

FGFR1 signaling in rheumatoid arthritis: Mechanisms of bone destruction and therapeutic targeting (Review)

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Abstract. Rheumatoid arthritis (RA) is an inflammatory, systematic and articular autoimmune disease characterized by progressive cartilage degradation and bone erosion, leading to irreversible joint deformity. Fibroblast growth factor receptor 1 (FGFR1) is a key mediator of RA-associated bone loss. Within inflamed joints, FGFR1 expression is markedly upregulated in synovial fibroblasts, osteoclasts and chondrocytes. Ligand engagement drives receptor dimerization and kinase activation, activating PI3K/Akt, MAPK and STAT signaling cascades that amplify cytokine release, matrix metalloproteinase expression and osteoclastogenesis. These converging signals promote cartilage degradation and cortical bone erosion, fueling progressive deformity. Targeting FGFR1 markedly attenuates bone loss and disease severity in both murine and humanized models. The present review aimed to summarize the potential of FGFR1 as a tractable therapeutic node for RA bone destruction.

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1. Introduction

Rheumatoid arthritis (RA) is a chronic (1-5), persistent autoimmune inflammatory joint disease with an unknown pathogenesis, primarily characterized by chronic erosive arthritis (6-8). Despite affecting 0.5-1.0% of the global population with female predominance (9,10), current treatments typically fail to halt irreversible bone erosion. For example, methotrexate, the first-line conventional disease-modifying anti-rheumatic drugs (DMARD), can only attenuate inflammation but fails to prevent long-term progressive bone damage in many patients (11,12), while cost-effective, typically exhibit incomplete efficacy in preventing structural damage, and their mechanisms remain incompletely understood. Moreover, certain patients experiences inadequate response or intolerable side effects, underscoring the need for novel therapeutic strategies targeting the core pathogenic processes, particularly bone destruction.

Fibroblast growth factor receptor (FGFR)1 has recently emerged as a critical regulator of bone remodeling in RA pathogenesis (13-20). FGFR1 is widely expressed in bone, cartilage and synovial tissue, where it regulates skeletal development, remodeling and inflammatory responses (21-26). Dysregulation of FGFR1 signaling is implicated in various pathological conditions, including RA, where excessive activation contributes to synovial hyperplasia, cartilage degradation and bone erosion (14,27-29). FGFR1, activated by FGFs, signals through key downstream effectors including MAPK, PI3K/AKT and phospholipase C γ (PLC γ) (30,31). Dysregulated FGFR1 signaling has been implicated in the aberrant bone remodeling central to RA (32).

The present review aimed to summarize the structural biology of FGFR1, its multifaceted roles in bone homeostasis and its pathological contributions to RA-associated joint damage, as well as FGFR1 as a therapeutic target and the translational potential of FGFR1-modulating strategies for RA treatment. The present study aimed to provide a framework for developing targeted interventions to prevent structural progression in RA and associated osteolytic disorders.

2. Molecular structure of FGFR1

FGFRs are widely distributed, highly conserved transmembrane tyrosine kinase (TK) receptors (33). FGFR adopts a

bilobal kinase architecture defined by an N- and a C-terminal lobe. These two structural domains form a catalytic groove that accommodates both ATP and peptide substrates. This serves an important role in the receptor kinase activity and regulation (34). FGFR1 is one of four main members of the FGFR family, which includes FGFR1, FGFR2, FGFR3 and FGFR4. Located at 8p11.23 and comprising 68,620 bases (35). FGFR1 is a cell surface TK receptor. FGFR1 comprises a triad of extracellular Ig-like modules (D1-D3), followed by a transmembrane α -helix and a pair of cytoplasmic TK units, TK1 and TK2. Numerous junctional regions are interspersed between these domains, playing a crucial role in maintaining the structural integrity of FGFR1 (36). Notably, the linkage between D1 and D2 is facilitated by a short sequence consisting of 7-8 amino acids. Composed of a stretch rich in acidic and serine residues, the acid box cooperates with Ig-like domain 1 to impose an autoinhibitory constraint on FGFR (37,38) (Fig. 1). D2 has a heparan sulfate (HS)-binding site, consisting of a conserved positively charged region (39). The D2 and the D3 region are key for ligand binding and specificity (40). FGFR1-3 undergo alternative splicing, generating b and c isoforms that modulate ligand specificity through structural alterations in the ligand-binding region (41-43). This regulatory mechanism is achieved by modifying the primary amino acid sequence within the C-terminal half of immunoglobulin-like domain D3, a key determinant of ligand-receptor interactions. Such isoform-specific variations in the extracellular domain enable differential recognition of FGFs, thereby regulating signaling responses in a tissue- and context-dependent manner (44,45). A fifth non-TK FGFR, FGFR5, is homologous to FGFR1-4 in the extracellular ligand-binding domain, but does not have an intracellular TK domain. FGFR5 was first discovered in human cartilage (46). The four FGFRs exert protein TK activity in the cell, while FGFR5 has a short non-enzymatic intracellular element of 105 amino acids (47). FGFR5 was originally hypothesized to function as a non-signaling decoy receptor, exerting an inhibitory effect on the classical FGFR signaling pathway (48). This regulatory role is hypothesized to be mediated through competitive binding to ligands, thereby decreasing their availability for interaction with canonical FGFRs and modulating downstream signaling responses (49,50). FGFR5 not only serves as a negative regulator but also actively engages in the canonical FGFR signaling pathway (48,51-53). This dual role includes mediating key biological functions such as the promotion of cell differentiation, suggesting a more complex regulatory mechanism. These findings highlight the context-dependent nature of FGFR5 activity, where its interaction with canonical FGFR components can inhibit or enhance downstream signaling outcomes depending on cell context and ligand availability. The expression of FGFR5 increases with FGFR2 and FGFR1 when mesenchymal cells differentiate into osteoblasts or adipocytes (54). In β cells of the pancreas, FGFR5 interacts with SHP-1 and promotes ERK1/2 signaling (55). FGFR5 is inflammation-inducible and serves as a FGFR1 coreceptor to enhance survival signaling (52). Deletion of FGFR1 in osteocytes leads to an increase in trabecular bone mass and cortical bone thickness, which is associated with increased bone formation and impaired bone resorption (56). FGFR1 can regulate bone mass in osteocytes by modulating

Wnt/ β -catenin signaling (35). This provides genetic evidence that FGFR1 serves a crucial role in bone cells during bone remodeling and suggests FGFR1 may be a potential therapeutic target for preventing bone loss (35). Activation of the FGFR1 signaling pathway is implicated in various chronic inflammatory diseases, including RA (14,36,52,57).

3. FGFR1 signaling pathways and mechanisms

FGFR signaling pathways and mechanisms. FGFR1-3 use alternative splicing to generate isoforms with distinct ligand-binding properties, exhibiting lineage-specific expression patterns in epithelial and mesenchymal tissues (58). This splicing-mediated diversification enables context-dependent modulation of receptor-ligand interactions, contributing to tissue-specific signaling outcomes (48). FGFRb variants are predominantly expressed in epithelial lineages and interact with mesenchymal-derived FGFs (FGF7/10), reflecting a paracrine signaling paradigm (59). Conversely, FGFRc isoforms localize to mesenchymal compartments and bind FGF ligands produced in both epithelial and mesenchymal tissues, enabling autocrine/paracrine signaling flexibility (60,61). This splicing-mediated receptor diversification creates tissue-specific receptor-ligand interfaces that modulate developmental and homeostatic processes through differential ligand availability and binding kinetics.

