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Review

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Bioactive lipids and cancer metastasis to bone

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Abstract

Bioactive lipids constitute a large family of molecules considered as inflammatory mediators. Among them, lysophosphatidic acid (LPA), sphingosine 1-phosphate (S1P), and eicosanoids (prostanoids such as PGE2 and leukotrienes such as LTB4, LTC4, and LTD4) play a central role in the pathophysiology of several inflammatory diseases. However, it has long been known that these bioactive lipids are also involved in cancer, mainly because of their ability to control the pro-inflammatory microenvironment of tumors as well as their ability to act directly on tumor cells promoting cell proliferation, migration, and survival. Recently, there has been increased interest in determining how these lipid mediators orchestrate tumor development and metastasis. Bone metastases result from a complex dialogue between tumor cells and bone cells. Recent findings demonstrate that all these bioactive lipids can profoundly affect bone metabolism by acting positively or negatively on both osteoblasts and osteoclasts. This review gives an overview of previous findings demonstrating direct involvement of LPA, S1P, and PGE2 in bone metastasis. This review also emphasizes the recent findings that characterize the activity of these bioactive lipids directly on bone cells and how these activities could be integrated into the complex molecular mechanisms leading to bone metastasis formation and progression.

Keywords: Lysophosphatidic acid, sphingosine 1-phosphate, eicosanoids, prostaglandins, leukotrienes, cancer, bone cells

INTRODUCTION

Bone is a highly dynamically regulated tissue which undergoes continuous homeostatic and reactive remodeling by the coordinated action of bone cells, namely osteoblasts, osteoclasts, and osteocytes, and controlled by endocrine factors, immune cells, and mechanical forces. Sir Paget's "seed and soil" theory was the first still valid concept explaining why certain types of cancers have remarkably high propensity to form bone metastases such as breast and prostate cancers[1]. During the 1990s, works released from Greg Mundy's lab led to the development of an additional theory leading to the notion of the "vicious cycle" established at the sites of bone metastases, reflecting the reciprocal stimulation between tumor growth and bone resorption[2]. The vicious cycle theory is also still valid with even more clinical impact, as it is the current target of the best systemic therapies against bone metastases that use anti-resorptive agents (i.e., bisphosphonates and denosumab)[3]. Unfortunately, even under these best standards of care, patients with bone metastases still have limited overall survival, indicating the existence of additional molecular mechanisms. Bioactive lipids are widely present in the organism and affect almost all vital systems. In this review, we focus on two lysophospholipids, lysophosphatidic acid (LPA) and sphingosine 1-phosphate (S1P), and two classes of eicosanoids, prostanoids and leukotrienes, because all of these molecules can regulate cancer progression including bone metastasis as well as important biological processes directly related to bone such as skeletal development, mineralization, regulation of bone mass and homeostasis, osteoblast-osteoclast coupling, and bone resorption and formation.

LYSOPHOSPHATIDIC ACID

Structure, synthesis, and receptors

LPA is the simplest phospholipid which is composed of a glycerophosphate backbone linked to a single fatty acid chain. LPA can be synthesized from two pathways. In the first one, phospholipid precursors such as phosphatidylcholine (PC), phosphatidylserine (PS), or phosphatidylethanolamine (PE) can be converted to lysophosphatidylcholine (LPC), lysophosphatidylserine (LPS), and lysophosphatidylethanolamine (LPE), respectively, through the action of phosphatidylserine-specific phospholipase A1 or secretory phospholipase A2 such as in blood platelets[4,5] [Figure 1]. LPC appears to be the most abundant LPA precursor in the blood. These precursors can then be converted to LPA by a lysophospholipase D (LysoPLD). LPA can also be generated by a distinct mechanism, namely the acylation of glycerol-3-phosphate by glycerophosphate acyltransferase and the phosphorylation of monoacylglycerol by monoacylglycerol kinase[6]. LPA level is tightly tuned by degradation mechanisms mediated by different classes of enzymes such as lipid phosphate phosphatases (LPPs)[7] or LPA acyltransferase[8,9].

Autotaxin (ATX or ENPP2) is responsible for LPA levels in the blood, as evidenced by LPA concentrations in serum that are half normal values in *Enpp2*$^{+/-}$ heterozygous mice[10]. As a unique member of the family of the seven ectonucleotide pyrophosphatase/phosphodiesterase (ENPP) that hydrolyze pyrophosphate and phosphodiester bonds in nucleotides and their derivatives[11], ATX possess a LysoPLD activity, allowing the hydrolysis of LPC and other lipid precursors to produce LPA. ATX is present at high concentration in the blood circulation[12]. However, the origin of ATX in blood remains to be determined. Nevertheless, adipose tissue is likely one of the main sources, as revealed in *aP2-Cre*/*Enpp2*$^{fl/fl}$ mice presenting 30% decrease in LPA levels in plasma[13]. ATX is also highly expressed in the brain and lymphatic high endothelial venules[14]. Although ATX is capable of hydrolyzing nucleotides *in vitro*, its biological function relies on its lysoPLD activity, as the apparent affinity for LPC is 10 times higher than that of nucleotides[15] and as

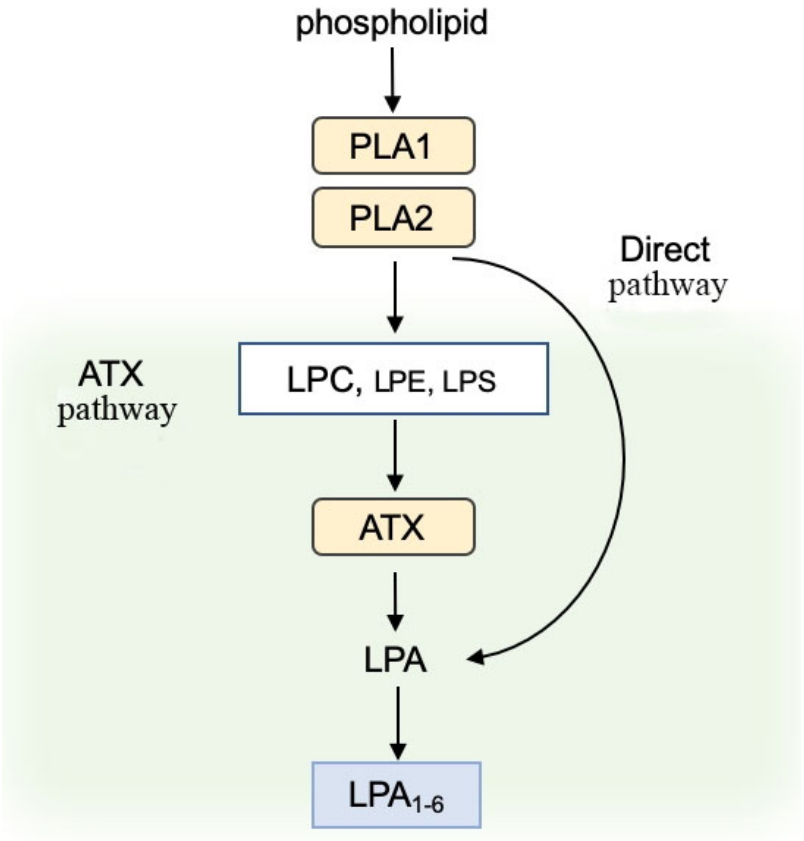

Figure 1. Overview of LPA biosynthesis and receptors. Phospholipase A1 or A2 (PLA1 and PLA2) catabolize membrane phospholipids producing LPA either directly or through the release of LPA precursors (LPC, LPE, and LPS) that are metabolized in LPA by autotaxin (ATX) due to its lysophospholipase D activity. LPA activates six specific G protein-coupled receptors (LPA_{1-6}). LPC: Lysophosphatidylcholine; LPE: lysophosphatidylethanolamine; LPS: lysophosphatidylserine; LPA: lysophosphatidic acid.

extracellular nucleotides are rare.

