Citation: BoneKEy Reports **3**, Article number: 527 (2014) | doi:10.1038/bonekey.2014.22

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REVIEW

Osteoimmunology: oncostatin M as a pleiotropic regulator of bone formation and resorption in health and disease

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Bone remodeling in health and disease is carried out by osteoblasts and osteoclasts, which respectively produce bone matrix and resorb it. Endocrine and paracrine control of these cells can be direct, but they are also exerted indirectly, either by influencing progenitor cell differentiation or by stimulating paracrine signals from local accessory cells including osteocytes (which form a critical communication and regulation network within the bone matrix), macrophages and T lymphocytes. Here we review the osteotropic actions of the interleukin-6 family member cytokine oncostatin M (OSM), which is of particular interest because of its ability to stimulate bone accrual. OSM is produced within the bone microenvironment by cells of both mesenchymal and hematopoietic origin, including osteocytes, osteoblasts, macrophages and T lymphocytes, and can act via two receptor complexes: OSM receptor:gp130 and leukemia inhibitory factor receptor (LIFR):gp130. Although OSM can directly stimulate osteoblast mineralization activity and differentiation, it can also stimulate mesenchymal stem cell osteoblastic commitment at the expense of adipogenesis. In osteocytes, OSM can suppress the production of the bone formation inhibitor sclerostin, an action that is mediated by LIFR:gp130. OSM also stimulates the production of receptor activator of nuclear factor κB ligand by osteoblasts and thereby drives the formation of osteoclasts particularly in pathological conditions. Thus, cellular effects of OSM on bone metabolism include direct and indirect actions mediated by two related receptor/ligand complexes. OSM therefore provides an example of paracrine and endocrine control mechanisms that regulate bone mass by controlling both bone formation and resorption.

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Introduction: Oncostatin M (OSM)

To design new therapies to improve bone health, we need to understand the key mechanisms that influence bone metabolism in both physiological and pathological conditions. Here we focus on OSM, a member of the interleukin (IL)-6 family of cytokines, as this hormone strongly influences both bone formation and resorption.

OSM is a pleiotropic cytokine first identified by Zarling *et al.*[1] as a secreted product of macrophage-like cells that inhibited the proliferation of melanoma-, neuroblastoma- and lung cancer-derived cell lines. In contrast to these early roles, OSM also has stimulatory roles in a number of human cancers including Kaposi's sarcoma[2] and breast cancer.[3] Frequently acting in conjunction with inflammatory factors or other gp130-dependent cytokines, OSM has been implicated in diverse disorders including pulmonary tissue fibrosis,[4] cardiac disease and repair,[5] prostate cancer,[6] asthma,[7] periodontal disease[8] and both rheumatoid arthritis and osteoarthritis.[9] In the context of skeletal biology, OSM is of particular interest as it displays anabolic effects on both cortical and trabecular bone (which would be clinically desirable to emulate) while at the same time driving osteoclast formation; notably, both influences are at least in part mediated by OSM action on the osteoblast lineage. It is also becoming clear that OSM has numerous strong influences on other less well-characterized cell types within the bone microenvironment. The existence of multiple pathways of influence raises questions about which cellular mechanisms are most critical in influencing bone anabolism.

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Received 27 November 2013; accepted 7 January 2014; published online 14 May 2014

Multiple Cellular Interactions Regulate Bone Structure

Bone mass in health and disease is determined by the actions of two unique cell types: myelomonocyte-derived multinucleated osteoclasts that resorb bone, and mesenchymal-derived osteoblasts that form bone matrix and regulate its mineralization. The coordinated actions of these two cell types are central to the life-long process of skeletal renewal, termed bone remodeling. Their actions are also coordinated during fetal development, bone growth, fracture repair, changes of bone structure in response to mechanical loading and in non-mechanical functions such as serum calcium and phosphate maintenance. Any disruption in the balance of their activities may result in skeletal disease.

