Clinical Section / Mini-Review

Gerontology

Gerontology 2016;62:128–137
DOI: 10.1159/000431091

Received: February 5, 2015
Accepted: May 4, 2015
Published online: June 17, 2015

Immunology of Osteoporosis: A Mini-Review

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Key Words
Osteoporosis · Immune response · Aging · B cells · Activation-induced cytidine deaminase · Plasma cells · Advanced glycation end products · Autoantibody

Abstract
Osteoporosis is a major cause of fractures and associated morbidity in the aged population. The pathogenesis of osteoporosis is multifactorial; whereas traditional pathophysiological concepts emphasize endocrine mechanisms, it has been recognized that also components of the immune system have a significant impact on bone. Since 2000, when the term 'osteoimmunology' was coined, novel insights into the role of inflammatory cytokines by influencing the fine-tuned balance between bone resorption and bone formation have helped to explain the occurrence of osteoporosis in conjunction with chronic inflammatory reactions. Moreover, the phenomenon of a low-grade, chronic, systemic inflammatory state associated with aging has been defined as 'inflamm-aging' by Claudio Franceschi and has been linked to age-related diseases such as osteoporosis. Given the tight anatomical and physiological coexistence of B cells and the bone-forming units in the bone marrow, a role of B cells in osteoimmunological interactions has long been suspected. Recent findings of B cells as active regulators of the RANK/RANKL/OPG axis, of altered RANKL/OPG production by B cells in HIV-associated bone loss or of a modulated expression of genes linked to B-cell biology in response to estrogen deficiency support this assumption. Furthermore, oxidative stress and the generation of advanced glycation end products have emerged as links between inflammation and bone destruction.

Introduction

Osteoporosis is a frequent age-related disorder characterized by a systemic impairment of bone mass and of the microarchitecture that results in fragility fractures [1]. From the point of view of cellular pathophysiology, osteoporosis results from a preponderance of activity of osteoclasts over that of osteoblasts [1, 2]. Despite this common pathogenic mechanism, osteoporosis is a heterogeneous disease; determinants of bone strength include bone mineral density (BMD), bone geometry, the microstructure of bone, bone mineralization and properties of the bone matrix. Traditionally, osteoporosis has been regarded as an endocrine (and, in particular, estrogen deficiency-me-

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Table 1. Selected regulators of bone remodeling

	Osteoblasts	Osteoclasts
Stimulatory	BMPs	**IL-1**
	FGFs	**IL-6**
	Insulin	IL-17
	PTH	**M-CSF**
	TGF-β	RANKL
	Wnt	**TNF-α**
Inhibitory	DKK1	**IFN-γ**
	IL-1	IL-3
	IL-6	IL-4
	SOST	**IL-10**
	TNF-α	**IL-12**
		OIP-1
		OPG

Regulators are listed in alphabetical order. Mediators that have been reported to be involved in inflammaging [68, 69] are set in bold letters. BMP = Bone morphogenetic protein; DKK1 = Dickkopf-related protein 1; FGF = fibroblast growth factor; IFN-γ = interferon-γ; OIP-1 = osteoclast inhibitory peptide-1; PTH = parathyroid hormone; SOST = sclerostin; TGF-β = transforming growth factor-β.

diated) disease; nevertheless, it is also well established that chronic inflammatory diseases [e.g. rheumatoid arthritis (RA), ankylosing spondylitis, Crohn's disease, ulcerative colitis, chronic obstructive pulmonary disease and certain viral infections] are associated with osteoporotic fractures. Over the years, our knowledge about the cross talk between the immune system and osseous tissue has significantly increased; in 2000, the term 'osteoimmunology' was coined [3, 4]. Since then, osteoimmunology has become a prosperous and promising research field. The aim of this paper is to review the immunology of osteoporosis with a special emphasis on gerontological aspects. We will present 'classic players' in osteoimmunology and also cover topics less often reviewed, such as the role of B cells, antibodies and advanced glycation end products (AGEs) at the immune-skeletal interphase.

