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Review

Post-Transcriptional Regulation of FGF Signaling: Insights from Musculoskeletal System

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Abstract

Fibroblast growth factor (FGF) signaling plays a pivotal role in the development, maintenance, and regeneration of musculoskeletal tissues. While its transcriptional regulation has been extensively characterized, accumulating evidence indicates that FGF activity is also modulated by a diverse array of post-transcriptional mechanisms. In this review, microRNAs, long non-coding RNAs, alternative splicing, and RNA modifications are examined as key regulators of FGF ligands and receptors across bone, cartilage, muscle, and tooth. Enhancer RNAs and RNA-binding proteins are also discussed as potential modulators of FGF transcript stability and translation. By integrating both established and emerging layers of RNA-level regulation, this review outlines a complex, tissue-specific architecture that fine-tunes FGF signaling in development and repair. To highlight this layered regulatory dimension, the concept of a *pathway-specific RNA regulome* is introduced, referring to the network of RNA-based mechanisms that modulate signaling cascades, such as FGF, across distinct biological processes. The therapeutic implications of targeting post-transcriptional nodes, particularly through non-coding RNAs and epitranscriptomic marks, are highlighted as promising avenues for future musculoskeletal interventions.

Keywords: FGF signaling; post-transcriptional regulation; musculoskeletal development; non-coding RNA; RNA modifications

1. Introduction

Fibroblast growth factor (FGF) signaling is a key modulator of embryonic development and adult tissue homeostasis, with particularly well-defined roles in the formation and maintenance of musculoskeletal structures (Su et al., 2014; Teven et al., 2014; Ornitz and Itoh, 2015; Ornitz and Marie, 2015). In vertebrates, the FGF family comprises 22 members, of which 18 secreted ligands interact with four transmembrane tyrosine kinase receptors (FGFR1–FGFR4) and can also bind the atypical receptor FGFRL1. FGFRL1 lacks an intracellular kinase domain and modulates signaling through decoy or scaffolding functions (Park et al., 2022). In contrast, ligand binding to FGFR1–FGFR4 activates downstream cascades including the RAS–MAPK, PI3K–AKT, PLCγ, and STAT pathways, each of which exerts context-dependent effects on cell proliferation, differentiation, survival, and

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migration (Dailey et al., 2005; Ornitz and Itoh, 2015). FGF signaling is strongly influenced by co-receptors that help assemble and stabilize the active ligand–receptor complex. Heparan sulfate proteoglycans (HSPGs) act as co-receptors for the paracrine/autocrine FGFs (FGF1–10, FGF16-18, FGF20 and FGF22), increasing their local concentration and promoting productive binding to FGFRs. In contrast, the Klotho family proteins (α-Klotho and β-Klotho) function as obligate co-receptors for the endocrine FGFs (FGF19, FGF21 and FGF23), conferring ligand specificity and enabling efficient long-range, hormone-like FGF signaling. Within musculoskeletal tissues, such signaling governs critical processes such as skeletal patterning, osteogenesis, chondrogenesis, myogenesis, and tooth morphogenesis (Li et al., 2014; Su et al., 2014; Teven et al., 2014; Ornitz and Marie, 2015; Pawlikowski et al., 2017; Du et al., 2018).

During bone development, FGF signaling is required for the proper proliferation and differentiation of mesenchymal stem cells (MSCs) into osteoblasts (Chen and Deng, 2005; Su et al., 2014; Teven et al., 2014; Ornitz and Marie, 2015). Genetic knockout studies have shown that FGF18 is essential for both osteogenesis and chondrogenesis (Liu et al., 2002; Ohbayashi et al., 2002). For example, FGF2 and FGF18 have been shown to stimulate osteoprogenitor proliferation and to modulate differentiation and matrix production, via the upregulation of *Bmp2* and *Runx2* (Hamidouche et al., 2010; Nagayama et al., 2013). Meanwhile, FGF23 plays a distinct endocrine role in phosphate homeostasis and exerts indirect effects on bone mineralization through its actions on kidney and bone cells (Chen and Deng, 2005; Wang et al., 2008; Hori et al., 2011; Su et al., 2014; Teven et al., 2014; Guo and Yuan, 2015). Beyond bone, FGFs also play pivotal roles in cartilage, where FGFs modulate chondrocyte proliferation and hypertrophy, particularly in the growth plate, where spatial gradients of FGFR expression intersect with Indian Hedgehog (Ihh) and parathyroid hormone-related protein (PTHrP) signaling to control longitudinal bone growth (Minina et al., 2001; Su et al., 2014; Teven et al., 2014; Ornitz and Marie, 2015). FGFR3, in particular, has been implicated in chondrodysplasias due to its inhibitory role in chondrocyte expansion (Su et al., 2014; Teven et al., 2014; Ornitz and Marie, 2015; Ornitz and Legeai-Mallet, 2017), while its over overactivation leads to skeletal dysplasias (Kimura et al., 2021).

In muscle tissue, FGF signaling contributes to the activation and proliferation of satellite cells during regeneration (Fu et al., 2015; Pawlikowski et al., 2017). FGFs such as FGF2 and FGF6 are upregulated or released in response to injury and promote satellite-cell and myoblast proliferation (Floss et al., 1997) (Allen and Boxhorn, 1999), whereas sustained FGF signaling must be attenuated to permit efficient differentiation (Armand et al., 2006; Fu et al., 2015; Pawlikowski et al., 2017). Dysregulation of FGF activity in muscle has been associated with impaired regeneration, muscular dystrophies, and tumorigenesis, including rhabdomyosarcoma, in which aberrant FGFR signaling contributes to malignant growth (Crose et al., 2012; Fu et al., 2015; Pawlikowski et al., 2017; Milton et al., 2022). In odontogenesis, members of the FGF family regulate epithelial–mesenchymal interactions essential for tooth bud initiation, enamel organ formation, and root development, often in coordination with Wnt and BMP signaling pathways (Kettunen and Thesleff; Li et al., 2014; Du et al., 2018; Vaseenon et al., 2020). For example, FGF3 and FGF10 are expressed in the dental mesenchyme during early morphogenesis (Kettunen et al., 2000), while FGF4 serves as a signaling hub for cusp formation (Jernvall et al., 1994).

Although the functional consequences of FGF signaling in musculoskeletal tissues have been extensively studied, the regulatory mechanisms that determine the intensity, timing, and duration of this pathway remain incompletely understood. Historically, research has focused on ligand availability, receptor expression, and feedback antagonists such as Sprouty proteins and other extracellular or intracellular inhibitors that dampen FGF–FGFR activity (Hacohen et al., 1998; Dailey et al., 2005; Ornitz and Itoh, 2015; Xie et al., 2020; Szybowska et al., 2021). However, increasing attention has been directed toward the regulation of FGF signaling at the RNA level. This includes not only transcriptional control, but also a range of post-transcriptional mechanisms that govern RNA processing, stability, localization, and translation, some of which have been shown to fine-tune FGF output in specific developmental contexts (Li et al., 2019a; Copeland and Simoes-Costa, 2020;

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Ding et al., 2024). These regulatory layers are of particular interest in dynamic tissues such as bone and muscle, where rapid and reversible shifts in gene expression are required for development, adaptation, and repair (Su et al., 2014; Teven et al., 2014; Fu et al., 2015; Pawlikowski et al., 2017). In the sections that follow, the post-transcriptional regulation of FGF signaling will be examined in detail, with emphasis on mechanisms such as microRNA interference, long non-coding RNA interaction, alternative splicing, and RNA modifications (Imbriano et al., 2023; Yi and Yang, 2023). These regulatory layers collectively form what we propose here as a pathway-specific RNA regulome: a complex, tissue-specific architecture that modulates FGF signaling cascade in development and repair. This review will integrate established and emerging evidence across bone, cartilage, muscle, and tooth to highlight how RNA-level regulation fine-tunes FGF signaling in musculoskeletal biology.