Precise osteoclast–osteoblast coordination is a particular requirement for bone remodeling. This process maintains bone strength and quality throughout life by osteoclastic resorption of areas of old or damaged bone and replacement with a similar amount of new bone at the same site by osteoblasts.[10] Although early studies suggested that such coordination between osteoclast and osteoblast activity occurred in relative isolation in the basic multicellular unit, it is now clear that several important local accessory cell types influence bone metabolism through their paracrine secretions,[11] and may mediate many of the effects of drugs and cytokines on bone metabolism. These accessory cells include osteocytes,[12] bone marrow stromal cells and osteal macrophages;[13] some less well-delineated influences include those from local endothelial cells,[14] nerve cells[15,16] and cell populations of the bone marrow cavity such as lymphocytes, as discussed below.

OSM is produced by several cell types found in the bone microenvironment, and it influences the skeleton both by direct actions on the osteoblast lineage and by indirect actions through other accessory cells. These will be discussed below with reference to their contributions to normal physiology, pathological bone disorders and possibilities for therapeutic application of this knowledge.

The Influences of OSM on the Cells of Bone: Osteoclasts, Osteoblasts and Osteocytes

OSM stimulates osteoclast formation via osteoblastic receptor activator of nuclear factor κB ligand (RANKL) expression. OSM probably does not affect osteoclasts or their progenitors directly, but its action does strongly increase osteoclast formation both *in vivo* and in hematopoietic populations cocultured with osteoblasts.[17] The latter is due to an OSM-induced increase in osteoblastic expression of RANKL.[18] This action is mediated by the OSM receptor (OSMR):gp130 receptor complex and downstream initiation of JAK/STAT signaling (principally STAT3 activation[19]) in osteoblastic cells.[20] OSM induces RANKL transcription by promoting STAT3 and RNA polymerase II binding to a subset[21] of 5 distal enhancer regions of the RANKL gene also utilized by parathyroid hormone (PTH) and 1,25-dihydroxyvitamin-D_3,[22] and a third more distal enhancer region.[23] Notably, genetic deletion of the distal control region led to a significant increase in bone mass owing to a low level of RANKL expression and limited bone resorption,[24] a phenotype strikingly similar to that of OSMR-null mice.[25]

The influence of OSM in driving osteoclast formation was the focus of much early work in osteoclast biology, particularly in the context of osteolytic bone disease. Indeed, OSM participates significantly in osteoclast formation in the context of breast cancer invasion of bone,[26] and may also be involved in the increased bone destruction associated with inflammatory arthritis.[27,28] The low osteoclast numbers observed in the OSMR-null mice also suggested a role for OSM in normal physiological levels of resorption in the process of bone remodeling.[25] However, osteoclast generation from OSMR-deficient marrow cells is similar to that of wild-type bone marrow. This indicates that changes in osteoclast numbers are not caused by the OSMR-null hematopoietic phenotype, and probably does not reflect a change in osteoclast progenitor number or responsiveness to RANKL.[29] Rather, our studies using osteoblast/bone marrow cocultures have indicated that osteoclast differentiation is defective when it is supported by osteoblasts that lack the OSMR. This is the case not only when the hormonal stimulus inducing osteoblastic RANKL is OSM, but also when it is 1,25-dihydroxyvitamin-D_3; this points to a previously unsuspected influence of OSMR in osteoblast RANKL production that may be critical to osteoclast formation and bone metabolism.[25] As neither osteocyte-specific nor osteoblast-lineage-specific gp130-null mice exhibit any alteration in osteoclast numbers,[30] the reduced osteoclast formation observed in OSMR-null mice may reflect an influence mediated by early osteoblast progenitors rather than by mature osteoblasts or osteocytes.

The Influence of OSMR in the Action of PTH

Although the above observations indicate that the presence of OSMR increases the osteoblastic capacity to produce RANKL, we also made an observation that strikingly deviated from this pattern. This was seen when OSMR-null osteoblasts or mice were treated with PTH.

