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Wedelolactone inhibits osteoclastogenesis but enhances osteoblastogenesis through altering different semaphorins production

Xue Deng[a,1], Li-Na Liang[a,1], Di Zhu[a], Lu-Ping Zheng[a], Jing-Hua Yu[b], Xiang-ling Meng[b], Yi-Ning Zhao[a], Xiao-Xin Sun[a], Tao-Wen Pan[a], Yan-Qiu Liu[a,*]

[a] Institute (College) of Integrative Medicine, Dalian Medical University, Dalian 116044, China
[b] Institute of Virology and AIDS Research, The First Hospital of Jilin University, Jilin University, Changchun, Jilin Province 130000, China

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ABSTRACT

Our previous study showed that wedelolactone, isolated from Ecliptae herba, enhanced osteoblastogenesis but inhibited osteoclastogenesis through Sema3A signaling pathway. This study aims to investigate the role of other semaphorins in wedelolactone-enhanced osteoblastogenesis and -inhibited osteoclastogenesis. Wedelolactone inhibited RANKL-induced Sema4D and Sema7A production, but had no effect on RANKL-reduced Sema6D expression in osteoclastic RAW264.7 cells. In mouse bone marrow mesenchymal stem cells (BMSC), wedelolactone reversed osteogenic medium(OS)-reduced Sema7A expression and OS-enhanced Sema3E mRNA expression, but no effect on OS-reduced Sema3B mRNA expression. Addition of Sema4D antibody promoted wedelolactone-reduced TRAP activity and bone resorption pit formation. Wedelolactone combined with Sema4D antibody inhibited the formation of Sema4D-Plexin B1 complex. In co-culture of BMSC with RAW264.7 cells, Sema7A antibody, similar with Sema 3A antibody, reversed wedelolactone-enhanced ALP activity and mineralization level, but promoted wedelolactone-inhibited TRAP activity. However, Sema3E and Sema3B antibodies had no effect. Further, wedelolactone enhanced the binding of Sema7A with PlexinC1 and Beta1, but addition of Sema7A antibody partially blocked this binding. Our data demonstrated that wedelolactone inhibited Sema4D production and Sema4D-PlexinB1 complex formation in RAW264.7 cells, thereafter inhibiting osteoclastogenesis. At the same time, wedelolactone enhanced osteoblastogenesis through promoting Sema7A production and Sema7A-PlexinC1-Beta1 complex formation in BMSC.

1. Introduction

Bone homeostasis is maintained by osteoblast-mediated bone formation and osteoclast-mediated bone resorption. The excess of osteoclastic bone resorption over osteoblastic bone formation results in bone-related diseases such as osteoporosis. Anti-resorptive drugs such as alendronate are most frequently used in clinic for curing osteoporosis, but treatment with alendronate for a long time concurrently impaired bone formation [1]. For the anabolic agent parathyroid hormone (PTH), a concomitant increase in bone resorption can be observed [2]. Therefore, it is crucial to identify a new class of agents that can regulate both formation and resorption [3].

Wedelolactone is a major component isolated from Ecliptae herba, which has been used as “Kidney-tonifying” traditional Chinese medicine for several thousand years and thereafter have the potential to strengthen bones [4]. Wedelolactone is reported to inhibit 5-lipoxygenase and trypsin [5,6], antagonize myotoxins [7], and induce caspase-dependent apoptosis [8]. We previously reported that wedelolactone inhibited pre-osteoclastic proliferation and differentiation [9], but enhanced osteoblast differentiation from BMSC through stimulation of Sema3A production [10,11].

Semaphorins are a family of cell-surface or soluble proteins that are able to regulate cell-cell interactions as well as cell differentiation, morphology and function. In the mammalian system, 20 semaphorins have been identified and fall into five classes (semaphorins 3–7) that are characterized by particular structural properties [12]. Among semaphorins, Sema3A and 3E are produced from osteoblasts, while Sema4D and 6D are expressed by osteoclasts. Sema7A can be expressed in both osteoblasts and osteoclasts. The role of semaphorin family proteins in osteoblast and osteoclast is different [13]. The effects of semaphorins are mediated by plexins, a group of nine transmembrane receptors that can be subdivided into four classes, plexins A–D. The

* Corresponding author at: No. 9 West Section Lvshun South Road, Institute (College) of Integrative Medicine, Dalian Medical University, Dalian 116044, China.
E-mail address: yqliu@dmu.edu.cn (Y.-Q. Liu).
[1] These authors contributed equally to this work.

