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The Role of The EphrinB2-EphB4 Bidirectional Signalling on Bone Remodeling: A Review

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Abstract: Postmenopausal osteoporosis is a prevalent disease that can lead to serious outcomes such as fractures. Oestrogen deficiency during menopause and postmenopause increases bone turnover, with elevated bone resorption and formation. However, resorption surpasses formation, resulting in bone loss. Identifying intervention targets in bone physiology to restore bone remodeling balance and normal bone mass is the initial aim in developing new effective therapies. Currently, EphrinB2/EphB4, one of the membrane coupling factors between osteoclasts (OCs) and osteoblasts (OBs), is a prominent topic in bone disease research. However, the regulatory mechanisms of EphrinB2-EphB4 bidirectional signalling on OC and OB and its effects remain incompletely understood. This review seeks to clarify the physiological roles and mechanisms of known EphrinB2-EphB4 bidirectional signalling in bone remodeling, providing insights for future studies on modulating this signalling pathway.

Keywords: EphrinB2, EphB4, Bone remodeling, Osteoclast, Osteoblast.

1. Introduction

Osteoporosis is a metabolic bone disease characterized by reduced bone mass, microstructural deterioration of bone tissue, decreased bone strength, and increased bone fragility, making patients susceptible to fractures (NIH Consensus Development Panel On Osteoporosis Prevention, 2001). Osteoporosis is categorized into primary and secondary types based on the causative factors. Primary osteoporosis is further divided into postmenopausal osteoporosis, which is associated with postmenopausal oestrogen deficiency, and senile osteoporosis, which is linked to aging (Raisz, 2005). Secondary osteoporosis results from various other diseases or as an adverse effect of the treatment of certain diseases (Feng & McDonald, 2011). Maintaining bone health crucially depends on preserving bone remodeling homeostasis, which is the dynamic balance between the bone resorption by osteoclasts and the bone formation by osteoblasts. When factors shift the balance towards increased bone resorption by osteoclasts over bone formation by osteoblasts, continuous bone loss occurs, eventually causing osteoporosis.

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During human development, bones accumulate mass as bone formation exceeds bone resorption. In adulthood, bone remodeling is in dynamic equilibrium, with bone resorption equal to bone formation. In the aging stage, bone mass is lost as bone resorption surpasses bone formation. When bone mass loss reaches a certain level, it can result in osteoporosis. Maintaining bone remodeling homeostasis in the aging stage can reduce the incidence of osteoporosis. Within the bone-remodeling compartment, bone remodeling is carried out by the cells of the basic multicellular units, passing through five steps: activation, bone resorption, reversal, bone formation, and termination (Kenkre & Bassett, 2018). These steps involve the migration and maturation of osteoclast precursors to the damaged bone surface. Mature osteoclasts then perform bone resorption. This is followed by the suppression of osteoclast bone resorption function. Next, osteoblast precursors are recruited and mature at the resorbed bone surface. They produce new bone matrix and mineralize it. Finally, the process concludes (Kenkre & Bassett, 2018). Therefore, the coupling of osteoclast resorption of old bone with osteoblast formation of an equivalent new bone is crucial for precisely maintaining bone remodeling homeostasis. The factors involved in the coupling between osteoclasts and osteoblasts fall into two main categories. First, soluble coupling factors include transforming growth factor-beta (TGF-β) (Tang et al., 2009) and Insulin Growth Factor 1 (IGF1) (Durdan et al., 2022; Xian et al., 2012) from bone matrix, as well as leukemia inhibitory factor (LIF) (Weivoda et al., 2020) and cardiotrophin-1 (CT-1) (Walker et al., 2008) from OCs. Second, membrane coupling factors include EphrinB2-EphB4 (Zhao et al., 2006), semaphorin4D-PlexinB1 (Negishi-Koga et al., 2011; Shindo et al., 2022), and RANKL-RANK signalling (Durdan et al., 2022). For the treatment of osteoporosis, a monoclonal antibody Denosumab (DMAb) targeting the membrane coupling factor RANKL-RANK

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signalling has been developed, which neutralizes RANKL, inhibits osteoclast differentiation and resorptive activity (Khosla & Hofbauer, 2017), and induces multinucleated osteoclast apoptosis to reduce osteoclast numbers (McDonald et al., 2021). However, this drug, besides inhibiting osteoclasts, does not significantly enhance bone formation. Given that most current osteoporosis treatments primarily target anti-resorptive effects, the development of drugs that both counteract bone resorption and stimulate bone formation to restore normal bone mass is increasingly important. Therefore, the EphrinB2-EphB4 bidirectional signalling that exists between osteoclasts and osteoblasts and among osteoblasts has become a significant topic in the research of bone diseases.

Inhibiting excessive bone resorption by osteoclasts and promoting bone formation by osteoblasts is essential for restoring the balance of bone remodeling. This balance is critical for preventing and treating osteoporosis. EphrinB2-EphB4 bidirectional signalling exists between osteoclasts and osteoblasts, as well as among osteoblasts themselves. This makes it a promising therapeutic target that can both inhibit bone resorption and promote bone formation. Understanding how EphrinB2-EphB4 bidirectional signalling affects the generation and function of osteoblasts and osteoclasts is important. It will support conducting animal experiments targeting this signalling pathway. The aim is to explore drugs that can effectively restore the balance of bone remodeling. Successful animal studies will lay the basis for future clinical trials of such drugs.