Figure 1: Mechanism of post-transcriptional regulation of FGF signaling

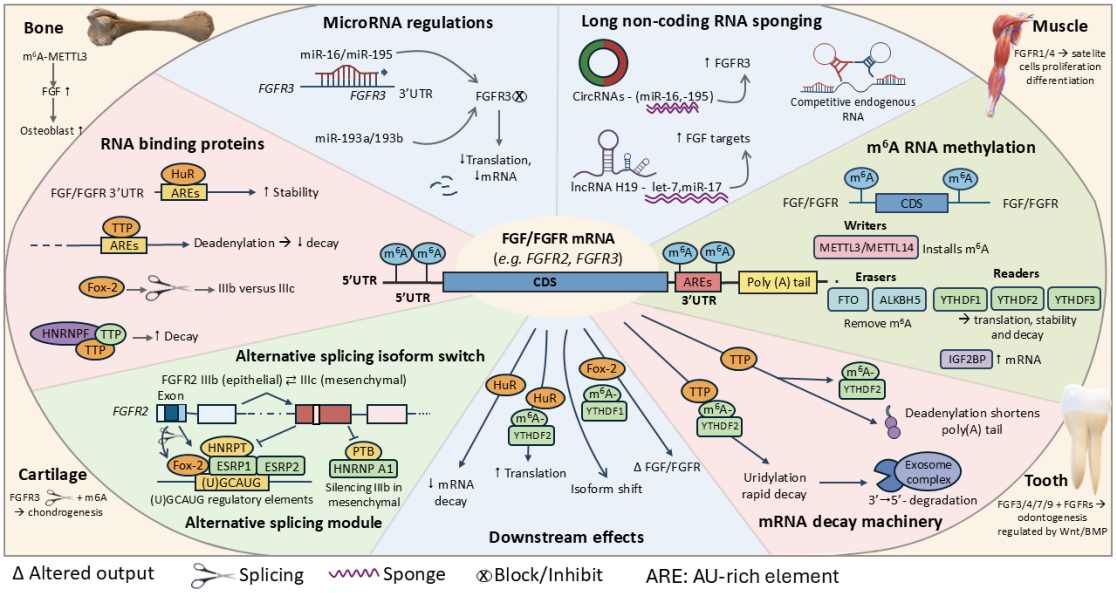


Figure 1. Layered post-transcriptional control of FGF/FGFR mRNAs across musculoskeletal tissues. FGF/FGFR transcripts are regulated by integrated RNA-based mechanisms acting on 5′UTR, CDS, and ARE-containing 3′UTR regions. MicroRNAs (miR-99a, miR-193a/b) repress FGFR3 translation and promote decay, counteracted by lncRNA/circRNA sponging (e.g., H19). RNA-binding proteins exert opposing effects, with HuR stabilizing and TTP–hnRNP F promoting degradation. Alternative splicing of FGFR2 (IIIb/IIIc) is controlled by Fox-2 and ESRP1/2, opposed by PTB/hnRNP A1. m6A modification, installed by METTL3/14 and interpreted by YTHDF and IGF2BP proteins, directs transcript stability, translation, or decay. These layers converge on mRNA turnover, isoform balance, and FGF/FGFR output in bone, muscle, cartilage, and tooth.

2. MicroRNA-Mediated Regulation of FGF Signaling

MicroRNAs (miRNAs) are well-known critical post-transcriptional regulators of gene expression in multicellular organisms. They typically act through sequences in the 3′ untranslated regions (UTRs) of target transcripts to repress translation or promote mRNA degradation (Bartel, 2009; Ha and Kim, 2014). In the context of musculoskeletal biology, several miRNAs have been linked to cell differentiation, growth, and repair by modulating growth factor–driven pathways, including the fibroblast growth factor (FGF) signaling axis (Lian et al., 2012; Mirzamohammadi et al., 2014; Horak et al., 2016; Loh et al., 2023; Thakore and Delany, 2025).

Evidence from experimental musculoskeletal models indicates that members of the miR-16/15/195 family directly or indirectly target FGF2, a mitogenic growth factor involved in osteoblast proliferation and matrix production (Chang et al., 2017; Chen et al., 2017; Qi et al., 2020; Yang et al., 2024; Nikeghbal et al., 2025). In mesenchymal stem cells derived from bone marrow, overexpression

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of miR-16 reduces FGF2 expression and impairs osteogenic differentiation, an effect that can be rescued by restoring FGF2 expression or inhibiting miR-16 (Qi et al., 2020). A related miRNA, miR-195-5p, has been observed to inhibit FGF2 expression in human periodontal ligament stem cells under mechanical stretch, suggesting that miRNA–FGF interactions may respond to biomechanical stimuli during skeletal remodeling (Chang et al., 2017; Chen et al., 2017; Wang et al., 2018b; Nikeghbal et al., 2025). While earlier work focused largely on FGF2, recent studies brought forth evidence of the implication of other critical ligands such as miR-455 directly targeting FGF18 (Niu et al., 2025). The loss of this miRNA leads to dysregulated bone turnover and impaired skeletal homeostasis, providing a clear example of how specific miRNA–ligand pairs maintain the adult bone architecture through post-transcriptional control.

Additional work in ligamentogenic and craniofacial mesenchymal stem-cell models further supports this regulatory concept. These studies show that miR-15/16 family members (miR-16/miR-16-5p, miR-16a-5p and the closely related miR-195-5p) repress FGF2 expression and thereby influence lineage allocation of mesenchymal stem cells in response to mechanical or growth factor cues (Chang et al., 2017; Chen et al., 2017; Li et al., 2022a; Yang et al., 2024; Nikeghbal et al., 2025). In avian and mammalian species, differential miRNA expression patterns have also been correlated with cartilage growth plate maturation, although specific FGF targets have not always been experimentally validated in these models (Lin et al., 2016, 2018; Li et al., 2020; Yao et al., 2023).

Beyond bone, muscle tissue exhibits a distinct set of miRNAs known as myomiRs, including miR-1, miR-133, and miR-206 (Chen et al., 2005; Sweetman et al., 2006; Mitchelson and Qin, 2015; Horak et al., 2016). These miRNAs play essential roles in myogenesis and muscle repair, in part by targeting components of pro-proliferative signaling cascades that intersect with FGF pathways (Chen et al., 2005; Sweetman et al., 2006; Feng et al., 2013; Mitchelson and Qin, 2015; Ballarino et al., 2016; Galimov et al., 2016; Mok et al., 2017; Fochi et al., 2020). In embryonic and adult muscle, FGF–ERK signaling can antagonize or delay the induction of myomiRs, most clearly demonstrated for miR-206 in chick somite development. This delay maintains muscle progenitors in a proliferative state. As myomiR expression subsequently increases, these miRNAs feedback to restrict cell-cycle progression and promote myotube differentiation (Sweetman et al., 2006; Mok et al., 2017). A direct link to FGF receptor signaling has been demonstrated for miR-133, which post-transcriptionally represses FGFR1 and the ERK pathway component PP2AC in C2C12 myoblasts. this repression dampens FGF-dependent ERK1/2 activation and favors differentiation over proliferation (Feng et al., 2013). miR-206 promotes terminal myoblast differentiation by targeting multiple inhibitors of myogenesis, including Pax7, HDAC4, thereby counteracting pro-proliferative signals such as FGF2 (Chen et al., 2005; Mitchelson and Qin, 2015; Ballarino et al., 2016; Galimov et al., 2016; Fochi et al., 2020). Together with other FGF-responsive miRNAs such as miR-29a, these myomiRs ensure that proliferative FGF signals are attenuated once satellite cells have committed to differentiation (Chen et al., 2005; Ballarino et al., 2016; Galimov et al., 2016; Mok et al., 2017; Fochi et al., 2020). A similar proliferation–differentiation switch has been described for miR-1 in vertebrate muscle, where it cooperates with miR-133 to promote differentiation and repress cell-cycle genes. Its expression is modulated by pathways including FGF–ERK signaling, although direct FGF ligands or receptors by miR-1 has not been conclusively demonstrated (Chen et al., 2005; Sweetman et al., 2006; Mok et al., 2017; Fochi et al., 2020).

Cartilage provides another example of miRNA-driven modulation of FGF-related genes (Miyaki et al., 2010; Mirzamohammadi et al., 2014; Duan et al., 2020; Si et al., 2020; Li and Wu, 2021; Chaudhry et al., 2022). In porcine and human chondrocytes, miR-140 regulates cartilage homeostasis by targeting matrix degrading enzymes such as ADAMTS5, thereby limiting aggrecan degradation and indirectly influencing the extracellular environment in which FGF2 ligands function (Miyaki et al., 2010; Duan et al., 2020; Li and Wu, 2021; Chaudhry et al., 2022). More recent CRISPR–Cas9-based target validation has confirmed FGF2 as a mechanosensitive miR-140 target in human articular chondrocytes, demonstrating that miR-140 can directly regulate FGF2 expression under conditions of injury or inflammatory stress (Chaudhry et al., 2022). These findings complement *in vivo* studies

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showing that loss of miR-140 leads to defects in cartilage development and early-onset osteoarthritis, whereas miR-140 overexpression attenuates chondrocyte senescence and matrix degradation (Miyaki et al., 2010; Duan et al., 2020; Si et al., 2020; Li and Wu, 2021).

