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Mini Review

GP130 cytokines and bone remodelling in health and disease

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Cytokines that bind to and signal through the gp130 co-receptor subunit include interleukin (IL)-6, IL-11, oncostatin M (OSM), leukemia inhibitory factor (LIF), cardiotrophin-1 (CT-1), and ciliary neutrophic factor (CNTF). Apart from contributing to inflammation, gp130 signalling cytokines also function in the maintenance of bone homeostasis. Expression of each of these cytokines and their ligand-specific receptors is observed in bone and joint cells, and bone-active hormones and inflammatory cytokines regulate their expression. gp130 signalling cytokines have been shown to regulate the differentiation and activity of osteoblasts, osteoclasts and chondrocytes. Furthermore, cytokine and receptor specific gene-knockout mouse models have identified distinct roles for each of these cytokines in regulating bone resorption, bone formation and bone growth. This review will discuss the current models of paracrine and endocrine actions of gp130-signalling cytokines in bone remodelling and growth, as well as their impact in pathologic bone remodelling evident in periodontal disease, rheumatoid arthritis, spondylarthropathies and osteoarthritis. [BMB reports 2010; 43(8): 513-523]

Gp130 cytokines

Glycoprotein 130 (gp130) is a receptor subunit capable of intracellular signalling that is required for the cellular action of a wide range of cytokines. The most well known of these are interleukin (IL-) 6 and IL-11, leukemia inhibitory factor (LIF), cardiotrophin-1 (CT-1), oncostatin M (OSM) and ciliary neurotrophic factor (CNTF). Every cytokine that binds to gp130 generates specific intracellular signalling events by forming specific receptor:ligand complexes, each with distinct components and/or architecture (Fig. 1) (1).

The simplest complexes formed are those made by IL-6 and IL-11, which bind to their own (non-signalling) ligand-specific receptor (IL-6R or IL11R), and then recruit a homodimer of gp130 (2, 3) which is responsible for all intracellular signalling events. However, the majority of gp130-binding cytokines, including LIF, CT-1, CNTF, cardiotrophin-2 (also known as neuropoietin), and cardiotrophin-like-cytokine (CLC) (4, 5) bind the LIF receptor (LIFR) followed by gp130. The LIFR subunit, like gp130, activates intracellular signaling pathways via Janus kinase (JAK) activation (6, 7). OSM is unique among gp130-binding cytokines as it binds first to gp130 and then forms a signalling complex with either LIFR or the closely-related OSM receptor (OSMR) which are both capable of intracellular signalling (8, 9). The composite cytokine IL-27 signals through gp130 bound to the WSX-1 (IL-27R) receptor subunit (10). It has recently been shown that humanin, which is not yet described in bone, signals through gp130 : WSX-1 : CNTFR (11).

Like all cells of the body, cells within bone and joint tissue express gp130, and each population expresses a distinct array of the ligand-specific receptors (Table 1) giving them the ability to respond to gp130-family cytokines. Consequently, many of these cytokines have been shown to regulate the processes of bone formation and bone resorption (destruction) that are required for skeletal development, growth and maintenance. These cytokines have also been shown to function in the pathogenesis of bone and joint disorders. We will discuss the role of gp130 signalling in bone remodelling in health and disease in this review.

Bone remodelling: osteoblasts, osteoclasts, osteocytes

Bone remodelling is the process by which bone is continually renewed. This process occurs both within the thick cortical bone that surround the marrow space and on the surfaces of the internal network of bone (trabecular bone). Continual replacement of bone structure provides a mechanism by which calcium levels in the blood can be maintained, a method to restore microscopic regions of damage, and a way of responding to load-bearing, dietary or hormonal changes.