2. EphB4 and EphrinB2

EphB4 is a member of the Eph receptor family, which belongs to the largest subgroup within the tyrosine kinase receptor family. The Eph receptor family can be divided into two subclasses: EphA and EphB. EphA receptors bind to EphrinA ligands anchored by glycosylphosphatidylinositol (GPI), whereas EphB receptors bind to EphrinB ligands containing transmembrane and cytoplasmic domains (Matsuo, 2010). In humans, there are 14 Eph receptors (EphA1-A8, EphA10, EphB1-B4, and EphB6) and 8 Ephrin ligands (EphrinA1-A5 and EphrinB1-B3) (Kania & Klein, 2016; Liang et al., 2019; Nguyen et al., 2016), with receptor-ligand mixed binding within subclasses (Lindsey et al., 2018). Eph receptors structurally consist of nine domains, including an extracellular N-terminal ligand-binding domain (LBD), a region rich in cysteine residues composed of sushi-like and EGF-like motifs, two fibronectin (FN) domains, a transmembrane domain (TM), a juxtamembrane domain (JM), a tyrosine kinase domain (TK), a sterile alpha motif (SAM) domain, and a C-terminal PDZ domain. Ephrin-As contain only a receptor-binding domain (RBD) and a GPI anchor. In contrast, Ephrin-Bs are integral membrane proteins composed of an extracellular RBD, a transmembrane domain, and an intracellular PDZ domain (Nguyen et al., 2016) (Figure 1). Ephrins and Ephs are membrane-bound proteins. They generate bidirectional signalling upon binding. This affects both the cells expressing the receptor and those expressing the ligand. The signalling through Ephs is termed forward signalling, whereas signalling through Ephrins is termed reverse signalling (Pasquale, 2005). Eph receptors and their Ephrin ligands play essential roles in various cells, regulating cell migration, repulsion, and adhesion in processes such as neuron, vascular, and intestinal development (Arvanitis & Davy, 2008; Pasquale, 2008). They are also closely associated with bone development (Davy et al., 2006) and bone homeostasis (Zhao et al., 2006). EphrinB2 is the preferred ligand for EphB4, showing weak binding to EphrinB1 or EphrinB3, with an affinity for EphrinB2 100 to 1000 times stronger than that for EphrinB1 (Flanagan & Vanderhaeghen, 1998). In bone tissue, osteoclasts express EphrinB2, which is encoded by Efnb2, one of the target genes of NFATc1, and its expression depends on the RANKL-induced c-Fos/NFATc1 transcriptional cascade (Ge et al., 2020; Zhao et al., 2006). Osteoblasts co-express the EphB4

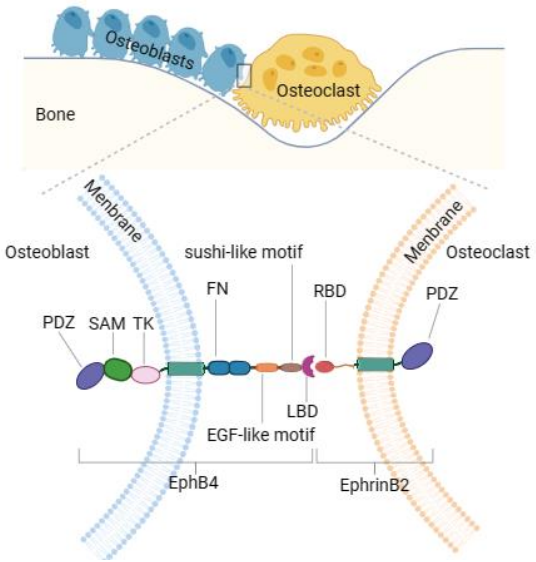

Figure 1. The basic components of EphrinB2 and EphB4

FN: fibronectin domain, LBD: ligand-binding domain, TK: tyrosine kinase domain, SAM: sterile alpha motif domain, RBD: receptor-binding domain.

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receptor and EphrinB2 ligand (Zhao et al., 2006). The reverse EphrinB2-EphB4 signalling between osteoclasts and osteoblasts inhibits osteoclast differentiation, while forward signalling promotes osteoblast differentiation (Zhao et al., 2006).

3. Roles of EphrinB2-EphB4 bidirectional signaling in osteoblast lineage cells

Since the osteoblast lineage expresses EphB4 and EphrinB2, and the osteoclast lineage expresses EphB4, understanding of EphB4-EphrinB2 interaction has evolved over the past 15 years from heterotypic interactions between osteoblast lineage cells and osteoclast lineage cells to homotypic interactions within the osteoblast lineage (Arthur & Gronthos, 2021). However, Blank M et al. argue that the primary role of EphrinB2 in bone is in the osteoblast lineage (Blank & Sims, 2019).