Major Regulatory Factors of Osteoblast and Osteoclast Proliferation and Differentiation

Bone remodeling ensures the quality of the skeleton. Many molecules impact on the balance of bone resorption by osteoclasts and bone formation by osteoblasts. Osteoblasts originate from mesenchymal progenitor cells. Among the beneficial factors for osteoblast function and survival are bone morphogenetic proteins, transforming growth factor-β, Wnt, insulin, neurotransmitters, fibroblast growth factors and parathyroid hormone [1, 5] (table 1). Following binding and intracellular signaling, these molecules activate diverse transcription factors. A key factor for osteoblast differentiation is Runt-related transcription factor 2. Consequently, bone matrix proteins such as type I collagen (COL I) and others are released. Moreover, osteoblasts produce positive and negative regulators of osteoclastogenesis such as receptor activator of nuclear factor (NF)-κB ligand (RANKL) and the natural decoy receptor for RANKL, osteoprotegerin (OPG), respectively [6].

Negative regulators of osteoblasts include Dickkopf-related protein 1 and sclerostin, which are mainly produced by osteocytes and interfere with the Wnt signaling pathway. Moreover, cytokines such as interleukin (IL)-6 or tumor necrosis factor-α (TNF-α) suppress osteoblast function [7].

Osteoclasts originate from hematopoietic stem cells. Macrophage colony-stimulating factor (M-CSF), derived from osteoblasts, leads to the proliferation and survival of osteoclast progenitor cells following binding to its receptor, c-Fms. Osteoclast differentiation is initiated by binding of RANKL, a TNF family cytokine, to the receptor activator of NF-κB (RANK). Osteoblasts are a major source of RANKL, but the cytokine is also expressed by osteocytes, fibroblasts or cells of the immune system, including antigen-stimulated T cells and mature dendritic cells. RANKL-RANK interaction leads to activation of the master transcription factor for osteoclastogenesis, nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1) [8]. NFATc1 cooperates with other transcription factors to induce osteoclast-specific genes such as tartrate-resistant acid phosphatase, calcitonin receptor and cathepsin K [8].

Among the negative regulators of osteoclastogenesis are the RANKL decoy receptor OPG, which is produced not only by osteoblasts but also by B lymphocytes or dendritic cells [9] as well as a host of cytokines including interferon-γ, IL-3, IL-4, IL-10 or IL-12 [10] (table 1).

Although RANKL and M-CSF are important factors for osteoclastogenesis, the process requires further co-stimulatory molecules. Among them are several proteins with structures containing immunoreceptor tyrosine-based activation motif (ITAM) or immunoreceptor tyrosine-based inhibition motif (ITIM).

Firstly, the ITAM-containing adaptor molecules DNAX-activating protein 12 (DAP12) and Fc receptor

common γ chain (FcRγ) are required for osteoclastogenesis. This was demonstrated in mice lacking both molecules, which were severely osteopetrotic (reviewed in [11]). FcRγ and DAP12 associate with plasma membrane receptors such as osteoclast-specific activating receptor or the triggering receptor expressed in myeloid cells 2, respectively. Ligands for these receptors are currently unknown. However, data from in vitro cultures suggest that receptors associated with FcRγ are activated by ligands expressed by osteoblasts, while those associated with DAP12 are activated by ligands expressed on osteoclast precursor cells and, possibly, also by ligands on osteoblasts. Once ITAM is activated via phosphorylation, intracellular calcium-calcineurin signaling is initiated, which, in cooperation with the RANKL signal, is critical for NFATc1 induction and osteoclastogenesis [8, 12].

Secondly, ITAM and ITIM are important for Fcγ receptor (FcγR) signaling. In humans, all FcγRs, with the exception of FcγRIIIB, contain a transmembrane region and a cytoplasmic tail, which mediates the signal into the cell after the receptors have been cross-linked through binding of immune complexes (ICs). The cytoplasmic regions of human FcγRIIA and FcγRIIC contain an ITAM, while FcγRI and FcγRIIIA associate with the ITAM-containing FcRγ [13]. Recently, all FcγRs have been demonstrated on human osteoclasts, and cross-linking of all activating FcγRs stimulated osteoclastogenesis [14].