The biological activity of FGF is enhanced by interactions with HS and other sulphated glycosaminoglycans (38,62). The protein class present on the cell surface and extracellular matrix is primarily composed of HS proteoglycan (HSPG), which includes HS covalently bound to a protein core. HSPG consists of membrane-spanning proteins on the cell surface, cell surface proteins anchored by glycosylphosphatidylinositol and diffusible protein components of the extracellular matrix such as basement membrane and agrin (38). Cell surface HSPGs and extracellular matrix regulate FGF diffusion dynamics in tissue, acting as cofactors stabilizing FGF-FGFR heterodimer complexes through electrostatic interactions, thereby enhancing ligand receptor affinity and intensifying downstream receptor activation cascades (63-65). Endocrine FGF differs from classical FGF in that it requires protein cofactors to promote receptor binding and activation. Members of the Klotho family fulfil this role, as evidenced by phenotypic similarities observed in α Klotho and FGF23 knockout (KO) mice (66-68).

The binding of FGF ligands to FGFRs induces dimerization and juxtaposition of the TK domains, thereby initiating the sequential transphosphorylation of at least six tyrosine residues (38,69,70). Activation of the FGFR TK domain induces direct phosphorylation of FGFR substrate 2 α (FRS2 α) docking binding proteins and promotes the recruitment of downstream signaling molecules, including PLC γ , STAT1, STAT3 and STAT5, through the formation of receptor-substrate complexes (38). In fibroblasts, FGF ligand stimulation triggers FGFR3 to activate STAT (71,72). Phosphorylated FRS2 α activates the MAPK pathway through Son of sevenless. Additionally, phosphorylated FRS2 α binds growth factor receptor-bound protein 2 (GRB2), which subsequently recruits GRB2-associated binder 1 to trigger the PI3K/AKT signaling pathway (73,74). Downstream from RAS and PI3K, FGFs activate several distinct MAPKs, including ERK1/2, JNK

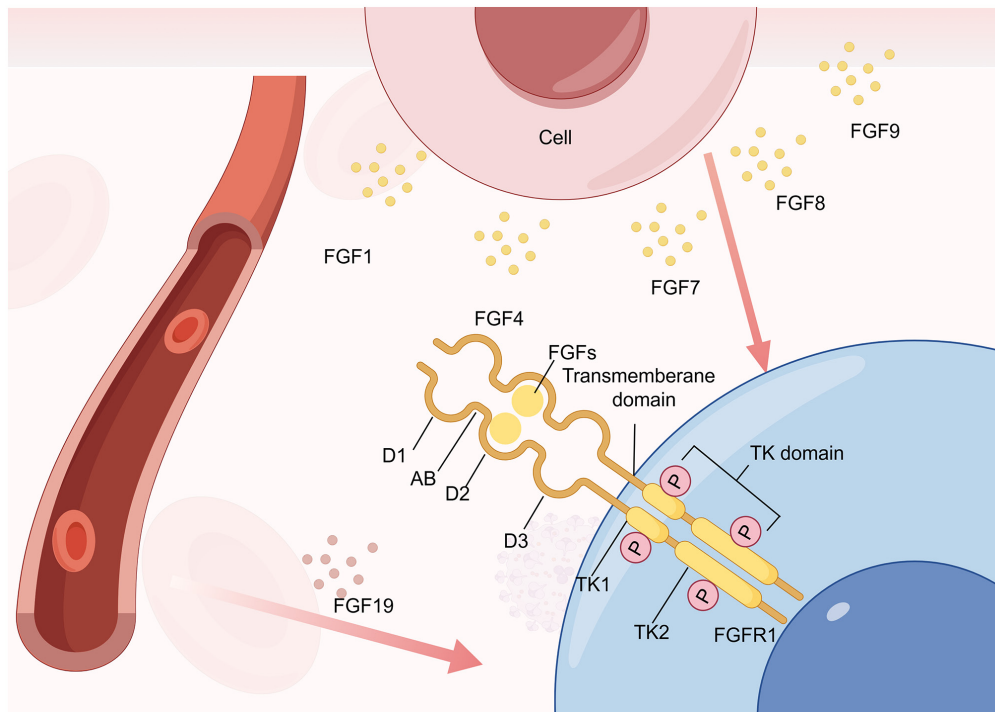


Figure 1. Source, species and molecular structure of FGFR1 ligands. FGFR1 comprises an extracellular region with three Ig-like domains, a transmembrane helix and a split TK domain. FGF interacts with extracellular structures and binds to activate intracellular TK domain. FGFR, fibroblast growth factor receptor; TK, tyrosine kinase.

and p38 (75-79). The binding of v-crk sarcoma virus CT10 oncogene homolog-like to the activated FGFR enhances the phosphorylation of FRS2 α , as well as the MAPK pathway signaling and the activation of ERK1/2 (80).

FGFR intracellular signaling cascades are subject to inhibitory regulation mediated by molecules such as GRB2. GRB2, which binds to FRS2 α , forms a complex with the casitas B-lineage lymphoma (CBL) E3 ligase, which transfers ubiquitin molecules to FGFR and FRS2 α , leading to their polyubiquitination (81). The ubiquitinated receptor and adaptor proteins are targeted by lysosomes or proteasomes for degradation, effectively shutting down ongoing signaling and achieving negative feedback inhibition (81). Sprouty proteins, which interact with GRB2 to suppress downstream MAPK and PI3K pathway activation (82,83). In the downstream region, similar expression to fibroblast growth factor antagonizes the MAPK pathway through its interaction with MEK (84), while dual-specificity phosphatase 6 suppresses MAPK signaling through the dephosphorylation of ERK1/2 (85). CBL E3 ligase has been shown to inhibit FGFR signaling by forming a triple complex with phosphorylated FRS2 and GRB2, where it promotes ubiquitination and degradation of FGFR and FRS2 (86). CBL interacts with PI3K, resulting in its ubiquitination and degradation (87). The GRB14 adapter protein binds phosphorylated FGFR of Tyr766, thereby interfering with phosphorylation and activation of PLC γ (88).

FGFR1 signaling and mechanisms. As aforementioned, FGFR1 is a TK cell surface receptor, the expression of which is primarily observed in the extracellular matrix and smooth muscle tissue, which constitutes a notable component of cartilage tissue. RA primarily affects cartilage tissue, leading to

bone destruction (35,56,58,89). Consequently, FGFR1 may serve a pivotal function in the progression of RA. *In vitro*, attenuation of the FGFR1 signaling pathway may lead to attenuation of bone decay and beneficial therapeutic effects in rat models of arthritis (14,90). The immunoglobulin-cell sII and III domains of FGFR1, together with the interdomain hinge regions, serve a key role in the regulation of FGF ligand binding specificity (91). The acidic amino acid motif AB, located within the interdomain region between extracellular immunoglobulin-like domains I and II of FGFR1, demonstrates an inhibitory effect on FGFR ligand-receptor interactions when acting in concert with domain I (92). The intracellular TK domain of FGFR1 demonstrates constitutive TK activity. In the absence of FGF, the receptor exists as a monomeric unit with the TK domain maintained in a phosphorylated state. Following FGF engagement, receptor dimerization facilitates the formation of a functional 2FGF:2FGFR1 complex, leading to kinase activation and trans-phosphorylation events. This results in full TK activation and subsequent downstream signal transduction cascades (59,93-95).