LPA activates a series of six different G-protein coupled receptors (LPA_{1-6}). Overall, LPA receptors link to all types of heterotrimeric G proteins, $G_{\alpha 12/13}$, $G_{\alpha q/11}$, $G_{\alpha i/o}$, and $G_{\alpha s}$, but, due to specific interactions, LPA receptors can have redundant, synergic, or opposite actions. LPA_1 is the most ubiquitous LPA receptor in adults, with prevalence in brain, heart, testis, ovary, prostate, colon, thymus, and pancreas. Eukaryotic cells frequently express multiple LPA receptors. Mature osteoclasts express LPA_1, LPA_2, LPA_4, LPA_5, and LPA_6[16], whereas osteoblasts express mostly LPA_1 and LPA_4 and traces of LPA_5[17]. As a marked specificity, LPA_6 is the sole LPA receptor whose mutation is involved in a human pathology of congenital alopecia[18]. The impact of LPA_6 mutation on bone homeostasis has not been reported yet.

Role of LPA on bone cells

LPA is produced at the bone site, as we previously showed in the context of bone metastasis [Figure 2]. Through its action on both cancer cells and osteoclasts, LPA promotes the progression of osteolytic lesions[19]. LPA plays a key role during bone development. However, origin of LPA in bone is still incompletely understood, although adipocytes[13] and osteoblasts[20] are potential sources that may account for bone homeostasis and bone metastasis. *Lpar1*$^{-/-}$ mice revealed growth retardation due multiple alteration at levels of both the central nervous and the musculoskeletal systems, including inhibition of chondrocyte proliferation, defects in endochondral ossification, and a low bone mass phenotype linked to decreased

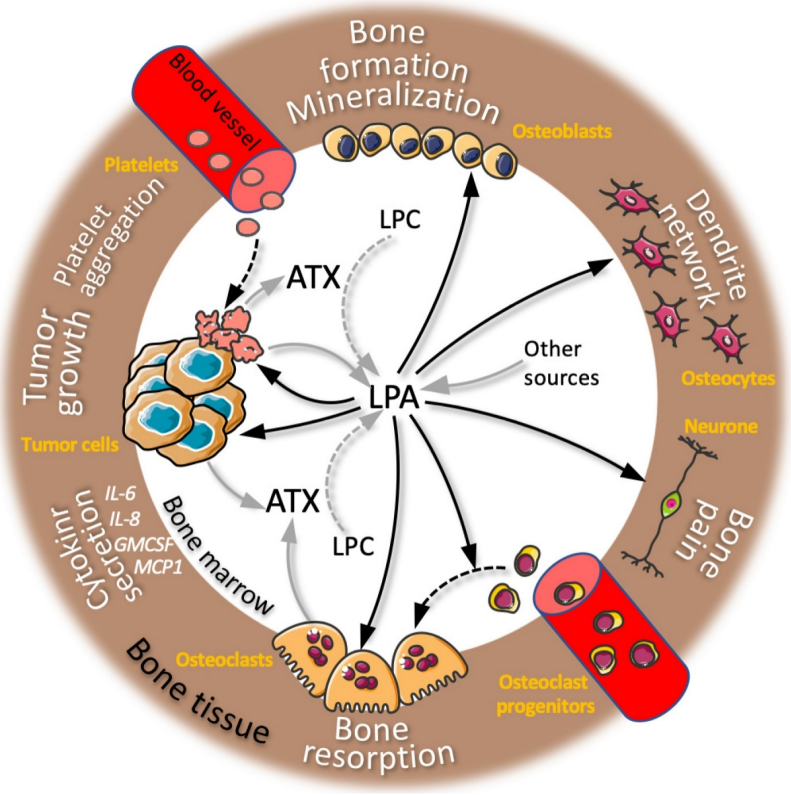

Figure 2. LPA activity in bone metastasis microenvironment: overview of actions of lysophosphatidic acid (LPA) on bone cells, cancer cells, and neurons. Black arrows indicate LPA activity on different cell types from the bone microenvironment (names in orange) resulting in multiple biological functions (text in white). Grey arrows indicate LPA or autotaxin (ATX) cell secretion. Dotted black arrows indicate cell differentiation and platelet aggregation. Dotted grey arrows indicate LPC catabolism by ATX. LPC: Lysophosphatidylcholine.

osteoblast activity[21]. On the other hand, *Lpar4*$^{-/-}$ animals show increased bone formation[22], suggesting that LPA_1 and LPA_4 may have opposite functions in the control of bone formation during development. LPA_4 activates the $G_{\alpha s}$ pathway, whereas LPA_1 signals through $G_{\alpha i}$, resulting in inverse control of adenylated cyclase activation and cAMP accumulation. LPA_1 is expressed in chondrocytes and all bone cells including osteoblasts, osteoclasts, and osteocytes[21,23]. As a result, the bone phenotype of *Lpar1*$^{-/-}$ mice is likely due to a combination of numerous cellular defects that even individually may impact bone remodeling. To elucidate the physiological role of LPA_1 expressed by osteoblasts, we generated conditional knockout mice for *Lpar1* in osteoblastic cell lineage (*Lpar1*-△Ob)[17]. These mice revealed reduced bone mineralization and increase in the areas of both osteocytic lacunaes and osteocyte apoptosis. We have known since the release of Karin lab's work that LPA can promote dendrite outgrowth in MLO-Y4 osteocyte cell line[24]. Osteocyte network was remarkedly reduced in the cortical bone of *Lpar1*-△Ob mice and dendrite connections were drastically reduced in *Lpar1*-△Ob osteocytes in vitro in response to fibroblast growth factor 2. These data reveal that, by acting on osteoblastic LPA_1, LPA produced in the bone environment controls bone quality via bone mineralization and osteocyte function [Figure 2].

LPA also acts on osteoclasts by promoting survival and cytoskeleton rearrangement[23], which involves c-SRC signaling and phosphorylation of Thyroid Hormone Receptor Interactor 6 that drive sealing zone formation and bone resorption[25]. Furthermore, we demonstrated that LPA is mandatory at least *in vitro* for macrophage colony-stimulating factor/receptor activator of nuclear factor-kappa B (NF-κB) (RANK)-ligand

(RANK-L)-induced osteoclastogenesis. Both genetic ablation and pharmacological inhibition of LPA_1 remarkably alter mineral matrix resorption of mature osteoclasts and prevent ovariectomy-induced bone loss[16,26]. These results demonstrate that, under pathophysiological context, the production of LPA in bone might profoundly affect osteoclast function. Mice with global deletion of *Lpar1* revealed remarkable resistance to bone destruction in an arthritis model induced by type II collagen injection[27], confirming the LPA-dependence of osteoclast function here under an inflammation context. This study showed decreased infiltration of macrophages and differentiation into Th17, but not Th1 or Th2, which were also suppressed under pharmacological inhibition of LPA_1. Thus, in the context of bone metastasis, in addition to its action on osteoclasts by stimulating osteolysis, LPA could also promote the recruitment of immune cells that may contribute to the progression of metastases. Furthermore, we recently showed that mature osteoclasts produce functionally active ATX, thereby highlighting these cells as an additional source of LPA in bone[28]. Intriguingly, although osteoclast-derived ATX was revealed to be dispensable for bone development as well as in the classical pathological model of bone loss induced by ovariectomy, we found that autocrine activity of ATX on osteoclasts is required for systemic bone loss and bone erosion induced by inflammation, as observed in tumor necrosis factor (TNF)-transgenic(tg) mice, or after mouse treatment with LPS as well as in the arthritic mouse model using K/BxN-serum transfer[28]. In the context of bone metastasis, treatment with BMP22 of mice harboring pre-established bone metastases from the ATX-null MDA-BO2 breast cancer cells significantly reduced the progression of osteolytic lesions[29]. This clearly demonstrates that non-tumoral ATX controls osteoclastic bone resorption. It is of course possible that ATX produced by different types of cells from the bone environment could act in a paracrine manner on osteoclasts; however, as we found under inflammatory conditions, osteoclast-derived ATX might act in an autocrine manner to stimulate malignant osteolysis. However, this assertion requires further investigation.