The regulatory mechanism of the FGF-miRNA axis is not limited to mammalian systems, and in fact appears to be deeply conserved across vertebrates. The same proliferation-differentiation switches that govern mammalian muscle and bone development can be observed during tissue regeneration in lower vertebrates fish models such as medaka and zebrafish. Thus fish models also provided valuable insight into miRNA regulation during fin development and regeneration, a process involving both FGF ligands and receptors (Thatcher et al., 2008; Yin et al., 2008; Ellman et al., 2013; Xie et al., 2020; Ribeiro et al., 2022; Fan et al., 2024). In zebrafish, global impairment of miRNA biogenesis or experimental manipulation of specific miRNAs, including miR-133 and miR-203, disrupts caudal fin regeneration, and FGF receptor inhibition alters miRNA expression profiles within the regeneration blastema (Thatcher et al., 2008; Yin et al., 2008; Fan et al., 2024).

FGF-dependent depletion of miR-133 promotes blastemal cell proliferation and appendage regrowth, highlighting a regulatory cascade, in which FGF signaling first reshapes the miRNA landscape, which in turn modulates downstream regenerative gene networks (Yin et al., 2008). Whether these miRNAs directly target FGF transcripts or act predominantly through parallel pathways, such as Wnt, BMP, or cell-cycle regulators, remains under investigation. Nonetheless, current evidence supports a conserved functional integration of FGF signaling with miRNA regulatory programs during vertebrate appendage regeneration (Thatcher et al., 2008; Yin et al., 2008; Ribeiro et al., 2022; Fan et al., 2024).

Altogether, these findings support the existence of tissue-specific and context-dependent miRNA networks that modulate FGF signaling across vertebrate species. The dynamic regulation of FGF ligands, receptors, and FGF-responsive downstream effectors by miRNAs enables precise temporal and spatial control of signaling outcomes during musculoskeletal development and repair (Table 1). However, only limited subsets of FGF ligands and receptors, most prominently FGF2 and FGFR1, have been validated as direct miRNA targets. Expanding functional studies to additional FGF family members and non-mammalian systems remains an important frontier for future research.

Table 1. Examples of microRNA regulation of FGF signaling components in musculoskeletal tissues.

miRNA	FGF target(s)	Tissue / cell type	Species	Mechanism affected	References
miR-16-5p	FGF2	Bone marrow MSCs (osteogenic differentiation)	Human	Represses FGF2–ERK; reduces osteogenesis	Qi et al., 2020
miR-16a-5p	FGF2	Human amniotic MSCs (ligamentogenic differentiation)	Human	Represses FGF2; inhibits ligamentogenesis	Yang et al., 2024
miR-16-5p (via UCA1)	FGF2	Human amniotic MSCs (ligament regeneration)	Human	lncRNA/miR axis elevates FGF2; promotes ligament repair	Yang et al., 2025
miR-195-5p	FGF2	Periodontal ligament cells under cyclic strain	Human	Represses FGF2; reduces osteogenesis under load	Chang et al., 2017; Chen et al., 2017; Nikeghbal et al., 2025
miR-23c	FGF2	Bone marrow MSCs / damaged articular cartilage	Rat	Represses FGF2; limits chondrogenesis and repair	Shen et al., 2019
miR-140-5p/-3p	FGF2	Primary articular chondrocytes	Human / mouse	Represses FGF2; tunes mechanosensitive response	Chaudhry et al., 2022

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miR-195	FGF18	Articular chondrocytes	Human / rat	Represses FGF18; reduces anabolic signaling	Wang et al., 2017
miR-21-5p	FGF18	Knee articular cartilage (osteoarthritis)	Mouse / human	Represses FGF18; worsens OA changes	Wang et al., 2019; Chen et al., 2021
miR-21-5p	Spry1	TMJ articular cartilage (TMJOA)	Mouse / human	Represses Spry1; enhances ERK–MAPK and ECM loss	Ma et al., 2020
miR-133a/b	FGFR1	C2C12 skeletal myoblasts	Mouse	Represses FGFR1; shifts from proliferation to differentiation	Feng et al., 2013; Horak et al., 2016
miR-133a-3p	FGFR1	Primary myoblasts (lncR-133a axis)	Goat	Represses FGFR1; modulates ERK1/2 and myogenesis	Zhan et al., 2022
miR-338-3p	FGFR2	Bone marrow stromal stem cells	Mouse	Represses FGFR2; impairs osteoblast differentiation	Liu et al., 2014
miR-223-3p	FGFR2	MSC/osteoblasts, PDL-derived cells	Mouse / human	Represses FGFR2; shifts lineage toward adipogenesis	Guan et al., 2015; Xie et al., 2015; Wang et al., 2021
miR-300	FGFR2	Bone marrow MSCs (osteoporotic vs control)	Mouse	Represses FGFR2; lncRNA sponge restores osteogenesis	Guo et al., 2020
miR-607	FGFR4	Skeletal muscle myotubes	Human	Predicted to repress FGFR4; impairs insulin–Akt signaling	Ling et al., 2024

3. Single Nucleotide Variants Linked to miRNA–FGF Interaction

Single nucleotide polymorphisms (SNPs) located within the 3′ untranslated regions (3′UTRs) of mRNAs can influence post-transcriptional regulation by disrupting or enhancing microRNA (miRNA) binding sites (Saunders et al., 2007; Sethupathy and Collins, 2008; Liu et al., 2012; Moszyńska et al., 2017). These variants, often termed miRNA target-site SNPs, miRSNPs, or poly-miRTSs, can create, destroy, or quantitatively modulate miRNA recognition elements, thereby altering mRNA stability or translation efficiency (Saunders et al., 2007; Sethupathy and Collins, 2008; Liu et al., 2012; Moszyńska et al., 2017). Within the FGF pathway, miRSNPs have now been implicated in both craniofacial malformations and bone mineral density (BMD) variation, illustrating context-dependent effects on FGF ligand dosage (Lei et al., 2011; Dole and Delany, 2016; Li et al., 2016; Zhu et al., 2017; Yalaev et al., 2024). Although the majority of functional evidence has been derived from genetic studies in humans, bioinformatic surveys and GWAS-based fine-mapping suggest that similar regulatory principles are likely to apply across vertebrate species (Saunders et al., 2007; Yerges et al., 2010; Zmuda et al., 2011; Liu et al., 2012; Wu et al., 2014; Moszyńska et al., 2017; Yalaev et al., 2024).

In the context of craniofacial development, SNPs within the 3′UTRs of FGF2 (rs1048201), FGF5 (rs3733336), and FGF9 (rs546782) have been implicated in altered susceptibility to nonsyndromic orofacial clefts in a Han Chinese population (Li et al., 2016). These variants are thought to affect miRNA binding efficiency, thereby modulating transcript stability or translation. Li and colleagues systematically selected miRNA-binding site SNPs in FGFs/FGFRs. They showed that rs1048201 in the FGF2 3′UTR alters binding of miR-496, rs3733336 in the FGF5 3′UTR affects miR-145 binding, and rs546782 in the FGF9 3′UTR modulates miR-187 binding, as demonstrated by allele-specific dual-luciferase assays (Li et al., 2016). For FGF2/rs1048201, the T allele attenuated miR-496-mediated repression compared with the C allele and was associated with a slightly increased FGF2 mRNA level

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and a reduced risk of nonsyndromic orofacial cleft, suggesting that a marginally higher FGF2 dosage can be protective during lip and palate morphogenesis (Li et al., 2016). Similarly, rs3733336-G strengthened miR-145-dependent repression of FGF5, whereas rs546782-T weakened miR-187-mediated repression of FGF9, indicating that both increased and decreased miRNA binding can act in a protective manner, depending on the baseline requirement for each ligand during craniofacial development (Li et al., 2016). These data provide one of the clearest examples in which miRNA–FGF interactions, modified by 3′UTR SNPs, contribute directly to variation in craniofacial phenotype.