Following exposure to FGFs and heparin/klotho, FGFR1 kinases undergo dimerization in the active aspartate-phenylalanine-glycine motif-aspartate-in conformation (DFG-Asp-in) conformation, a process mediated by co-receptor interactions that stabilize the signaling complex and promote kinase activation (96). FGF demonstrates preferential binding to the extracellular domains of FGFR, with a marked affinity for the D2 and D3 immunoglobulin-like domains and their intervening interdomain linker regions. This binding stabilizes the FGF-FGFR-HS complex and promotes receptor dimerization (97). Upon receptor dimerization, the FGFR kinase domain undergoes conformational reorganization,

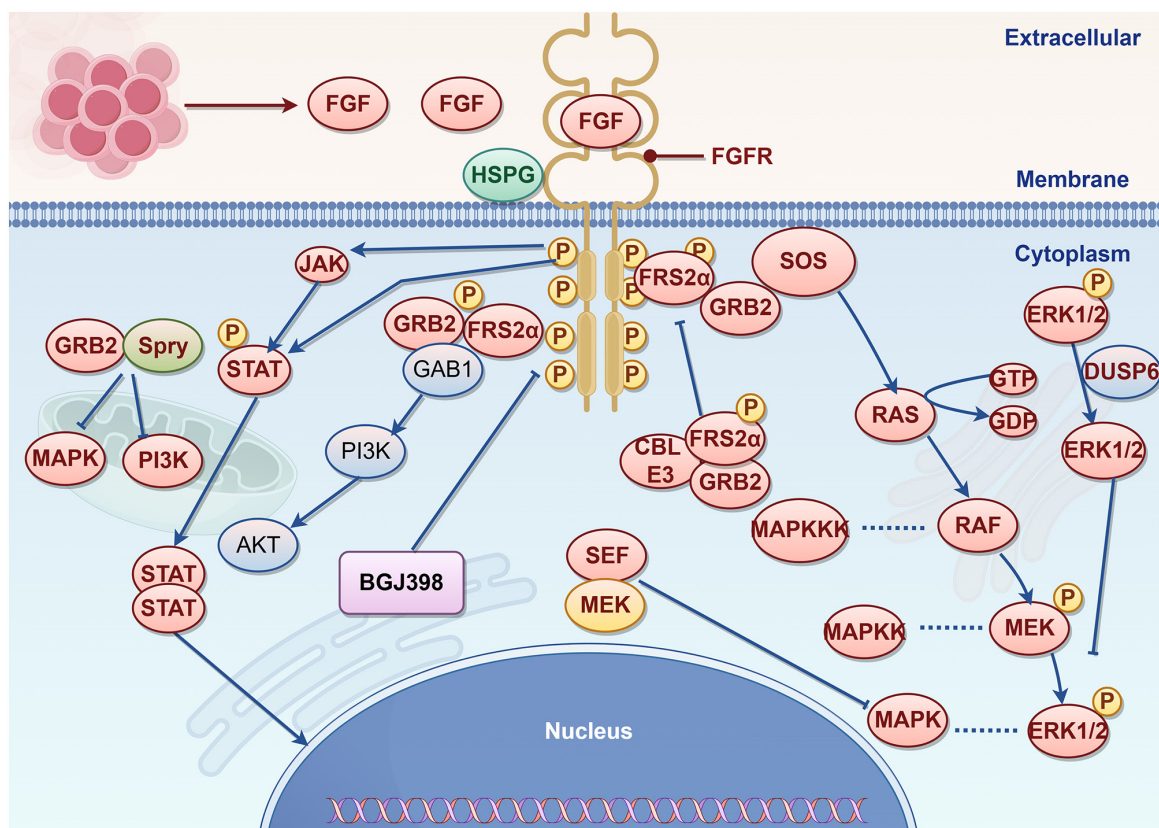


Figure 2. FGFR1-mediated signaling pathways associated with bone destruction. Upon ligand binding, FGFR dimerizes and autophosphorylates intracellular tyrosines, recruiting adaptors such as FRS2 α , GRB2, and GAB1. This triggers multiple cascades, including RAS-MAPK (ERK1/2), PI3K-AKT, and JAK-STAT pathways. Negative regulators (DUSP6, SEF) and the inhibitor BGJ398 are indicated. Nuclear ERK1/2 and STAT regulate gene expression. FGFR, fibroblast growth factor receptor; HSPG, HS proteoglycan; GRB, growth factor receptor-bound protein; Spry, sprouty; MAPKK, mitogen-activated protein kinase kinase; MAPKKK, mitogen-activated protein kinase kinase kinase; FRS, FGFR substrate; GAB, GRB2-associated binder family proteins; BGJ398, infgratinib; SEF, similar expression to FGF; DUSP6, dual-specificity phosphatase 6; SOS, Son of Sevenless; CBL E3, casitas B-lineage lymphoma E3 ligase.

transitioning from an Upon receptor dimerization, the FGFR kinase domain shifts from the autoinhibitory DFG-out conformation to the catalytically active DFG-in conformation (97). This structural rearrangement facilitates ATP-binding pocket alignment and activation loop stabilization, enabling kinase activation and downstream signaling initiation. In its active DFG-in conformation, the FGFR kinase domain DFG motif aspartate residue orients toward the catalytic site, enabling ATP coordination and substrate phosphorylation (97,98). Following FGF and heparin/klotho engagement, FGFR1 kinases assemble into active DFG-in conformational dimers, a process stabilized by co-receptor interactions. Trans-phosphorylation of tyrosine residues within the activation loop amplifies kinase catalytic efficiency through allosteric modulation of the catalytic site (99,100). The intramolecular regulatory element within the FGFR kinase domain, composed of the conserved never in mitosis gene A-related kinase triplet, undergoes conformational disengagement. This structural rearrangement disrupts the hydrogen-bonding network that stabilizes the autoinhibited state, thereby enabling the kinase domain to adopt a catalytically competent conformation (96). In this active conformation, the activated kinases trigger downstream signaling cascades through the recruitment of cytoplasmic adaptor proteins, thereby activating key intracellular pathways including RAS/MAPK, PI3K/AKT, PLC γ and STAT signaling. This process involves the formation of multi-protein

complexes that transduce extracellular signals to nuclear effectors, modulating cell responses such as proliferation, differentiation and survival (38) (Fig. 2).

