Biochemical and Biophysical Research Communications xxx (2017) 1–9

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Cyclic compressive stress-induced scinderin regulates progress of developmental dysplasia of the hip

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ARTICLE INFO

Article history:
Received 25 January 2017
Accepted 12 February 2017
Available online xxx

Keywords:
Developmental dysplasia of the hip
Cyclic compressive stress
Scinderin
Osteoblast
Chondrocyte

ABSTRACT

Developmental dysplasia of the hip (DDH) is a common musculoskeletal disorder characterized by a mismatch between acetabulum and femoral head. Mechanical force plays an important role during the occurrence and development of abnormities in acetabulum and femoral head. In this study, we established a mechanical force model named cyclic compressive stress (Ccs). To analyze the effect of Ccs on DDH, we detected special genes in chondrocytes and osteoblasts. Results showed that Ccs downregulated chondrogenesis of ADTC5 in a concentration-dependent manner. Moreover, the mRNA level of Scinderin (Scin) considerably increased. We established lentivirus-SCIN(GV144-SCIN) to transfect hBMSCs, which were treated with different Ccs levels (0.25 Hz*5 cm, 0.5 Hz*5 cm, and 1 Hz*10 cm); the result showed that overexpression of Scin upregulated osteogenesis and osteoclastogenesis. By contrast, expression of chondrocyte-specific genes, including ACAN, COL-2A, and Sox9, decreased. Further molecular investigation demonstrated that Scin promoted osteogenesis and osteoclastogenesis through activation of the *p*-Smad1/5/8, NF-κB, and MAPK P38 signaling pathways, as well as stimulated the expression of key osteoclast transcriptional factors NFATc1 and *c*-Fos. Moreover, Scin-induced osteogenesis outweighed osteoclastogenesis in defective femur in vivo. The results of the analysis of Micro-CT confirmed these findings.

Overall, Ccs influenced the development of DDH by promoting osteogenesis and cartilage degradation. In addition, Scin played a vital role in the development of DDH.

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1. Introduction

Developmental dysplasia of the hip (DDH) is one of most common diseases in pediatric orthopedics with an incidence rate of 2.5%–5% [1]. The pathogenesis of DDH remains unknown, although some risk factors have been identified, including being female and firstborn, as well as genetic factors and wearing swaddling clothes [2,3]. Studies have well documented the contribution of DDH to the high morbidity of osteoarthritis (OA), which is the most common degenerative disease characterized by cartilage degradation, loss of joint space, subchondral sclerosis, and formation of osteophytes [4,5].

Articular cartilage is a biologically active and a relatively acellular complex tissue that allows near frictionless joint motion, which is crucial for the long-term functioning of diarthrodial joints, such as hip joint [6]. Cartilage comprises primarily water, type II collagen, and proteoglycans [7]. Phenotypically, articular chondrocytes are characterized by their ability to synthesize type II collagen and aggrecan, and the matrix allows them to withstand changes in mechanical environment [8]. An etiological study speculates that variation in type II collagen gene is related to the development of DDH [9].

Bone is continuously remodeled in a dynamic balance involving

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http://dx.doi.org/10.1016/j.bbrc.2017.02.065
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Please cite this article in press as: C.-L. Wang, et al., Cyclic compressive stress-induced scinderin regulates progress of developmental dysplasia of the hip, Biochemical and Biophysical Research Communications (2017), http://dx.doi.org/10.1016/j.bbrc.2017.02.065

osteoblasts that produce new bone tissues and osteoclasts that destroy and reabsorb bone tissues [10]. Studies have shown the role of certain substances, such as estrogen, osteoprotegerin, and osteocalcin, which are triggered by biomechanical stress in bone tissue metabolism [11,12]. These outcomes indicate that mechanical stress plays an important role in the maintenance of bone homeostasis.

Scinderin (Scin), also termed Adseverin, is a member of the gelsolin family and has been identified to perform secretory activity in several bovine tissues [13,14]. Recent data suggest that Scin regulates osteoclast formation [15,16], and this phenomenon was confirmed by microarray analysis [17]. Although the role of Scin in osteoclasts has been well characterized, the role of Scin in chondrocytes and osteoblasts is relatively unknown, especially in mechanical environment. This study found that Scin expression is upregulated in DDH patients and in DDH rat model. By using an overexpression lentivirus for Scin, we observed the upregulation of osteoblast and osteoclast in human bone marrow-derived mesenchymal stem cells (HBMSCs) and bone marrow-derived macrophages (BMMs) treated with cyclic compressive stress (Ccs). Furthermore, osteogenesis outweighs osteoclastogenesis in defective femur model. Therefore, we concluded that Scin is a novel regulator in DDH.