The significance of EphrinB2-EphB4 signalling in the late-stage differentiation and survival of osteoblasts has been demonstrated in several experiments. Results from gain-of-function experiments indicate that overexpression of EphrinB2 in osteoblasts promotes their differentiation, evidenced by increased expression of osteoblast differentiation markers, such as alkaline phosphatase, Col1a1, and osteocalcin (Zhao et al., 2006). Additionally, the expression of distal-less homeobox 5 (Dlx5), osterix (Osx), and runt-related transcription factor 2 (Runx2), which are key transcription factors for osteoblast differentiation, is significantly upregulated (Zhao et al., 2006). Mechanistically, EphrinB2 stimulation may promote osteoblast formation by enhancing ERK1/2 phosphorylation and reducing RhoA activity, but this stimulatory effect is believed to be independent of EphrinB2 cytoplasmic domain (Zhao et al., 2006). Loss-of-function experiments by Tonna S et al. demonstrated that specific deletion of EphrinB2 mediated by Osx-Cre leads to impaired late-stage osteoblast differentiation, accompanied by increased osteoblast and osteocyte apoptosis (Tonna et al., 2014). The compromised osteoblast differentiation and delayed initiation of bone mineralization result in reduced bone strength in adult bones, leading to osteomalacia (high osteoid content) (Tonna et al., 2014). While osteocytes differentiate from osteoblasts embedded in osteoid, they still retain expression of EphrinB2 and EphB4 (Allan et al., 2008; Arthur et al., 2011; Takyar et al., 2013). EphrinB2-specific knockout osteocytes exhibit increased autophagic activity, resulting in enhanced secondary mineralization processes and increased bone fragility as stimulation with EphrinB2-Fc inhibited the increase in autophagosomes in EphrinB2-deficient osteocytes via the RhoA-ROCK signalling pathway (Vrahnas et al., 2019). Treatment of cultured osteoblasts with soluble EphB4 (sEphB4), a specific inhibitor blocking EphrinB2-EphB4 bidirectional signalling, inhibits EphB4 and EphrinB2 phosphorylation. It also decreases the mRNA levels of late-stage osteoblast/osteocyte differentiation markers, such as osteocalcin and sclerostin. Moreover, in vivo administration of sEphB4 increases osteoblast formation and the mRNA levels of early osteoblast markers, such as Runx2 and alkaline phosphatase. This significantly increases the number of osteoblasts. However, there is no significant change in bone formation rate or late-stage markers of osteoblast/osteocyte differentiation. This indicates that EphrinB2/EphB4 signalling within the osteoblast lineage is critical for the late-stage differentiation of osteoblasts (Takyar et al., 2013). These research findings suggest that EphrinB2-EphB4 signalling plays an essential role in the normal differentiation and functional regulation of the osteoblast lineage, but whether these effects are achieved through forward or reverse signalling remains unclear.

Following EphB4-Fc treatment in vivo, immunofluorescence analysis revealed an increase in OPG protein expression and a decrease in RANKL protein expression in osteoblasts, indicating that the reverse signalling of EphrinB2-EphB4 elevated the OPG/RANKL ratio. Examination of the forward signalling of EphrinB2-EphB4 showed that EphrinB2-Fc significantly increased the OPG/RANKL ratio both in vivo and in vitro; however, in vitro stimulation with EphrinB2-Fc resulted in a significant decrease in RANKL mRNA expression in osteoblasts, while the change in OPG mRNA expression was not significant (Ge et al., 2020). These findings suggest a clear distinction in the effects of the forward and reverse signalling of EphrinB2-EphB4 in osteoblasts (Figure 2).