Bone remodelling is made up of three key steps: resorption of old or damaged bone by osteoclasts, a reversal phase, and formation of new bone by osteoblasts. This process takes place at multiple sites, asynchronously, throughout the skeleton and throughout life in a multicellular unit termed the bone remodelling unit. The balance between bone resorption and formation at each bone remodelling unit changes throughout life. During periods of bone growth, or in response to repetitive

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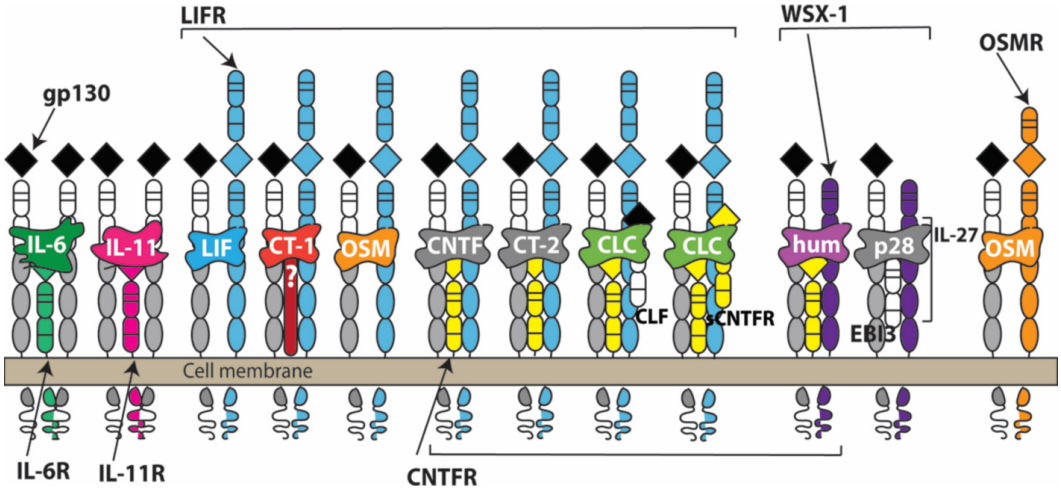

Fig. 1. Ligand : receptor signaling complexes formed with gp130. gp130 itself is shown on the left of each complex. IL-6 and IL-11 bind to ligand specific β-receptor subunits (IL-6R and IL-11R, respectively) and form a complex that contains gp130 homodimers. The LIF receptor is used by multiple cytokines and these complexes are shown in the central portion of the figure. LIF itself signals through a trimer of the ligand coupled to LIFR and gp130. CT-1 also signals through LIFR and gp130 as well as, potentially, a CT-1 specific receptor subunit which remains undefined. Oncostatin M (OSM) has two receptor : ligand conformations, signaling through gp130 in a heterodimeric complex with either LIFR or OSMR (shown to the right of the figure). CNTF, CT-2 and the cytokine complexes CLC/CLF and CLC/sCNTFR signal through a LIFR : gp130 heterodimer complexed to the membrane-bound CNTFR. Finally, the WSX-1 receptor heterodimerised with gp130 is utilized by IL-27 (p28/EBI3) and humanin, which also requires CNTFR for signalling.

Table 1. Expression patterns of gp130 cytokines and receptor subunits in bone and joint cells. +indicates a report of positive expression in this cell type, - indicates a confirmed report of expression lacking in this cell type

	Osteoclast	Osteoblast	Osteocyte	Chondrocyte	Synovial fibroblast
Receptors:					
gp130	+(105)	+(22)	+(43)	+(104)	+(111)
IL-6R	+(105)	+(107)	+(109)	+(110)	−(112)
IL-11R	+(22)	+(22)	Not reported	Not reported	−(111)
LIFR	−(106)	+(106)	+(43)	−(104)	−/+(111)
CNTFR	Not reported	+(108)	Not reported	Not reported	Not reported
OSMR	−(43)	+(43)	+(43)	+(104)	+(111)
WSX-1	Not reported	+(37)	Not reported	Not reported	+(113)
Ligands:					
IL-6	Occasional (25)	+(114)	Occasional (25)	+(117)	+(70)
IL-11	Not reported	+(22)	Not reported	+(118)	+(22)
LIF	Not reported	+(115)	Not reported	+(119)	+(70)
OSM	−(43)	+(43)	+(43)	Not reported	−(70)
CT-1	+(14)	−(14)	−(14)	+(120)	Not reported
CNTF	+(28)	+(116)	+(28)	+(28)	Not reported
IL-27	Not reported	Not reported	Not reported	Not reported	Not reported

mechanical forces such as increased exercise, the remodelling balance is in favour of bone formation. In contrast, in periods where calcium needs to be released (e.g. during lactation) or during periods of inactivity the remodelling balance is in favour of bone resorption, and bone mass is lost.

