Title

CYR61/CCN1 Regulates Sclerostin Levels and Bone Maintenance

Journal

Journal of Bone and Mineral Research, 33(6)

ISSN

0884-0431

Authors

Zhao, Gexin

Huang, Bau-Lin

Rigueur, Diana

et al.

Publication Date

2018-06-01

DOI

10.1002/jbmr.3394

Peer reviewed

J Bone Miner Res
2018 Jun;33(6):1076-1089.
doi: 10.1002/jbmr.3394. Epub 2018 Mar 5.

CYR61/CCN1 Regulates Sclerostin Levels and Bone Maintenance

Gexin Zhao[1], Bau-Lin Huang[2], Diana Rigueur[1], Weiguang Wang[1], Chimay Bhoot[1], Kemberly R Charles[1], Jongseung Baek[1,3], Subburaman Mohan[4,5], Jie Jiang[1,6,7], Karen M Lyons[1,3,7]
Affiliations expand

- PMID: 29351359
- PMCID: PMC6002906
- DOI: 10.1002/jbmr.3394

Abstract

CYR61/CCN1 is a matricellular protein that resides in the extracellular matrix, but serves regulatory rather than structural roles. CYR61/CCN1 is found in mineralized tissues and has been shown to influence bone healing in vivo and osteogenic differentiation in vitro. In this study we generated Cyr61 bone-specific knockout mice to examine the physiological role of CYR61/CCN1 in bone development and maintenance in vivo. Extensive analysis of Cyr61 conditional knockout mice showed a significant decrease in both trabecular and cortical bone mass as compared to WT littermates. Our data suggest that CYR61/CCN1 exerts its effects on mature osteoblast/osteocyte function to modulate bone mass. Specifically, changes were observed in osteocyte/osteoblast expression of RankL, VegfA, and Sost. The increase in RankL expression was correlated with a significant increase in osteoclast number; decreased VegfA expression was correlated with a significant decrease in bone vasculature; increased Sost expression was associated with decreased Wnt signaling, as revealed by decreased Axin2 expression and increased adiposity in the bone marrow. Although the decreased number of vascular elements in bone likely contributes to the low bone mass phenotype in Cyr61 conditional knockout mice, this cannot explain the observed increase in osteoclasts and the decrease in Wnt signaling. We conducted in vitro assays using UMR-106 osteosarcoma cells to explore the role CYR61/CCN1 plays in modulating Sost mRNA and protein expression in osteocytes and osteoblasts. Overexpression of CYR61/CCN1 can suppress Sost expression in both control and Cyr61 knockout cells, and blocking Sost with siRNA can rescue Wnt responsiveness in Cyr61 knockout cells in vitro. Overall, our data suggest that CYR61/CCN1 modulates mature osteoblast and osteocyte function to regulate bone mass through angiogenic effects as well as by modulating Wnt signaling, at least in part through the Wnt antagonist Sost. © 2018 American Society for Bone and Mineral Research.

Keywords: ANIMAL MODELS; BONE MODELING AND REMODELING; CELL/TISSUE SIGNALING; CELLS OF BONE; GENETIC ANIMAL MODELS; MOLECULAR PATHWAYS; OSTEOCYTES; PARACRINE PATHWAYS; REMODELING; WNT/BETA-CATENIN/LRPS.