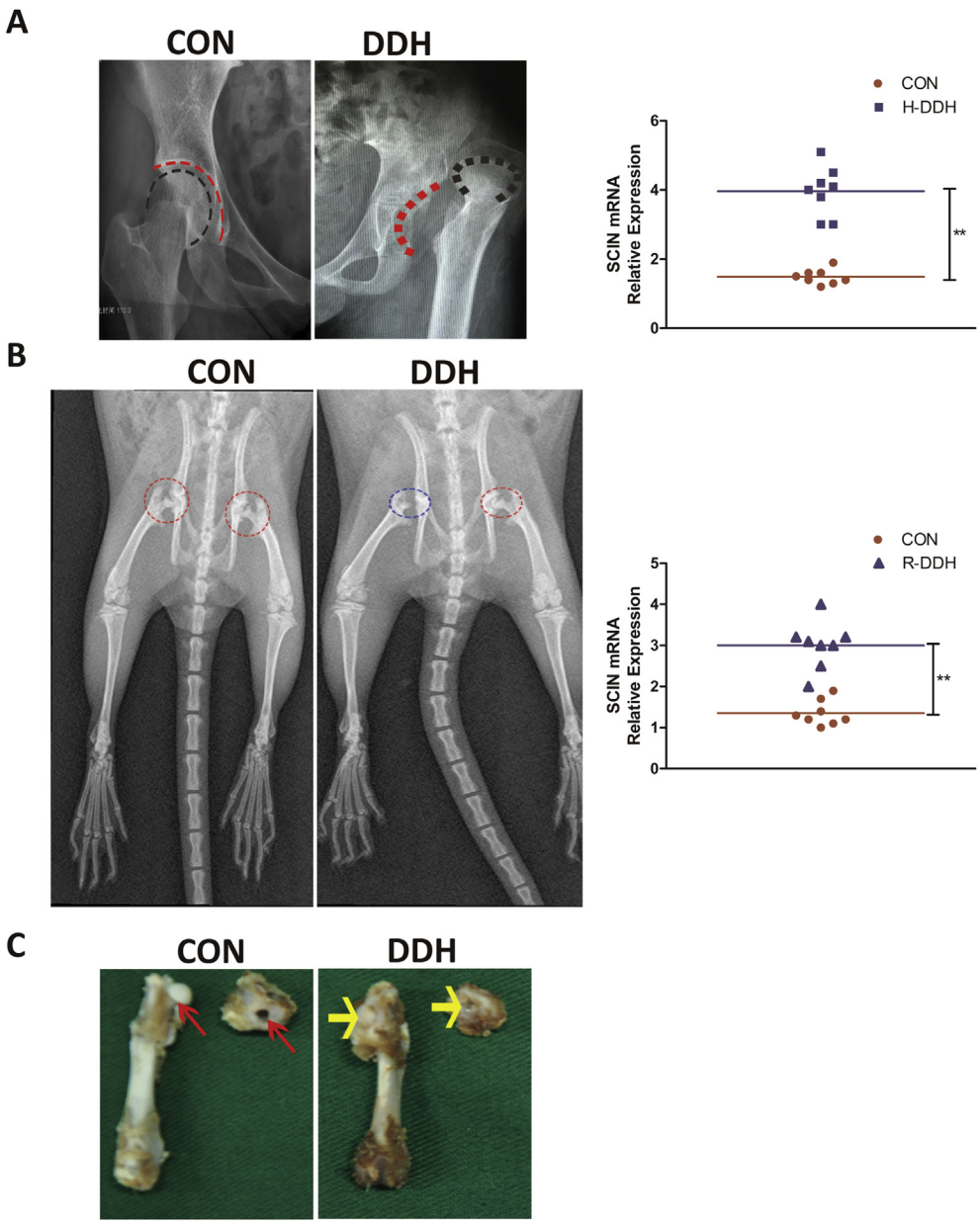

Fig. 1. Radiographs and experimental data of patients and rats with or without Developmental dysplasia of the hip (DDH). **(A)** Radiographic results of patients with DDH (H-DDH) or without DDH (Trauma fracture). Acetabulum is indicated by red dotted line, whereas the femoral head is indicated by black dotted line; Scin mRNA expression was detected in both groups (right); ($n = 8$; $^{**}P < 0.01$). **(B)** Radiographic results for rats with DDH (R-DDH) or without DDH. Normal hip joint is indicated by red dashed circles, whereas the hip joint of DDH is indicated by blue dashed circles; Scin mRNA expression was detected in both groups (right). ($n = 8$; $^{**}P < 0.01$); **(C)** General observation of samples obtained from rats with or without DDH. Normal acetabulum and femoral head are indicated by red arrows, whereas the acetabulum and femoral head of DDH are indicated by yellow arrows. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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