Treatment with PTH injection (which results in intermittently high PTH serum levels) has two particular effects *in vivo*: it stimulates RANKL production in osteoblasts and stimulates bone formation by promoting proliferation and differentiation of osteoblasts while inhibiting their apoptosis.[31] As PTH treatment also induces OSMR expression, we suggested that some PTH actions may depend on OSMR signaling.[32] However, when OSMR-deficient osteoblasts *in vitro* were stimulated with PTH, their support of osteoclast formation was much greater than that of wild-type osteoblasts.[32] Increased osteoclast formation was also seen *in vivo* when OSMR-null mice were treated with PTH to the degree that a PTH injection regimen that showed anabolic effects in control mice was actually *catabolic* in OSMR-null mice. Anabolic effects of intermittent PTH treatment are normally associated with only a short and transient induction of RANKL[31] and a similarly transient increase in osteoclast activity,[33] two actions that probably contribute to an anabolic action by the release of osteoclast-derived coupling factors.[34,35] In contrast, persistently high circulating PTH, induced by PTH infusion or other means, is catabolic,[36] owing to a corresponding persistently high level of RANKL[31] that increases osteoclast formation. In OSMR-null osteoblasts, an unusual persistently high RANKL mRNA response to PTH injection was observed; this could thus explain the conversion of a normally PTH anabolic treatment to catabolic response in the OSMR-null mouse.[32] The reason why OSMR-null osteoblasts have a persistent RANKL response to PTH (and not to other osteolytic hormones) remains unclear. If these catabolic effects of PTH in

OSMR-null mice *in vivo* are wholly osteoblast mediated, it suggests that under some circumstances OSMR signals can result in both procatabolic actions (via increased RANKL levels) and anticatabolic actions. It is possible that OSMR induction by PTH provides negative feedback that limits the duration of RANKL response. Indeed, recent work has indicated that OSM stimulates the production of Wnt16, an osteoblast-derived stimulus of OPG production, suggesting that OSMR signaling may restrain osteoclast formation through this pathway.[37] As PTH treatment induces many gene responses in osteoblasts,[38] including increased expression of many cytokines, OSMR has much scope to modify PTH action.

It should be noted that OSMR also associates with the gp130-like receptor IL-31RA to form a receptor for the Th2 cytokine IL-31; another consequence of OSMR deletion is a lack of IL-31 response.[39] Although we could find no effect of IL-31 on osteoblast or osteoclast differentiation *in vitro*,[25] IL-31RA deletion has been noted to increase hepatic cytokine response to OSM.[40] This suggests that OSMR deletion may increase responses to other gp130-dependent cytokines by increasing the availability of other receptor components.

OSM Stimulates Osteoblast Differentiation and Bone Formation by Actions on Both Osteocytes and Osteoblast Progenitors

OSM suppresses osteocytic sclerostin

Osteocytes have recently emerged from their relative obscurity to be recognized as major regulatory cells, with a critical role in regulating bone mass through their production of an anti-anabolic inhibitor of osteoblast activity, sclerostin,[41] and (like all osteoblast-lineage cells) their production of RANKL.[42,43] In mice, injected OSM has a strongly anabolic effect on bone, and this is associated with a strong suppression of sclerostin *in vivo*, which is also observed in cultured cells.[25] However, unlike OSM stimulation of RANKL, suppression of sclerostin is not mediated by the classical OSMR:gp130 heterodimer but is mediated by the leukemia inhibitory factor receptor (LIFR), presumably in a LIFR:gp130 heterodimer.[25] Notably, injected OSM is still anabolic in mice that lack OSMR.[25] The degree to which the suppression of osteocyte sclerostin mediates the anabolic OSM influence is unclear, as it has yet to be examined in sclerostin-null animals. Nevertheless, since the anabolic action of OSM is lost in mice that lack the gp130 signaling unit specifically in osteocytes,[30] it is clear that the anabolic action of OSM is mediated by its action in the osteocyte.

One technical problem with interpreting many of the early studies of OSM and bone has been the tendency of such studies to use human OSM and murine OSM somewhat interchangeably. This has complicated matters, as human OSM has equal affinity for both human LIFR and human OSMR,[44] whereas in murine cells human OSM acts exclusively through mouse LIFR.[45] Different again is murine OSM, which binds at a much higher affinity to murine OSMR than to murine LIFR.[45] It is notable that, in rodent cells, suppression of sclerostin levels is a property that other cytokines that act through the LIFR:gp130 heterodimer also possess; this includes human OSM, cardiotrophin-1 and leukemia inhibitory factor (LIF).[25] The suppression of sclerostin by IL-11, a cytokine that does not recruit LIFR, is far less potent.[25] As sclerostin is the only target of LIFR:gp130 thus far identified, it is possible that the use of this receptor complex is specific to osteocytes, and it may depend on other factors such as scaffolding proteins, present in these cells, or altered receptor availability.

