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Mechano-growth factor protects against mechanical overload induced damage and promotes migration of growth plate chondrocytes through RhoA/YAP pathway

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Abstract

Epiphyseal growth plate is highly dynamic tissue which is controlled by a variety of endocrine, paracrine hormones, and by complex local signaling loops and mechanical loading. Mechano growth factor (MGF), the splice variant of the IGF-I gene, has been discovered to play important roles in tissue growth and repair. However, the effect of MGF on the growth plate remains unclear. In the present study, we found that MGF mRNA expression of growth plate chondrocytes was upregulated in response to mechanical stimuli. Treatment of MGF had no effect on growth plate chondrocytes proliferation and differentiation. But it could inhibit growth plate chondrocytes apoptosis and inflammation under mechanical overload. Moreover, both wound healing and transwell assay indicated that MGF could significantly enhanced growth plate chondrocytes migration which was accompanied with YAP activation and nucleus translocation. Knockdown of YAP with YAP siRNA suppressed migration induced by MGF, indicating the essential role of YAP in MGF promoting growth plate chondrocytes migration. Furthermore, MGF promoted YAP activation through RhoA GTPase mediated cytoskeleton reorganization, RhoA inhibition using C3 toxin abrogated MGF induced YAP activation. Importantly, we found that MGF promoted focal adhesion(FA) formation and knockdown of YAP with YAP siRNA partially suppressed the activation of FA kinase, implying that YAP is associated with FA formation. In conclusion, MGF is an autocrine growth factor which is regulated by mechanical stimuli. MGF could not only protect growth plate chondrocytes against damage by mechanical overload, but also promote migration through activation of RhoA/YAP signaling axis. Most importantly, our findings indicate that MGF promote cell migration through YAP mediated FA formation to determine the FA-cytoskeleton remodeling.

Key words: Mechano-growth factor; RhoA/YAP; Migration; Focal adhesion; Cytoskeleton

INTRODUCTION

Longitudinal growth of long bones is a tightly regulated process achieved by endochondral ossification, in which cartilage is replaced by bone tissue. The coordinated recruitment, proliferation, hypertrophy and apoptosis of chondrocytes play a crucial role to ensure physiological growth[1]. This extremely complex process is regulated by a variety of endocrine, paracrine, autocrine hormones, and by complex local signaling loops and mechanical loading[2]. It is widely recognized that mechanical loading exerts crucial effects on the development of cartilage and bone tissue at the levels of gene expression, protein transcription, and growth factors secretion [3, 4].

Mechano-growth factor (MGF) is an alternative splice variant of the IGF-I gene and serves as a protective growth factor in response to changes in physiological conditions or environmental stimuli[5]. Insulin-like growth factor 1 (IGF-1) plays an important role in regulating embryonic development and postnatal growth[6]. The IGF-1 gene contains 6 exons and generates three isoforms in humans, which are IGF-I Ea, IGF-I Eb, and IGF-I Ec, but only two isoforms in rat, namely IGF-I Ea and IGF-I Eb[7]. Human IGF-1Ec and rodent IGF-1 Eb are named MGF for its up-regulation in exercised and damaged muscles [8]. IGF-1Ea is the predominant isoform which is produced