In mice, FcγRI, FcγRIII and FcγRIV are activating receptors signaling through the ITAM-bearing FcRγ chain. The inhibitory FcγRIIB mediates its downstream signaling through ITIM phosphorylation and subsequent counteraction of the activating FcγRs or other ITAM-bearing receptors [13]. All FcγRs are present on mouse osteoclasts and/or their progenitor cells [14, 15]. Osteoclast inhibitory peptide-1, an inhibitor of osteoclast differentiation, binds to FcγRIIB expressed on osteoclast progenitor cells and, via ITIM, downregulates the ITAM signaling of FcRγ [16]. On the other hand, cross-linking of the activating FcγRIV on mouse preosteoclasts with specific antibodies resulted in increased osteoclast formation. In line with this, decreased bone resorption was shown in arthritic mice lacking FcγRIV under the osteoclast-specific cathepsin K promoter [14].

Inconsistent with this concept of osteoclast activation by ICs are two other reports, which observed an inhibitory effect of ICs on osteoclastogenesis [15, 17]. These conflicting results may be caused by the different cell types and antibodies used, and they clearly call for further investigation. However, it should be considered in this context that the risk of RA patients of developing osteoporosis is two-fold higher than in a control population [18]. Besides the well-known effects of locally and systemically produced cytokines on enhanced osteoclast formation in RA, autoantibodies of the IgG isotype are critically involved in the disease process. In fact, the presence of anti-citrullinated protein antibodies is one of the strongest risk factors for RA. RA patients with autoantibodies have higher disease activity and more severe bone loss than patients who are negative for these antibodies [19]. Nevertheless, the role of autoantibodies in osteoporosis has so far been largely neglected.

Impact of Inflammation on Bone Cells

In the course of any inflammation, cells of the immune system, such as T cells, B cells, macrophages or dendritic cells, become activated and produce inflammatory cytokines, which are among the most important mediators in osteoimmunology. Many of these cytokines stimulate osteoclasts, but antiosteoclastogenic cytokines are also known [6]. Especially activated T cells are major stimulators of osteoclastogenesis by increasing the production of so-called bone-resorbing cytokines, especially TNF-α and RANKL; consequently, activated T cells are suggested to have a major role in osteoporosis [6, 20]. Already in the 1980s had it been recognized that TNF-α and IL-1 are potent stimulators of bone resorption and inhibitors of bone formation [21, 22]. IL-6 is also among the 'classic' bone-resorbing proinflammatory cytokines [23] and is thought to be the most abundant and effective cytokine in blood. In the presence of RANKL, the cytokines TNF-α, IL-6 and IL-1 can lead to a massive upregulation of osteoclasts and inhibition of osteoblast activities. TNF-α stimulates osteoclast development and function directly as well as indirectly by increasing the production of M-CSF by bone marrow (BM) stromal cells and decreasing the release of the RANKL decoy receptor OPG by osteoblasts, respectively. Overall, the activation of osteoclasts via these cytokines leads to exaggerated systemic, and in some diseases associated with osteoporosis (periodontitis, RA) also local, bone loss. IL-17 is a further example of a proinflammatory cytokine that – by upregulation of RANKL – promotes bone resorption [24]. IL-17 has become the signature cytokine of a specific T-cell subset (Th17 cells, $CD4^+$ T cells) and is of crucial importance for bone destruction in RA [25].

