast-induction medium with IL-17A or without IL-17A. The osteogenic differentiation of BMSCs was confirmed by the alkaline phosphatase and alizarin red staining. The lentiviral plasmid was used to construct the sFRP1-shRNA expression vector. The associated osteogenic differentiation marks (RUNX2, ALP, OPN), Wnt signaling pathway inhibitor (sFRP1), and modulators of Wnt signaling pathway (Wnt3, Wnt6) were detected by qRT-PCR and Western blot method.

Results: The results showed that the addition of IL-17A inhibited osteogenic differentiation of BMSCs. IL-17A induced up-regulated expression of sFRP1 and down-regulated expression of Wnt3 and Wnt6 in BMSCs. In addition, sFRP1-shRNA abolished the inhibition effect of IL-17A in osteogenic differentiation of BMSCs and induced up-regulated expression of Wnt3 and Wnt6 in the Wnt signaling pathway in BMSCs.

Conclusions: Our findings show that IL-17A inhibits osteogenic differentiation of bone mesenchymal stem cells via the Wnt signaling pathway.

MeSH Keywords: **Cell Differentiation • Receptors, Interleukin-17 • Stem Cells • Wnt Signaling Pathway**

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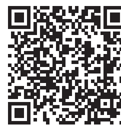

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Background

Bone marrow-derived mesenchymal stem cells (BMSCs) are multipotent progenitor cells, and are reported to have the potential to differentiate into bone, cartilage, muscle, and adipose tissue [1]. Osteogenic differentiation of BMSCs is an important part of differentiation of BMSCs, which is used to clinical apply materials of bone regeneration and repair [2–5]. Therefore, to efficiently harness these therapeutic potentials, it is very important to understand the molecular mechanisms underlying osteogenic differentiation of BMSCs and to improve the osteogenic capacity of BMSCs.

Many studies have reported that proinflammatory cytokines are involved in diseases associated with bone destruction, had can inhibit bone formation and osteogenic differentiation [6–9]. Interleukin-17A (IL-17A) is an important member of the interleukin-17 family, which is a group of proinflammatory cytokines produced by helper T cells. IL-17A is not only involved in the systemic inflammatory response, but also plays the key role in bone metabolism [10,11]. Some studies also have shown that IL-17A is involved in the osteogenic differentiation and inhibit this differentiation [12–14].

Growing evidence shows that the IL-17A inhibits osteoblast and osteocyte function via the Wit signaling pathway, IL-17A can weaken the Wnt signaling pathway, and pharmacological blockade of IL-17A activates the Wnt signaling pathway *in vitro* [15]. The Want signaling pathway is involved in osteogenic differentiation of BMSCs, and activation of the Wnt signaling pathway promotes this differentiation [16–18]. In the Wnt signaling pathway, sFRP1, a member of the secreted frizzled-related protein (SFRP) family and a specific Wnt inhibitor, is repressed in osteogenic differentiation [19]. In addition, Wnt3 and Wnt6, which are representative canonical Wnt family members, are activated in the osteogenic differentiation of BMSCs [20,21].

However, the role IL-17A in osteogenic differentiation of BMSCs and the molecular mechanisms of IL-17A in governing osteogenic differentiation of BMSCs remain to be fully elucidated. Based on the above studies, we investigated the role of IL-17A in osteogenic differentiation of BMSCs to determine whether IL-17A affects osteogenic differentiation of BMSCs via the Wnt signaling pathway and whether inhibiting the Wnt signaling pathway blocks the role of IL-17A in osteogenic differentiation of BMSCs, and provide novel strategies for more successful MSC-mediated repair.

Material and Methods

Isolation and culture of BMSCs

Bone marrow tissues were harvested from adult donors and hBMSCs were isolated from human bone marrow tissue. The hBMSCs were cultured in cell medium composed of α-MEM medium (Lonza, Belgium), 10% fetal bovine serum, 2 mM L-glutamine, 100 ug/ml penicillin, and 100 ug/ml streptomycin. Cells from passages 3–6 (cells were >99%) were used for experiments. This study was approved by the Ethics Committee of the First Affiliated Hospital of Chengdu Medical College and written consent was obtained from donors.