In skeletal tissues, miRSNPs influencing FGF signaling have been most clearly characterized for FGF2, where multiple 3′UTR variants have been associated with BMD. Lei et al. identified three polymorphisms (rs6854081, rs1048201, rs7683093) in the FGF2 3′UTR that lie within predicted miRNA-binding motifs, including sites for miR-146a/b, and found significant associations with femoral neck BMD in Caucasian women (Lei et al., 2011). Follow-up work in independent cohorts and meta-analyses confirmed that rs6854081 and rs1048201 are reproducibly associated with BMD, with allele-specific differences in predicted miRNA binding at these sites (Dole and Delany, 2016; Zhu et al., 2017; Tyurin et al., 2021; Yalaev et al., 2024). Zhu et al. subsequently provided direct functional evidence for rs1048201, by showing that the C allele enhances repression of FGF2 by miR-196a-3p, whereas the T allele weakens this interaction, leading to higher FGF2 expression and higher spinal BMD in Chinese subjects (Zhu et al., 2017). Together, these studies support a model in which FGF2 3′UTR miRSNPs fine-tune FGF2 abundance in osteoblast-lineage cells, thereby contributing to interindividual differences in bone mass and osteoporosis risk (Lei et al., 2011; Dole and Delany, 2016; Zhu et al., 2017; Tyurin et al., 2021; Yalaev et al., 2024).

Beyond FGF2, variants at or near FGF18 and FGFR3 loci have been linked to bone-related traits, although their roles as miRSNPs remain speculative. Candidate-gene and GWAS analyses have identified FGF18-region polymorphisms associated with vertebral trabecular BMD and with knee osteoarthritis risk, and FGFR3-region variants associated with volumetric BMD and fracture susceptibility (Yerges et al., 2010; Zmuda et al., 2011; Wu et al., 2014). However, most of these FGF18 and FGFR3 variants reside in intronic or coding regions rather than in experimentally confirmed miRNA recognition elements, and their effects on miRNA–mRNA binding have not yet been tested. *In silico* predictions sometimes place these SNPs close to putative miRNA seed sites, but functional validation in bone cells is lacking. In agricultural species, FGF-related loci such as FGFBP1 show polymorphisms associated with BMD and carcass traits, and FGF2-based SNP markers for growth traits in chickens have been described, but no clear miRNA target-site mechanisms have been reported yet in these settings (Hoppman et al., 2010; Wells et al., 2012; Felício et al., 2013).

In muscle regeneration, there is growing interest in the role of genetic variability in modulating satellite-cell responsiveness to FGF signals, As recently highlighted by Liu and Dong, 2025, these miRNA-mediated signals, including those within the FGF pathway, are increasingly recognized as part of a complex exosomal communication network that orchestrates skeletal muscle repair. While direct examples of FGF-focused miRSNPs in these myogenic exosomal pathwways are still emerging, variant in regulatory regions likely affect how efficiently FGFR transcripts are silenced by miRNAs such as miR-133 amd miR-206, which are known to target FGF signaling components or their downstream effectors in myoblasts and satellite cells (Chen et al., 2005; Feng et al., 2013; Pawlikowski et al., 2017; Liu and Dong, 2025). To date, however, no SNP in the 3′UTRs of FGFR1–FGFR4 has been functionally shown to alter myomiR binding in skeletal muscle, and evidence for miRNA target-site variants shaping FGF-dependent regeneration remains largely hypothetical. Population-level studies in livestock and zebrafish indicate that natural genetic variation in FGF pathway genes can influence muscle mass, body composition, or appendage regeneration (Xu et al., 2013; Wu et al., 2014), but the causal variants have generally not been mapped to specific miRNA–mRNA interfaces. However, GWAS for muscle mass in livestock have identified specific SNPs in the 3′UTRs of FGFR4 and FGF6 (Xu et al. 2013), which are prime candidates for future miRSNP testing to determine if they functionally alter the “proliferation-differentiation switch” during myogenesis.

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The potential for miRSNPs to influence FGF signaling has also raised interest in personalized medicine. Functional FGF2 miRSNPs that modify BMD or craniofacial risk illustrate how allelic differences in miRNA-mediated repression can contribute to musculoskeletal phenotypes and might, in principle, influence responses to anabolic or anti-resorptive therapies (Lei et al., 2011; Dole and Delany, 2016; Li et al., 2016; Zhu et al., 2017; Tyurin et al., 2021; Yalaev et al., 2024). These functional miRSNPS constitute the regulatory architecture of the RNA regulome, illustrating how inherited sequence variation pre-determines the baseline efficiency of the FGF signaling cascade and explains inter-individual differences in development and disease susceptibility. If specific alleles confer increased or decreased sensitivity to miRNA-mediated repression, therapeutic strategies involving miRNA mimics or inhibitors may require genotype-based adjustment (Saunders et al., 2007; Moszyńska et al., 2017; Rykova et al., 2022). Moreover, the identification of functional miRSNPs in musculoskeletal disease genes could improve genetic risk prediction models by capturing regulatory variation that is not explained by coding SNPs alone (Saunders et al., 2007; Rykova et al., 2022; Bhatia et al., 2024). While very promising, this area of research is still emerging, and much of the current understanding is based on predictive algorithms rather than experimental confirmation (Saunders et al., 2007; Liu et al., 2012; Moszyńska et al., 2017; Rykova et al., 2022; Bhatia et al., 2024). Functional assays validating altered miRNA–mRNA interactions in musculoskeletal contexts remain sparse. Moving forward, integrative studies that combine fine-mapping of GWAS signals with 3′UTR reporter assays, CLIP-based mapping of miRNA–mRNA contacts, and allele-specific expression analyses in bone, cartilage, and muscle will be needed to determine how sequence variation modifies post-transcriptional FGF regulation and influences tissue phenotype.

4. Long Non-Coding RNAs and FGF Signaling

Long non-coding RNAs (lncRNAs), defined as transcripts exceeding 200 nucleotides that lack significant protein-coding capacity, have emerged as regulators of diverse biological processes, including gene expression, chromatin remodeling, and post-transcriptional regulation (Mercer et al., 2009; Fatica and Bozzoni, 2013; Kopp and Mendell, 2018; Statello et al., 2020). In musculoskeletal tissues, lncRNAs have been implicated in modulating signaling pathways that govern progenitor cell fate and tissue remodeling (Ballarino et al., 2016; Huynh et al., 2017; Silva et al., 2019; Wang et al., 2019; Sufianov et al., 2023), among which the FGF axis is increasingly recognized as a node that can be tuned either directly, via interactions with FGF ligands or receptors, or indirectly through control of downstream effector pathways (Razmara et al., 2019; Silva et al., 2019; Wang et al., 2022a; Sufianov et al., 2023; Jiang et al., 2024).

In osteogenic systems, several lncRNAs have been shown to modulate the expression or activity of FGF pathway components through competing endogenous RNA (ceRNA) mechanisms or direct protein interactions (Razmara et al., 2019; Silva et al., 2019; Li, 2022; Wang et al., 2022a; Sufianov et al., 2023; Jiang et al., 2024). For example, lncRNA MALAT1, well studied in cancer biology, has been reported to enhance osteogenic differentiation of bone marrow–derived mesenchymal stem cells (BMSCs), adipose-derived stem cells, and periodontal ligament stem cells by acting as a molecular sponge for miR-124-3p and other miRNAs, thereby upregulating IGF2BP1, RUNX2, and Wnt/β-catenin signaling (Lanzillotti et al., 2021; Li, 2022; Liu et al., 2022; Huang et al., 2023; Zhang et al., 2023; Gu et al., 2024). Rather than stabilizing FGFR1, current evidence indicates that MALAT1 promotes osteogenesis primarily by relieving miR-124-3p-mediated repression of IGF2BP1 and other osteogenic regulators, placing MALAT1 upstream of pathways that synergize with FGF-driven MAPK activity rather than directly targeting FGF receptors (Lanzillotti et al., 2021; Li, 2022; Liu et al., 2022; Huang et al., 2023; Zhang et al., 2023; Gu et al., 2024). A similar ceRNA mechanism has been described for lncRNA H19, which supports bone formation by regulating miR-22 and miR-141; in mesenchymal and dental stem cell populations, H19 sponging of these miRNAs increases SPAG9 and Wnt/β-catenin–Runx2 signaling, thereby promoting osteogenic commitment and modulating MAPK cascades that intersect with FGF signaling outputs (Li et al., 2019b; Zhou et al., 2021; Ping et al., 2022; Zhang et al., 2025b).