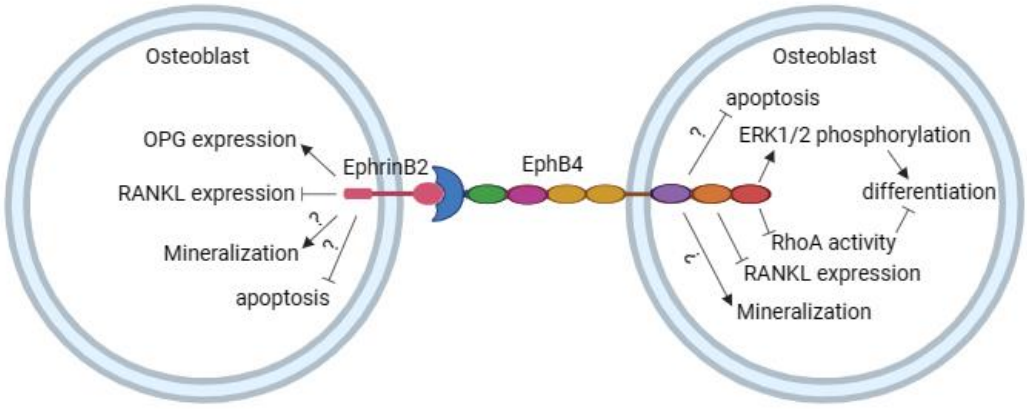

Figure 2. EphrinB2-EphB4 bidirectional signalling in osteoblast lineage cells

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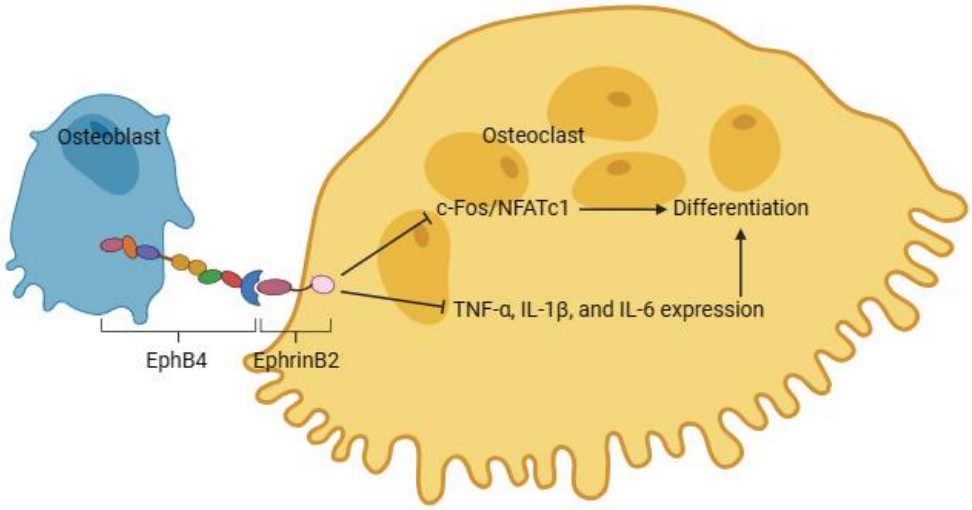

Figure 3. EphrinB2-EphB4 reverse signalling in osteoclasts.

Differentiating the effects of the forward and reverse signalling of EphrinB2-EphB4 in osteoblast differentiation, function, and survival holds potential significance for the treatment of bone diseases.

4. The roles of reverse signaling of EphrinB2-EphB4 in osteoclasts

Osteoclasts have been shown to express the ligand EphrinB2 for the receptor EphB4. Research by Zhao et al. and Baek et al. indicates that the reverse signalling of EphrinB2 entering osteoclast precursors inhibits osteoclast differentiation and maturation by negative feedback suppression of c-Fos and NFATc1 transcription in osteoclasts (Figure 3) (Baek et al., 2018; Zhao et al., 2006). The inhibitory signalling in osteoclasts is mediated by the C-terminal DYKV motif of EphrinB2 intracellular domain binding with PDZ domain proteins (Zhao et al., 2006). The detailed mechanism of EphrinB2-EphB4 reverse signalling in osteoclasts is poorly understood. Experiments using Icariin intervention in a glucocorticoid-induced osteoporotic mouse model have shown that Icariin can counteract osteoporosis via EphB4-EphrinB2 signalling, while also increasing the expression of Grb4 adaptor protein (Huang et al., 2020). This suggests that elevated Grb4 binding with the EphrinB2 intracellular domain amplifies the inhibitory effect of EphrinB2 reverse signalling on osteoclasts. Moreover, it has been found that monomeric EphrinB2 cannot initiate signal transduction (Kertesz et al., 2006). A study revealed that in cells expressing EphrinB2, kindlin2 can interact with the highly conserved NIYY motif in the cytoplasmic tail of EphrinB2, promoting EphrinB2 clustering to regulate EphB4 activation across cells. This indicates that kindlin2 facilitates bidirectional EphB4/EphrinB2 signalling (Li et al., 2022). These research findings suggest that developing a drug that can enhance EphrinB2 clustering may be used to treat osteoporosis by strengthening the EphrinB2-EphB4 bidirectional signalling.

In an in vivo experiment demonstrating the use of EphB4 inhibitors to intervene in orthodontic tooth movement in rats, an increase in tooth movement, a significant increase in bone trabecular separation, a decrease in bone trabecular number, an increase in osteoclast number and activity, and inhibition of osteoblast differentiation and function were observed (Jiang et al., 2023). The researchers believe that by inhibiting EphB4, the reverse signalling of EphrinB2-EphB4 is blocked, leading to a weakening of the inhibition of c-Fos-NFATc1 transcription and osteoclast differentiation, thereby promoting bone resorption on the tension side (Jiang et al., 2023). In addition to in vivo, enhancing osteoclastogenesis by using sEphB4 monomer to block EphrinB2-EphB4 interaction was also reproduced in vitro, but osteoblast presence was necessary. These facts, combined with the result that sEphB4 treatment enhances RANKL expression in osteoblasts, suggest that EphrinB2-EphB4 signalling within the osteoblast lineage limits RANKL production to some extent, thereby suppressing osteoclastogenesis (Takyar et al., 2013). In vitro, treatment with EphB4-Fc inhibited the release of pro-inflammatory factors TNF-α, IL-1β, and IL-6 mediated by titanium particles in BMMs, confirming the inhibition of osteoclast differentiation and bone resorption function through the EphrinB2 signalling pathway by EphB4-Fc(Ge et al., 2020). This suggests that the reverse signalling of EphrinB2-EphB4 can induce a decrease in the expression of factors like TNF-α and indirectly inhibit osteoclast formation (Figure 3).