Osteogenic differentiation of BMSCs

For osteogenic differentiation, after RNA and protein isolation, the density of BMSCs reached 5×10^3 cells/cm^2, then the growth medium was replaced with osteogenic differentiation medium composed of osteogenic base medium, 100 nM dexamethasone (Sigma), 10 mM β-glycerophosphate (Sigma), and 50 μM ascorbic acid (Sigma). The medium was changed every 3 days for 15 days, with or without the IL-17A (50 ng/ml, R&D systems, France).

ALP and Alizarin Red staining

An alkaline phosphatase detection kit (Jiancheng Bioengineering, China) and an ALP staining kit (Blood institute, Chinese Academy of Medical Sciences) were used to assess ALP activity and ALP staining, according to the manufacturers' protocols. The BMSCs were induced for 15 days, fixed with 70% ethyl alcohol, then stained with the 2% Alizarin Red S (Sigma) to detect matrix mineralization.

Quantitative RT-PCR analysis

For quantitative RT-PCR analysis, total RNA was extracted using the RNeasy plus mini kit (Qiagen). Total RNA concentrations were determined by NanoVue Plus (GE Healthcare, Piscataway, NJ, USA). cDNA was synthesized with the PrimeScript RT reagent kit (TaKaRa, Dalian, China). PCR amplification was performed using the SYBR Premix Ex Taq II kit (TaKaRa, Dalian, China) and the Applied Biosystems ABI Prism 7500 HT sequence detection system. The expression of genes was normalized with β-actin. The list of primers is shown in Table 1. The PCR conditions were: 1 cycle at 95°C for 2 min, 40 cycles at 95°C for 5 s, and 60 °C for 30 s. Gene expression was evaluated based on the threshold cycle (Ct) as $n=2^{-\Delta\Delta Ct}$.

Western blot analysis

Lysis buffer (Beyotime, Nanjing, China) was used to lyse BMSCs. Protein samples were loaded and separated, loaded onto a

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Table 1. The primers of genes.

Genes	Forward (5'-3')	Reverse (5'-3')
ALP	ACGTGGCTAAGAATGTCATC	CTGGTAGGCGATGTCCTTA
OPN	ACTCGAACGACTCTGATGATGT	GTCAGGTCTGCGAAACTTCTTA
Runx2	TCTTCACAAATCCTCCCC	TGGATTAAAAGGACTTGG
sFRP1	TGAGGCCATCATTGAACATC	TCATCCTCAGTGCAAACTCG
Wnt3	CCACAACACGAGGACGGAG	CGCCCAGCCACACACTTC
Wnt6	AAGGTACCATGCTGCCGCCCTTACC	GCAAGCTTTCACAGGCAGGCTGAGCT
β-actin	GCGCGGCTACAGCTTCA	CTTAATGTCACGCACGATTTCC

10% sodium dodecyl sulfate (SDS) polyacrylamide gel, blotted onto a PVDF membrane, blocked in 5% BSA, and incubated with the primary and secondary antibodies. After washing, antibody and antigen complexes were detected using chemiluminescent ECL reagent (Millipore, USA) and protein bands were visualized using an LiDE 100 scanner (Canon, Japan).

Constructing the shsFRP1

The lentiviral plasmid, obtained from GenePharma (China), was used to construct the shsFRP1 expression vector, and shRNA coding sequences were used to direct against sFRP1 mRNA. The 293T cells (Invitrogen, USA) with the vectors of pLVX-control and pLVX-shsFRP1 were used to produce the Lenti-control and Lenti-shsFRP1. The lentiviral particles and siRNA were transfected into the BMSCs. After 12 h, more than 95% of the BMSCs were still viable, and the osteogenic differentiation medium with or without the IL-17A was used to replace the original medium. After 15 days, the transfected BMSCs were harvested and used for further experiments.

Statistical analysis

Data are presented as mean values and standard deviation, and statistical analysis was performed using SPSS (Chicago, IL, USA). The independent-samples *t* test and ANOVA were used to identify differences among all groups, and p value <0.05 was considered to be a statistically significant difference.