Role of LPA in cancer and bone metastasis

Autotaxin's name was originally attributed due to its action on melanoma cells as a new autocrine factor stimulating tumor cell invasion[30]. The ATX/LPA axis was later recognized as a major regulator of tumorigenesis through its action on cancer cell proliferation and survival, as well as through the promotion of angiogenesis and the control of the metastatic cascade by stimulating cell migration and invasion[31,32]. Increased LPA levels are found in different types of cancers[33-35]. Endogenous expression of *ATX* in 4T1 mouse carcinoma cells as well as high *ATX* expression in human MDA-BO2-ATX transfected breast cancer cells provide a higher propensity to these cells of generating bone metastases[26]. The main reason is likely to reside in the fact that these cells express high levels of LPA_1 receptor, resulting in high sensitivity to LPA stimulation. By activating LPA_1, LPA promotes cell motility and proliferation, but the prominent action of LPA/LPA_1 signaling in the context of bone metastasis might be linked to the increase in the secretion of growth factors such as vascular endothelial growth factor (VEGF)[36,37] and cytokines [such as interleukin (IL)-6, IL-8, granulocyte-macrophage colony-stimulating factor, and monocyte chemoattractant protein 1] that are known to affect bone remodeling. Osteomimetism was shown to characterize breast cancer bone-seeking cells[38]. Gene signature of LPA signaling was not associated with osteomimetism. However, cancer cells and bone cells (osteoblasts and osteocytes) share the characteristics that, by activating LPA_1 receptor, LPA also stimulates the secretion of IL-6 and IL-8 [chemokine (C-X-C motif) ligand 15 protein in mouse][39,40]. Overexpression of LPA_1 in MDA-BO2/LPA_1 transfected cells dramatically increases the extent of osteolytic lesion areas, whereas pharmacological inhibition of this receptor using Ki16425 and Debio 0719, two $LPA_{1/3}$ antagonists, reduced cytokine production and the progression of osteolytic bone metastasis. Intriguingly, endogenous expression of *ATX* was revealed to be dispensable for cancer cells to metastasize to bone, as shown by the above-mentioned MDA-BO2 cells that do not express ATX but which are a sub-clone of MDA-MB-231 cells isolated *in vivo* for their exclusive bone tropism[41].

High *ATX* expression in primary tumors is frequently associated with a poor prognosis in cancer patients[42-44]. Intriguingly, the expression of *ATX* directly by tumor cells is often low, as found in most breast cancer cell lines. It has been well established by Brindley *et al.*[45] that tumor microenvironment is a major source of ATX[45]. We showed that challenging mature osteoclasts with inflammatory molecules such as TNF and LPS upregulates the secretion of ATX through a NF-κB pathway[28]. In addition, inflammatory cytokines and chemokines released by breast and thyroid cancer cells have been shown to induce the expression of *ATX* in tumor-associated fibroblasts and adipocytes[46]. Furthermore, during our study on the role of non-tumoral ATX in the formation of bone metastases, we found that blood platelets uptake circulating ATX that is naturally present in the bloodstream and store ATX in their granular compartments, which is eventually released under tumor cell-induced platelet aggregation[29]. Non-tumoral ATX released by platelets is functionally active as it catalyzes the production of LPA, which ultimately acts on cancer cells to promote survival, invasion, and bone metastasis[19,29]. Overall, ATX present in the tumor environment appears as a major promoter of tumor growth and metastasis. Therefore, a new paradigm is emerging at the level of bone metastasis where multiple vicious cycles establish and interconnect together. The first well-known vicious cycle was characterized in 1997 by T Guise, establishing the cross talk between tumor growth and bone resorption[47] [Figure 2]. We showed that the production and activity of LPA following tumor cell-induced platelet aggregation constitute a second vicious cycle between tumor cells and blood platelets taking place at the bone metastasis site[19]. Non-tumoral ATX released by activated platelets is likely to contribute to this bone resorption-independent vicious cycle. Furthermore, by acting on fibroblasts, adipocytes, and, potentially, osteoclasts, tumor cell-derived inflammatory cytokines might contribute to an additional vicious cycle through the secretion of ATX.

Role of LPA in bone pain

Bone pain is the most common complication of bone metastases for cancer patients[48]. LPA is well known to promote neuropathic pain[31], but pain occurring in the context of bone metastasis depends on different mechanisms; as shown primarily by Yoneda *et al.*[49], the release of protons from vacuolar resorption pits during osteoclastic resorption create acidic microenvironments that stimulate sensory nociceptive neurons that innervate bone. This is likely to explain why anti-resorptive agents, such as bisphosphonates and denosumab, efficiently reduce bone pain in bone metastasis patients[3]. Although LPA might indirectly promote metastasis-induced bone pain through the stimulation of osteoclast activity, it might also have a direct action. Using an osteosarcoma-induced bone pain model in rat, Zhao *et al.*[50] showed that, two weeks after cancer cell implantation *in vivo*, sural C-fibers become more sensitive to LPA stimulation, an effect that was blocked after treatment with VPC32183, an antagonist of LPA_1 receptor. The analysis of dorsal root ganglion neurons showed increased LPA_1 receptor expression two weeks after cancer cell injection into the rat tibia[51]. In this context, bone pain was regulated by LPA through LPA_1 signaling in dorsal root ganglion neurons, potentiating potential vanilloid 1 (TRPV1) receptors via protein kinase Cε pathway. In addition, in this rat model, mechanical allodynia and thermal hyperalgesia were alleviated under treatment with VPC32183[51]. Furthermore, using paw withdrawal threshold and flinching behavior assays, Wu *et al.*[52] demonstrated that Rho/ROCK signaling mediates $P2X_3$-induced bone cancer pain downstream of LPA_1 activation. Collectively, these results strongly suggest that LPA might play an important role in pain associated with bone metastasis. However, which LPA receptor is involved is not well understood. Although LPA_1 is likely to mediate LPA-induced bone cancer pain, the analysis of conditional knock-out of *Lpar1* in dorsal root ganglion neurons and its impact on pain in bone metastasis has not been investigated yet.

SPHINGOSINE 1-PHOSPHATE

Structure, synthesis, and receptors

Sphingolipids are another class of phospholipids that are a part of cell membrane. They comprise a polar head and two non-polar tail domains. Sphingosine, a long chain amino-alcohol, is an integral component of

this class of lipids[53]. Sphingolipid metabolism involves three interconnected pathways, namely the *de novo* synthesis pathway, salvage pathway, and sphingomyelinase (SMase) pathway, all of which generate ceramide from complex lipids that is eventually converted into sphingosine and S1P[54,55]. These pathways were initially thought to be autonomous of each other in ceramide generation, but the metabolites synthesized in these three metabolic pathways are highly reversible, non-distinguishable, and hence interdependent.

Ceramide produced by these pathways is converted into sphingosine and eventually S1P by the concatenated effect of enzymes such as ceramidase and functionally redundant sphingosine kinases 1 and 2 (SphK1 and SphK2), respectively[56] [Figure 3]. This process is also reversible and ceramide synthase and sphingosine phosphate phosphatase can revert sphingosine into ceramide and S1P to sphingosine, respectively. S1P can be irreversibly degraded by S1P lyase (SPL) present on the cytosolic side of the endoplasmic reticulum to form non-sphingolipid products: phospho-ethanolamine and hexadecenal (a fatty aldehyde). While these enzymes are intracellular, LPPs reside on the cell membrane and keep extracellular S1P in check[57,58]. Although minimal roles of intracellular S1P signaling have been reported, the major biological functions of S1P (such as embryonic and postnatal vascular development, vascular integrity and tone, hematopoiesis and trafficking of immune and stem cells, and platelet formation and activation in addition to bone homeostasis) are suggested to be receptor dependent and necessitate an efficient export of S1P into the blood and lymph where the levels of S1P are higher as compared to the tissue parenchyma[58-60]. The two bona fide transporters of S1P identified thus far are spinster homolog 2 (Spns2) that is expressed on lymphatic and blood endothelial cells and major facilitator superfamily transporter 2b that exports S1P from erythrocytes and activated platelets[61], therefore making these cells "sources of S1P". This exported S1P needs chaperons to promote aqueous solubility of S1P, increase resistance against degradation and dephosphorylation, and accelerate release of S1P from cellular sources, and they may alter receptor selectivity and signaling bias[59,62,63]. These chaperons include high-density lipoprotein bound to apolipoprotein M, albumin, low-density lipoprotein, very low-density lipoprotein, and the recently identified chaperon apolipoprotein A4[64,65]. While blood chaperones are well described, less is known about what chaperones S1P associates within the lymph and interstitial fluids.

Highly regulated local differences in the synthesis, export, and intracellular and extracellular degradation of S1P lead to marked differences in its abundance among blood (~1 μM), lymph (~0.1 μM), and the tissue parenchyma (< 1 nM), as well as the formation of local S1P gradients within tissues. Sensing of this S1P gradient by the receptors drives biological processes such as immune cell trafficking and vascular homeostasis[58,66,67]. Factors such as presence of *de novo* synthesis machinery, lack of degradation machinery, and expression of *S1P* transporters govern whether a cell can be deemed as a source of S1P.