This balance between bone resorption and bone formation is to some extent controlled by endocrine hormones, but finer elements of cellular control are determined by multiple paracrine signalling pathways within the bone remodelling unit (12, 13). Osteoblasts produce paracrine factors that influence the formation and activity of osteoclasts, the key example of which is RANKL, a factor required for osteoclast formation. The same is true in the other direction, although osteoclast- derived factors that influence osteoblast function have been elusive, and are only now being identified (14, 15). Within the bone remodelling unit, there are also signals from osteocytes; these are "retired" osteoblast-lineage cells embedded within the bone matrix. These cells, unlike osteoblasts, have long cel-

lular processes that reside within channels (canaliculi) and form a cell-cell communication network throughout the bone matrix that connects and communicates to osteoblasts on the cell surface. Recent work has identified that these cells also release locally-acting factors that influence both bone formation and bone resorption (16, 17).

Gp130 actions on the skeleton

Paracrine or endocrine involvement?

gp130 cytokines are expressed in the cells of bone (Table 1), but early work focussed on their levels in the circulation. However, levels of each of these cytokines are generally very low, being detected at high levels only in pathological states. For example, there is an increase in circulating CNTF in neurodegenerative disorders (18), in LIF during septic shock (19) and in CT-1 in cardiovascular disease (20). Serum IL-6 levels are also elevated with age (21) and circulating gp130 cytokines and soluble receptor isoforms are increased during inflammation (see below).

In contrast, gp130 cytokine expression by cells within the bone remodelling unit are high throughout life (Table 1). Furthermore, the expression of gp130 cytokines by osteoblasts in particular, is strongly influenced by bone-active hormones and inflammatory cytokines including PTH, 1,25-dihydroxyvitamin D_3, IL-1, estradiol and testosterone (22-25). This indicates that gp130 cytokines, like RANKL, may play important paracrine roles to regulate bone formation and resorption within the bone remodelling unit during normal bone development, growth and remodelling. Furthermore, paracrine actions of these cytokines regulate local cellular activation during localised inflammation including periodontal disease and arthritic disorders.

Gp130 cytokine action on osteoclasts

The formation of bone resorbing osteoclasts from mononuclear haemopoietic precursors is stimulated by many gp130 cytokines *in vitro*, including IL-11, IL-6, OSM, CT-1, and, to a lesser extent, LIF (26, 27). In contrast, CNTF, neuropoietin and CLC do not stimulate osteoclast formation (28). The pro-osteoclastic gp130 cytokines generally stimulate osteoclast formation by acting on osteoblast lineage cells to enhance expression of the key osteoclastogenic factor RANKL, and by reducing osteoblastic expression of its inhibitor OPG (29-31). Furthermore, studies using the gp130 knockout mouse, and a gp130 neutralising antibody have demonstrated that a gp130-dependent pathway is involved in the stimulation of osteoclast formation by other factors, including 1,25-dihydroxyvitamin D_3, parathyroid hormone (PTH), and inflammatory cytokines such as IL-1, (22, 32). Neutralising antibody studies also indicated that PTH-stimulated osteoclast formation requires at least IL-6R (24) and IL-11 (33).

The influence of gp130 cytokines on osteoclast formation is not entirely mediated by osteoblasts however. LIF has also been reported to have a direct pro-osteoclastic influence by increasing CSF-1R expression by osteoclast precursors (34). Furthermore, cell culture studies in which osteoclasts were generated by RANKL/M-CSF treatment of bone marrow precursors from knockout mice indicated that gp130, CT-1 and IL-11 signaling in osteoclast precursor cells are all required for optimal osteoclast differentiation (14, 35, 36). Finally, IL-27 has been shown to inhibit osteoclast formation through a T-cell dependent mechanism (37).

Surprisingly, despite the pro-osteoclastic influence of most gp130 cytokines, mice lacking gp130 had very high osteoclast numbers, even though the osteoclastogenic response to PTH in *ex vivo* cultures was impaired (32, 38). These mice die at the time of birth, so the osteoclast defect could relate specifically to the role of gp130 in osteoclast formation during embryonic bone development, or the osteoclast defect could be secondary to haemopoietic and cardiovascular defects that cause early death.