Results

IL-17A inhibits osteogenic differentiation of BMSCs

To determine whether IL-17A affected osteogenic differentiation of BMSCs, BMSCs were cultivated with osteogenic differentiation medium (OM) and IL-17A (50 ng/ml), the expression of osteoblastic markers (RUNX2, ALP, and OPN) was detected, and the level of osteogenic differentiation in BMSCs was confirmed. The results showed that the expression of RUNX2, ALP, and OPN was significantly increased after cultivation with OM and without IL-17A; however, the expression of RUNX2, ALP, and OPN was no significantly different after cultivation with OM and IL-17A (Figure 1A–1D). Compared with cultivation with OM and without IL-17A, the expression of RUNX2, ALP, and OPN was also significantly decreased after cultivation with OM and IL-17A (Figure 1A–1D). The ALP and Alizarin Red staining experiments confirmed that IL-17A inhibited osteogenic differentiation level of BMSCs (Figure 1E).

IL-17A blocked the Wnt signaling pathway in BMSCs

To determine whether IL-17A affected the Wnt signaling pathway in osteogenic differentiation of BMSCs, BMSCs were cultivated with IL-17A, and the expression of Wnt signaling pathway inhibitor (sFRP1) and modulators of Wnt signaling pathway (Wnt3, Wnt6) were detected. The results showed that the expression of sFRP1 was significantly up-regulated and the expression of Wnt3 and Wnt6 was significantly down-regulated after cultivation with IL-17A (Figure 2A–2D).

Knockdown of the expression of sFRP1 abolished the inhibition effect of IL-17A in osteogenic differentiation of BMSCs

To analyze whether sFRP1 changed the effect of IL-17A in osteogenic differentiation of BMSCs, Lenti-control and Lenti-shsFRP1 were transfected into BMSCs, BMSCs were cultivated with OM and IL-17A, the Wnt signaling pathway inhibitor (sFRP1) and modulators of the Wnt signaling pathway (Wnt4, Wnt5a) were detected, and the osteogenic differentiation level of BMSCs was confirmed. The results showed that, compared with OM, the expression of sFRP1 was significantly up-regulated, and Wnt4 and Wnt5a were significantly down-regulated in cultivation with OM and IL-17A (Figure 3A–3D). Compared with cultivation with OM and IL-17A, the expression of sFRP1 was significantly up-regulated and Wnt3 and Wnt6 were significantly down-regulated in cultivation with OM and IL-17A