An excessive production of the aforementioned bone-resorbing cytokines thus explains, at least to a significant extent, the occurrence of osteoporosis in conjunction

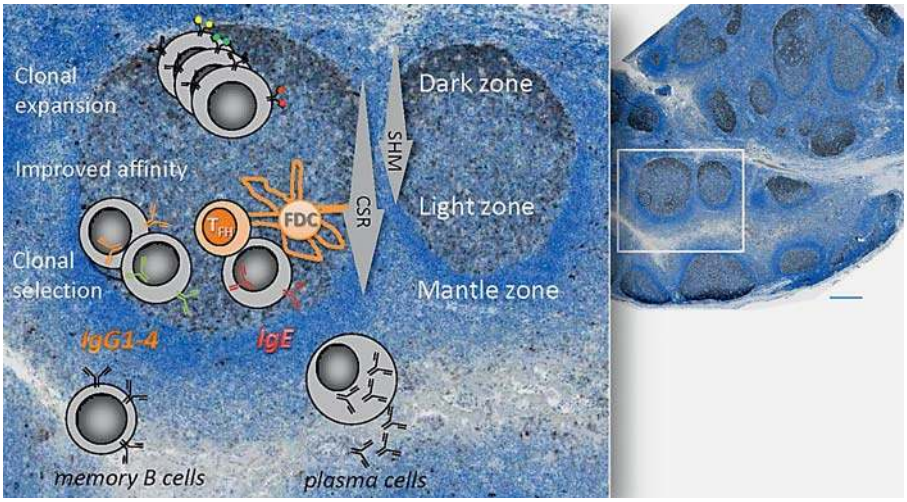

Fig. 1. AID is expressed within GCs. Tonsil tissue specifically stained for AID (brown) and counterstained with hematoxylin to visualize the nuclei (blue). Scale bar = 500 μm. **Insert** Enhanced view of GC structure. A dark zone (area with dominantly proliferating and mutating B cells), a light zone (area of B-cell selection) and a mantle zone (a compact outer rim of small lymphocytes) are clearly visible. CSR = Class switch recombination; FDC = follicular dendritic cell; SHM = somatic hypermutation; T_{FH} = follicular helper T cell.

with chronic inflammatory reactions. Interestingly, these cytokines also are of pathogenic importance in 'primary' forms of osteoporosis, i.e. in postmenopausal and age-related osteoporosis. In pioneering work, the group of Pacifici had established that estrogen deficiency leads to an increased production of IL-1 by mononuclear cells [26]; Eghbali-Fatourechi et al. [27] convincingly demonstrated an upregulation of RANKL in early postmenopausal women. Data from our laboratory show that in postmenopausal women with osteoporotic fractures, the proportion of $CD8^+$ cells that express TNF-α is expanded when compared to age-matched control women [28]. Our findings are in line with those of D'Amelio et al. [20], who described an increased production of TNF-α by T cells (and monocytes) in postmenopausal women with osteoporosis. Aging is associated with a (initially subclinical) proinflammatory state that has been termed 'inflamm-aging' by Claudio Franceschi [29]. The overproduction of proinflammatory (and often bone-resorbing) cytokines by macrophages is a hallmark of inflamm-aging (table 1); classic age-related diseases such as atherosclerosis, dementia, sarcopenia and also osteoporosis were proposed to result – at least in part – from manifestations of inflamm-aging.

Role of B Cells beyond the Generation of Antibodies: The B Lymphocyte-Skeletal Interface

B lymphocytes – comprising multiple subsets and subpopulations and allocated in BM, the blood stream, secondary lymphoid organs such as lymph nodes, the spleen, tonsils, Peyer's patches and mucosal tissues as well as peripheral tissues – belong to the key players in both innate and adaptive immunity. The driver of B-cell immunological diversity is the enzyme activation-induced cytidine deaminase (AID), which converts cytidine to uracil in DNA and thus is responsible for Ig class switch recombination and somatic hypermutation events [30]. AID is predominantly expressed in germinal center (GC) B cells within secondary lymphoid organs (fig. 1) [31]. Another unique functionality of B lymphocytes is linked to their capacity to form active GC-like ectopic lymphoid structures outside secondary lymphoid tissues, thereby impacting the pathophysiology of diseases [32–34]. Notably, at the end of the GC reaction, long-lived plasma cells migrate to the BM, where their homing and survival is provided by a specialized niche [35, 36].