In mice null for individual ligands and receptors involved in gp130 signalling, the osteoclastic phenotype varies. Adult IL-6 null mice demonstrate normal numbers of osteoclasts, indicating that this cytokine plays a role in osteoclastogenesis that can be compensated for by other factors. However, IL-6 appears to play a unique role in contributing to the osteoclastic effects of ovariectomy (39), PTH infusion (40), and experimental inflammatory arthritis (see below). Genetic deletion of CT-1, LIF and LIFR all lead to increased osteoclast formation *in vivo* (14, 41, 42), while osteoclast numbers are low in IL-11R and OSMR deficient mice (36, 43). This indicates that these cytokines are required for normal osteoclastogenesis and normal bone remodelling, but that their roles are not redundant.

Some gp130 signalling components are expressed in mature osteoclasts (Table 1), but whether gp130 signalling plays a significant biological role in the mature osteoclast remains unresolved. Osteoclast size appears to be regulated by both CT-1 and LIF, since osteoclasts are enlarged in mice null for either of these factors, or the LIFR (14, 41, 42). It remains unclear whether this is because CT-1 and LIF influence osteoclast fusion, or substrate/bone attachment, or if this has any consequence in the ability of osteoclasts to resorb bone. While impaired resorption by CT-1 and gp130 null osteoclasts has been reported (14, 32), this has only been tested on bone substrate from the same null mouse. It is possible then that this could also reflect a defect in the nature of the bone formed in these mice, that is, an influence of gp130 cytokines on osteoblast function.

Gp130 cytokine action on osteoblasts and osteocytes

Both osteoblasts and osteocytes are capable of responding to gp130 cytokines, since they express not only gp130, but also many of the ligand-specific subunits required for cytokine action (Table 1). While much work on the influence of gp130 cytokines on osteoblasts has focussed on the regulation of RANKL, and thereby, osteoclast formation, IL-6, OSM and IL-

11 were also reported to stimulate the differentiation of primary calvarial osteoblasts themselves (44). Surprisingly, although IL-6 stimulated primary calvarial osteoblast differentiation, osteoblast numbers were unchanged in IL-6 deficient mice (36, 39). Furthermore, genetically induced overexpression of IL-6 in two transgenic mouse models (45, 46) led to a significant reduction in osteoblast numbers, suggesting that the sum total physiological role of IL-6 in bone formation *in vivo* may be inhibitory.

OSM, CT-1, IL-11 and LIF all stimulate osteoblast differentiation by stromal cells, and at the same time reduce the ability of these cells to differentiate into adipocytes (14, 43). The influence of CT-1 and OSM on osteoblast commitment appears to involve rapid regulation of C/EBP family members that then activate runx2-dependent osteocalcin transcription (14, 43). No defect in bone formation or adipocyte generation has been reported in LIF knockout mice (41). In contrast, even though OSM, CT-1 and IL-11 have the same action on cells in culture, their effects *in vivo* are not redundant, since CT-1, IL-11R and OSMR deficient mice all demonstrate a low level of bone formation *in vivo* (14, 36, 43). Since adipocyte volume within the marrow space is also modified in these mice, their influences on adipocyte formation are also unique. These unique roles may stem from the cell-types and conditions under which these cytokines are expressed. For example, in the bone remodelling unit, CT-1 is expressed only by the osteoclast, making it a putative coupling factor; i.e. one of those factors that ensures matching of osteoblast activity to that of the osteoclast, while OSM is not expressed in osteoclasts, but is expressed in all osteoblast-lineage cells.