S1P binds to and activates a family of cognate G-protein coupled receptors, $S1P_{1\text{-}5}$. Due to overlap and divergence in Gα subunit selectivity, S1P receptors can act in synergy or in opposition to each other[68,69]. Notable examples include antagonistic activities of the exclusively $G\alpha_i$-coupled $S1P_1$ and the predominantly $G\alpha_{12/13}$-coupled $S1P_2$ and sometimes synergistic activities of $S1P_1$ and $S1P_3$, which can also couple to $G\alpha_i$. $S1P_1$ is the most widely expressed receptor, which is well studied for its role in maintaining vascular, immune, and bone homeostasis. S1PR1, S1PR2, and S1PR3 transcripts in primary osteoblasts and S1PR1 and S1PR2 in osteoclasts have been detected with negligible or null quantity of S1PR4 and S1PR5, but this could be attributed to poor sensitivity of the tools available to detect these receptors rather than the actual absence of these receptors.

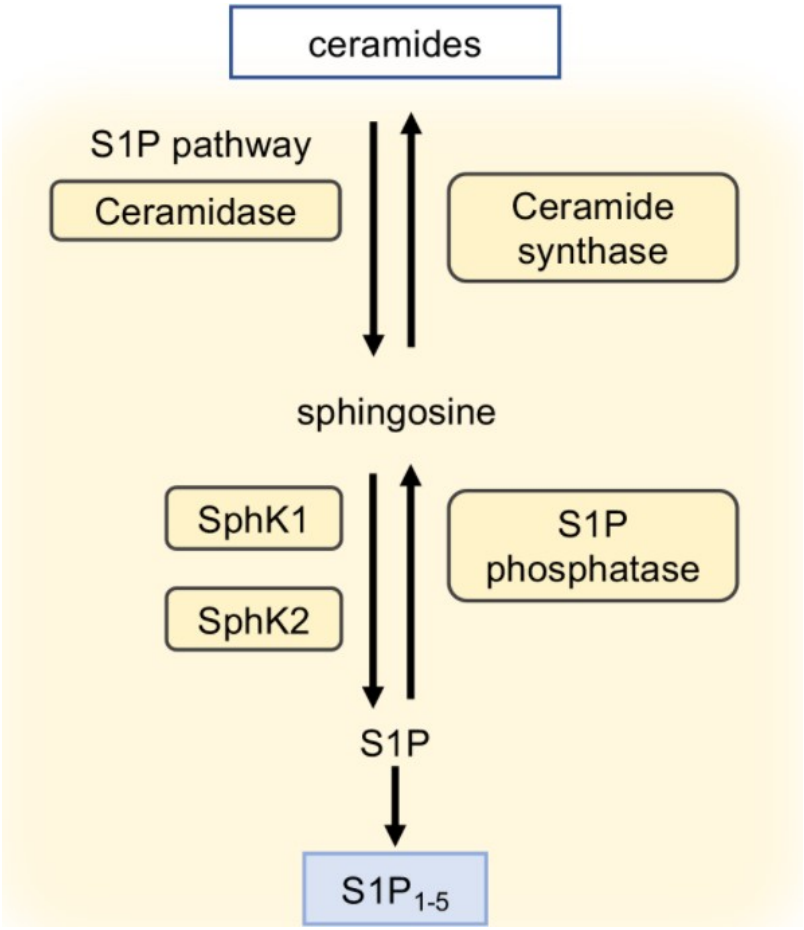

Figure 3. Overview of sphingosine 1-phosphate (S1P) biosynthesis and receptors. Ceramides are converted into sphingosine under the action of ceramidase. Sphingosine is then metabolized in S1P by the action of two sphingosine kinases (SphK1 and SphK2). All biosynthesis steps are reversible in cells. S1P activates five specific G protein-coupled receptors ($S1P_{1-5}$).

Role of S1P on bone cells

Initially, the S1P contribution to bone homeostasis has been mainly assigned to bone remodeling with particular emphasis on possible roles in the circulation of osteoclast progenitors[70-72]. Accordingly, a S1P gradient between blood and bone marrow has been proposed that chemoattracts osteoclast progenitors away from the bone microenvironment (and hence fewer of them differentiating to mature osteoclasts) towards blood through $S1P_1$. Accordingly, mice lacking $S1P_1$ in CD11b+ cells were mildly osteopenic. Ishii *et al.*[73,74] argued that this process was at equilibrium with another regulated by $S1P_2$ causing exactly the opposite - chemorepulsion of osteoclast progenitors away from blood towards bone resulting in their prolonged dwelling there and hence accelerating osteoclastogenesis. How the two mechanisms may interact physiologically remains unclear as $S1P_1$ and $S1P_2$ possess the same K_d for S1P and are expressed to the same extent in osteoclast progenitors. On the contrary, we showed that elevating S1P levels *in vivo* by genetic SPL knockout and pharmacological SPL inhibitors resulted in a dramatic increase of bone mass and bone mechanical strength in adult mice. If S1P actions on osteoclast progenitors were crucial, bone mass would have decreased as high S1P levels under these circumstances would have desensitized $S1P_1$ leading to enhanced osteoclastogenesis. In the following years, much more potent mechanisms have been identified for how stimulating S1P signaling enhances net bone growth, bone remodeling, and bone mechanical strength[75] [Figure 4].

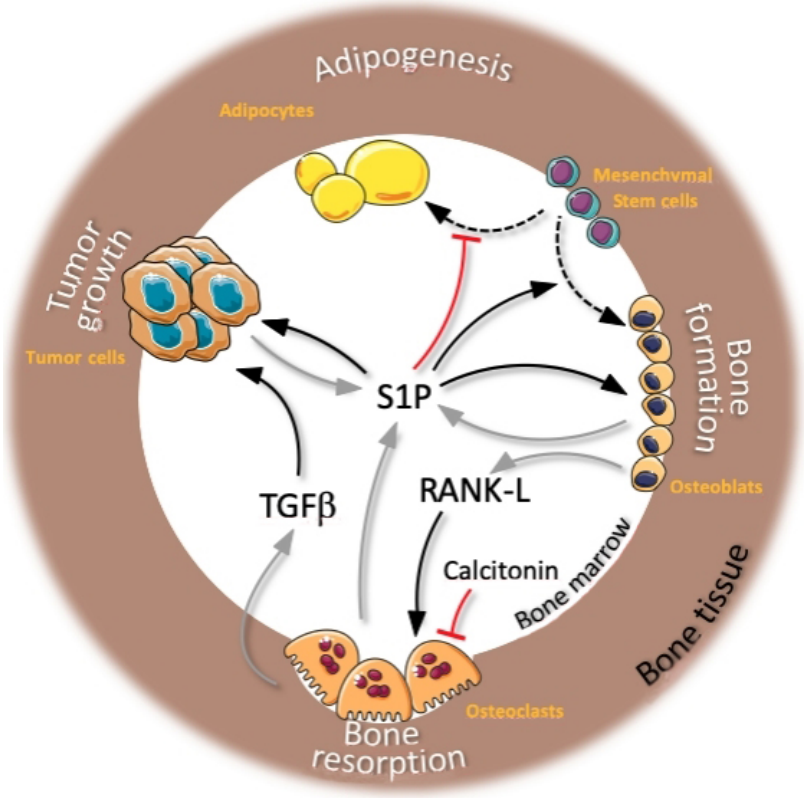

Figure 4. Sphingosine 1-phosphate (S1P) activity in bone metastasis microenvironment: overview of actions of S1P on bone cells, cancer cells, and adipocytes. Black arrows indicate activities of S1P, receptor-activated NF-κB ligand (RANK-L), and tumor growth factor β (TGFβ) on different cell types from the bone microenvironment (names in orange) resulting in multiple biological functions (text in white). Grey arrows indicate S1P and RANK-L secretions and TGFβ release from resorbed bone matrix. Dotted black arrows indicate cell differentiation (adipogenesis and osteoblastogenesis). Red lines indicate S1P and Calcitonin inhibitory activities.