FGFR1 signaling, through its downstream effectors including RAS/MAPK and PI3K/AKT pathways, serves a crucial role in numerous physiological processes. During embryogenesis, FGFR1 plays a pivotal role in regulating essential cell behaviors, including proliferation, differentiation and migration, which are fundamental for the proper formation of tissue and organs (101-103). FGFR-mediated signaling coordinates the morphogenesis of neural, skeletal and cardiovascular systems, ensuring precise spatiotemporal integration and functional maturation of developing organ structures (104-106). FGFR1 exerts key functions in regulating developmental processes and sustaining metabolic homeostasis during infancy and postnatal maturation. Its signaling is key for driving tissue expansion, orchestrating organogenesis and modulating nutrient utilization pathways to ensure proper growth trajectories and metabolic equilibrium (107). FGFR1 modulates adipogenic differentiation and governs glucose homeostasis alongside lipid metabolic pathways, thereby serving as a key regulator of systemic energy balance (108). This multifaceted role positions FGFR1 signaling at the nexus of metabolic regulation, integrating nutrient sensing with cell energy utilization (109). FGFR1 serves a pivotal role in metabolic regulation, which is key for the adaptation of the body

Table I. Effects of FGFR1 knockout in mice.

Authors, year	FGFR1 cKO mouse strain	Pathological changes	(Refs.)
Jacob <i>et al</i> , 2006	Col2a1-cre	Bone mass increases, osteoblast differentiation is delayed, osteochondral progenitor cell proliferation increases	(135)
Pirvola <i>et al</i> , 2002	Coll1-cre	Bone mass, osteoblast differentiation and mineralization increase	(233)
Lu <i>et al</i> , 2009	LysM-cre	Bone mass increases, osteoclast formation and activity are inhibited	(147)
McKenzie <i>et al</i> , 2019, Zhang <i>et al</i> , 2014	OC-cre	Bone mass and number of osteoblasts increase without any effect on bone length	(129,138)
Tang <i>et al</i> , 2023, Xiao <i>et al</i> , 2014	Dmp1-Cre	Bone tissue exhibits downregulation of FGF23 transcript levels and circulating FGF23 concentration. No significant alterations in broader markers of osteoblast differentiation, exemplified by the stable expression of osteopontin and osteocalcin	(35,139)
Wang <i>et al</i> , 2013	Wnt1-Cre	Severe craniofacial defect, frontal bone ectopic chondrogenesis and osteogenesis at the anterior interface	(234,235)
Kawai <i>et al</i> , 2019	K14-Cre	Loss of FGFR1 disrupts ameloblast arrangement during the enamel secretory stage and impedes normal enamel formation	(236)
Takamori <i>et al</i> , 2008	Gli1-CreER	Loss of FGFR1 in dental mesenchymal progenitors leads to abnormal cementum and bone formation with narrowed periodontal space	(237)
Pei <i>et al</i> , 2024	Cdx2 Cre/+	Embryonic development is unimpaired between the fore and hindlimb buds, whereas a selective attenuation of caudal elongation is observed in the region extending from the hindlimbs to the caudal body terminus	(238)

Col2a1, collagen type II alpha 1 chain; LysM, lysozyme 2; OC, Osteocalcin; Dmp1, dentin matrix acidic phosphoprotein 1; K14, keratin 14; Gli1, GLI family zinc finger 1; Cdx2, caudal type homeobox transcription factor 2.

to fluctuating nutritional and energy demands throughout the growth and maturation process (110). FGFR1 signaling coordinates tissue repair and regeneration in adults via stem cell activation modulation, angiogenesis promotion and extracellular matrix remodeling regulation (111,112). FGFR1 serves a pivotal role in orchestrating cellular injury responses (113). It boosts the proliferation and migration of stromal fibroblasts, vascular endothelial cells, and other typical reparative cells including mesenchymal stem cells and pericytes, all of which are key for tissue regeneration (114,115). This signaling axis modulates the recruitment and activation of cells following tissue injury via context-dependent transcriptional programs, and thus orchestrates the full sequence of wound repair, ranging from hemostasis to remodeling (116-118). FGFR1-mediated signaling serves a key role in wound repair by orchestrating neovascularization, extracellular matrix synthesis and structural reorganization of damaged tissue. This multifaceted regulation ensures coordinated progression through healing phases, culminating in functional restoration and preservation of tissue architectural integrity (119).

Genetic ablation of FGFR1 in murine models results in increased trabecular bone mass and cortical thickness, accompanied by impaired osteoclast function and enhanced osteoblast activity (Table I) (35,120,121). These findings are supported by pharmacological studies demonstrating that FGFR1 inhibition attenuates bone erosion and synovitis in experimental arthritis models (13,122,123). However, the cell type-specific mechanisms through which FGFR1 coordinates

bone destruction in RA remain incompletely understood, particularly regarding its interplay with inflammatory mediators and other signaling pathways such as MAPK, NF- κ B and PI3K/AKT pathways (32,123,124).

4. Cell mechanisms of FGFR1 in RA-associated bone destruction

Role of FGFR1 in osteocyte-mediated bone remodeling. RA bone destruction is associated with bone tissue remodeling and maintenance of bone homeostasis. Bone tissue contains three types of cell: Osteocytes, osteoblasts and osteoclasts. The most abundant type of cell in adult bones is osteocytes, which are osteoblasts that differentiate and control bone remodeling (89,125). Osteocytes regulate osteoblast differentiation and anabolic action, as well as osteoclastic activity, either by direct dendritic contact or by the secretion of regulatory factors such as sclerostin receptor activators and NF- κ B B binders (B ligand-factor nucleic receptor activators, RANKL) (126). Bone cells are one of the primary sources of RANKL and FGFR1 serves an important role in bone development and bone homeostasis. FGFR1 activation promotes the expression of MMP 2 and RANKL by promoting ERK1/2 phosphorylation (127,128). Mice with FGFR1 and/or FGFR2 deficiency exhibit normal phenotypes at birth, yet develop a high bone mass phenotype with age (129). These animals show enhanced periosteal adhesion, expanded and disorganized intracortical bone and elevated porosity, as well as improved

mechanical strength and stiffness consistent with higher bone mass (129). While KO of specific FGFRs increases bone mass, mechanical properties such as fracture toughness are impaired. Despite higher overall bone mass, these bones show inferior mechanical performance compared with normal bone. These data establish the role of FGFR1 signaling in osteoblasts, indicating that FGFR1 is essential for osteoblast survival and regulation of bone mass during postnatal bone growth (129). Loss of FGFR1 in osteocytes activates the Wnt/ β -catenin signaling pathway, promotes trabecular and cortical bone formation and increases osteoprotegerin mRNA expression and osteoblast activity (35). In addition, the loss of FGFR1 in osteocytes leads to decreased osteoclast formation, expression of RANKL mRNA in cortical bone and primary osteocytes and mRNA expression of genes associated with bone resorption, such as MMP 9 and catechins K, suggesting that the signals produced by FGFR1 loss in osteocytes inhibit osteoclast formation (35). However, these structural alterations paradoxically coincide with impaired biomechanical properties, indicating that complete ablation of FGFR1 may disrupt the equilibrium between bone quantity and quality. While genetic deletion studies have elucidated the role of FGFR1 in bone development, the ramifications of pharmacological inhibition in established RA remain unclear (35,130). Secondly, FGFR1-mediated regulation of both Wnt/ β -catenin and RANKL pathways poses a challenge in achieving a balanced therapeutic outcome, necessitating dual pathway modulation strategies. Thirdly, the net impact of FGFR1 modulation is contingent on its differential effects on osteocytes, osteoblasts and osteoclasts, underscoring the importance of cell type-specific responses. Collectively, these findings position FGFR1 as a promising therapeutic target for mitigating RA-associated bone loss, and future investigations should ascertain whether selective, partial inhibition of FGFR1 signaling preserves its physiological functions while curbing pathological bone destruction in RA.