However, a conclusion drawn by Tonna S and colleagues is that EphrinB2 signalling induced by EphB4 in the osteoclast lineage does not suppress osteoclastogenesis. This conclusion is based on their finding that knocking down EphB4 in Kusa 4b10 cells (pre-osteoblasts) did not change their support for osteoclast formation, and that the number of osteoclasts generated from bone marrow mesenchymal stem cells (BMMs) under conditions with or without EphrinB2 knockout was comparable, and even stimulation with clustered EphB4-Fc did not inhibit osteoclastogenesis (Tonna et al., 2014). The explanation for this finding may relate to the fact that RANKL is a major stimulatory factor necessary for osteoclast differentiation and formation. This is because knocking down EphB4 in Kusa 4b10 osteoblasts may reduce the EphrinB2-EphB4 bidirectional signalling between

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osteoblasts. It caused increased RANKL expression and decreased OPG expression in osteoblasts. Conversely, inhibiting osteoclast differentiation and formation may not be the primary function of EphrinB2-EphB4 reverse signalling between osteoclasts and osteoblasts. The infrequent direct contact between mature osteoclasts and osteoblasts suggests that the interaction of EphrinB2-EphB4 between OC and OB is unlikely to be crucial for normal bone mass, and the role of EphrinB2 expression and signalling in osteoclasts remains unresolved (Vrahnas & Sims, 2015). Considering that during the reversal stage of bone remodeling, it is still unclear how the bone resorption activity of mature osteoclasts terminates, cells leave the resorbing bone surface, or cell apoptosis is initiated. We speculate that the interaction of EphB4 and EphrinB2 in contact between osteoclasts and osteoblasts may relate to this: at the start of the reversal phase, osteoblast precursors migrate to the resorption site of osteoclasts, direct contact between the two leads to the binding of EphrinB2 and EphB4, promoting osteoblast precursor differentiation into mature cells through forward signalling, and inducing cessation of bone resorption activity in mature osteoclasts and initiating the apoptosis program of osteoclasts, preparing for the migration of osteoblasts into the resorption pit.

Furthermore, contrary to previous reports, one study found weak expression of EphB4 in cultured BMMs (Baek et al., 2018). Therefore, further experimental validation is needed on this issue.

5. Prospects of drug development research on EphrinB2-EphB4 signalling

EphrinB2 and EphB4 are expressed in various organs and tissues, including tumor tissues, and their interaction leads to complex biological effects, such as affecting the proliferation, migration, and invasion capacity of tumor cells (Hadjimichael et al., 2022). Many researchers have attempted to study EphrinB2-EphB4 bidirectional signalling as a potential target for intervening in several diseases, such as cardiovascular diseases, neurological disorders, cancer, and bone diseases.

Pharmacological inhibition of EphrinB2/EphB4 interaction impairs osteoblast differentiation both in vitro and in vivo (Allan et al., 2008; Takyar et al., 2013), and intermittent administration of parathyroid hormone (PTH) increases bone mass by upregulating EphrinB2 (Vrahnas & Sims, 2015). This implies that increasing the expression of EphrinB2/EphB4 in osteogenic lineage cells and enhancing EphrinB2-EphB4 bidirectional signalling among bone tissue cells might be a potential research direction for preventing bone loss in osteoporosis and restoring normal bone mass in the future.

Regarding the regulation of EphrinB2/EphB4 expression, Wang R et al. found that silencing Jumonji domain-containing 3 (Jmjd3, a histone demethylase) in osteoblasts inhibits H3K27me3 demethylation in the EphB4 promoter region, reducing EphB4 expression. This also leads to upregulation of RANKL in osteoblasts, with soluble RANKL levels increasing, but RANKL elevation can be suppressed by EphB4 overexpression (Wang et al., 2023). This indicates that Jmjd3 participates in regulating bone resorption and formation by increasing EphB4 expression and inhibiting RANKL levels. Prior research shows that Erythropoietin (EPO) can increase EphB4 expression in ST2 cells (osteoblast precursors) and EphrinB2 expression in RAW264.7 cells (osteoclast precursors) (Li et al., 2015). Additionally, a novel vitamin D analog, Eldecalcitol (ED-71), can prevent bone loss and reduce the number of osteoclasts in Glucocorticoid-Induced Osteoporosis rats and OVX rats in vivo (Rong et al., 2022; Zhang et al., 2022). Moreover, it can also promote new bone formation and osteoblast activity (Rong et al., 2022). The inhibitory effect of ED-71 on osteoclasts was mediated by increasing EphrinB2 expression in osteoclasts, as this effect could be reversed by knocking down EphrinB2 (Zhang et al., 2022). The study also found that ED-71 enhances EphB4 expression in osteoblasts both in vitro and in vivo (Zhang et al., 2022).