OSM directs stromal cell commitment to osteoblastogenesis

The action of OSM on osteoblast differentiation is probably not restricted to its effects on sclerostin. As OSMR is expressed by mesenchymal stem cells (MSCs), it is likely that direct effects of OSM stimulate osteoblast differentiation and activity in both murine and human MSCs while reducing adipocyte formation in the same populations.[25,46,47] Some of the influences of OSM can be attributed to suppression of sclerostin as noted above; however, enhanced differentiation of osteoblasts and impaired adipogenesis occurs in primary osteoblast cultures and osteoblastic cell lines even when little sclerostin is detectable. This suggests some direct action on immature osteoblastic cells, as indicated by rapid effects on the expression of C/EBPα and PPARγ.[25] Furthermore, it should be noted that all bone formation depends to some degree on the recruitment of new, primitive osteoblast progenitors. Indeed, OSM shares a number of direct gene targets with PTH in osteoblasts; these include RANKL,[48] IL-33[49] and the transcription factor Zfp467, a factor that regulates osteoblast/adipocyte commitment.[50] This is consistent with the similarity of OSM and PTH effects on bone even though their physiological roles otherwise seem to be quite different.

Although OSM and LIF have similar effects *in vitro* on osteoblast and adipocyte differentiation,[25,51] it should be noted that both LIF- and OSMR-null mice demonstrate reduced osteoblast differentiation and enhanced adipogenesis *in vivo,*[25,51] indicating that the roles of LIF:LIFR and OSM:OSMR signaling that regulate stromal cell differentiation to osteoblasts are not redundant in normal physiology. It remains unknown whether OSM:gp130:LIFR and LIF:gp130:LIFR complex formations elicit redundant or distinct influences on the undifferentiated stromal cell, osteoblast or osteocyte. If there are differences, this would suggest altered receptor conformation and/or recruitment of different accessory proteins, but the structures of the OSM:gp130:LIFR and LIF:gp130:LIFR complexes remain unresolved. Furthermore, it is not yet known whether the phenotypes of the OSMR-null mice and mice lacking OSM (and therefore lacking both OSM:gp130:LIFR and OSM:gp130:OSMR signaling) are similar. These experiments would resolve the lingering question about redundancy between LIF and OSM signaling.

The Source of OSM: Osteoblasts, Macrophages, T Cells and Malignant Cells

OSM as a paracrine factor within the osteoblast lineage

Significant levels of OSM mRNA and protein have been detected at all stages of differentiation in the osteoblast lineage, including bone lining cells, matrix-producing osteoblasts and osteocytes in murine bone.[25] In human bone, OSM mRNA has been detected in bone marrow stromal cells and osteoblasts from normal and arthritic specimens, although this has yet to be confirmed at the protein level.[52] Osteoblastic cells express all three receptor subunits than can be used by OSM (gp130, OSMR and LIFR),[25] and their expression of OSM, gp130 and OSMR is strongly stimulated by PTH and PTH related protein

(PTHrP).[32] Furthermore, in whole bones subjected to mechanical loading, OSM and OSMR are both significantly upregulated.[53] The regulation of both osteoblastic and osteocytic genes by OSM indicate functions for OSM at multiple stages of osteoblast differentiation to regulate bone metabolism in response to anabolic and catabolic stimuli, as described above.

