

EDITORIAL

Bone Loss in Intestinal Inflammation Disease Yields to Osteoclastogenesis Inhibition



In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Peek et al¹ provide important new insight into the osteoclast signaling that underlies the bone loss occurring in inflammatory bowel disease (IBD). Initially, these investigators show, using both noninfectious and infectious murine models, that loss of trabecular bone is a universal consequence of gut inflammation. They then go on to show that this is associated with increased bone levels of an array of cytokines and chemokines, most notably granulocyte colony-stimulating factor (CSF), tumor necrosis factor α (TNF- α), interleukin (IL)-12, and MCP-1 (Monocyte Chemoattractant Protein-1 (CCL-2 (Chemokine (C-C Motif) Ligand 2)), but no increases in levels of downstream effector cytokines, IFN (interferon)- γ and IL-17. In addition, these increases occurred *pare passu*, with increases in various osteoclast progenitor cells (OPCs) such as lineage-negative Sca-1⁺ (Stem Cell Antigen-1) cells, c-Kit⁺ (Tyrosine protein kinase KIT) cells, and CD11b^{-/lo}Ly6C^{hi} cells within the bone marrow. These findings were taken as evidence that the cytokines and chemokines were acting by promoting osteoclast progenitor development and trafficking; however, the possibility that they also were stimulating osteoclast formation and activity was not ruled out. In accompanying further studies, the investigators found that macrophage CSF, a major inducer of osteoclastogenesis, was increased only modestly and relatively late during DSS (dextran sodium sulfate)-colitis inflammation; in addition, whereas RANK (Receptor Activator of nuclear factor K B), another major inducer, was not measured; its receptor was decreased on OPCs during colitis. This indicates that gut inflammation-associated bone loss is not caused primarily by changes in the level/activity of these major inducers, as perhaps equivocally suggested in previous studies.^{2,3} On the other hand, the osteoclastogenesis was associated with enhanced OPC expression of RANK/CSF1Receptor co-receptors, especially MDL-1 (Myeloid Dap12-Associating Lectin 1, CLEC5A (C-type Lectin domain family 5)). Thus, it emerged that bone loss in IBD is owing to increased expression of 1 (or more) receptor providing co-stimulation, rather than those providing primary stimulation of osteoclast precursors. Based on these findings, Peek et al¹ examined the effect of administration of antagonistic anti-MDL-1 on bone loss occurring during colitis and, indeed, showed that MDL-1 neutralization impeded such loss. The question therefore arises as to whether IBD-associated bone loss can and should be treated with an MDL-1 inhibitor.

MDL-1, a C-type lectin, is a component of the remarkably complex signaling program that guides the

development and/or activation of osteoclasts.⁴ A somewhat simplified description of its function is that MDL-1 is one of several co-receptors whose activation is necessary for stimulation of osteoclastogenesis by the primary osteoclast activators RANKL (acting via RANK) and/or macrophage CSF (acting via CSF1Receptor).⁵ When stimulated by its ligand, MDL-1 provides such co-activation via activation of intracellular signaling adaptors adjacent to the cell membrane, ITAM (immunoreceptor tyrosine-based activating motif)-harboring proteins called DAP 12 and DAP10.⁶ In this respect, MDL-1 is closely related to another co-receptor, TREM2 (Triggering Receptor Expressed on Myeloid Cells 2), which also signals through DAP12 and DAP10 and is distantly related to other co-receptors, PIR-A and OSCAR, that use another ITAM-harboring protein. The latter also serves yet other osteoclastogenic co-stimulators, various Fc γ receptors. As if this signaling program was not complicated enough, it should be added that osteoclastogenesis also is regulated by an Fc γ receptor acting through an ITIM (immunoreceptor tyrosine-based inhibitory motif)-harboring protein that in this case results in a negative signal. Why this complexity? One possibility is that each co-receptor, by acting through its specific ligand, allows regulation of osteoclastogenesis to be tailored to particular microenvironments and/or situations. The endogenous ligand for MDL-1 is not known and therefore it is not known whether increases in its level is unique to gut inflammation and as such is specifically necessary for bone loss occurrence in this circumstance.