Indeed, we and others demonstrated numerous effects of S1P on osteoblast behavior instead: (1) osteoclast-secreted S1P stimulated osteoblast production of RANK-L and bone morphogenic protein 6 and promoted osteoblast differentiation from mesenchymal stem cells[72,76]; (2) deletion of the bone matrix-degrading enzyme cathepsin K in osteoclast increased osteoblastic bone formation by inducing Sphk1 activity and S1P production[77]; and (3) the hormone calcitonin induced bone formation by osteoblast through $S1P_3$ and did so by controlling osteoclast S1P secretion though regulation of the S1P transporter Spns2[71]. These studies have established S1P as a bona fide trophic factor for osteoblasts as well as a novel factor in the functional coupling of osteoclasts and osteoblasts [Figure 4].

Nevertheless, despite all the molecular insights, the most relevant question of all remains: What exactly are the consequences of pharmacological or genetic alteration of endogenous S1P for bone health and diseases *in vivo*, and which S1P receptors are responsible? This is particularly relevant if S1P-based drugs were to be considered for the therapy of osteoporosis or any other bone-related diseases. Studies in preclinical models of human diseases have shown that interventions that elevate whole body S1P concentration successfully corrected age-related osteoporosis, osteoporosis caused by estrogen deficiency, and the severe genetic osteoporosis caused by osteoprotegerin deficiency (a genetic model of human juvenile Paget disease)[75]. At least two major mechanisms have been identified behind the potent osteoanabolic actions of S1P. The first involves an osteoclast suppressive action of osteoblasts, where $S1P/S1P_2$ signaling stimulated osteoblasts to produce Wnt oncogene analog 5 (Wnt5a) and osteoprotegerin through a p38-dependent glycogen synthase

kinase-3 (GSK3)/β-catenin pathway, thus inhibiting both osteoclastogenesis and osteoclast activity. The second mechanism was even more fundamental: S1P had profound effects on the lineage commitment of the common osteoblast/adipocyte stem cell precursor by tilting the differentiation equilibrium in favor of osteoblastogenesis at the expense of adipogenesis [Figure 4]. This occurred by S1P activating the ostoblastogenic transcription factors osterix and Wnt5a and suppressing major adipogenic ones such as peroxisome proliferator-activated receptor gamma and CCAAT/enhancer-binding protein alpha. Accordingly, mice with high S1P had not only a higher bone mass but also less adipose tissue[75].

In humans, data on bone health or disease in relation to S1P are scarce. Several small observational studies have negatively associated blood S1P and certain parameters of osteoporosis and have even linked S1P to increased risk of bone fracture[78]. In over 4000 participants of the SHIP-Trend population study, we also found an inverse relation of plasma S1P to QUS-based bone stiffness as surrogate for classical bone mineral density but uncovered a positive association of plasma S1P with clinical bone formation markers[75]. This indicated that high S1P is not necessarily causally detrimental for bone mass but, instead, may serve as a counter-regulatory measure to boost decreasing bone quality.

As altering S1P metabolism by SPL inhibition has undesired side effects, $S1P_2$ agonists have already been successfully used instead to correct osteoporosis caused by estrogen deficiency in mice[79], thereby opening new avenues for osteoporosis treatment in men. Considering the lack of drugs aimed at stimulating new bone formation rather that inhibiting its degradation (virtually all osteoporosis drugs are anti-resorptive in nature), S1P-targeting drugs may become part of the therapeutic quest for the osteoanabolic "Holy Grail" in the treatment of osteoporosis. On a broader perspective, any therapy successful at increasing new bone growth will certainly find applications not only in the treatment of primary and secondary osteoporosis but also in the therapy of rare genetic skeletal diseases, bone trauma and bone regeneration medicine, osteoprosthetics, and bone-related tumor and metastasis medicine.

Rolls of S1P in cancer and bone metastasis

SphK/S1P metabolic pathway has been thoroughly investigated because of its implication in all stages of tumorigenesis, in cancer cell dissemination, and in the onset and development of metastasis[56,80]. Interestingly, the exact role of SphK/S1P/S1P receptor signaling in cancer-derived bone metastasis remains somehow unexplored; only a few studies propose the imbalance of S1P metabolism as a central driver of bone metastasis.

Recently, the analysis of tumor transcriptome of 3999 breast cancer patients showed that an increase in SPHK1, a suppression of SPHK2, and an increase in SPNS2 and S1PR1 were associated with high score tumors. All of these protein partners are implicated in the production and secretion of S1P and the promotion of angiogenesis[81]. *S1PR1* expression was indeed elevated in different models of human breast cancer with bone metastatic potential such as luminal and basal/triple-negative subtypes of breast cancer cell lines and several breast tumors. Furthermore, breast cancer tumors with a correlation between *IL-22R1* and *S1PR1* expression were more prone to cause bone metastases[82]. *S1PR3* expression and S1P secretion were significantly increased in MDA-MB-231 subline 1833, derived from a breast cancer-derived bone metastasis[83]. *SphK1* expression was increased by TGF-β and associated to the metastatic potential of MDA-MB-231 breast cancer cell model[84] [Figure 4].

Up to a third of advanced renal cell carcinoma patients will also develop osteolytic bone metastases[85]. SphK/S1P signaling has been implicated in several aspects of the pathophysiology of renal cell carcinoma, notably in the regulation of tumor hypoxia and angiogenesis[86,87]. Moreover, upregulation of *SphK1*

expression was correlated to sunitinib resistance and poor prognosis of a large cohort of renal cell carcinoma patients[88]. An antibody directed against S1P (sphingomab/sonepcizumab) was proposed as a new therapy for resistant renal cell carcinoma after encouraging results in mouse models[89]. Finally, a phase 2 study of the effect of sonepcizumab in patients with advanced renal cell carcinoma who have previously failed up to three therapies, including VEGF and/or mammalian target of rapamycin inhibitors, was conducted. This study did not accomplish its primary endpoint (two-month progression-free survival of the disease), but a median overall survival of 21.7 months was monitored. Moreover, treatment with sonepcizumab was considered as safe[90].

Osteoblastic bone metastases are currently found in lung cancer patients and prostate cancer patients with advanced disease. Osteoblasts actively synthetize bone in localized zones such as ribs, clavicles, or spinal vertebrae. Newly synthetized bone is extremely fragile, generally provoking fractures and therefore intensive pain. In the case of lung cancer, the five S1P receptors were expressed in several non-small and small lung cancer-derived cell lines. Exogenous S1P had a pro-metastatic effect in these lung cancer cell models, increasing cell migration and their chemotactic responsiveness to different growth factors, especially HGF[91]. SphK/S1P metabolic pathway has been extensively studied in the case of prostate cancer[92,93]. Importantly, *SphK1* activity and expression were increased in human prostate cancer resection specimens and correlated with higher prostate specific antigen levels, higher tumor volumes, and disease relapse[94]. There is only one study reporting the implication of S1P metabolic pathway in prostate cancer-derived bone metastasis. SphK1 activity was significantly increased in murine and human osteoblastic cell models. Osteoblasts triggered proliferation of different prostate cancer cell lines through extracellular secretion of S1P. In addition, osteoblast-derived S1P was able to induce chemo - or radioresistance of prostate cancer cell models. Furthermore, blockade of SphK1 inhibited the proliferative effects of osteoblasts on prostate cancer cells[95].

Finally, mixed bone metastases have zones of both active bone resorption and active bone formation. As mentioned above, a small population of breast cancer patients can suffer from mixed bone metastasis, and they can be found in, for example, colorectal cancer, which is the most common cause of death in these patients. SphK/S1P signaling has been extensively described to have oncogenic roles in colorectal cancer or colitis-associated colorectal cancer[96,97]. SphK1 activity was important for the promotion of metastasis in colorectal cancer[98]. *SphK1* expression was indeed significantly increased in patients, and an elevated SphK1 was an independent predictor of distal metastasis[99]. Other components of S1P signaling such as irreversibly S1P-degrading enzyme, SPL[100] and S1P transporter, and Spns2[101] or S1P receptors such as $S1P_2$[102] or $S1P_4$[103] were recently implicated in different aspects of colorectal cancer or colitis-associated colorectal cancer.

PROSTAGLANDINS/LEUKOTRIENES

Prostaglandins and leukotrienes belong to the super-family of eicosanoids. This family is composed of bioactive lipids that all derive from arachidonic acid (AA). AA is released from cellular membranes predominantly by cytosolic phospholipase A2α activity. Then, AA is processed by cyclooxygenases (COXs) to form prostanoids, including prostaglandins (PGs), prostacyclin (PGI_2), and thromboxane A2 (TXA2), and by 5-lipoxygenase (5-LOX) to form leukotriene B_4 (LTB_4) and the cysteinyl leukotrienes (CysLTs): LTC_4, LTD_4, and LTE_4 [Figure 5].