Macrophage-derived OSM supports osteoblast differentiation

Macrophages come in many varieties capable of distinct (but often as yet poorly defined) activities and secretory profiles. They are highly responsive to many influences, notably emanating from the immune system, that exert strong and malign effects in osteolytic bone diseases associated with chronic inflammation, particularly rheumatoid arthritis. Macrophages also have a wide secretory repertoire, and inflammatory macrophages produce factors such as tumor necrosis factor and dickkopf WNT signaling pathway inhibitor 1 (Dkk1) that have strong negative influences on osteoblast activity,[54–57] but proanabolic influences involving IL-6 family cytokines, notably OSM, are also beginning to emerge. Resident osteal macrophages are present at or near the bone surface in intimate proximity to osteoblasts and bone lining cells,[13] and their paracrine secretions are likely to influence bone formation. Close cooperative interactions between resident macrophages and mesenchymally derived cells are seen in many tissues, such as joint synovial membranes, but such interactions in bone are now receiving renewed attention. It is not clear whether osteal macrophages differ from other local mature macrophages, as they cannot be studied in isolation. However, bone-derived macrophages can enhance mineralization of osteoblasts *in vitro*,[13] and specific deletion of macrophages (c-fms-expressing cells) greatly reduces bone mass and is catastrophic for the process of fracture repair,[58] pointing to a significant role of macrophages in stimulating bone formation.

Three research groups, Guihard *et al.*, Nicolaidou *et al.* and ourselves, have observed that monocyte-derived macrophages strongly stimulate the osteoblastic commitment of human MSCs.[59–61] Guihard *et al.*[59] observed that this depended on a diffusible factor released by M1 (classically) activated adult macrophages. Work with neutralizing antibodies showed that this was principally dependent upon their production of OSM, although IL-6 and LIF also contributed to the pro-osteoblastic actions. As detailed above, OSM had indeed previously been demonstrated to drive human and murine MSC commitment to mineralizing osteoblasts,[25,46,47] and LIF has similar effects.[51]

Although an increase in osteoblast progenitor maturation induced by M1-activated macrophages may be surprising, given their production of tumor necrosis factor, this may shed some light on the patterns of abnormal bone formation seen in inflammatory bone diseases such as ankylosing spondylitis and in osteophyte formation. However, OSM can clearly be produced by macrophages under other stimulatory conditions, including in rheumatoid arthritis.[55,62,63] Nicolaidou *et al.*[60] observed a similarly strong OSM-dependent osteoblastic influence of monocyte-derived macrophages not with activation but when stimulated by contact with MSCs themselves. This might point to a very localized paracrine control of MSC maturation by macrophages in close proximity; the activity of bone resorption itself may attract MSCs[64] that interact with local OSM-producing osteal macrophages, and this could lead to osteoblastic formation by such MSCs at or near the bone resorption site. Our own work identified that immature proliferative macrophages (probably naïve or M2 polarized), nevertheless, stimulated osteoblast maturation in MSCs in an OSM-dependent manner.[61] Collectively, these observations suggest that macrophages of various types can be persuaded to provide an OSM-dependent stimulus of osteoblastic maturation of MSCs.

These studies emphasize the importance of MSCs themselves in bone formation, and their potential, in addition to mature osteoblasts and osteocytes, as targets for anabolic therapies. As MSCs are attracted to sites of bone resorption,[64] it is plausible that they could participate in the bone formation that occurs in response to osteoclast-derived coupling factors in remodeling. Osteoclast formation at a site of resorption involves the recruitment of osteoclast progenitors (immature macrophages), but it remains to be seen whether these also influence MSCs.

T cells as a source of OSM

T cells also have the capacity to greatly influence bone metabolism, although the degree of their influence is controversial. T cells both produce and respond to OSM, which, for example, stimulates extrathymic T-cell development.[65] In rheumatoid arthritis, both activated T cells and macrophages produce OSM, which, as described above, could thereby locally stimulate both focal bone destruction, by stimulating osteoclastogenesis, and periosteal bone formation, through actions on the osteoblast lineage. Although there is clear evidence that T cells might influence bone formation and resorption in inflammation, their influence in normal bone physiology is less certain given their relative paucity in the bone microenvironment and bone marrow cavity in normal physiological conditions. Activated T cells produce RANKL, which can drive osteoclast formation,[66] and indeed ablation of RANKL in T cells mildly increases trabecular bone mass.[67] However, as T cells do not express the OSMR subunit,[68] it is unlikely that T-cell expression of RANKL is regulated by OSM.