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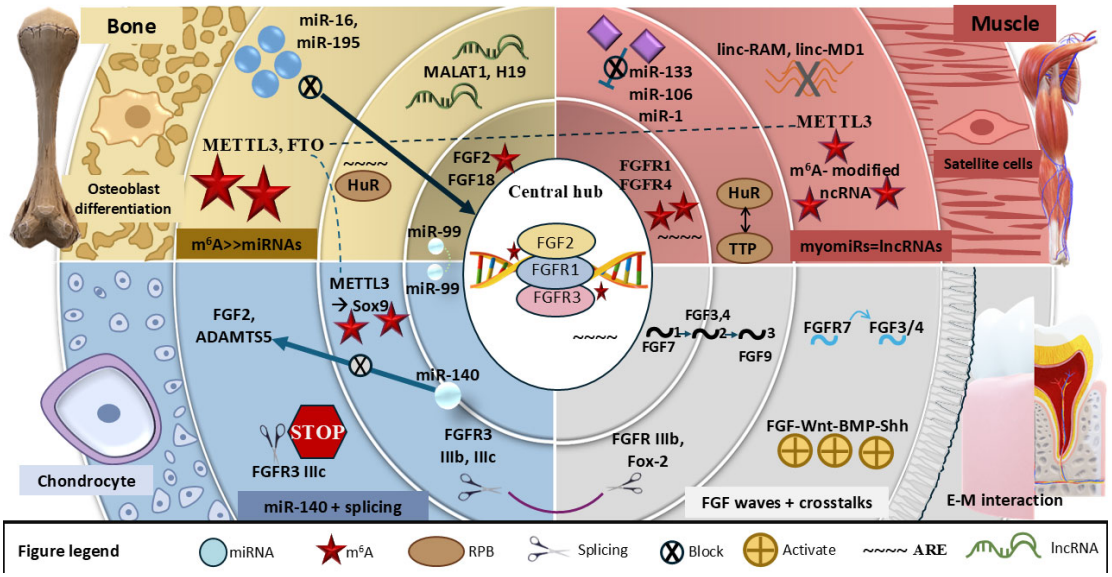


Figure 2. Tissue-specific RNA regulome of FGF signaling. A central FGF2–FGFR1–FGFR3 hub integrates m6A and AU-rich element regulation across four tissue contexts. In bone, METTL3/FTO-dominated m6A regulation intersects with miR-16/195, MALAT1/H19, and HuR to control osteoblast differentiation. In muscle, myomiRs (miR-1/133/206), lincRNAs, and HuR↔TTP balance regulate FGFR1/4 and satellite cell state. In cartilage, FGFR3 IIIb/IIIc splicing, miR-140 targeting, and METTL3–Sox9 signaling govern chondrocyte function. In tooth, sequential FGF3/4/7/9 signaling, FGFR2 IIIb splicing, and FGF–Wnt–BMP–Shh crosstalk drive epithelial–mesenchymal interactions. Shared regulators (METTL3, HuR, miRNAs, splicing factors) connect tissue modules.

Beyond ceRNA control of transcription factors, more direct connections between lncRNAs and FGF ligands have been uncovered in bone and tendon-related cells. lncRNA TUG1 promotes the osteogenic differentiation of tendon stem/progenitor cells by physically interacting with FGF2 and enhancing its ubiquitination, leading to reduced intracellular FGF2 protein levels and a shift from FGF2-driven proliferation toward mineralizing differentiation (Yu et al., 2020; Chen et al., 2024). In periodontal ligament stem cells, TUG1 also facilitates osteogenic differentiation by binding the RNA-binding protein Lin28A and regulating downstream pro-osteogenic transcripts (He et al., 2018), again converging on pathways that couple to FGF2 activity in the periodontal niche. More recently, NEAT1 has been shown to bind the 18-kDa FGF2 isoform, which in turn decreases FGF2-KPNB1 (importin-β) association in BMSCs, thereby modulating FGF2 nuclear localization, BMSC proliferation, and osteogenic differentiation. NEAT1 overexpression sequesters FGF2 away from KPNB1 and limits nuclear import, whereas NEAT1 knockdown enhances FGF2–KPNB1 interaction, FGF2 nuclear accumulation, and bone regeneration *in vivo* (Wang et al., 2025). In this context, NEAT1 is therefore a post-transcriptional regulator of BMSC aging through direct modulation of FGF2 intracellular transport. Together, these studies support a model in which osteogenic lncRNAs tune FGF signaling at multiple levels, from ligand abundance and subcellular trafficking to integration with Wnt and MAPK pathways.

In muscle tissues, lncRNAs are increasingly being recognized for their roles in satellite cell activation and differentiation (Ballarino et al., 2016; Wang et al., 2019; Martone et al., 2020; Lv et al., 2022). The lncRNA linc-MD1, for instance, modulates myoblast differentiation in mice by sponging miR-133 and miR-135, thereby derepressing MAML1 and MEF2C, two transcription factors that drive myogenic gene expression programs (Cesana et al., 2011; Legnini et al., 2014; Fu et al., 2015). Although linc-MD1 does not directly bind FGF transcripts, it operates in the same temporal window in which FGF2–ERK signaling maintains myoblast proliferation, suggesting that linc-MD1-mediated relief of miR-133/miR-135 repression is one mechanism by which cells transition from an FGF-responsive proliferative state to a differentiation-competent state (Cesana et al., 2011; Legnini et al., 2014; Fu et al., 2015; Martone et al., 2020). Another muscle-associated lncRNA, LncMyoD, is induced by MyoD

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and regulates cell-cycle exit and differentiation timing by interacting with MyoD and modulating chromatin accessibility at myogenic gene loci (Gong et al., 2015; Dong et al., 2020).

Importantly, several muscle lncRNAs show more direct regulatory relationships with FGF2. Linc-RAM, a MyoD-regulated lncRNA, enhances myogenic differentiation by facilitating assembly of the MyoD–BAF60c–Brg1 complex, and FGF2 represses Linc-RAM transcription through the Ras–Raf–MEK–ERK pathway; overexpression of Linc-RAM can rescue FGF2-induced inhibition of C2C12 differentiation, indicating that Linc-RAM functions as a critical intracellular mediator of FGF2's anti-differentiation effects in satellite cells (Yu et al., 2017; Zhao et al., 2018; Hitachi and Tsuchida, 2020). In human periodontal ligament stem cells, downregulation of a "linc-RNA activator of myogenesis" transcript has been reported to participate in FGF2-mediated proliferation, further supporting the idea that FGF2 shapes lncRNA expression profiles, creating a feedback on musculoskeletal progenitor behavior (Wu et al., 2020). Additional muscle lncRNAs, such as lncMUMA and lncMREF, have been implicated in mechanical unloading–induced atrophy and regeneration, respectively, and are regulated in contexts where FGF2 is an established mitogenic cue (Cesana et al., 2011; Lv et al., 2022; Du et al., 2024), although direct binding to FGF components has yet to be fully defined.

Chondrogenic models offer fewer characterized lncRNAs directly linked to FGF, but several examples intersect with FGF-regulated matrix remodeling. In rat and human osteoarthritic cartilage, lncRNA-CIR (cartilage injury–related lncRNA) is upregulated and promotes extracellular matrix degradation by increasing the expression of MMP3, MMP13, and ADAMTS5, while also modulating autophagy (Liu et al., 2014; Li et al., 2017; Wang et al., 2018a; Tu et al., 2020). Because FGF2 can both induce matrix-anabolic responses and, under chronic or inflammatory conditions, stimulate MMP and ADAMTS expression, lncRNA-CIR-driven shifts in catabolic enzyme levels are likely to influence how chondrocytes respond to FGF2 during cartilage degeneration and attempted repair (Hu et al., 2018; Tu et al., 2020; Iantomasi et al., 2025). Additional lncRNAs such as HOTAIR, GAS5, MEG3, and XIST have been implicated in chondrocyte apoptosis, inflammatory signaling, and matrix turnover (Hu et al., 2018; Sun et al., 2019; Tu et al., 2020; Wang et al., 2021; Iantomasi et al., 2025). While these molecules have not been shown to bind FGF ligands or receptors directly, they regulate pathways (NF-κB, Wnt/β-catenin, Notch, and JAK/STAT) that functionally intersect with FGF signaling in articular cartilage and growth plate physiology (Ellman et al., 2013; Hu et al., 2018; Sun et al., 2019; Tu et al., 2020; Wang et al., 2021; Iantomasi et al., 2025).

In zebrafish, lncRNA expression patterns have been correlated with regenerative responses in fins and skeletal structures, where FGF signaling is essential for blastemal proliferation and position-dependent growth (Lee et al., 2005; King et al., 2018; Li et al., 2022b; Cudak et al., 2023). Whole-transcriptome profiling during caudal fin regeneration has revealed hundreds of differentially expressed lncRNAs, including lincRNA-154324, whose disruption impairs regenerative outgrowth (Li et al., 2022b). Although direct mechanistic links between specific lncRNAs and FGF pathway components have not been established in zebrafish fins, co-expression analyses and cis-regulatory relationships with genes in FGF-responsive domains suggest that lncRNAs may participate in wiring the transcriptional and epigenetic landscape through which FGF signals control appendage regeneration.