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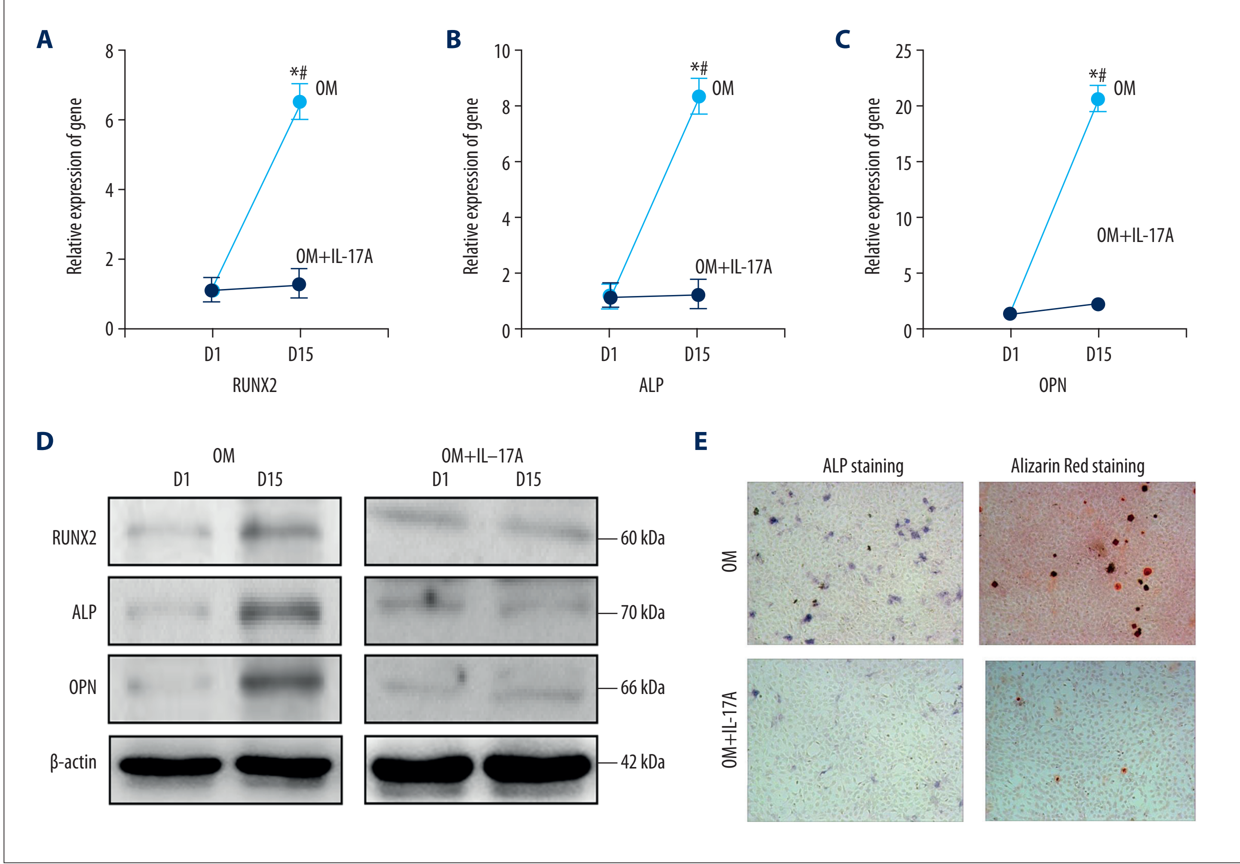

Figure 1. IL-17A inhibited osteogenic differentiation of BMSCs; (**A–C**) The osteoblastic markers were detected by qRT-PCR method; (**D**) The osteoblastic markers were detected by Western blotting; (**E**) ALP staining and Alizarin Red staining were used to assess osteogenic differentiation level of BMSCs; OM – osteogenic differentiation medium; OM+IL-17A – osteogenic differentiation medium with IL-17A; D1 – 1 day; D15 – 15 days; * compared with before induction of differentiation, P value <0.05; # compared with induction of differentiation without IL-17A, P value <0.05.

and Lenti-shsFRP1(Figure 3A–3D). The IL-17A inhibited osteogenic differentiation level of BMSCs, and down-regulated expression of sFRP1 abolished the inhibition effect of IL-17A in osteogenic differentiation level of BMSCs (Figure 3E).

Discussion

Bone loss is the most common complication in chronic inflammatory and metabolic diseases, including diabetes, arthritis, and periodontitis [22–24] The high inflammatory reactions in these diseases have been reported to be involved in the progression of these diseases and to inhibit bone formation. Transplantation therapy, such as BMSCs-based transplantation, is a promising approach to bone regeneration and repair in these diseases [25,26]. Therefore, it is very important to understand the osteogenic capacity of BMSCs in the inflamed environment. In this study, we found that the proinflammatory cytokine IL-17A inhibits osteogenic differentiation of BMSCs through blocking the Wnt signaling pathway, and knockdown of the Wnt signaling pathway abolished the inhibition effect of IL-17A in osteogenic differentiation of BMSCs. Therefore, it is critical to understand the role of proinflammatory cytokines and the Wnt signaling pathway in the process of osteogenic differentiation of BMSCs, and to provide novel strategies for overcoming inflammation to improve the osteogenic capacity of BMSCs and the therapeutic effect.