Concluding Statements

OSM is a multifactorial cytokine, expressed by a range of cells within the bone microenvironment (**Figure 1**), which thereby exert both anabolic and catabolic effects on bone. It appears that both these effects are mediated through the osteoblast lineage. OSM action via two different receptor complexes that activate JAK-STAT signaling (OSMR/gp130 and LIFR/gp130) give different cellular outcomes via different target cells, affecting osteoblast/stromal cell RANKL and osteocyte sclerostin, respectively, *in vivo* and *in vitro*.[25] Its actions on bone have a number of parallels with those of PTH, which also exerts its actions via several different cellular targets,[69] including OSMR and gp130. This suggests that the careful dissection of intracellular pathways elicited by OSM (and related cytokines) and evaluating the roles of its target cells in bone could lead to important insights into the design of novel anabolic therapies for bone.

Conflict of Interest

The authors declare no conflict of interest.

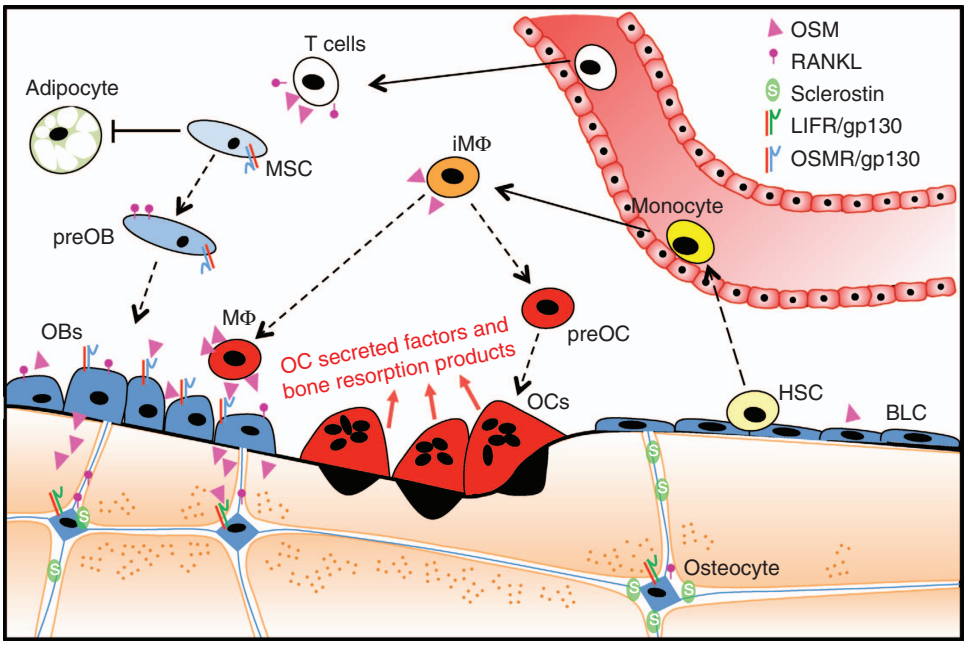

Figure 1 Oncostatin M (OSM) is produced both by cells derived from hemopoietic stem cells (HSCs,; including T cells, immature macrophages (iMΦ), mature macrophages (MΦ)) and by the osteoblast lineage, including osteoblasts on the bone surface (OBs), bone lining cells (BLCs) and osteocytes. When preosteoblasts (preOBs), OBs and osteocytes are stimulated by OSM through the OSMR:gp130 complex, their differentiation (dotted lines) from mesenchymal stem cells (MSCs) is stimulated, and adipogenesis is inhibited. In addition, RANKL production is increased in these cells with OSM response through OSMR:gp130; T cells also produce soluble RANKL when activated, but do not express OSMR. RANKL stimulates the differentiation of osteoclast precursors (preOC) to mature osteoclasts (OCs) that resorb the bone matrix. OCs release factors (by secretion and through breakdown of bone matrix) that also stimulate osteoblast differentiation. In contrast to its action on RANKL mediated by OSMR:gp130, OSM acts on osteocytes through LIFR:gp130 to inhibit sclerostin production. This action results in increased bone formation by OBs on the bone surface.

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