B-cell-mediated functional activities in health and disease, however, go far beyond the antigen-dependent T-cell priming and generation of antibodies. The variety of B-cell-mediated actions additionally includes the secretion of cytokines and chemokines that mediate (promote or inhibit) cell differentiation and inflammation [37]. Particularly relevant for the current review is the knowledge that B lymphocytes are active regulators of the RANK/RANKL/OPG system [9], which – as described above – is known to play a key effector role in basal bone homeostasis, osteoclast formation and the regulation of bone resorption.

Given the tight anatomical proximity and physiological coexistence between B cells – representing the abundant population of the BM – and bone-forming units, bidirectional interactions have long been suspected. In-

deed, from early B-cell development in the BM to the plasma cell stage when antigen-experienced B cells return back to the BM niche, B cells produce active mediators for bone maintenance and, furthermore, share a number of regulatory cytokines and chemokines and their receptors as well as downstream signaling molecules with bone-forming or bone-resorbing cells. Reciprocally, it is now well recognized that BM stromal cells and osteoblasts produce growth factors that provide support for hematopoiesis and early B-cell development; among these are: C-X-C motif chemokine 12; Skp, Cullin, F-box-containing complex; granulocyte M-CSF; IL-7; RANKL, and OPG.

One long-known example which highlights the tight relationship between B-cell development and bone homeostasis is based on the experimental outcome of the manipulation of the IL-7/IL-7R axis in mice, which allows to make the important statement that perturbation of B lymphopoiesis in the BM is closely linked to changes in bone mass [38].

Already in the year 1998, it was demonstrated that human B cells secrete the antiosteoclastogenic factor OPG [39]. These studies were considered important for an understanding of the role of OPG in immune regulation; however, the significance of these findings was overlooked in respect to bone biology, while, historically, the major source of OPG has been attributed to osteoblasts. Almost a decade later, in mouse models, a link was established to bone homeostasis, showing that under physiological conditions B cells are the dominant source of OPG in mouse BM; the B lineage (including multiple subsets such as B-cell precursors, immature B cells and plasma cells) was found to be responsible for 64% of total BM OPG production [40]. In line, B-cell KO mice were found to be osteoporotic and deficient in BM OPG; both OPG deficiency and development of osteoporosis were rescued by transplantation of B cells back into B-cell KO mice. On the contrary, under inflammatory circumstances, B cells serve as a significant source of the proresorptive cytokine RANKL [41]. Of note, B-cell OPG production was shown to be upregulated in human tonsil-derived B cells via activation of B-cell costimulatory CD40 signaling by an activating antibody [39] and in mouse splenic B cells by a soluble ligand to CD40 (sCD40L) [40], thus mimicking the action of activated T cells. Furthermore, mouse models using CD40 KO and CD40L KO mice as well as T-cell-deficient nude mice translated these findings in vivo and confirmed that BM OPG production is significantly diminished with any of those deficiencies and that those mice display osteoporosis [40].

Although many questions are still open, discoveries covering the sources and regulation of RANKL and OPG as well as their defined ratio in physiological bone turnover versus an imbalance in their expression under pathological conditions including osteoporosis demonstrated a strong association between the mechanisms controlling skeletal integrity and the immune response, with particular emphasis placed on the functionality of B cells. This new way of thinking revises our understanding of the pathogenesis of several diseases with osteopenia and osteoporosis development under altered function or deficiency in B cells. Some examples will be discussed below.

The results of the Immunos study, which aimed to analyze the immune changes in postmenopausal osteoporosis, revealed that the number of $CD19^+$ B lymphocytes and, interestingly, the magnitude of various subpopulations of memory B cells were significantly lower in women with osteoporosis when compared to healthy controls [42]. Furthermore, the basal levels of granulocyte M-CSF secreted by B cells were found to be higher in osteoporotic patients and showed a negative correlation with lumbar spine BMD (independent of estrogen levels). The authors postulated that the observed perturbations of B-cell populations are the consequence of physical changes in the BM microenvironment. However, the data do not exclude the inverse possibility when altered B-lymphocyte functions, survival mechanisms and/or abnormal branching point to either memory or plasma cells possibly contributing to the development of such a multifactorial disorder as osteoporosis.