Dual regulation of FGFR1 in osteoblast differentiation and mineralization. Osteoblasts are key for bone formation and development and growth (131). These cells secrete extracellular matrix proteins such as type I collagen, osteopontin, osteocalcin and alkaline phosphatase. Osteoblast differentiation and maturation are divided into three stages: Preosteoblast, bone precursor and osteoblast (132). Genetic studies in mice and humans have highlighted the key role of FGFR1/2 signaling in controlling gene expression and bone formation in osteoblasts (133,134). Conditional inactivation of FGFR1 in bone progenitor cells leads to increased cell proliferation, delayed differentiation and matrix mineralization, while deletion of FGFR1 in osteoblasts leads to increased mineralization and expression of FGFR3 (135). Therefore, it has been hypothesized that FGFR1 promotes the differentiation of mesenchymal progenitor cells into preosteoblasts but inhibits the proliferation of mesenchymal progenitor cells and the maturation and mineralization of osteoblasts (135). However, in postnatal bone, FGFR1 expression in mature osteoblasts and osteocytes is necessary for skeletal balance and maintenance of osteocyte viability (136). *In vivo* studies have demonstrated that FGFR1 regulates the differentiation and maturation of osteoblasts across distinct developmental

stages (135,136). FGFR1 and FGFR2 are expressed in immature osteoblasts and osteoblasts; immature osteoblasts cultured *in vitro* express relatively high levels of FGFR1, while mature osteoblasts express high levels of FGFR2 (137). Mature osteoblast-specific FGFR1 gene KO is achieved by using specific genetic manipulation techniques, such as the collagen- and osteocalcin-cyclization recombination enzyme (Cre) systems. However, this genetic manipulation has no notable effect on linear bone growth, suggesting that the role of FGFR1 in osteoblasts is primarily associated with regulation of bone mass rather than bone length growth (135,138). By contrast, another study generated dentin matrix protein 1-Cre cKO mice to delete *Fgfr1* specifically in mouse osteocytes (139). In the aforementioned model, FGFR1 mRNA expression was reduced by 50%. The transcript levels of osteocyte-specific genes, including FGF23, bone morphogenetic protein inhibitor protein, phosphorylase, tension protein homologue, *Dmpl* and matrix outer membrane phosphoprotein, were also down-regulated. However, the expression of bone marker genes osteopontin and osteocalcin remained unchanged (139). In addition, no significant differences were found in bone volume and mass and histological features between *Fgfr1* cKO mice and wild-type controls (139). Lee *et al* (140) showed that the FGFR inhibitor dovitinib enhances osteoblast differentiation *in vitro* by increasing the expression of osteoblast target genes. FGFR1 activation in osteoblasts enhances FGF23 secretion in adult mice, while concurrently suppressing renal phosphate reabsorption (141). FGFR1 serves a role in maintaining bone balance and osteocyte vitality: It promotes the maturation of early osteoblasts and inhibits the mineralization of mature osteoblasts, thereby promoting bone metabolism and inhibiting bone formation (135). FGFR1 inhibitors promote osteoblast differentiation *in vitro*, and FGFR1 activation modulates phosphate metabolism (13). Overall, FGFR1 maintains bone balance by modulating osteoblast activities, but the mechanisms and its full therapeutic potential require further exploration.

FGFR1-mediated osteoclast activation and bone resorption. Osteoclasts are large multinucleated cells whose primary function is the absorption of bone (142). These cells originate in the hematopoietic system and differentiate into mature osteoclasts through the interaction between macrophage colony-stimulating factors and RANKL. Macrophage colony-stimulating factor promotes the expansion of osteoclast precursors, whereas RANKL induces their differentiation into functional osteoclasts (132). FGFR1 serves an important role in osteoclast differentiation and function. Studies have shown that activated FGFR1 and MAPK act directly on mature osteoclasts to stimulate bone resorption (143,144). FGFR1 expression is detected on isolated mouse osteoclasts (145). In addition, FGFR1 expression is also detected in osteoclasts near fracture sites (146). To explore the direct effect of FGFR1 on osteoclasts, Lu *et al* (147) knocked out FGFR1 in mouse bone marrow mononuclear cells and mature osteoclasts: Mutant mice showed abnormal bone remodeling, decreased numbers of osteoclasts, impaired osteoclast function and decreased expression of tartrate-resistant acid phosphatase and MMP 9. Loss of FGFR1 decreases the number and activity of osteoclasts in mice, indicating that FGFR1 has a positive regulatory effect

on osteoclasts. FGFR1 is key for the complete differentiation and activation of mouse osteoclasts (147). FGFR1 directly promotes the differentiation and activation of osteoclasts by enhancing ERK 1/2 pathway signaling, thus enhancing their ability to decompose bone (143,147). Aukes *et al* (148) showed that in the co-culture environment of osteoclasts and breast cancer cells, FGFR inhibitor BGJ398 decreases the activation of FGFR-mediated signaling and expression of osteoclast target genes (149). FGFR1 inhibitors enhance osteoblast differentiation *in vitro* and FGFR1 activation inhibits phosphate metabolism. Overall, FGFR1 maintains bone balance by modulating osteoblast activities, but the mechanisms and its full therapeutic potential require further exploration (150,151).

FGFR1-mediated chondrocyte catabolism in cartilage homeostasis. The FGF signaling pathway serves a key role in bone and cartilage development (38). FGFR1 and FGFR3 are the primary FGFRs expressed in cartilage. During the formation of the growth plate, FGFR1 is primarily expressed in the pre-hypertrophic zone and the hypertrophic zone and FGFR3 is mainly expressed in the proliferative zone and the pre-hypertrophic zone (152). Expression of FGFR3 in chondrocytes inhibits cell proliferation, while expression of FGFR1 in hypertrophic chondrocytes promotes terminal maturation (135,153). In mice with chondrocyte-specific FGFR1 conditional KO and wild-type littermates were followed for 18 months. Spontaneous degeneration of the temporomandibular joint (TMJ) surface was observed in wild-type controls, whereas the FGFR1 KO mice were protected from pathological changes (154). However, the role of FGFR signaling in articular chondrocytes has been less studied (155). FGFR1 and FGFR3 are primarily expressed in human articular chondrocytes. FGFR1 mediates catabolic activity and FGFR3 mediates anabolic activity of chondrocytes (156). Activation of FGFR1 upregulates expression of MMP 1 and 13 in adult articular chondrocytes to promote matrix degradation (157). FGFR1 deficiency in adult mouse articular chondrocytes suppresses cartilage degeneration progression, accompanied by downregulation of metalloproteinase 13 and upregulation of FGFR3 (157). The molecular mechanism of FGFR1 signaling on chondrocyte catabolism remains unclear. Runt-related transcription factor 2 is a transcription factor that serves a key role in cartilage homeostasis by promoting the expression of extracellular matrix-degrading enzymes and chondrocyte hypertrophy, thereby accelerating the development of osteoarthritis (158). Zhou *et al* (159) showed that FGFR1 signaling positively regulates intramembranous bone formation by upregulating the expression of Runt-related transcription factor 2. FGFR1 with P250R mutation promotes the expression of Runt-related transcription factor 2 *in vivo* (159). In addition, deletion of FGFR1 decreases expression of Runt-related transcription factor 2 *in vivo* and *in vitro* to protect TMJ cartilage from degeneration (160). IL-1 β treatment upregulates FGFR3 expression and downregulates FGFR1 expression in rat chondrocytes (161). FGF18 enhances FGFR3 expression while suppressing FGFR1 expression in rat chondrocytes (162). Delucchi *et al* (163) extracted tibias from fetal mice and established an *in vitro* model of fetal mouse tibial explants for studying skeletal growth, development and disease. Expression analysis of FGFRs in tibial explants shows that