MDL-1 is expressed on myeloid cells other than osteoclasts or their precursors and in fact is highly expressed on macrophages upon stimulation by TNF- α (but not interferon- γ).⁷ This suggests that MDL-1 signaling subtends a range of responses other than those related to osteoclastogenesis. This possibility is supported by the observation that mice lacking MDL-1 show decreased experimental arthritis and mice administered agonistic anti-MDL-1 show increased arthritis and cytokines driving the latter.⁷ In addition, it is supported by the fact that in the study under discussion, antagonistic anti-MDL-1 administration ameliorated DSS colitis to some extent. This opens the door to the possibility that the decreased bone loss observed was in part the result of decreased underlying inflammation.

The question posed earlier and still to be addressed is whether prevention of bone loss by specific blockade of osteoclast activity, such as that achieved with anti-MDL-1, rather than by blockade of the underlying inflammation, is a

worthwhile clinical goal. Peek et al¹ are conservative in their answer to this question in that they suggest that specific therapy may be limited to those patients whose disease cannot be completely controlled by standard antibiologic therapy and then only in conjunction with the latter. However, they did not provide data on whether biologic therapy such as administration of anti-TNF- α or anti-IL12p40 alone provide as much amelioration of bone loss as anti-MDL-1. Until this question is answered, use of anti-MDL-1 must be held in abeyance.

WARREN STROBER, MD

Mucosal Immunity Section

Laboratory of Clinical Immunology and Microbiology

National Institute of Allergy and Infectious Diseases,

National Institutes of Health

Bethesda, Maryland

References

1. Peek CT, Ford CA, Eichelberger KR, Jacobse J, Torres TP, Maseda D, Latour YL, Piazuelo MB, Johnson JR, Bynloss MX, Wilson KT, Rathmell JC, Goettel JA, Cassat JE. Intestinal inflammation promotes MDL-1⁺ osteoclast precursor expansion to trigger osteoclastogenesis and bone loss. *Cell Mol Gastroenterol Hepatol* 2022;14:731–750.
2. Moschen AR, Kaser A, Enrich B, Ludwiczek O, Gabriel M, Obrist P, Wolf AM, Tilg H. The RANKL/OPG system is activated in inflammatory bowel disease and relates to the state of bone loss. *Gut* 2005; 54:4479–4487.
3. Franchimont N, Reenaers C, Lambert C, Belaiche J, Bours V, Malaise M, Delvenne P, Louis E. Increased expression of receptor activator of NF- κ B ligand (RANKL), its receptor RANK and its decoy receptor osteoprotegerin in the colon of Crohn's disease patients. *Clin Exp Immunol* 2004;138:491–498.
4. Humphrey MB, Nakamura MC. A comprehensive review of immunoreceptor regulation of osteoclasts. *Clin Rev Allergy Immunol* 2016;51:48–58.
5. Teitelbaum SL. Bone resorption by osteoclasts. *Science* 2000;289:1504–1508.
6. Inui M, Kikuchi Y, Aoki N, Endo S, Maeda T, Sugahara-Tobinai A, Fujimura S, Nakamura A, Kumanogoh A, Colonna M, Takai T. Signal adaptor DAP10 associates with MDL-1 and triggers osteoclastogenesis in cooperation with DAP12. *Proc Natl Acad Sci U S A* 2009;106:4816–4821.
7. Joyce-Shaikh B, Bigler ME, Chao C-C, Murphy EE, Blumenschein WM, Adamopoulos IE, Heyworth PG, Antonenko S, Bowman EP, McClanahan TK, Phillips JH, Cua DJ. Myeloid DAP12-associating lectin (MDL)-1 regulates synovial inflammation and bone erosion associated with autoimmune arthritis. *J Exp Med* 2010; 207:579–589.

Correspondence

Address correspondence to: Warren Strober, MD, Mucosal Immunity Section, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland. e-mail: wstrober@niaid.nih.gov.

Conflicts of interest

The author discloses no conflicts.



Most current article

© 2022 The Author. Published by Elsevier Inc. on behalf of the AGA Institute. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

2352-345X

<https://doi.org/10.1016/j.jcmgh.2022.07.015>