In previous experiments, results of the effects of IL-17 on osteogenic differentiation were conflicting. For example, IL-17 was reported to inhibit the proliferation and migration of periodontal ligament stem cells and the osteogenic differentiation of these cells through ERK1,2 and JNK mitogen-activated protein kinases [13]. It was also reported that the presence of IL-17 reduced alkaline phosphatase and alizarin red staining and inhibited osteogenic differentiation of calvarial osteoblast precursor cells [12]. It was also reported that zoledronic acid enhanced osteogenic differentiation of BMSCs; however, this effect was not associated with the numbers of regulatory T cells or Th17 levels and IL-17a levels, when co-cultured

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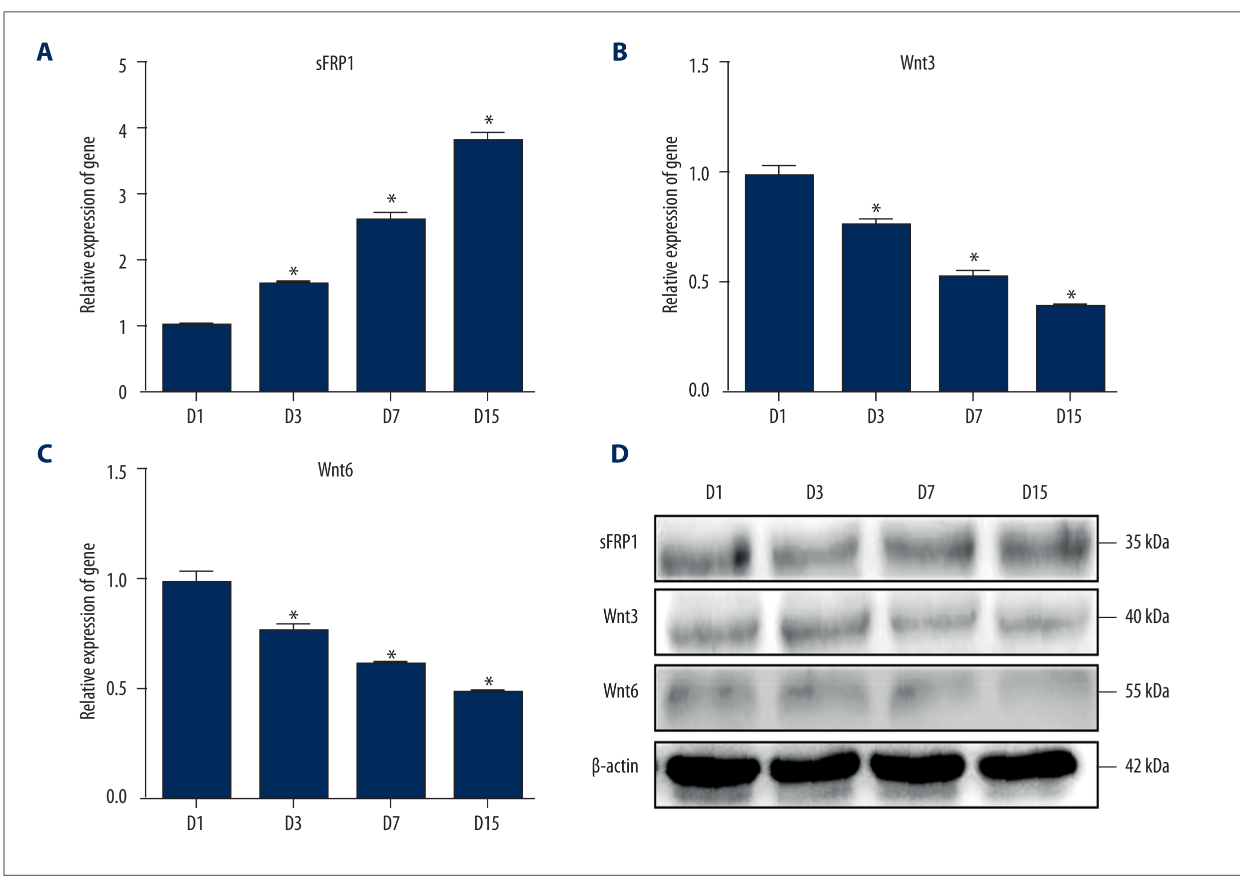