glucocorticoids downregulates expression of FGFR1, while FGFR3 is upregulated (163). Mutations in FGFR1 disturb the progression of endochondral osteogenesis. Genetic ablation of FGFR1 also induces notable enlargement of the hypertrophic zone of growth plates (163). Increased FGFR1 in human osteoarthritis chondrocytes leads to cartilage destruction, while KO of FGFR1 decreases the development of cartilage destruction in surgically induced knee instability mice (157). By contrast, increased FGFR3 in human osteoarthritis chondrocytes promotes cartilage synthesis (164) and FGFR3 deficiency accelerates osteoarthritis in mice (156,165). Therefore, activation of FGFR1 may promote chondrocyte catabolism, and FGFR1 deficiency may have a protective effect on cartilage degeneration. FGFR1 signaling in chondrocytes serves a complex role. It promotes hypertrophic chondrocyte maturation but induces articular cartilage degeneration via catabolic activity (13,95,123,166). The crosstalk between FGFR1 and FGFR3, together with modulation by GFs, cytokines and intracellular adaptor proteins, further increases the complexity of FGFR1 signaling cascades. Elucidating these mechanisms is critical for developing targeted therapies against cartilage disorders such as osteoarthritis and rheumatoid arthritis (95).

FGFR1 as a dual regulator of macrophage-driven inflammation. FGFR1 is expressed in human mononuclear macrophages (95) and influences the migration and survival of tumor macrophages through downstream signaling pathways such as PI3K/Akt and MEK1/2/ERK1/2. Activation of FGFR1 can promote macrophage migration and aggregation, indirectly promoting inflammatory responses in cellular microenvironment (167). In addition, FGFR1 directly affects macrophage polarization induced by high-fat diet and increases inflammatory cytokine levels. Specifically, FGFR1 on macrophages is activated by multiple growth factors such as FGFs, PDGF and TGF- β , triggering downstream signaling cascades including ERK, PI3K/AKT and STAT3 pathways. These pathways promote the synthesis and secretion of inflammatory mediators, thereby amplifying the inflammatory response (168). Knockdown of FGFR1 in macrophages decreases pro-inflammatory cytokine expression (168). FGFR1 activation leads to downregulation of transforming growth factor- β (TGF- β) gene expression in macrophages, thereby attenuating TGF- β /Smad3 signaling pathway activity (169). The TGF- β /Smad3 pathway plays inhibits the inflammatory response, and its downregulation leads to upregulation of inflammatory cytokine and chemokine expression. In conclusion, activation of FGFR1 on macrophages affects macrophage migration and survival and aggravates macrophage inflammatory responses (170,171). FGFR1 signaling in macrophages plays a dual-faceted role in inflammation: It facilitates macrophage migration and aggregation, regulates macrophage polarization toward the pro-inflammatory M1 phenotype, and increases the secretion of inflammatory cytokines. Its downregulation of TGF- β /Smad3 signaling exacerbates inflammation. Targeting FGFR1 in macrophages could be a potential strategy for controlling inflammatory disease.

Dual roles of FGFR1 in synovial fibroblasts mediating synovial homeostasis and invasive destruction. Fibroblast-like synoviocytes play a key role in the pathophysiology of

Table II. US Food and Drug Administration-approved FGFR1 inhibitors.

Drug	Target	Clinical trial no.	Indications	Patients	(Refs.)
Erdaftinib	FGFR1, FGFR2, FGFR3, FGFR4	NCT02365597	Locally advanced or metastatic urothelial carcinoma	Adults	(239)
Pemigatinib	FGFR1, FGFR2, FGFR3, FGFR4	NCT03011372	Relapsed or refractory myeloid/lymphoid neoplasm	Adults	(240)
Futibatinib	FGFR1, FGFR2, FGFR3, FGFR4	NCT02052778	Previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma	Adults	(241,242)
Selpercatinib	FGFR1, FGFR2, FGFR3	NCT03157128	Locally advanced or metastatic solid tumors with RET gene fusion	≥2 years	(243-247)

FGFR, fibroblast growth factor receptor; RET, rearranged during transfection.

RA (172), regulating joint homeostasis and the pathological process of RA (173). Under physiological conditions, fibroblast-like synoviocytes are responsible for synthesizing joint lubricant and hyaluronic acid to maintain the stability of the joint cavity environment (174). However, under arthritic conditions, fibroblast-like synoviocytes transform into proinflammatory and tissue-destructive phenotypes, triggering degenerative changes in cartilage and bone (175,176). These destructive fibroblast-like synoviocytes upregulate MMP, promote cartilage breakdown and express NF- κ B ligands, activating osteoclast maturation and function, thereby exacerbating bone destruction (177-179). Based on their role in RA, fibroblast-like synovial cells have attracted attention as potential therapeutic targets (180,181). Single-cell sequencing analysis of knee synovial cells isolated from patients with active RA and patients in clinical remission demonstrates robust activation of the FGFR1 signaling pathway within fibroblast-like synoviocytes located in the synovial lining layer of the joint cavity, which serves as the primary barrier of synovial tissue, and promotes local inflammatory lesions during active RA (14). In an *in vitro* pannus bone slice erosion assay, human recombinant FGF10 protein and FGFR1 inhibitor were administered to verify the potential influence of FGF10/FGFR1 signaling on the bone erosion capability of pannus cells (14,182). *In vivo*, blocking FGFR1 signaling pathway decreases arthritis, synovial erosion and joint destruction in collagen-induced arthritis rats (14). Although the US Food and Drug Administration (FDA) has not approved any treatment method directly targeting fibroblast-like synovial cells (183), four FGFR1-targeted small molecule inhibitors, namely erdaftinib, pemigatinib, infigratinib and derazantinib, have received FDA approval and proceeded to clinical trials (Table II). FGFR1 activation is associated with RA disease activity and promotes synovial fibroblast migration (184,185), invasion (185-187) and bone erosion progression (188,189), but its direct or indirect role needs further verification. Despite the promising results from preclinical studies showing decreased arthritis severity following FGFR1 blockade (188,190), the direct and indirect mechanisms by which FGFR1 influences synovial fibroblast behavior and RA disease progression need to be fully elucidated (191).