The functional relevance of lncRNA–FGF interactions is further underscored by the responsiveness of lncRNAs to environmental cues such as mechanical loading, oxidative stress, and cytokine exposure (Huynh et al., 2017; Silva et al., 2019; Tu et al., 2020; Sufianov et al., 2023; Deng and Wan, 2025). Mechanical strain and inflammatory mediators modulate the expression of MALAT1, H19, TUG1, NEAT1, and other lncRNAs in osteoblasts, BMSCs, chondrocytes, and tendon stem/progenitor cells, often in parallel with changes in FGF ligand production or FGF receptor expression (Huynh et al., 2017; Silva et al., 2019; Yu et al., 2020; Deng and Wan, 2025; Wang et al., 2025). These observations support a model in which lncRNAs act as context-dependent integrators, translating biomechanical and inflammatory inputs into post-transcriptional adjustments of FGF ligand abundance, receptor signaling competence, and downstream pathway sensitivity, thereby contributing to dynamic signaling adaptation under physiological and pathological conditions (Table

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2). Within the framework of the pathway-specific RNA regulome, lncRNAs may occupy unique and versatile regulatory role, acting primarily at the level of mRNA stability and translation, they can simultaneously modulate FGF ligand subcellular localization, protein ubiquitination, and chromatin accessibility (LncMyoD), potentially representing a qualitatively distinct and multi-modal layer of post-transcriptional control. Despite growing evidence, direct lncRNA–FGF interactions remain limited to a handful of examples (TUG1, NEAT1, Linc-RAM). Expanding functional studies to cartilage and regenerative models will be critical to determine whether lncRNAs broadly act as modulators of FGF signaling or only in selected contexts.

Table 2. Examples of long non-coding RNA regulation of FGF signaling components in musculoskeletal tissues.

lncRNA	FGF target(s)	Tissue / cell type	Species	Mechanism affected	References
MALAT1	FGF2	Periodontal ligament stem cells (PDLSCs)	Human	Upregulates FGF2; enhances PDLSC proliferation	Chen et al., 2019
TUG1	FGF2 (bFGF)	Tendon stem/progenitor cells (TSPCs)	Mouse	Binds bFGF; promotes its ubiquitination and degradation; promotes osteogenic differentiation	Yu et al., 2020
TUG1	FGFR1	MC3T3-E1 osteoblasts (fluid shear stress)	Mouse	Sponges miR-34a; upregulates FGFR1; promotes proliferation and inhibits apoptosis	Wang et al., 2021
NEAT1	FGF2 (via KPNB1)	Bone marrow mesenchymal stem cells (BMSCs) and alveolar bone	Human / Mouse	Binds FGF2 and KPNB1; high NEAT1 impairs FGF2 nuclear import; inhibits bone regeneration	Wang et al., 2025
Linc-RAM	FGF2 signaling output	C2C12 myoblasts / satellite cells	Mouse	Mediates FGF2 repression of differentiation; overexpression rescues FGF2-induced block of myogenesis	Zhao et al., 2017; Zhao et al., 2018
Linc-RAM	FGF2	Periodontal ligament stem cells (PDLSCs)	Human	Downregulated in periodontitis; FGF2 further suppresses Linc-RAM; Linc-RAM attenuates FGF2-driven proliferation	Wu et al., 2020
SNHG1	FGF2	Osteosarcoma cell lines (e.g. MG-63, Saos-2)	Human	Sponges miR-424-5p; upregulates FGF2; promotes proliferation and migration	Li et al., 2021
MAGI2-AS3	FGFR2 (via miR-223-3p)	MC3T3-E1 osteoblasts; fracture callus	Mouse / Human	Sponges miR-223-3p; upregulates FGFR2; enhances osteogenesis and fracture healing	Dong et al., 2024

5. Alternative Splicing and Isoform Regulation of FGF Components

Alternative splicing serves as a critical mechanism for expanding the functional diversity of the FGF signaling pathway across musculoskeletal tissues (Gong, 2014; Ornitz and Itoh, 2015; Ornitz and Legeai-Mallet, 2017; Xie et al., 2020). Both FGF ligands and their receptors (most prominently the FGFR1–3 pre-mRNAs) undergo alternative splicing or alternative translation initiation events that alter their biological activity, receptor-binding affinity, or cellular localization (Werner et al., 1992; Warzecha et al., 2009; Gong, 2014; Ornitz and Itoh, 2015; Xie et al., 2020; Derham and Kalsotra, 2023). These modifications allow cells to fine-tune signaling outputs in response to developmental stage, tissue type, or environmental conditions (Gong, 2014; Ornitz and Itoh, 2015; Ornitz and Legeai-Mallet, 2017; Xie et al., 2020). Among the FGFRs, FGFR1, FGFR2, and FGFR3 are known to exhibit isoform

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variation, particularly through mutually exclusive inclusion of exon IIIb or IIIc in the immunoglobulin-like domain III (Werner et al., 1992; Warzecha et al., 2009; Bebee et al., 2015; Derham and Kalsotra, 2023). This alteration modifies ligand-binding specificity and is especially relevant to epithelial–mesenchymal interactions that underlie bone, cartilage, and muscle development (Su et al., 2014; Bebee et al., 2015; Ornitz and Itoh, 2015; Ornitz and Marie, 2015; Ornitz and Legeai-Mallet, 2017).

In skeletal systems, the FGFR2 IIIc isoform is expressed predominantly in mesenchymal-derived cells such as osteoblasts and chondrocytes and functions as a positive regulator of ossification in these lineages (Eswarakumar et al., 2002; Su et al., 2014; Zhao et al., 2023; Zhou et al., 2023). Targeted deletion of Fgfr2IIIc in mice reduces osteoblast proliferation, delays bone collar formation, and shortens long bones, whereas Fgfr2c gain-of-function alleles that increase signaling cause craniosynostosis and bent-bone dysplasia (Eswarakumar et al., 2002, 2004; Merrill et al., 2012; Zhao et al., 2023; Zhou et al., 2023). At the biochemical level, the IIIc isoforms of FGFR1–3 preferentially bind mesenchymal FGFs such as FGF2, FGF4, FGF8, FGF9, and FGF18, whereas the IIIb isoforms bind epithelial FGFs of the FGF7 subfamily (including FGF7 and FGF10) with high affinity (Yeh et al., 2003; Olsen et al., 2004; Zhang et al., 2006; Zinkle and Mohammadi, 2019). In contrast, the FGFR2 IIIb isoform is more commonly expressed in epithelial tissues and responds to ligands like FGF7 and FGF10, which drive epithelial proliferation and branching morphogenesis in multiple organs (Miralles et al., 1999; Yeh et al., 2003; Olsen et al., 2004; Zinkle and Mohammadi, 2019). Together, reciprocal expression of FGFR2b in epithelia and FGFR2c in adjacent mesenchyme establishes epithelial–mesenchymal feedback loops that are reused during craniofacial skeletogenesis, limb bud outgrowth, and long-bone development (Miralles et al., 1999; Eswarakumar et al., 2002; Yeh et al., 2003; Su et al., 2014; Ornitz and Marie, 2015; Zinkle and Mohammadi, 2019; Zhao et al., 2023; Zhou et al., 2023). Rather than altering splicing per se, several disease-associated mutations at the D3–ligand interface of FGFR2c relax normal ligand specificity, allowing aberrant binding to FGF10 and other FGFR2b ligands and leading to craniosynostosis and limb malformations, underscoring the developmental importance of maintaining distinct IIIb and IIIc signaling domains (Yu et al., 2000; Eswarakumar et al., 2004; Ibrahimi et al., 2004; Merrill et al., 2012).

Alternative isoforms of FGF ligands have also been described, although in the musculoskeletal system FGF2 remains the best-characterized example (Warzecha et al., 2009; Xiao et al., 2009, 2010, 2014; Derham and Kalsotra, 2023). The Fgf2 gene encodes multiple high molecular weight (HMW; ≈21–24 kDa) isoforms initiated from upstream CUG codons and a low molecular weight (LMW; 18 kDa) isoform initiated at the canonical AUG (Xiao et al., 2009, 2010, 2014). The HMW isoforms contain nuclear localization sequences and accumulate predominantly in the nucleus, where they act in an intracrine manner to regulate gene expression and bone cell activity (Xiao et al., 2009, 2010, 2014; Homer-Bouthiette et al., 2014). In contrast, the LMW FGF2 isoform is exported, associates with the extracellular matrix, and participates in autocrine–paracrine signaling by activating FGFRs on neighboring cells (Xiao et al., 2009, 2010, 2014). Genetic dissection of these isoforms in mice has revealed that LMW FGF2 promotes endochondral bone formation and increases bone mass, whereas nuclear HMW FGF2 tends to suppress mineralization and elevate expression of Fgf23 and Sost, thereby exerting a negative influence on bone and phosphate homeostasis (Xiao et al., 2010, 2014; Homer-Bouthiette et al., 2014; Burt et al., 2016; Douglas Coffin et al., 2018) . Through these opposing actions, the balance between LMW and HMW FGF2 isoforms provides an additional layer of control over osteoblast proliferation, differentiation, and the coupling of osteogenesis with angiogenesis and phosphate metabolism (Xiao et al., 2010, 2014; Homer-Bouthiette et al., 2014; Burt et al., 2016; Douglas Coffin et al., 2018; Nickle et al., 2024).