In terms of enhancing EphrinB2-EphB4 signalling, Baek JM et al. discovered that Cldn11, the key component of tight junctions (TJs), had the potential to treat bone diseases (Baek et al., 2018). Cldn11 exerted a negative effect on osteoclast differentiation and function by targeting the reverse signalling of EphrinB2 in OCs. It had a positive regulatory effect on osteoblast differentiation by targeting the forward signalling of EphB4 in OBs. Consistent with in vitro effects, subcutaneous injection of recombinant Cldn11 protein in mouse models demonstrated anti-resorptive effects and increased osteogenic activity (Baek et al., 2018). Combined with the research results of Li W et al. showing that kindlin2 promoted EphrinB2 clustering (Li et al., 2022), it provides a clue that factors which promote EphrinB2/EphB4 clustering on the membranes of osteoblasts and osteoclasts or enhance the phosphorylation of the intracellular segment of EphrinB2/EphB4 are also worth investigating.

6. Conclusion

Currently, most clinical drugs for the treatment of primary osteoporosis primarily focus on inhibiting bone resorption. It is difficult to achieve the outcome of reversing bone loss and restoring normal bone mass simultaneously. The development of targeted therapeutic drugs that consider both anti-resorptive and pro-formative effects represents the trend. Further research into the detailed regulatory mechanism of EphrinB2-EphB4 bidirectional signalling in bone resorption and bone formation will help identify key nodes in the signalling process that can significantly enhance osteoblast production, survival, and bone formation. This will pave the way for future interventions in animal models targeting these points, to observe and evaluate their regulatory effects, and establish the foundation for subsequent clinical trials.

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8. References

Allan, E. H., Hausler, K. D., Wei, T., Gooi, J. H., Quinn, J. M., Crimeen-Irwin, B., Pompolo, S., Sims, N. A., Gillespie, M. T.,

DOI: https://doi.org/10.22452/mjs.vol44sp1.1
Malaysian Journal of Science 44 (Special Issue 1): 1-7 (December 2025)

Onyia, J. E., & Martin, T. J. (2008). EphrinB2 regulation by PTH and PTHrP revealed by molecular profiling in differentiating osteoblasts, *Journal of Bone and Mineral Research.* 23(8):1170-1181.

Arthur, A., Zannettino, A., Panagopoulos, R., Koblar, S. A., Sims, N. A., Stylianou, C., Matsuo, K., & Gronthos, S. (2011). EphB/ephrin-B interactions mediate human MSC attachment, migration and osteochondral differentiation, *Bone.* 48(3):533-542.

Arthur, A., & Gronthos, S. (2021). Eph-Ephrin Signaling Mediates Cross-Talk Within the Bone Microenvironment, *Front Cell Dev Biol.* 9:598612.

Arvanitis, D., & Davy, A. (2008). Eph/ephrin signaling: networks, *Genes Dev.* 22(4):416-429.

Baek, J. M., Cheon, Y., Kwak, S. C., Jun, H. Y., Yoon, K., Lee, M. S., & Kim, J. (2018). Claudin 11 regulates bone homeostasis via bidirectional EphB4-EphrinB2 signaling, *Experimental & Molecular Medicine.* 50(4):1-18.

Blank, M., & Sims, N. A. (2019). Cellular Processes by Which Osteoblasts and Osteocytes Control Bone Mineral Deposition and Maturation Revealed by Stage-Specific EphrinB2 Knockdown, *Current Osteoporosis Reports.* 17(5):270-280.

Davy, A., Bush, J. O., & Soriano, P. (2006). Inhibition of gap junction communication at ectopic Eph/ephrin boundaries underlies craniofrontonasal syndrome, *Plos Biology.* 4(10):e315.

Durdan, M. M., Azaria, R. D., & Weivoda, M. M. (2022). Novel insights into the coupling of osteoclasts and resorption to bone formation, *Seminars in Cell & Developmental Biology.* 123:4-13.

Feng, X., & McDonald, J. M. (2011). Disorders of Bone Remodeling, *Annual Review of Pathology: Mechanisms of Disease.* 6(1):121-145.

Flanagan, J. G., & Vanderhaeghen, P. (1998). The ephrins and Eph receptors in neural development, *Annual Review of Neuroscience.* 21:309-345.

Ge, Y., Feng, K., Liu, X., Chen, H., Sun, Z., Wang, C., Liu, Z., Wang, H., Zhang, J., Yu, D., & Mao, Y. (2020). The Recombinant Protein EphB4-Fc Changes the Ti Particle-Mediated Imbalance of OPG/RANKL via EphrinB2/EphB4 Signaling Pathway and Inhibits the Release of Proinflammatory Factors In Vivo, *Oxidative Medicine and Cellular Longevity.* 2020:1-15.

Hadjimichael, A. C., Pergaris, A., Kaspiris, A., Foukas, A. F., Kokkali, S., Tsourouflis, G., & Theocharis, S. (2022). The EPH/Ephrin System in Bone and Soft Tissue Sarcomas' Pathogenesis and Therapy: New Advancements and a Literature Review, *International Journal of Molecular Sciences.* 23(9):5171.

Huang, M., Wang, Y., & Peng, R. (2020). Icariin Alleviates Glucocorticoid-Induced Osteoporosis through EphB4/Ephrin-B2 Axis, *Evidence-Based Complementary and Alternative Medicine.* 2020:1-8.