The influence of gp130 cytokines on bone formation is not restricted to an influence on osteoblast commitment. OSM, CT-1 and LIF have been recently reported to strongly inhibit expression of sclerostin by osteocytes (43). This protein is a specific and essential inhibitor of bone formation that acts as a Wnt signalling antagonist (16). Antibodies to sclerostin are currently under development as a new therapeutic agent for osteoporosis (47). Sclerostin expression by osteocytes is also inhibited by administration of PTH (48), and by mechanical loading (49). While OSM, CT-1 and LIF all inhibited sclerostin expression, IL-11, IL-6, CNTF, CLC and CT-2 did not (28, 43). Although OSM is capable of signalling through a receptor complex containing either LIFR or OSMR (Fig. 1), it appears that its influence on both sclerostin expression and bone formation is mediated specifically by the LIFR, while its influence on osteoblast/adipocyte commitment is mediated by the OSMR (43). This receptor-specific divergence of influence of a single cytokine on osteoblasts and osteoclasts appears to be unique to OSM, since LIF and CT-1 both stimulate osteoclast formation and inhibit sclerostin through the LIFR (14); the specific structural interaction between OSM and the LIFR compared to the interaction of LIFR with its "native" ligands CT-1 and LIF is not yet solved.

In contrast to the above, some gp130 cytokines that bind to CNTFR inhibit mineralisation by osteoblasts *in vitro* (28). Furthermore, in the absence of CNTF, enhanced bone formation is observed in the trabecular bone of female mice, but not males, indicating a possibility of interaction between the sex steroids and CNTF (28).

Gp130 cytokine action on growth plate chondrocytes

Gp130 cytokines also play clear roles in regulating chondrocyte metabolism. In growing bones, chondrocytes are found at the growth plate and are responsible for longitudinal bone growth. At the joint, articular chondrocytes form articular cartilage, which covers the boney surfaces enabling smooth movement and dispersion of force during daily activities. Gp130 cytokines regulate the function of chondrocytes at both of these sites.

Longitudinal bone growth is determined by the proliferation of chondrocytes at the growth plate. Significant dwarfism has been reported in mice null for gp130 and mice with a mutation in STAT3 signalling downstream of gp130 (32, 50), indicating that gp130 is required for normal bone growth, but the cytokines that signal through gp130 to stimulate chondrocyte proliferation have not yet been identified. Since human LIFR mutations that lead to impaired LIF binding also lead to a syndrome that features shortened, curved bones with irregular trabecular bone (51), the key cytokines for longitudinal growth are likely to be LIFR-dependent. LIF, CT-1 and CNTF expression have all been reported in growth plate chondrocytes (Table 1), but dwarfism has not been described in mice deficient in these ligands (14, 41, 43).

Gp130 in physiology and pathology

The effects of gp130 on osteoblasts, osteoclasts, adipocytes and chondrocytes are important in normal physiology, as indicated by phenotypes of mice with genetic modifications in expression of gp130 and its ligands (see above, and a detailed review (52)). In humans, normal function of these cells also depends on gp130 signalling. There is severe developmental pathology when LIFR signalling is mutated such that LIF binding is impaired (51). It remains unclear whether polymorphisms in IL-6 are associated with bone mineral density, body mass index and adiposity, or if this is population-specific (53-55). In localised skeletal disorders, including arthropathies and periodontal disease, gp130 has also been reported to play a role and this will be discussed below.

Gp130 and periodontal disease

Periodontitis is characterised by bone loss mediated by increased osteoclast formation in the presence of inflammation near the tooth. Many cytokines participate in this process and there is some evidence that gp130 signalling cytokines may also be involved. *In vitro* studies have reported that treatment of healthy human periodontal ligament cells with lipopolysaccharide (LPS) from inflammatory pathogens involved in perio-

dontal disease stimulates IL-6 release (56). Local expression of IL-6 at periodontic sites is higher than levels in similar sites in healthy controls (57, 58). Surprisingly however, periodontal lesions induced by pulp exposure were larger in IL-6 null mice than wild type, but this model does not involve infection (59). OSM has also been detected at high levels in periodontal endothelial and inflammatory cells (60), in gingival fluid (61) and in the circulation of patients with chronic periodontal disease (62), but is not observed in these locations in healthy subjects, suggesting that OSM may contribute to ongoing pathogenesis in this condition. In contrast, local expression of IL-11 is high in pockets of gingivitis (early stage periodontitis), but is low in established chronic periodontitis, suggesting a role for IL-11 in disease establishment only (58). No involvement of CT-1, CNTF or LIF in periodontal disease has been reported.

