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# Compression loading of osteoclasts attenuated microRNA-146a-5p expression, which promotes angiogenesis by targeting adiponectin

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Osteoclastogenesis in alveolar bone induced by compression stress triggers orthodontic tooth movement. Compression stress also stimulates angiogenesis, which is essential for osteoclastogenesis. However, the effects of osteoclastogenesis induced by compression on angiogenesis are poorly understood. *In vivo*, we found the markers of angiogenesis increased during orthodontic bone remodeling. *In vitro*, osteoclast-derived exosomes increased proliferation, migration, and tube formation of human umbilical vein endothelial cells (HUVECs), as well as expression of vascular endothelial growth factor and CD31. The promotive effects of exosomes derived from compressed osteoclasts were greater than those derived from osteoclasts without compression. Next, we analyzed changes in the microRNA transcriptome after compression stress and focused on microRNA146a-5p (miR-146a), which was significantly decreased by compression. Transfection of an inhibitor of miR-146a stimulated angiogenesis of HUVECs while miR-146a mimics repressed angiogenesis. Adiponectin (ADP) was confirmed to be a target of miR-146a by dual luciferase reporter assay. In HUVECs treated with exosomes, we detected increased ADP which promoted angiogenesis. Knockdown of ADP in HUVECs reduced the promotive effects of exosomes. Our results demonstrate that the decreased miR-146a observed in osteoclasts after compression promotes angiogenesis by targeting ADP, suggesting a novel method to interfere with bone remodeling induced by compression stress.

**microRNA-146a-5p, adiponectin, angiogenesis, compression stress, osteoclastogenesis, exosomes**

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## INTRODUCTION

Orthodontic tooth movement is a biological consequence of alveolar bone remodeling induced by mechanical force and is controlled by osteoclasts and osteoblasts (Zheng et al., 2017). Osteoclasts originate from the compressive side of the periodontal ligament (PDL) by the fusion of pre-osteoclasts recruited during orthodontic tooth movement (Rody Jr et al., 2001). Because the efficiency of orthodontic tooth movement depends on bone resorption, osteoclastogenesis and the biological changes in osteoclasts under compression force are crucial to orthodontic treatment (Soma et al., 1999).

The function of bone tissue is influenced by many factors including hormones, growth factors, mechanical loading, and vascularization (Peng et al., 2020; Rumney et al., 2019; Su et al., 2018). Angiogenesis is the formation of new blood vessels from pre-existing vasculature, which involves the proliferation and migration of endothelial cells and finally tube formation (Azad et al., 2019; Ratajczak et al., 2018; Xie et al., 2014). Angiogenesis in the PDL can be induced by orthodontic compression forces (Niklas et al., 2013). Following application of orthodontic force, an occlusion of vascularization appears on the compressive side of the PDL, resulting in the induction of angiogenesis to adapt to the hypoxic situation (Niklas et al., 2013). In addition, earlier studies highlighting the coupling of angiogenesis and os-

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