Jiang, Y., Tao, G., Guan, Y., Chen, S., He, Y., Li, T., Zou, S., & Li, Y. (2023). The role ofephrinB2-EphB4 signalling in bone remodelling during orthodontic tooth movement, *Orthodontics & Craniofacial Research.* 26(1), 107-116.

Kania, A., & Klein, R. (2016). Mechanisms of ephrin-Eph signalling in development, physiology and disease, *Nat Rev Mol Cell Biol.* 17(4):240-256.

Kenkre, J. S., & Bassett, J. (2018). The bone remodelling cycle, *Annals of Clinical Biochemistry: International Journal of Laboratory Medicine.* 55(3):308-327.

Kertesz, N., Krasnoperov, V., Reddy, R., Leshanski, L., Kumar, S. R., Zozulya, S., & Gill, P. S. (2006). The soluble extracellular domain of EphB4 (sEphB4) antagonizes EphB4-EphrinB2 interaction, modulates angiogenesis, and inhibits tumor growth, *Blood.* 107(6):2330-2338.

Khosla, S., & Hofbauer, L. C. (2017). Osteoporosis treatment: recent developments and ongoing challenges, *Lancet Diabetes Endocrinol.* 5(11):898-907.

Li, C., Shi, C., Kim, J., Chen, Y., Ni, S., Jiang, L., Zheng, C., Li, D., Hou, J., Taichman, R. S., & Sun, H. (2015). Erythropoietin Promotes Bone Formation through EphrinB2/EphB4 Signaling, *Journal of Dental Research.* 94(3):455-463.

Li, W., Wen, L., Rathod, B., Gingras, A., Ley, K., & Lee, H. (2022). Kindlin2 enables EphB/ephrinB bi-directional signaling to support vascular development, *Life Science Alliance.* 6(3):e202201800.

Liang, L. Y., Patel, O., Janes, P. W., Murphy, J. M., & Lucet, I. S. (2019). Eph receptor signalling: from catalytic to non-catalytic functions, *Oncogene.* 38(39):6567-6584.

Lindsey, R. C., Rundle, C. H., & Mohan, S. (2018). Role of IGF1 and EFN-EPH signaling in skeletal metabolism, *Journal of Molecular Endocrinology.* 61(1):T87-T102.

Matsuo, K. (2010). Eph and ephrin interactions in bone, *Advances in Experimental Medicine and Biology*, 658, 95-103.

McDonald, M. M., Khoo, W. H., Ng, P. Y., Xiao, Y., Zamerli, J., Thatcher, P., Kyaw, W., Pathmanandavel, K., Grootveld, A. K., Moran, I., Butt, D., Nguyen, A., Corr, A., Warren, S., Biro, M., Butterfield, N. C., Guilfoyle, S. E., Komla-Ebri, D., Dack, M., Dewhurst, H. F., Logan, J. G., Li, Y., Mohanty, S. T., Byrne, N., Terry, R. L., Simic, M. K., Chai, R., Quinn, J., Youlten, S. E., Pettitt, J. A., Abi-Hanna, D., Jain, R., Weninger, W., Lundberg, M., Sun, S., Ebetino, F. H., Timpson, P., Lee, W. M., Baldock, P. A., Rogers, M. J., Brink, R., Williams, G. R., Bassett, J., Kemp, J. P., Pavlos, N. J., Croucher, P. I., & Phan, T. G. (2021). Osteoclasts recycle via osteomorphs during RANKL-stimulated bone resorption, *Cell.* 184(5):1330-1347.

Negishi-Koga, T., Shinohara, M., Komatsu, N., Bito, H., Kodama, T., Friedel, R. H., & Takayanagi, H. (2011). Suppression of bone formation by osteoclastic expression of semaphorin 4D, *Nature Medicine.* 17(11), 1473-1480.

DOI: https://doi.org/10.22452/mjs.vol44sp1.1
Malaysian Journal of Science 44 (Special Issue 1): 1-7 (December 2025)

Nguyen, T. M., Arthur, A., & Gronthos, S. (2016). The role of Eph/ephrin molecules in stromal-hematopoietic interactions, *International Journal of Hematology.* 103(2):145-154.

NIH Consensus Development Panel On Osteoporosis Prevention, D. A. T. (2001). Osteoporosis prevention, diagnosis, and therapy, *JAMA.* 285(6):785-795.

Pasquale, E. B. (2005). Eph receptor signalling casts a wide net on cell behaviour, *Nat Rev Mol Cell Biol.* 6(6), 462-475.

Pasquale, E. B. (2008). Eph-ephrin bidirectional signaling in physiology and disease, *Cell.* 133(1):38-52.

Raisz, L. G. (2005). Pathogenesis of osteoporosis: concepts, conflicts, and prospects, *Journal of Clinical Investigation.* 115(12):3318-3325.

Rong, X., Kou, Y., Zhang, Y., Yang, P., Tang, R., Liu, H., & Li, M. (2022). ED-71 Prevents Glucocorticoid-Induced Osteoporosis by Regulating Osteoblast Differentiation via Notch and Wnt/beta-Catenin Pathways, *Drug Des Devel Ther.* 16:3929-3946.