Figure 2. IL-17A blocked the Wnt signaling pathway in BMSCs; (**A–C**) The Wnt signaling pathway inhibitor (sFRP1) and modulators of Wnt signaling pathway (Wnt3, Wnt6) were detected by qRT-PCR method; (**D**) The Wnt signaling pathway inhibitor (sFRP1) and modulators of Wnt signaling pathway (Wnt3, Wnt6) were detected by Western blotting; D1 – 1 day; D3 – 3 days; D7 – 7 days; D15 – 15 days; *: P value <0.05.

with T cells [27]. Finally, IL-17 promotes osteogenic differentiation of C2C12 myoblastic cells through activating the ERK1,2 mitogen-activated protein kinase signaling pathway [28], the IL-17A promotes osteogenic differentiation in isolated fibroblast-like synoviocytes [29,30]. These contradictory data show that IL-17 has both stimulatory and inhibitory effects on osteogenic differentiation of MSCs. The causes of the emergence of this phenomenon still remain unclear. The possible reason is that different conditions of microenvironment and nature of progenitor cells affects the differentiation outcome [31–33]. These studies also further explain that the role of proinflammatory cytokines, such as IL-17A, in osteogenic differentiation of BMSCs is very complicated and understanding the mechanism of this in osteogenic differentiation of BMSCs is necessary and meaningful.

Possible mechanisms of IL-17A in osteogenic differentiation have been proposed. For example, IL-17A could activate osteoclastogenesis and promote bone loss through nuclear factor kappa B ligand (RANKL) and M-CSF [34,35], and IL-17A could further produce proinflammatory cytokines, inhibit osteoblastogenesis, and promote bone loss through Smad ubiquitin regulatory factor (Smurf)1 and NF-kB in the bone morphogenetic protein (BMP)-2 signaling pathway [6,36,37]. IL-17A could induce differentiation of human mesenchymal stem cells through reactive oxygen species (ROS) [38]. Therefore, multiple mechanisms of IL-17A are involved in osteogenic differentiation. In this study, we found that the expression of Wnt signaling pathway inhibitor (sFRP1) was up-regulated, and the modulators of Wnt signaling pathway (Wnt3, Wnt6) were down-regulated in osteogenic differentiation of BMSCs after cultivation with IL-17A. In addition, the down-regulated expression of sFRP1 and the up-regulated expression of Wnt3 and Wnt6 could abolish the inhibition effect of IL-17A in osteogenic differentiation of BMSCs. Growing evidence shows that the Wnt signaling pathway is involved in regulating osteoblast proliferation, maturation, and mineralization, and is an important modulator for the regulation of osteogenic differentiation [39]. The Wnt genes or other chemicals can activate the Wnt signaling pathway and further activate Wnt/β-catenin-responsive genes, such as c-Myc, CyclinD1, TCF-1 and LEF-1, and regulate the developmental processes of osteogenic