Structure, synthesis, and receptors

Prostaglandins are generated by the action of prostaglandin G/H synthases, colloquially known as COXs, bifunctional enzymes that contain both cyclooxygenase and peroxidase activity and exist as two distinct

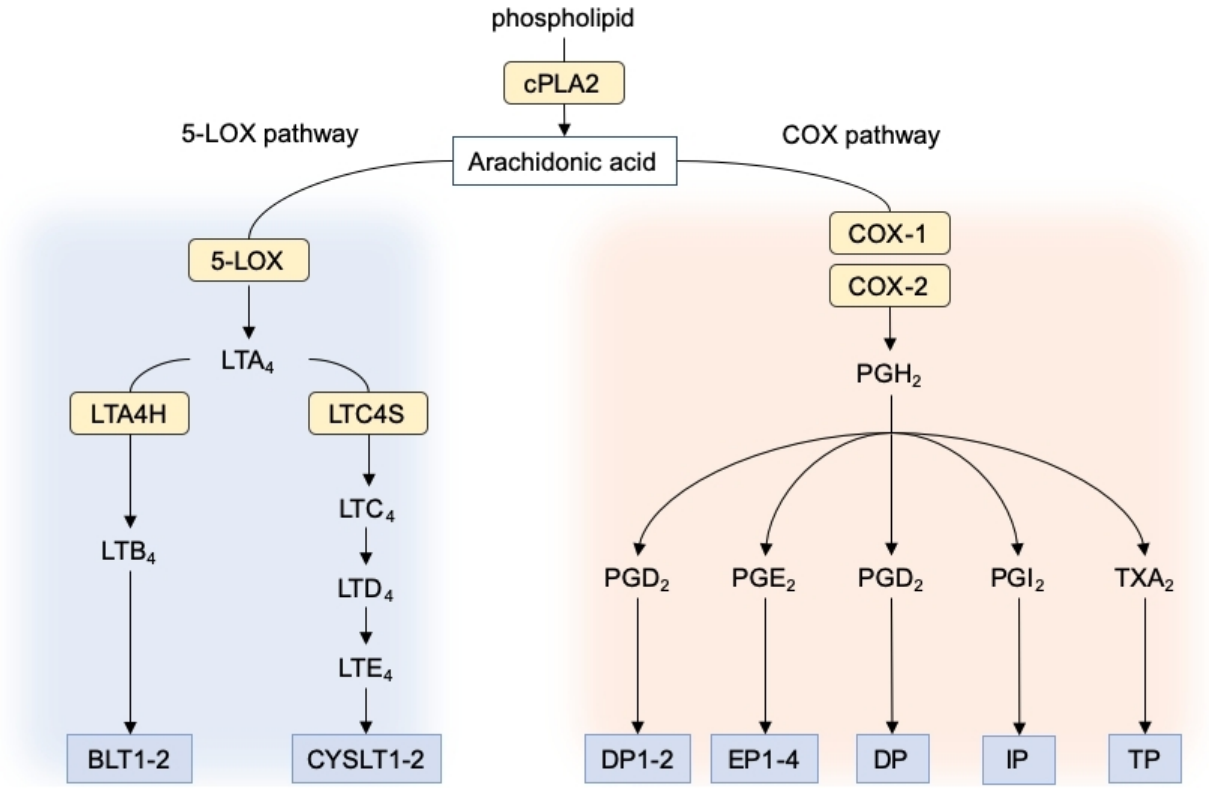

Figure 5. Overview of eicosanoid biosynthesis and receptor signaling. Arachidonic acid (AA) is liberated from the cellular membranes by cytoplasmic phospholipase A2 (cPLA2). Free AA can be metabolized by two main enzymes: cyclooxygenases (COXs) to form various prostanoids and 5-lipoxygenase (5-LOX) to form leukotrienes. In the COX pathway, the intermediate PGH2 is sequentially metabolized into prostaglandins and thromboxanes by specific prostaglandins and thromboxane synthases. In the 5-LOX pathway, AA is converted into the unstable leukotriene A4 (LTA4), which is subsequently converted to leukotriene B4 by LTA4 hydrolase (LTA4H) or to cysteinyl leukotriene LTC4 by LTC4 synthase (LTC4S). Each of the prostaglandins and leukotrienes exerts its biological effects through its cognate G protein-coupled receptor.

isoforms referred to as COX-1 and COX-2. COX isoenzymes catalyze the conversion of arachidonic acid to prostanoids, which include TXA2 and four different PGs: PGD_2, PGE_2, $PGF_{2\alpha}$, and PGI_2. COX-1 is expressed constitutively in most cells. It is the major source of prostanoids with housekeeping functions, whereas COX-2, which is induced by inflammatory stimuli, hormones, and growth factors, is the most important source of prostanoids in inflammation and cancer[104]. Prostaglandins signal in an autocrine or paracrine manner through G-protein-coupled receptors (GPCRs) designated as $DP_{1/2}$ for PGD_2, $EP_{1/2/3/4}$ for PGE_2, FP for $PGF_{2\alpha}$, IP for PGI_2, and TP for TXA_2[105] [Figure 5].

Leukotrienes (LT) are generated by the 5-LOX pathway in certain types of leukocytes, such as granulocytes (neutrophils, eosinophils, and basophils) and monocytes/macrophages. 5-LOX, in conjunction with 5-LOX-activating protein (FLAP), generates the unstable intermediate leukotriene A_4 (LTA_4). Depending on the cellular enzymes present, LTA_4 can be either converted to dihydroxy-LT LTB_4 by LTA_4 hydrolase or conjugated with glutathione by cysteinyl leukotriene C4 synthase (LTC_4S) to generate LTC_4. Subsequently, LTC_4 is exported out of the cell via multidrug resistance-associated proteins 1 and 4 and further processed into cysteinyl leukotriene D4 (LTD_4) and cysteinyl leukotriene E4 (LTE_4). LTB_4 and LTD_4 are the most potent leukotrienes[106]. LTs exert their biological effects by binding to two sets of GPCRs present at the cell surface: $BLT_{1/2}$ for LTB_4 and $CYSLT_{1/2}$ for the CysLTs. Chemotaxis, one of the principal effects of LTB_4, occurs via activation of the BLT_1 receptor subtype, which is the high-affinity LTB_4 receptor[107]. BLT_2 exhibits

low affinity to LTB_4 and responds in addition to various eicosanoids[108]. $CYSLT_1$ has a high affinity for CysLTs that is higher for LTD_4 than LTC_4, whereas $CYSLT_2$ has a lower overall affinity that is equal for LTC_4 and LTD_4[109,110]. *BLT_1* and *$CysLT_1$* expression is restricted to myeloid cells, whereas BLT_2 and $CysLT_2$ are expressed in a wide variety of cells [Figure 5].

Role of prostaglandins/leukotrienes in bone cells

Prostaglandins, particularly PGE_2, are major regulators of bone metabolism. However, their mechanisms of action are complex as they can stimulate both bone resorption and formation and auto-amplify their effects by inducing *COX-2* expression [Figure 6]. In bone, PGE_2 is primarily produced by osteoblasts and contributes indirectly to osteoclastic bone resorption through the upregulation of RANK-L in osteoblasts, leading to stimulated osteoclastogenesis and bone resorption[111]. Many cytokines and growth factors known to potentiate bone resorption, such as IL-1 and IL-6, enhance PGE_2 production by osteoblasts. In contrast, IL-4 and IL-13 inhibit bone resorption by suppressing PGE_2 production[112]. Analysis of the four EP receptor-deficient mice revealed that PGE_2 stimulates bone resorption in the cultured calvariae through the EP_4-cAMP signaling pathway[113]. *EP_4* expression on mouse osteoblasts is required for osteoclast formation[114]. This suggests that PGE_2-induced *RANK-L* expression is mediated through EP_4 [Figure 6]. In addition, PGE_2, synergistically with RANK-L and M-CSF, directly stimulates the differentiation of mouse osteoclast precursors into osteoclasts through EP_2 and EP_4, which are downregulated in mature osteoclasts[115,116]. This direct effect of PGE_2 on human osteoclasts is however controversial[112]. Paradoxically, prostaglandins also have inhibitory effects on bone formation. PGE_2 is known to inhibit bone resorption *in vitro*[111] and increase overall bone mass *in vivo*[117]. The anabolic effect of PGE_2 is notably mediated by the stimulation of osteoblastic differentiation via EP_4 and possibly EP_2[118]. PGE_2 has also been implicated in several bone-resorptive inflammatory disorders such as osteoarthritis, osteoporosis, and periodontitis[112]. PGE_2 and COX-2 promote bone formation in response to mechanical loading and endogenous PGE_2 participates in the recovery from osteoporosis and bone fracture[119].