Shindo, S., Savitri, I. J., Ishii, T., Ikeda, A., Pierrelus, R., Heidari, A., Okubo, K., Nakamura, S., Kandalam, U., Rawas-Qalaji, M., Leon, E., Pastore, M. R., Hardigan, P., & Kawai, T. (2022). Dual-Function Semaphorin 4D Released by Platelets: Suppression of Osteoblastogenesis and Promotion of Osteoclastogenesis, *International Journal of Molecular Sciences.* 23(6):2938.

Takyar, F. M., Tonna, S., Ho, P. W., Crimeen-Irwin, B., Baker, E. K., Martin, T. J., & Sims, N. A. (2013). EphrinB2/EphB4 inhibition in the osteoblast lineage modifies the anabolic response to parathyroid hormone, *Journal of Bone and Mineral Research*. 28(4):912-925.

Tang, Y., Wu, X., Lei, W., Pang, L., Wan, C., Shi, Z., Zhao, L., Nagy, T. R., Peng, X., Hu, J., Feng, X., Van Hul, W., Wan, M., & Cao, X. (2009). TGF-beta1-induced migration of bone mesenchymal stem cells couples bone resorption with formation, *Nature Medicine.* 15(7):757-765.

Tonna, S., Takyar, F. M., Vrahnas, C., Crimeen Irwin, B., Ho, P. W. M., Poulton, I. J., Brennan, H. J., McGregor, N. E., Allan, E. H., Nguyen, H., Forwood, M. R., Tatarczuch, L., Mackie, E. J., Martin, T. J., & Sims, N. A. (2014). EphrinB2 signaling in osteoblasts promotes bone mineralization by preventing apoptosis, *The FASEB Journal.* 28(10):4482-4496.

Vrahnas, C., Blank, M., Dite, T. A., Tatarczuch, L., Ansari, N., Crimeen-Irwin, B., Nguyen, H., Forwood, M. R., Hu, Y., Ikegame, M., Bambery, K. R., Petibois, C., Mackie, E. J., Tobin, M. J., Smyth, G. K., Oakhill, J. S., Martin, T. J., & Sims, N. A. (2019). Increased autophagy in EphrinB2-deficient osteocytes is associated with elevated secondary mineralization and brittle bone, *Nature Communications.* 10(1):3436.

Vrahnas, C., & Sims, N. A. (2015). EphrinB2 Signalling in Osteoblast Differentiation, Bone Formation and Endochondral Ossification, *Current Molecular Biology Reports.* 1(4):148-156.

Walker, E. C., McGregor, N. E., Poulton, I. J., Pompolo, S., Allan, E. H., Quinn, J. M., Gillespie, M. T., Martin, T. J., & Sims, N. A. (2008). Cardiotrophin-1 is an osteoclast-derived stimulus of bone formation required for normal bone remodeling, *Journal of Bone and Mineral Research.* 23(12):2025-2032.

Wang, R., Luo, H., Yang, D., Yu, B., Guo, J., Shao, L., Okamura, H., & Qiu, L. (2023). Osteoblast Jmjd3 regulates osteoclastogenesis via EphB4 and RANKL signalling, *Oral Diseases.* 29(4):1613-1621.

Weivoda, M. M., Chew, C. K., Monroe, D. G., Farr, J. N., Atkinson, E. J., Geske, J. R., Eckhardt, B., Thicke, B., Ruan, M., Tweed, A. J., McCready, L. K., Rizza, R. A., Matveyenko, A., Kassem, M., Andersen, T. L., Vella, A., Drake, M. T., Clarke, B. L., Oursler, M. J., & Khosla, S. (2020). Identification of osteoclast-osteoblast coupling factors in humans reveals links between bone and energy metabolism, *Nature Communications.* 11(1):87.

Xian, L., Wu, X., Pang, L., Lou, M., Rosen, C. J., Qiu, T., Crane, J., Frassica, F., Zhang, L., Rodriguez, J. P., Xiaofeng, J., Shoshana, Y., Shouhong, X., Argiris, E., Mei, W., & Xu, C. (2012). Matrix IGF-1 maintains bone mass by activation of mTOR in mesenchymal stem cells, *Nature Medicine.* 18(7):1095-1101.

Zhang, Y., Kou, Y., Yang, P., Rong, X., Tang, R., Liu, H., & Li, M. (2022). ED-71 inhibited osteoclastogenesis by enhancing EphrinB2–EphB4 signaling between osteoclasts and osteoblasts in osteoporosis, *Cellular Signalling.* 96:110376.

Zhao, C., Irie, N., Takada, Y., Shimoda, K., Miyamoto, T., Nishiwaki, T., Suda, T., & Matsuo, K. (2006). Bidirectional EphrinB2-EphB4 signaling controls bone homeostasis, *Cell Metabolism.* 4(2):111-121.

DOI: https://doi.org/10.22452/mjs.vol44sp1.1
Malaysian Journal of Science 44 (Special Issue 1): 1-7 (December 2025)