In a recent study by Pineda et al. [43] on a postmenopausal female cohort, an interesting methodological approach was used to find associations between bone density and SNPs within predefined, differentially expressed genes obtained from the ovariectomized (OVX) animal model using a genome-wide gene expression profiling. Thus, as a first step, the global gene expression data sets in BM of OVX mice were compared to those of control mice to identify genes with modulated expression in response to estrogen deficiency induced by OVX. Noteworthy, the analysis revealed that the top canonical pathways were attributed to B-cell biology and included B-cell development, primary immunodeficiency signaling, PI3K signaling in B cells and FcγRIIB signaling in B cells. Based on the mouse model's outcome, the authors selected four genes for further study to find their association with BMD in a cohort of 706 postmenopausal women; CD79a molecule, immunoglobulin-associated alpha gene *(CD79A* or *IGA)* was among those genes. The encoded protein transcript is necessary for the functionality of B-cell receptors

on the B-cell subsets. In this study, an association was detected between two SNPs within *CD79A* (rs3810153 and rs1428922) and lumbar spine BMD. In sum, these results strongly suggest the contributing role of B cells in bone metabolism and the pathology of osteoporosis. A potential follow-up question is whether the indicated SNPs can be used as prognostic/predictive biomarkers for the outcome of patients with osteoporosis.

The prevention of bone resorption and subsequent joint destruction is one of the main challenges in the treatment of patients with RA. The results of a recent study revealed that the percentages of $CD5^+$ B cells are positively correlated with the serum levels of the bone resorption marker CTX-1 in a cross-sectional cohort of RA patients [44]; however, the possible functional link and driving mediators still need to be identified. $CD5^+$ B cells have attracted considerable interest based on their association with self-reactivity (by production of low-affinity polyreactive autoantibodies), autoimmunity, mucosal immunity and leukemia (reviewed in [45]).

Another example of a severe disease which is associated with extensive damage to both cellular and humoral immunity on the one hand and with high rates of osteopenia and osteoporosis on the other hand is HIV infection/AIDS. Again, the mechanisms involved in pathological bone turnover are unclear. Based on the results for the HIV transgenic rat model, it was previously reported that the bone loss was associated with a significantly altered rheostat of RANKL/OPG produced by B cells; thus, upregulation of the key osteoclastogenic RANKL was accompanied by a decline in expression of its physiological moderator/decoy receptor OPG [46]. In HIV patients with increased bone resorption and osteopenia, B-cell expression of RANKL was significantly increased, while B-cell expression of OPG was significantly diminished, thus favoring osteoclast-mediated bone resorption [47]. Furthermore, a correlation analysis with variables such as BMD (g/cm^2, T-score and Z-score) at the hip, neck of femur and lumbar spine and B-cell OPG, RANKL and RANKL/OPG ratio revealed that (1) B-cell OPG was significantly correlated with neck of femur Z-score and (2) RANKL/OPG ratio was negatively correlated with all BMD measures and T- and Z-scores at the hip and neck of femur. This study for the first time demonstrated a possible role for B-cell dysfunction in HIV-associated bone loss in humans, and further emphasized the critical interrelation between immune and skeletal systems.