gp130 cytokines in rheumatoid arthritis

Rheumatoid arthritis (RA) is characterised by inflammation of the joint lining (synovium) which is accompanied by focal destruction of both cartilage and bone tissues within the affected joint. Focal bone erosion by osteoclasts (63, 64) is a distinguishing clinical feature of RA and is associated with patient pain and joint dysfunction (65). The cytokine milieu created by cells present within the inflammatory infiltrate in RA promotes increased expression of RANKL relative to OPG resulting in increased osteoclast differentiation and promotion of bone resorption at sites where the inflammatory tissue is adjacent to bone (66-68). In addition to increased osteoclastic bone resorption, differentiation of osteoblasts is compromised at bone surfaces adjacent to erosion (69), thereby contributing to net bone loss at this site.

Increased levels of IL-6, OSM, IL-11, LIF, IL-27 and the soluble form of IL-6R (sIL-6R) have been detected in RA synovial fluids and/or tissues (70-73) (Table 1). These cytokines contribute to RA inflammation by activating synovial fibroblasts to express various cytokines, chemokines and factors contributing to cartilage and bone destruction (for a more detailed review, see (74)). Supporting a role in RA pathogenesis, administration of soluble gp130 (72) or antibodies targeting IL-6 (75), IL-6R (75-78) or OSM (79) in rodent models of RA inhibit inflammation and attenuate both focal bone erosion and cartilage destruction. The roles of LIF, IL-11 and IL-27 in RA pathogenesis have not been clarified, nor has it been determined whether gp130 cytokines affect osteoblast function in this context.

IL-6 is expressed by fibroblast-like synoviocytes, macrophages and T cells, within RA synovial tissue (70, 80, 81). Its signalling via IL-6R has recently risen to prominence as a key therapeutic target in the treatment of RA (75, 76, 78). Inducing inflammatory arthritis in mice deficient in IL-6 expression (82); blockade of the IL-6 receptor (IL-6R) (83) or targeting of the soluble form of IL-6R (83, 84) in mouse models of arthritis reduced recruitment of T cells expressing IL-17 (Th17 cells) to the affected joint, and decreased inflammation and bone erosion. Th17 cells are a cellular source of RANKL within the arthritic joint. Therefore IL-6 can also indirectly promote osteclastogenesis by local recruitment of RANKL-expressing Th17 cells (82). Together this work laid the foundation for the development of a humanized monoclonal antibody specific to the IL-6R (Toculizumab), which has proven effective in reducing both inflammation and the progression of focal bone erosion in early RA patients, either as a monotherapy or in combination with the gold-standard disease-modifying drug, methotrexate (75, 77, 78).

When considering the role of the gp130 cytokines and their receptors in pathologic bone remodelling in RA it is important to remember that it is the cytokine mileu of the local bone microenvironment created by cells present within the inflammatory tissue that influence the extent of bone and cartilage destruction. Therefore treatments or genetic interference which reduces inflammation in response to arthritic challenge may, by default, lead to protection from bone and cartilage destruction. For this reason careful analysis and the use of bone-cell specific gene knockout models is required to determine consequences of inhibition of gp103 cytokine signalling on bone remodelling in RA.

Spondylarthropathies (e.g. ankylosing spondylitis, psoriatic arthritis)

Seronegative spondylathropathies (SpAs) including ankylosing spondylitis, psoriatic arthritis, reactive arthritis, and bone and joint diseases associated with inflammatory bowel disease share features with RA including synovial inflammation, focal bone erosion and cartilage destruction. The distinguishing feature of these rheumatic conditions is inflammation at entheseal sites, where ligaments attach to bone, which often results in calcification of the enthesis and formation of new bone (syndesmophytes) at this site and fusion of the joint (ankylosis) (85-88).

In mouse models of inflammatory arthritis that share features with SpAs, formation of new bone in the form of osteophytes and subsequent ankylosis has been linked to activation of the BMP (89) and Wnt signalling pathways (90). Recently down-regulation of the Wnt signalling antagonist sclerostin in osteocytes has been noted at sites adjacent to syndesmophyte formation in retrieved tissues from ankylosing spondylitis patients (91) suggesting that this may be one mechanism by which bone formation is induced in the context of inflammation and mechanical strain at the entheseal site.