In muscle tissues, most work has focused on changes in the overall abundance and signaling activity of FGFR1 and FGFR4 rather than on detailed mapping of IIIb/IIIc or kinase-domain splice choices (Templeton and Hauschka, 1992; Yu et al., 2004; Pawlikowski et al., 2017). Satellite cells and proliferating myoblasts express high levels of FGFR1 and respond to FGF1 and FGF2 with sustained ERK activation and cell-cycle progression, whereas differentiation is accompanied by

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downregulation of FGFR1 signaling and increased expression of myogenic regulatory factors (Templeton and Hauschka, 1992; Yu et al., 2004; Pawlikowski et al., 2017). Unlike FGFR1–3, FGFR4 does not undergo the canonical IIIb/IIIc ligand-binding domain switch, exhibiting instead a distinct form of isoform diversity through kinase domain splicing. A novel splice variant of FGFR4 (FGFR4-Δ16) has been identified in mouse myogenic cells; its expression correlates with that of wild-type FGFR4 during differentiation, and the two isoforms differ in glycosylation and tyrosine phosphorylation, suggesting isoform-dependent tuning of FGF responses in myotubes (Kwiatkowski et al., 2008). Notably, unlike canonical FGFRs, neither isoform undergoes homodimerization-dependent autophosphorylation; instead, FGFR4 tyrosine phosphorylation appears to require the presence of a heterologous kinase such as FGFR1, suggesting that FGFR4 signaling in myotubes may be fundamentally co-receptor-dependent rather than autonomous (Kwiatkowski et al., 2008). Although analogous studies of FGFR1 IIIb/IIIc usage in regenerating skeletal muscle are scarce, the general principle that mesenchymal tissues predominantly express IIIc isoforms (Werner et al., 1992; Bebee et al., 2015; Ornitz and Marie, 2015) implies that isoform composition is likely to change as myogenic precursors transit from a proliferative, FGF-dependent state to terminally differentiated myofibers, even if the precise splicing events *in vivo* remain to be fully defined (Templeton and Hauschka, 1992; Yu et al., 2004; Kwiatkowski et al., 2008; Pawlikowski et al., 2017).

Despite these insights, the regulatory mechanisms controlling FGF-related splicing in musculoskeletal contexts remain only partially defined (Table 3). In epithelial systems, the epithelial splicing regulatory proteins ESRP1 and ESRP2 are well-established determinants of FGFR2 IIIb versus IIIc exon choice, and TGF-β–induced epithelial–mesenchymal transition causes downregulation of ESRPs and a concomitant switch from epithelial to mesenchymal FGFR isoforms (Warzecha et al., 2009; Horiguchi et al., 2011; Holzmann et al., 2012; Wendt et al., 2014; Bebee et al., 2015; Ranieri et al., 2015; Derham and Kalsotra, 2023). Comparable splicing regulators have not yet been delineated in osteoblasts, chondrocytes, or satellite cells, and it is not clear whether mechanical stress, inflammatory cytokines, or local growth factor cues (including FGF itself) directly modulate FGFR splicing in these tissues. From the perspective of the pathway-specific RNA regulome, this represents a mechanistic asymmetry: while FGFR2 splicing in epithelial systems has been mapped to specific RNA-binding proteins (ESRP1/2), the equivalent regulators in osteoblasts, chondrocytes, and satellite cells remain unknown, leaving a significant gap in our understanding of how the RNA regulome operates in musculoskeletal tissues specifically. Further research across vertebrate models, combining isoform-specific reporters with perturbation of splicing factors, will be required to determine under which conditions FGF isoforms are selected and how they interact with broader signaling networks during tissue remodeling.

Table 3. Alternative isoforms of FGF components relevant to musculoskeletal tissues.

FGF/FGFR isoform(s)	Isoform-generating mechanism	Musculoskeletal tissue / cell context	Species / model	Functional effect (concise)	References
FGFR2 IIIc vs IIIb	Mutually exclusive exon IIIc (mesenchymal) vs IIIb (epithelial) in D3	Osteoblast/chondrocyte precursors in craniofacial and long bones	Mouse	FGFR2IIIc promotes ossification; loss reduces bone growth; gain-of-function FGFR2c causes craniosynostosis/bent-bone dysplasia	Eswarakumar et al., 2002; Eswarakumar et al., 2004; Merrill et al., 2012; Su et al., 2014
FGFR3 IIIc vs IIIb	Alternative use of exon IIIc vs IIIb in D3	Growth-plate and articular chondrocytes (IIIc) vs epithelia (IIIb)	Human / mouse	FGFR3IIIc in chondrocytes inhibits proliferation and bone elongation; FGFR3IIIb mainly epithelial	Delezoide et al., 1997; Pandit et al., 2002; L'Hôte & Knowles,

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					2005; Su et al., 2010
FGFR1–3 b/c	Alternative “b” vs “c” exons in D3 ligand-binding domain	Epithelial vs mesenchymal compartments in limb buds and craniofacial primordia	Human / mouse	b-isoforms bind FGF7/10 in epithelia; c-isoforms bind FGF2/4/8/9/18 in mesenchyme; misexpression disrupts epithelial–mesenchymal FGF loops and skeletal patterning	Yeh et al., 2003; Olsen et al., 2004; Zhang et al., 2006; Ornitz & Itoh, 2015; Chen et al., 2023
FGF2 18-kDa LMW	Translation from canonical AUG start codon	Osteoblasts, BMSCs, periosteal cells; cortical and trabecular bone	Mouse	Secreted; activates FGFR1; increases osteoblast proliferation, bone mass and fracture repair	Xiao et al., 2009; Xiao et al., 2014; Coffin & Hurley, 2018; von Hövel et al., 2021
FGF2 HMW (22–24 kDa)	Upstream CUG initiation → N-terminally extended nuclear isoforms	Osteoblasts, BMSCs; bone–renal axis via FGF23	Mouse	Nuclear; induces Fgf23 and Sost; causes hypophosphatemia and low bone mass; deletion increases bone density	Xiao et al., 2010; Xiao et al., 2013; Homer-Bouthiette et al., 2014; Coffin & Hurley, 2018
FGFR4 (−16)	Exon 16 skipping in intracellular kinase domain	Satellite cell–derived myogenic cultures and C2C12 myoblasts	Mouse	Co-expressed with full-length FGFR4 during differentiation; weak phosphorylation; modulates FGF signaling strength	Kwiatkowski et al., 2008

6. Emerging Post-Transcriptional Mechanisms Regulating FGF Signaling

While microRNAs, long non-coding RNAs, and splicing variants have received the most attention as post-transcriptional regulators of FGF signaling in musculoskeletal biology, several other RNA-level mechanisms have been observed or hypothesized to influence this pathway (Van Pelt et al., 2019; Huang et al., 2021; Shi and Grifone, 2021; Pashay Ahi, 2025). Recent work in bone, muscle, and cartilage suggests that RNA-binding proteins, epitranscriptomic RNA modifications, and untranslated-region (UTR)–dependent mechanisms can modulate the abundance or responsiveness of FGF ligands and receptors, although the evidence is still fragmentary compared with miRNAs and lncRNAs (Van Pelt et al., 2019; Huang et al., 2021; Shi and Grifone, 2021; Wang et al., 2023a; Pashay Ahi, 2025). In addition, structured 5′UTR elements such as internal ribosome entry sites (IRESs) and embedded RNA G-quadruplexes, as well as circular RNAs arising from FGF receptor loci, have begun to emerge as non-canonical post-transcriptional modulators of FGF-related signaling in musculoskeletal cells (Bonnal et al., 2003; Ainaoui et al., 2015; Pan et al., 2021; Du et al., 2022; Yan et al., 2022).