FGFR1 dual roles in CD4⁺ T cell function during RA. FGFR1 expression in CD4⁺ T cells is significantly downregulated following methotrexate treatment in patients with newly diagnosed RA (192). Zhao *et al* (193) described FGFR1-positive T cells producing IL-2 and promoting cell proliferation upon activation. Studies have established a positive association between FGF concentrations and RA disease activity (194-196), but the role of FGFR1-positive T cells remains unclear. Studies have identified FGFR1-CD4⁺ T cells in patients with active and remission RA by screening smooth tissue cells (15,197). Among CD4⁺ T cells producing IFN- γ , levels of FGFR1-positive CD4⁺ T cells are higher than those of FGFR1-negative CD4⁺ T cells (15,198). However, there is no increase in the proportion of FGFR1-positive CD4⁺ T cells producing the pro-inflammatory factor IL-17A. Although FGFR1 expression is insufficient to acquire proinflammatory properties, FGFR1-positive cells may serve a role in inflammation induction in patients with RA (15). These findings demonstrate that FGFR1 in T cells has complex implications in RA. FGFR1 expression is downregulated following FGFR1 inhibitor treatment. Combined with its close association with T cell proliferation and inflammatory cytokine secretion, this expression pattern indicates that FGFR1 plays a vital regulatory role in immune inflammation. Yet, its exact mechanisms in promoting T cell inflammatory responses in RA remain unclear.

Angiogenic FGFR1 signaling in RA vascular endothelial (VE) cells. Angiogenesis serves a key role in maintaining and promoting the progression of RA (199). Studies have shown that angiopoietin, hypoxia-inducible factor, VEGF and FGF serve an important role in inhibiting synovial angiogenesis in RA, suggesting that targeting angiogenesis may be an effective treatment for RA (200,201). Binding of these GFs to their receptors leads to VE cell deformation, division, migration and proliferation, inducing neovascularization; in addition, angiogenesis in synovial tissue stimulates intravascular extravasation, exacerbating synovial inflammation and vessel formation (202). Targeting FGFR1 to inhibit angiogenesis has been demonstrated in tumor therapy (203-205). In RA neovascularization, many proangiogenic factors, including VEGF and sphingosine-1-phosphate, induce abnormal activation

Table III. Opportunities and risks of FGFR1 inhibitors and DMARDs.

Drug	Opportunities	Risks
FGFR1 inhibitor	Inhibits the bone-resorbing activity of osteoclasts, decreasing bone loss; inhibits the breakdown of chondrocytes and protects degenerative chondrocytes; inhibits macrophage activity and suppresses inflammatory responses; may inhibit the migration and invasion of synovial fibroblasts, exerting an inhibitory effect on bone erosion	Promotes early osteoblast maturation, inhibits mineralization of mature osteoblasts, promotes bone metabolism and inhibits bone formation; decreases protein levels of FGFR1; affects the function of endothelial cells, especially during angiogenesis
DMARDs	Fast-acting; effectively inhibit bone destruction; rarely cause serious adverse reactions	Systemic toxicity; poor bone-targeting ability; unable to restore bone homeostasis; gastrointestinal and cardiovascular adverse reactions FGFR, fibroblast growth factor receptor

FGFR, fibroblast growth factor receptor; DMARD, disease-modifying antirheumatic drug.

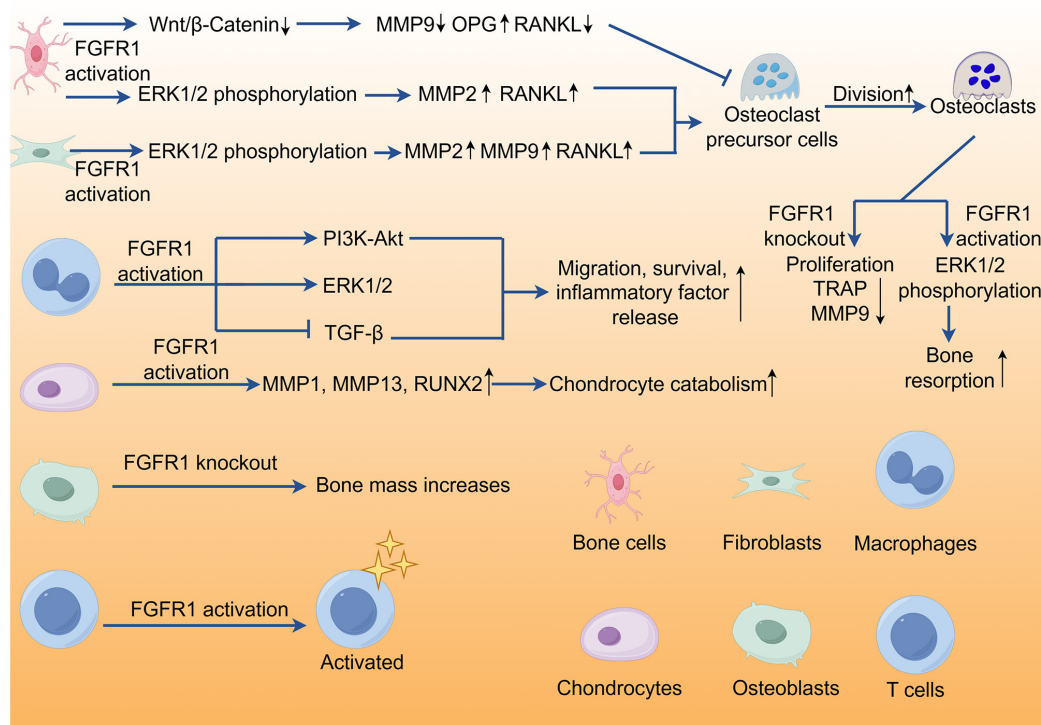


Figure 3. Role of FGFR1 in bone cells. This figure describes the regulatory effects of FGFR1 in different cells. When FGFR1 is activated, bone resorption in synovial fibroblasts and osteocytes increases, chondrocyte metabolism increases, and inflammatory factor release from macrophages increases. When FGFR1 is deficient, osteoblast mineralization increases, and osteoclast proliferation decreases. FGFR, fibroblast growth factor receptor; OPG, osteoprotegerin; TRAP, tartrate-resistant acid phosphatase.

of VE cells and promote angiogenesis (206). Studies have shown that activated FGFR1 upregulates VEGF A expression (207,208). Promoting VEGF A expression and secretion mediates FGFR1 activation to induce angiogenesis (209). Lowering FGFR1 protein levels impairs endothelial cell function, particularly during angiogenesis (210). FGFR1 activation promotes endothelial cell proliferation and migration by activating MAPK signaling pathways (211). To the best of our knowledge, no studies have linked FGFR1 with angiogenesis and bone destruction in RA. Therefore, investigating the role

of FGFR1 in inhibiting synovial vascularization in RA may facilitate treatment of RA vascularization and improvement of RA bone destruction. In RA, FGFR1 is associated with VEGFA production and key endothelial activities including proliferation and migration. Nevertheless, its specific roles in synovial angiogenesis and secondary bone damage remain unclear (Fig. 3).