Little is known about the role of gp130 cytokines in modulating inflammation and bone remodelling in the spondylarthropathies. Increased levels of serum IL-6 have been reported in psoriatic arthritis patients (92), and serum IL-6 levels were noted to correlate with disease activity in ankylosing spondylitis patients (93). Mice over-expressing human TNF (hTNF.Tg mice), which are characterised by focal bone erosion similar to RA, and bilateral sacroilitis associated with new bone for-

mation similar to ankylosing spondylitis, have been shown to have high serum IL-6 levels (94). Genetic deletion of IL-6 expression in this model, did not modify the development of inflammation and bone formation associated with the bilateral sacroilitis, suggesting that IL-6 may not mediate these features of ankylosing spondylitis (94). However, the potential for gp130 cytokines such as OSM to downregulate the expression of Wnt signalling antagonists such as sclerostin in osteocytes (43), leaves open the possibility for gp130 cytokines to mediate the enhanced bone formation in the form of syndesmophytes in the spondylarthropathies and should be further investigated in models not dependent on TNF over-expression.

Osteoarthritis

Osteoarthritis (OA) is characterized by progressive articular cartilage damage, driven by increased expression of matrix metalloproteinases and aggrecanases, thickening of the subchondral bone and formation of osteophytes (95). This leads to pain, dysfunction and loss of work capacity (95).

Several lines of evidence suggest that gp130 signalling may contribute to pathogenesis of OA. Osteoblasts isolated from sclerotic bone in OA-affected joints express increased levels of IL-6 (96). IL-6 and OSM can impair synthesis of aggrecan, which is required for normal cartilage formation, and can promote expression of the degradative metalloproteinases in chondrocytes *in vitro* (96). Furthermore, both cytokines can promote bone formation (see above) fitting with the pathologic features of OA.

OSM treatment is commonly used *in vitro* to model OA cartilage damage (97) and there is evidence that it may contribute to OA pathogenesis. For example, local over-expression of OSM in the mouse knee joint induces changes to the joint that resemble OA, including cartilage destruction and periosteal bone formation similar to osteophytes (98, 99). OSM also induces proteoglycan loss and cartilage damage *ex-vivo* (97, 100). Interestingly, decreased sclerostin expression was observed in bone from OA patients compared to normal or RA patients (91). Given that OSM can downregulate sclerostin expression in osteocytes (43) and promote bone formation, it is possible that OSM may function in this manner in OA to induce osteophyte formation and/or subchondral bone formation.

The potential for IL-6 to contribute to OA pathogenesis is not as clear, with some suggestion that IL-6 may protect against cartilage damage. Aged male IL-6 knockout mice develop more obvious OA-like cartilage damage compared to their wildtype counterparts (101). However no differences were observed in 3 month old mice when challenged with collagenase to induce OA-like cartilage damage (101). The female IL-6 knockouts showed no differences in incidence of OA, or severity of cartilage damage in the collagenase-induced OA model (101).

Similar to IL-6 and OSM, LIF has been demonstrated to induce expression of matrix metalloproteinases (MMP1, MMP-3 and TIMP1) in chondrocytes (102) and is upregulated in chondrocytes in response to IL-1 stimulation (103). However the role of LIF in OA-induced cartilage destruction and bone formation is yet to be investigated. CT-1 does not appear to influence cartilage breakdown (104), and is therefore unlikely to play a role in the cartilage damage associated with OA.

Concluding comments

In conclusion, it is clear that members of the gp130 cytokine signalling family have important roles in bone remodelling. However there are many questions remaining to be answered before we can fully understand the details of gp130 cytokine signalling and its role in regulating bone remodelling and maintenance of joint cartilage in health and disease. The generation of bone and cartilage specific gene knockout mouse models lacking expression of each gp130 signalling factor will be required to further dissect the paracrine roles of these factors and their signalling pathways in regulating bone structure and cartilage integrity. With greater understanding of the effects of these cytokines, independent of their roles in inflammation, it may be possible to identify novel therapeutic targets for the prevention of bone loss in RA and periodontitis, and abnormal bone gain in OA and spondylarthropathies, and cartilage destruction.

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