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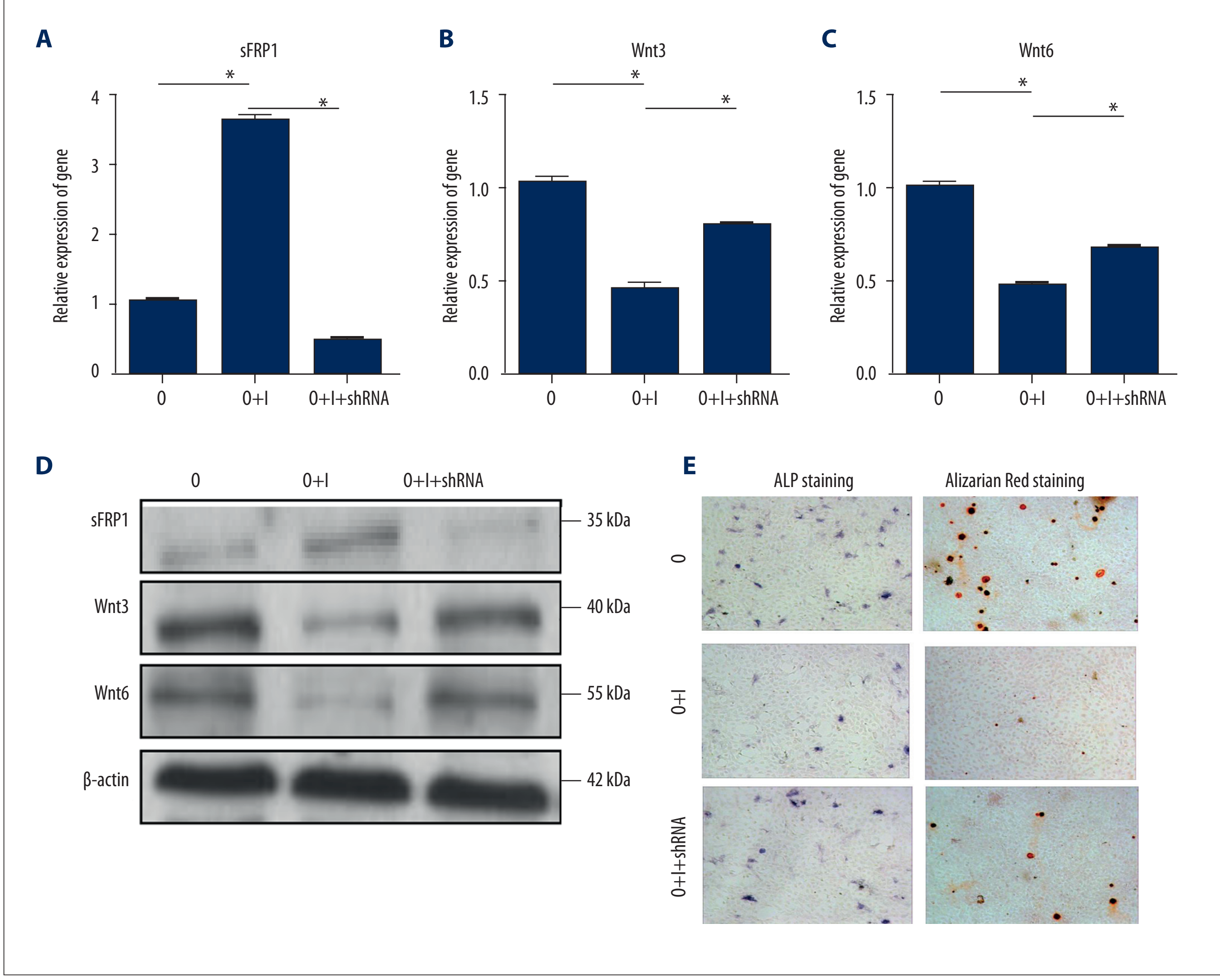

Figure 3. Knockdown of the expression of sFRP1 abolished the inhibition effect of IL-17A in osteogenic differentiation of BMSCs; (**A–C**) The Wnt signaling pathway inhibitor (sFRP1) and modulators of Wnt signaling pathway (Wnt3, Wnt6) were detected by the qRT-PCR method; (**D**) The Wnt signaling pathway inhibitor (sFRP1) and modulators of Wnt signaling pathway (Wnt3, Wnt6) were detected by Western blotting; (**E**) The ALP staining and Alizarin Red staining were used to analyze osteogenic differentiation level of BMSCs; O – osteogenic differentiation medium; O+I – osteogenic differentiation medium with IL-17A; O+I+shRNA – osteogenic differentiation medium with IL-17A+ sFRP1-shRNA; * P value <0.05.

differentiation [16,40]. In addition, the Wnt signaling pathway was involved in osteogenic differentiation of BMSCs, and activation of the Wnt signaling pathway promoted this process [41]. Finally, under inflammatory conditions, IL-17A inhibited osteoblast and osteocyte function and decreased Wnt signaling pathway *in vitro* [15]. Therefore, we conclude that IL-17A inhibited osteogenic differentiation of BMSCs through blocking the Wnt signaling pathway.

Conclusions

This study revealed that IL-17A significantly inhibited osteogenic differentiation of BMSCs through blocking the Wnt signaling pathway, which might be a target to improve the osteogenic capacity of BMSCs and provide novel strategies for bone regeneration and repair in relevant diseases.

Conflicts of interest

All authors declare that they have no conflicts of interest.

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