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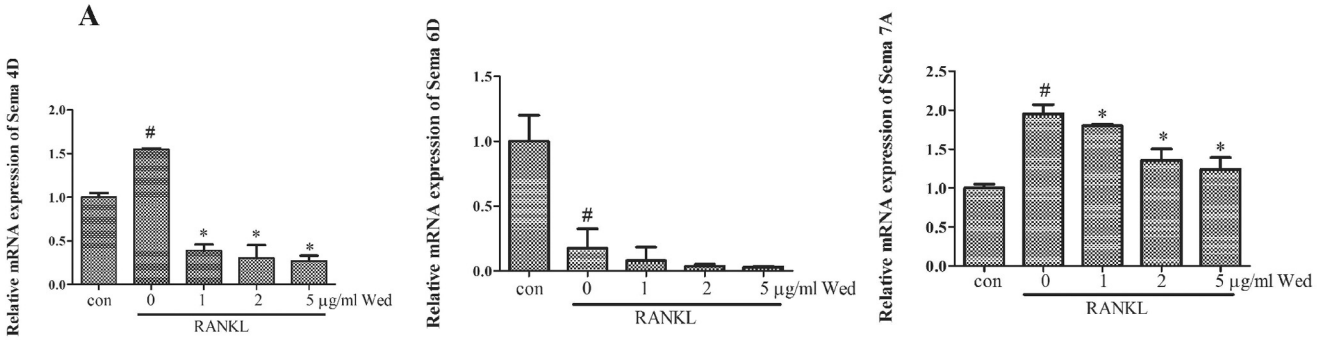

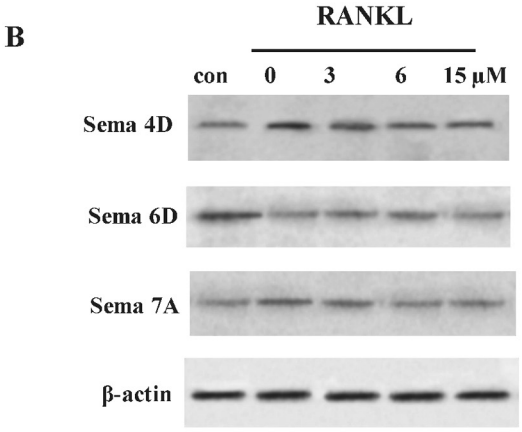

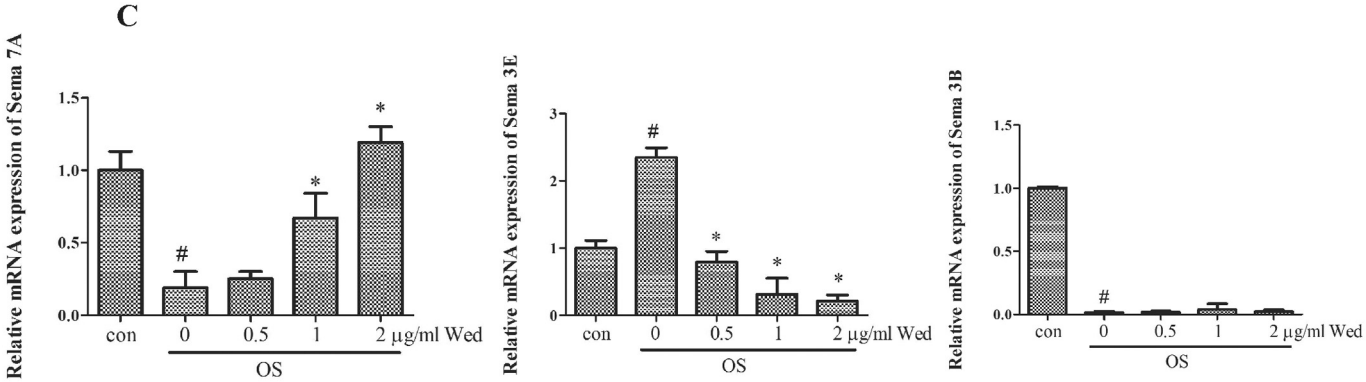

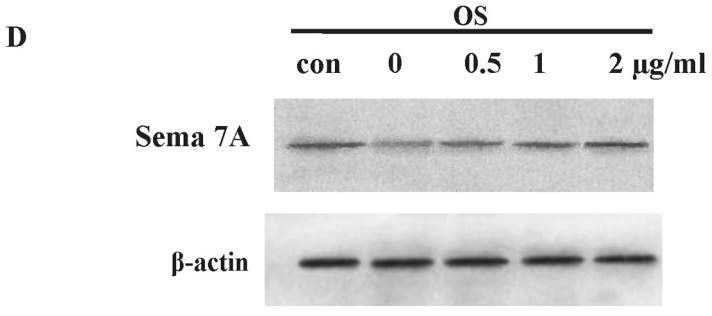

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