Dual roles of FGFR1 across cell types. The contradictory roles of FGFR1 in different cell types primarily stem from its complex

signaling network and cell type-specific responses (106,212). Environmental factors, cell type-specific characteristics and stages of disease influence the ultimate effects of FGFR1. Therefore, when studying FGFR1 functions, it is necessary to consider these factors to understand its mechanisms of action under different physiological and pathological conditions (106). Moreover, targeted therapeutic strategies against FGFR1 need to be adjusted according to the specific disease and cell type to achieve the best therapeutic outcome (213). In bone cells, FGFR1 activation promotes the formation of osteoclasts and bone resorption by upregulating the expression of MMP 2 and RANKL, leading to a decrease in bone mass and enhanced bone resorption; FGFR1 also serves a role in promoting bone formation in bone cells (127,128). The loss of FGFR1 in bone cells activates the Wnt/ β -catenin signaling pathway, promotes the formation of trabecular and cortical bone and increases the expression of osteoprotegerin mRNA, thereby enhancing bone formation (214). The microenvironment of bone cells, including extracellular matrix components and local concentrations of GF, may affect FGFR1 signaling pathways, causing it to promote bone resorption or enhance bone formation. In different stages of RA, bone cell responses may differ, with early stages dominated by inflammation and bone resorption, while later stages may involve reparative bone formation (215). In osteoblasts, FGFR1 expression is key for bone mineralization and formation (17). However, excessive activation of FGFR1 may inhibit osteoblast maturation and mineralization, leading to decreased bone formation. During osteoblast development, FGFR1 promotes the proliferation of progenitor cells and differentiation into pre-osteoblasts in the early phase. In mature osteoblasts, by contrast, FGFR1 restrains excessive mineralization to sustain bone homeostasis. Notably, these biological processes are tightly modulated by multiple downstream signaling pathways. In articular chondrocytes, FGFR1 activation upregulates the expression of MMP1 and MMP13 in the matrix, promoting matrix degradation and cartilage damage (216). However, in gene KO models (128,217), the loss of FGFR1 protects cartilage from degeneration and decreases cartilage destruction. In inflammatory diseases such as RA, inflammatory factors may alter the response of chondrocytes to FGFR1 signaling, causing its role to shift from protective to destructive (128,154).

5. Therapeutic strategies targeting FGFR1 for RA

As FGFR1 is key for bone resorption and bone reconstruction in the induction and development of RA, blockade of FGFR1 might represent a novel therapeutic strategy for the treatment of RA. There is evidence that mice lacking FGFR1 in osteocytes have increased trabecular bone mass and cortical bone thickness, which is attributed to increased bone formation and impaired bone resorption (35,129). Consequently, FGFR1 is hypothesized to be a good molecular target for decreasing bone loss in RA. Tang *et al* (35) used osteocyte-specific FGFR1 KO mice to demonstrate that FGFR1 deficiency enhances trabecular bone mass and cortical bone thickness through augmented bone formation and attenuated bone resorption. *In vitro*, Meng *et al* (14) showed that the FGF pathway is a critical signaling pathway in relapsed RA, and targeted tissue-specific inhibition

of FGF10/FGFR1 may provide new opportunities to treat patients with relapse RA. FGFR1 inhibitors could effectively improve the effectiveness of RA treatment. Additionally, treating rats with PD173074 (FGFR1 inhibitor) significantly decreases bone erosion (14).

Xiao *et al* (139) reported downregulation of sclerostin and Dickkopf-1 and FGFR1 may participate in the post-transcriptional control of FGF23 in FGFR1 dentin matrix acidic phosphoprotein 1 (Dmp1)-cKO-null mice. This not only highlights the molecular crosstalk between FGFR1 signaling and pivotal bone-derived endocrine factors including FGF23 and osteocalcin, but also defines FGFR1 as a key modulator of systemic mineral metabolism via post-transcriptional regulatory mechanisms. These are produced by osteocytes and serve as antagonists of the Wnt signaling pathway, which is an important anabolic signal for bone. Among hypophosphatemic (Hyp) mice with Dmp1-driven cKO of FGFR1, circulating FGF23 concentrations declined to a significantly greater extent than bone-derived FGF23 transcripts. These results demonstrate FGFR1 promotes the translation of FGF23 mRNA. FGF2/FGFR1 signaling modulates FGF23 protein translation in cultured cells through a PI3K/AKT signaling pathway-dependent mechanism. This establishes a post-transcriptional regulatory pathway wherein FGFR1 activation directly influences FGF23 biosynthesis via PI3K-mediated activation of the Akt kinase cascade. These results are consistent with prior reports showing the role of FGFR1 signaling in translational control in cancer and smooth muscle cells (218-220). FGFR1-mediated bifunctional regulation of FGF23 at transcriptional and post-transcriptional levels offers a mechanistic explanation for the discordance between bone FGF23 mRNA expression and circulating FGF23 levels (221). It may also offer an alternative therapeutic target, in addition to the regulation of transcription and degradation (222), for the modification of circulating FGF23 levels in disease states. While FGFR1 inhibition shows promise for RA-associated bone erosion, gaps remain in understanding its pleiotropic effects across cell types and disease stages. Future studies should perform high-resolution single-cell transcriptomic profiling of FGFR1 signaling cascades and spatiotemporal-controlled genetic models to determine pathological vs. metabolic FGFR1 functions.

FGFR1 inhibitors and disease-modifying anti-rheumatic drugs (DMARDs). Drugs used in clinical practice primarily include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and DMARDs (223,224). Clinical trials have demonstrated that these drugs effectively improve the condition of patients with RA (225,226). NSAIDs and glucocorticoids serve a role in relieving pain and reducing inflammation (227,228). DMARDs are effective first-line drugs for treating RA in clinical practice (229). FGFR1 inhibitors may inhibit inflammatory responses, counteract bone erosion, and reduce bone loss by suppressing the bone-resorbing activity of osteoclasts, inhibiting chondrocyte degradation, suppressing macrophage activity, and protecting degenerated chondrocytes. The advantages of FGFR1 inhibitors in the treatment of RA as well as potential risks are summarized in Table III.

6. Conclusion

FGFR1 is a key regulator in RA-associated bone destruction, orchestrating crosstalk between synovial angiogenesis, osteoclast activation and inflammatory signaling. However, the specific regulatory mechanisms remain unclear, particularly the signal transduction mechanisms of FGFR1 in the pathogenesis of RA and across different cell types, which require further validation. FGFR1 inhibition attenuates bone erosion and synovitis in preclinical models (230-232), suggesting its therapeutic potential. However, challenges persist, including the paradoxical roles of FGFR1 in different cell types and the need for targeted delivery strategies to minimize off-target effects. Advanced single-cell sequencing and spatial transcriptomics may delineate cell-type-specific FGFR1 signaling networks in RA joints. The therapeutic potential of selective FGFR1 inhibitors, particularly their capacity to simultaneously target bone erosion and synovitis, warrants validation in human clinical trials. By bridging these gaps, FGFR1-targeted therapies may redefine RA management, particularly for refractory cases with aggressive joint destruction.

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Authors' contributions

All authors have read and approved the final manuscript. CQ, ZZ, XW, XL and FLY conceived the study. CQ, HT, JW, ZY and ZZ constructed figures. CQ and FLY wrote the manuscript. Data authentication is not applicable.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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