The Effect of Aging and Inflamm-Aging-Related Accumulation of AGEs on Bone

In the aging skeleton, bone remodeling is reduced, leading to a negative bone balance. The number of osteoblasts decreases due to a reduced number of their stem cells, a defective proliferation and differentiation and diversion of these progenitors toward the adipocyte lineage as well as due to increased apoptosis. Aging also significantly increases stromal/osteoblastic cell-induced osteoclastogenesis and promotes an expansion of the osteoclast precursor pool [2, 48]. The osteoblast-derived osteocytes are long-living and interconnected bone cells that significantly impact the bone remodeling process. A decline in osteocyte number is paralleled by a decline in bone strength in both humans and mice. Osteocytes exhibit a dramatic loss of viability with age; Qiu et al. [49] estimated that at an age of 75 years, the osteocyte density has declined to about 40% of the value at the age of 20 years. Among other determinants of osteocyte death during aging, such as estrogen deficiency and reduced physical activity, oxidative stress is an important factor [48]. Aging is associated with inflamm-aging [29], which is paralleled by an increase in oxidative stress. Over time, this impairs the antioxidant and repair potential of cells and promotes diverse nonenzymatic modifications of macromolecules. Elevated oxidative stress and the increased glucose levels often found in elderlies support the generation of AGEs, a process further stimulated by and stimulating the inflammatory environment [50]. It should be noted in this context that glycemia and, subsequently, diabetes mellitus (DM) are a rising global hazard, with the number of adults with DM having more than doubled over nearly three decades [51]. Moreover, both type 1 and type 2 DM are associated with an increased risk of osteoporosis-associated fractures [7, 52]. AGEs, a major class of nonenzymatically modified macromolecules, are thought to contribute to many of the complications of aging including cataract formation or atherosclerosis [53], but they also interfere with bone physiology [50]. AGEs accumulate in the bone matrix with increasing donor age [54]. In line with a function of AGEs in osteoporosis, their serum levels are elevated in individuals with osteoporosis [55], and they are found in bone biopsies of osteoporotic patients [56].

AGEs impact cells and tissues in two major ways. Firstly, they act by modifying the structure and, subsequently, the function of proteins. Secondly, AGEs can bind and activate the receptor for AGEs (RAGE), which is expressed at low levels in many cells including those of the

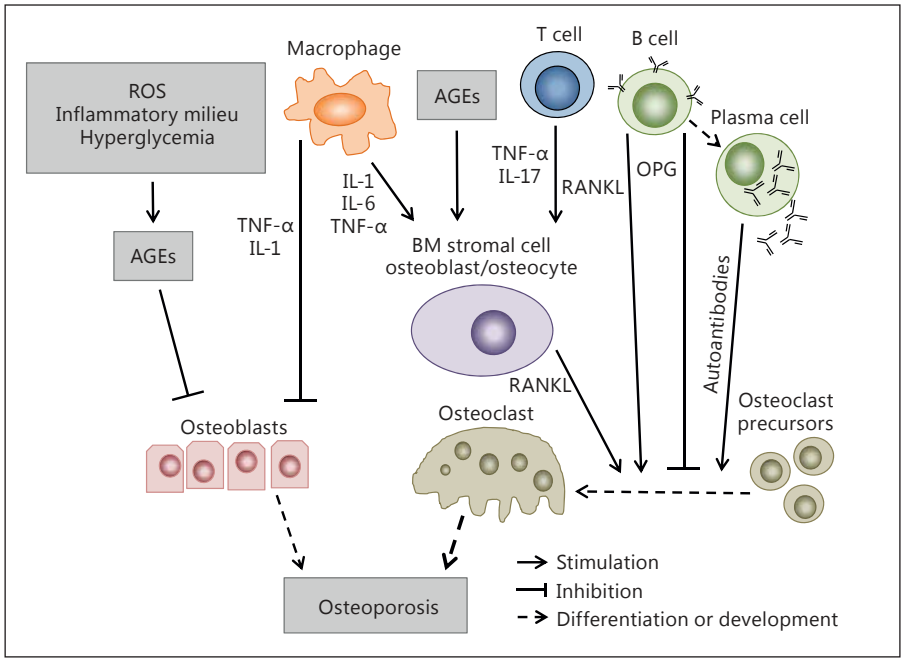

Fig. 2. A partly hypothetical model of the role of components of the immune system in the pathogenesis of osteoporosis. ROS = Reactive oxygen species.

bone and the immune system. Although AGEs can also bind to a diverse set of other receptors, it is most likely the RAGE activation which accounts for the pathogenicity associated with AGEs. RAGE signaling activates the NF-κB pathway, causes upregulation of RAGE itself, promotes the expression of adhesion molecules and the production of proinflammatory cytokines and enhances oxidative stress. Sustained RAGE activation leads to chronic perpetuation of inflammation and tissue damage [50].