Global deletion of 5-LOX in mice increases bone mass and protects against bone loss in the ovariectomy mouse model[120], although high-fat diet-induced bone loss was increased in *$5\text{-}LOX^{-/-}$* mice[121], suggesting an interaction between estrogen and leukotriene pathways. Both LTB_4 and LTD_4, in association with RANK-L, promote osteoclast differentiation and bone resorption[122]. Thus, 5-LOX metabolites may also act as regulators of bone metabolism. LTB_4, but not CysLTs, is responsible for *Aggregatibacter actinomycetemcomitans*-induced bone loss in mice[123]. By promoting osteoclastic bone resorption, LTB_4 may thereby inhibit bone formation. Osteoclasts express BLT_1, but not BLT_2, and produce LTB_4, suggesting that LTB_4/BLT_1 signaling increases osteoclastic activity through autocrine and paracrine pathways[112]. LTB_4 is involved in the induction of pain and bone damage in rheumatoid arthritis[124]. CysLTs also regulate osteoclast differentiation via $CYSLT_1$ receptor, supporting the role of CysLT in bone loss[125,126]. Importantly, LTD_4-$CYSLT_1$ signaling activates the mitogen-activated protein kinases (MAPK)/extracellular signal-regulated kinases (Erk)/c-Jun N-terminal kinase/p38 pathway, which is a key pathway for regulating osteoclast differentiation and bone resorption. This may explain why the $CYSLT_1$ antagonist montelukast inhibits M-CSF- and RANK-L-induced osteoclast differentiation[127]. In addition, montelukast prevents the association of RANK and TNF receptor associated factor 6 and suppresses reactive oxygen species generation, which are known to contribute to the pathophysiological development of osteoclastogenesis[128]. $LTD_4/CYSLT_1$ signaling also plays a role in inducing cellular senescence signaling in osteoblasts, a mechanism that has been described to control bone metastasis[129]. Montelukast also inhibits *MMP13* expression in osteoblast, a key factor of proteolytic degradation of membrane-linked RANK-L and extracellular matrix components[130]. LTD_4 induces chemotaxis and migration of CD34+ bone marrow progenitors and induces Erk/MAPK signaling in chronic lymphocytic leukemia (CLL) cells, suggesting that CysLTs may contribute to bone marrow accumulation and homing of CLL cells[131,132].

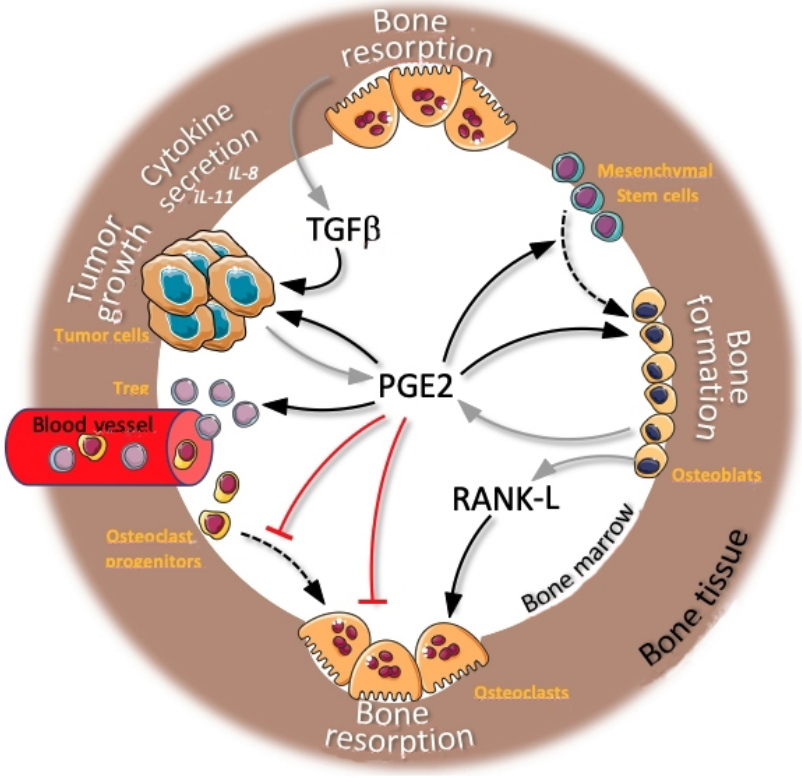

Figure 6. Prostaglandin E2 (PGE2) activity in bone metastasis microenvironment: overview of actions of PGE2 on bone cells, cancer cells, and blood cells. Black arrows indicate activities of PGE2, receptor-activated NF-κB ligand (RANK-L), and tumor growth factor β (TGFβ) on different cell types from the bone microenvironment (names in orange) resulting in multiple biological functions (text in white). Grey arrows indicate PGE2 and RANK-L secretions and TGFβ release from resorbed bone matrix. Dotted black arrows indicate cell differentiation (adipogenesis and osteoclastogenesis). Red lines indicate PGE2 inhibitory activity on osteoclast differentiation and activity.

Role of prostaglandins/leukotrienes in cancer and bone metastasis

Prostaglandins

Although negligibly expressed in normal cells, COX-2 is overexpressed in many types of cancers such as lung, colorectal, breast, prostate, skin, and hepatic cancers[133]. COX-2 overexpression increases the rate of cancer recurrence[134] and reduces survival in patients[135,136]. The use of non-steroidal anti-inflammatory drugs, which inhibit PGE_2 production, may reduce cancer risk of metastasis[137]. Expression of *COX-2* in tumors probably occurs as an early event[138] and is related to cancer cell resistance to chemo- and radiotherapy[139]. COX-2 exerts most of its functions on tumor cells through PGE_2, and elevated urinary PGE_2 metabolites serve as a biomarker to predict pancreatic cancer risk[140]. PGE_2 promotes tumor growth through autocrine and paracrine mechanisms by activating EP receptors present in both cancer and stromal cells. The variability of EP receptors expressed by cancer cells may influence cell response to PGE_2. Typically, EP_1 and EP_4 are associated with tumor cell migration, invasion, and metastasis, whereas EP_2 is associated with angiogenesis and immunosuppression. PGE_2 supports survival and proliferation of cancer cells by upregulating Bcl-2 and epidermal growth factor receptor (EGFR). Moreover, PGE_2 is an important player in tumor microenvironment, where it suppresses antitumor immunity[141]. Many *in vivo* studies have revealed the role of PGE_2 in colon cancer carcinogenesis and progression[142-144] and showed that microsomal prostaglandin E synthase-1 (mPGES-1) deletion suppresses intestinal and breast cancer progression[145,146]. Although clinical and *in vitro* studies have shown a potential for the use of COX-2 inhibitors to prevent and treat malignant diseases, toxicities due to global prostanoid suppression have limited their use[147]. For this

reason, EP receptors antagonists are now considered more relevant with some under clinical investigation[133] [Figure 6].

Blockade of prostaglandin synthesis with aspirin, in combination with APT102, an ADPase, decreases breast cancer and melanoma bone metastasis in mice[55,148]. B16 melanoma bone metastasis is also suppressed in *mPGES-1*-deficient mice, suggesting that prostaglandins may drive tumor invasion and metastasis[149]. Bone seeking cells express COX-2 and produce PGE_2. TGF-β released from resorbed bone matrix enhances *COX-2* expression in cancer cells, leading to a vicious cycle between bone resorption and tumor growth[150]. In addition, PGE_2 also indirectly contributes to bone resorption by stimulating the secretion of pro-osteoclastic cytokines (IL-8 and IL-11) by cancer cells[151,152]. PGE_2/EP_4 signaling upregulates matrix metallopeptidase (MMP)-2, MMP-9, RANK-L, and Runt-related transcription factor 2 (RUNX2) and contributes to prostate cancer cell proliferation and invasion via the cAMP-protein kinase A/phosphoinositide 3-kinase (PI3K)-Akt signaling pathway[153]. Overexpression of COX-2 in *TM40D* mouse breast cancer cells increased bone metastasis by recruiting Treg cells through their EP_2 and/or EP_4 receptors[154], thus providing a favorable metastatic environment against immune system surveillance. Nevertheless, in an immunocompromised mouse model, the COX-2 inhibitor MF-tricyclic inhibited bone metastasis in mice inoculated with human breast cancer cells, suggesting a direct antitumor action of COX-2 inhibitor and/or indirect action on bone cells[155]. Blockade of PGE_2-EP_4 signaling in mice was shown to decrease bone metastasis, in part via the abrogation of PGE_2-induced *RANK-L* expression in osteoblasts[156].