In bone, AGE adducts form predominantly on the long-living and abundant matrix protein COL I. This introduces intermolecular cross-links and side-chain modifications in COL I, reducing the solubility and flexibility and increasing the stiffness of the protein, thereby contributing to skeletal fragility [57]. Moreover, the AGE modification of collagen negatively impacts the interaction with preosteoblasts, decreasing the differentiation of preosteoblasts into osteoblasts [58]. Likewise, osteoblastic cells isolated from fetal rat calvariae and cultured on AGE-modified COL I exhibit altered cell differentiation and function [59]. Not only COL I, but also other AGE-modified proteins can disturb osteoblast proliferation, differentiation and function. This has been demonstrated in a variety of studies using preosteoblasts/osteoblasts of human, mouse and rat origin, although not all cell stages seem to be equally sensitive [58, 60, 61]. Furthermore, AGEs promote apoptosis of osteoblastic cells [62] and human mesenchymal stem cells [63].

In contrast to the clearly negative effect of AGEs on osteoblasts, more research is required to clarify the role of AGEs in osteoclastogenesis. AGE-modified BSA was shown to totally inhibit osteoclastogenesis in vitro, most likely by impairing the commitment of osteoclast progenitors into preosteoclastic cells [64]. Other research groups, however, found that the bone resorption activity of osteoclasts was positively correlated with the in situ concentration of AGEs and showed that this effect was enhanced with increasing donor age [54]. A stimulation of osteoclast activity due to AGEs is also supported by studies of Franke and colleagues [61, 65], who found increased RANKL production as well as TNF-α production in osteoblasts stimulated by AGEs. Both factors, as described above, are potent stimulators of osteoclast activity.

Therapeutic Aspects

Based on the central role of the RANKL/RANK/OPG system in the pathophysiology of osteoporosis, denosumab, a monoclonal antibody that targets RANKL, has been developed. Denosumab inhibits the generation and activity of osteoclasts; in clinical studies, the antibody was found to decrease bone resorption and to increase BMD [66]. In postmenopausal women with osteoporosis, denosumab significantly decreased the risk of vertebral, nonvertebral and hip fractures [67]. Denosumab is the

first monoclonal antibody that had been approved for patients with osteoporosis; currently, antibodies against sclerostin (an inhibitor of bone formation) are under clinical investigation. In RA and other inflammatory arthritides, anti-TNF-α therapies are effective in treating joint inflammation; consistent with the concept of osteoimmunology, antibodies against TNF-α have been shown to inhibit excessive bone resorption.

Conclusions

Although osteoimmunology is a relatively young discipline, this research field has already made significant contributions to our knowledge of the biology and pathophysiology of bones and the immune system. Figure 2 summarizes our current working model about how components of the immune system may induce an imbalance between osteoblasts and osteoclasts that ultimately results in osteoporosis. The identification of molecular disease mechanisms in osteoimmunology has fostered the development of novel treatment strategies: since several years, denosumab, a monoclonal antibody against RANKL, has been available for the treatment of osteoporosis [4]. Thus, osteoimmunology has very successfully made the transition from bench to bedside.

Acknowledgments

This work was supported in part by the Austrian Science Fund (FWF; http://www.fwf.ac.at/) project P20239-B13 to P.P. and projects P22441-B13 and P23228-B19 to D.M.

Disclosure Statement

P.P. has received research support and/or honoraria from Amgen GmbH, Eli Lilly GmbH, Fresenius Kabi Austria GmbH, Merck Sharp and Dohme GmbH, Novartis Pharma, Nycomed Pharma, Roche Austria, Servier Austria, Sanofi-Austria and Sinapharm. The remaining authors declare no conflicts of interest.

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