Leukotrienes

5-LOX is overexpressed in tissue samples of patients with bladder, breast, esophageal, kidney, oral, pancreatic, and prostate cancer, as well as in established cancer cell lines[157-161]. 5-LOX expression is present during the early neoplastic changes in cancers such as in pancreatic cancer, well before progression to invasive disease[158], supporting the role of 5-LOX in early stages of carcinogenesis. Furthermore, 5-LOX correlates with tumor stage and lymph node metastasis in colorectal adenocarcinomas[158]. Leukotrienes may modulate the initiation, progression, and metastasis of tumors through regulating the proliferation, apoptosis, migration, and invasion of cancer cells. Addition of *5-LOX* expression products to tumor cells led to increased cell proliferation and activation of anti-apoptotic pathways[162]. *$CYSLT_1$* receptor expression negatively correlates with survival of patients with prostate, breast, and colon cancers and metastatic uveal melanoma[105]. Conversely, low expression of *$CYSLT_2$* is associated with poor prognosis in colon cancer. In this context, $CYSLT_2$ signaling leads to terminal differentiation of colon carcinoma cells and growth inhibition[163]. LTC4S overexpression is found in patients with chronic myeloid leukemia, and high LTC4S levels are correlated with tumor aggressiveness in prostate cancer[164,165]. Activation of $LTD_4/CYSLT_1$ signaling has been shown to promote cell proliferation and survival through multiple parallel pathways, including GSK3β/β-catenin, PKC/Raf/ERK1, and ERK2 signaling[166,167]. LTD_4 increases cancer cell survival by upregulating *COX-2* expression and PGE_2 production[168], indicating a crosstalk between CysLTs and the prostaglandins pathways. $LTD_4/CYSLT_1$ promotes migration and invasion in colon cancer cells by regulating *MMP-9* expression[169], whereas $CysLT_2$ signaling reduces cancer cell migration[163], suggesting opposing roles of these receptors in cancer cell motility. LTB_4 levels are increased in human colon and prostate cancers[163]. Inhibition of LTB_4 synthesis reduced colon cancer cell growth in patient-derived xenograft mouse model and inhibited the burden of esophageal adenocarcinoma in a rat model[170,171]. Although *in vivo* LTB_4 may have both direct and indirect pro-tumor action, *in vitro* LTB_4/BLT_1 signaling directly stimulates colon cancer cell growth and survival through MAPK/ERK- and PI3K-Akt-dependent pathways[172,173]. LTB_4, by acting on BLT_2, increases mesenchymal markers and promotes epithelial-to-mesenchymal transition in several human cancer cell lines[174,175]. BLT_1 appears to also affect cancer progression through immune modulation. Notably, PD-1 blockade fails to reduce melanoma growth in

BLT1$^{-/-}$ mice due to deficiency in T cell infiltrations[176]. This might contribute to the escape of cancer patients to checkpoint inhibitor therapies. Although pharmacological leukotriene inhibitors have demonstrated promising cytotoxic and anti-proliferative effects on cancer cell lines and in animal models[162], few clinical trials have been conducted. LY293111, a well-tolerated inhibitor of BLT1, showed no significant difference in short-term survival in patients with pancreatic cancer and non-small cell lung cancer[177,178]. Conversely, cysteinyl leukotriene receptor antagonists (LTRAs), such as montelukast and zafirlukast, which are widely prescribed anti-asthmatic drugs, show more promising chemopreventive effects. A large epidemiological study on asthmatic patients showed that LTRA treatments decreased the risk of cancer development, especially lung, breast, colorectal, and liver cancers[179]. $CYSLT_1$ antagonists also confer promising chemopreventive effects in preclinical models[180-184].

Although the role of 5-LOX metabolites in carcinogenesis is well established both *in vitro* and in murine models, few studies have focused on tumor progression and metastasis. MK591, a 5-LOX inhibitor, inhibits *in vitro* invasion of C4-2B human prostate cancer cells[99]. Increased resorption in bone explants induced by the breast-cancer cell lines MDA-MB-231 and MCF-7 was inhibited by blocking prostaglandin and leukotriene synthesis[185]. These findings suggest that prostaglandins, as well as leukotrienes, may drive osteolytic bone lesions. Unexpectedly, 5-LOX deletion in an immunocompetent orthotopic model of lung cancer resulted in increased primary tumor growth and metastasis, suggesting an antitumorigenic role for some 5-LOX products[186]. Given the crosstalk between the different prostanoid pathways and their possible opposing effects, caution should be taken in targeting these pathways in cancer.

CONCLUSIONS

Inflammation plays a prominent role in carcinogenesis and metastasis[187]. Multiples reports have demonstrated during the past decade that inflammation can promote tumor initiation, cancer cell growth, and metastasis. Remarkably, chemotherapy, radiation therapy, and surgery frequently result in the production of pro-inflammatory and pro-angiogenic factors that significantly reduce or even counteract the efficacy of those anti-cancer therapies[188-195]. Increased knowledge of the tumor microenvironment composition has brought the concept of tumors as inflammatory sites that do not heal. Beyond their direct action on both cancer cells and bone cells, LPA, S1P, and eicosanoids also promote inflammation at the bone metastatic site by inducing the production of pro-inflammatory cytokines and the recruitment of immune cells. Therefore, therapeutic strategies combining anti-inflammatory drugs and blockers of bioactive lipids deserve future investigations. However, the recent success of immunotherapies against various types of cancers has shifted the paradigm that mobilizing the immune system is beneficial against cancer. Meanwhile, loss of resolution of inflammation has recently emerged as a new mechanism of cancer pathogenesis[196-202]. This suggests that resolution of inflammation rather than blocking it might be a better therapeutic approach[203,204]. Resolution of inflammation relates to the clearance of cellular debris by macrophages resulting in reduced localized pro-inflammatory cytokines[205]. Many specialized pro-resolving mediators (SPMs) have been characterized based on their endogenous inhibitory action of inflammation such as resolvins, lipoxins, protectins, and maresins[205]. Failure of resolution *vs.* inflammation in carcinogenesis has been reviewed in detail[206]. Interestingly, lipoxin A4 (LXA4), which is also a bioactive lipid derived from AA following combined activities of 5-LOX and 12-LOX[207], inhibited osteoclast differentiation and resorption activity[208]. As expected, *in vivo*, LXA4 treatment prevented ovariectomy-induced bone loss in mice. Interestingly, serum levels of pro-osteoclastic cytokines (TNF-α, IL-1β, IL-6, and RANKL) were significantly reduced in ovariectomized animals treated with LXA4. These results support the hypothesis for direct inhibition of osteoclasts *in vivo* by LXA4. They also reveal an additional indirect osteoclastic action of LXA4 via reducing the production of pro-osteoclastic mediators. Therefore, LXA4 appears as a potential new tool for the treatment of osteoporosis as well as bone metastasis. Although the

number of studies directly linking bioactive lipid/receptor axes to bone metastasis remains limited, the constant presence of these lipids in the tumor microenvironment as well as their potent direct activity on bone cells suggest a still underestimated action of these molecules among the complex integrated molecular mechanisms responsible for bone metastases progression. Even under the best standard of care, current targeted bone metastasis therapies are still provided in a palliative purpose with unfortunately no long-term curative benefit, highlighting the dramatic need for additional strategies. In this context, targeting bioactive lipids in combination with SPMs may potentially lead to the development of novel therapeutic approaches that undoubtedly deserve future investigations.

DECLARATIONS

Author's contributions

Made substantial contributions to writing and correcting the manuscript: Saier L, Niazi H, Brizuela L, Levkau B, Peyruchaud O

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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