RNA-binding proteins (RBPs) regulate mRNA localization, translation, and decay across many cell types (Khabar, 2017; Shi and Grifone, 2021). In skeletal muscle, RBPs such as HuR (ELAVL1), PTB (PTBP1), and RBM24 contribute to myogenic differentiation and satellite-cell activation (Miyamoto et al., 2009; Hausburg et al., 2015; Grifone et al., 2020, 2021; Shi and Grifone, 2021). These proteins stabilize or repress specific transcripts during the transition from quiescent satellite cells to proliferating myoblasts and differentiated myotubes (Miyamoto et al., 2009; Hausburg et al., 2015; Grifone et al., 2020, 2021; Shi and Grifone, 2021).

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HuR and the destabilizing factor TTP (ZFP36) cooperate to control the turnover of AU-rich element (ARE)–containing mRNAs in myogenic and stem-cell systems, and ARE catalogs indicate that several FGFR mRNAs (including FGFR1) harbor AU-rich motifs in their 3′UTRs, which are canonical binding sites for these RBPs (Peng et al., 1998; Khabar, 2017; Otsuka et al., 2019). Direct links between RBPs and FGF pathway mRNAs in musculoskeletal tissues are beginning to emerge: a recent study showed that the m^{6}A reader IGF2BP1 binds FGFR1 mRNA in skeletal myoblasts, increasing its stability and translation in an m^{6}A-dependent manner and thereby sustaining ERK signaling and inhibiting myogenic differentiation (Liu et al., 2024). In osteogenic contexts, the RBP Lin28 promotes proliferation and osteogenic differentiation of dental pulp and urine-derived stem cells by blocking let-7 maturation, thereby indirectly modulating networks (e.g., IGF2BP2/HMGA2, Wnt) that intersect with FGF-driven MAPK signaling (Wei et al., 2014; Ju et al., 2019; Wang et al., 2022b; Yan et al., 2024). Consistent with a broader role for RBPs in FGF control, the poly(C)-binding protein PCBP2 was recently identified as an intrinsic aging factor in human bone marrow mesenchymal stromal cells (hBMSCs): manipulating PCBP2 levels alters FGF2 expression and demonstrates that PCBP2 regulates replicative senescence through a ROS–FGF2 axis, although the precise post-transcriptional mechanism (direct versus indirect control of FGF2 mRNA) remains to be clarified (Chen et al., 2025). Whether Lin28 or other RBPs bind FGF ligands or FGFR transcripts directly in bone or cartilage remains unclear, but the combination of predicted AREs, RBP expression, and early IGF2BP1–FGFR1 data strongly supports RBP-mediated tuning of FGF receptor output in musculoskeletal cells (Peng et al., 1998; Khabar, 2017; Otsuka et al., 2019; Shi and Grifone, 2021; Liu et al., 2024).

RNA modifications, particularly N^6-methyladenosine (m^{6}A), have emerged as regulators of stem-cell differentiation and tissue regeneration (Yan et al., 2020; Wang et al., 2023a; Sun et al., 2024; Zhou et al., 2024). METTL3, a core component of the m^{6}A methyltransferase complex, is upregulated during osteogenic differentiation of bone marrow or periodontal ligament stromal cells; gain- and loss-of-function experiments show that METTL3 promotes mineralization and alkaline phosphatase activity by installing m^{6}A marks on key osteogenic transcripts such as RUNX2, OSX/SP7, and SMAD1, which are then stabilized or translationally enhanced by readers such as IGF2BP1 (Yan et al., 2020; Wang et al., 2023b; Bertels et al., 2024; Sun et al., 2024; Zhou et al., 2024). So far, FGF ligands and receptors have not been mapped as m^{6}A targets in bone or cartilage, but multiple studies in other tissues demonstrate that FGF pathway transcripts are epitranscriptomically modified: FGF2 mRNA carries METTL3-dependent m^{6}A marks that facilitate its expression in uterine spiral arteries and in breast cancer cells via the m^{6}A reader YTHDF3, and FGFR2 and FGF13 show altered m^{6}A methylation and expression after spinal cord injury (Ni et al., 2022; Gong et al., 2024; Liu et al., 2025a, 2025b). Within the skeleton itself, a newer layer of evidence has come from N^7-methylguanosine (m^{7}G): deletion of the m^{7}G methyltransferase METTL1 in mesenchymal lineage cells causes severe limb shortening and impaired osteoblast/chondrocyte differentiation, and m^{7}G-MeRIP sequencing identified Fgfr2 as a direct METTL1 target whose loss of m^{7}G reduces mRNA stability and attenuates PI3K–AKT and MAPK signaling; pharmacologic or genetic reactivation of FGFR2 signaling rescues the skeletal phenotype (Li et al., 2025). In skeletal muscle, m^{6}A methylation has been shown to regulate satellite-cell function: METTL3-mediated m^{6}A on MyoD mRNA supports exercise-induced muscle growth, and YTHDF2 promotes myogenic differentiation in part by controlling the maturation of miR-378, a microRNA enriched in muscle regeneration (Koopmans et al., 2023; Deng et al., 2024; Feng et al., 2024). Together with the IGF2BP1–FGFR1 axis, these findings support a model in which epitranscriptomic marks on both FGF receptors and their downstream effectors modulate the intensity and duration of FGF signaling in musculoskeletal tissues.

Beyond covalent RNA modifications, UTR-embedded structural elements provide an additional level of control over FGF translation. The 5′ leader of human FGF2 mRNA contains a highly structured internal ribosome entry site (IRES) that includes an RNA G-quadruplex; this IRES is required for cap-independent initiation at three CUG and one AUG codon and thus governs the relative production of low- and high-molecular-weight FGF2 isoforms (Bonnal et al., 2003). Given

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that these same isoforms exert opposing effects on bone mass and phosphate homeostasis, IRES/G-quadruplex-mediated control of FGF2 translation is likely to be relevant for osteoblast function even though it has not yet been dissected directly in skeletal cells. A related mechanism has been described for FGF1 in myogenesis: during C2C12 myoblast differentiation, promoter A–derived FGF1 transcripts are translated through an IRES that is activated by the paraspeckle proteins p54nrb/NONO and hnRNPM; these RBPs bind both the FGF1 promoter and the IRES, coupling transcriptional induction to enhanced IRES-dependent translation of FGF1 and promoting myotube formation (Ainaoui et al., 2015). Together, these studies establish G-quadruplex–containing IRES elements and their associated IRES trans-acting factors as non-canonical post-transcriptional switches for FGF output that are likely to operate in musculoskeletal lineages.

Other RNA modifications, including A-to-I RNA editing by ADAR enzymes, 3′ uridylation, and regulation of poly(A) tail length, have not yet been linked directly to FGF signaling in musculoskeletal tissues. Nonetheless, these processes are known to regulate transcript stability and translational efficiency in a variety of developmental contexts (Charlesworth et al., 2013; Buchumenski et al., 2021; Piasecka et al., 2021; Shi and Grifone, 2021). In zebrafish, ADAR1-mediated A-to-I editing is essential for early embryonic patterning and neural crest–derived craniofacial structures, illustrating the potential for editing to impact signaling pathways that shape the craniofacial skeleton, even though FGF ligands and receptors have not been identified as direct editing substrates (Buchumenski et al., 2021; Niescierowicz et al., 2022). In human muscle cells, MEF2C-dependent 3′ uridylation of miRNAs contributes to fine-tuning of myogenic gene expression, and perturbation of this process alters the spectrum and stability of myomiRs during differentiation (Piasecka et al., 2021). Poly(A) tail length and alternative polyadenylation are also emerging as regulators of myogenic transcripts: nuclear poly(A)-binding protein 1 (PABPN1) and other polyadenylation factors influence mRNA isoform usage and stability in muscle, and their dysfunction leads to myopathy (Charlesworth et al., 2013; Shi and Grifone, 2021). At present, neither uridylation nor poly(A) length control has been tied specifically to FGF or FGFR transcripts in bone, cartilage, or muscle, but the enrichment of regulatory motifs in their UTRs makes them plausible future targets of these pathways.

Enhancer RNAs (eRNAs) represent another emerging regulatory class with potential relevance to FGF gene expression. These non-coding RNAs are transcribed from active enhancers and have been shown to promote transcriptional elongation, recruit transcription factors, and alter chromatin accessibility (Tsai et al., 2018; Lee et al., 2021). In muscle differentiation, MyoD-bound enhancers at the core enhancer (CE) and distal regulatory region (DRR) produce eRNAs that are required for robust activation of MyoD and Myogenin; the DRR eRNA, for example, associates with cohesin and is recruited in trans to the Myogenin locus to promote myogenic transcription (Tsai et al., 2018; Zhao et al., 2019; Lee et al., 2021). Although no eRNAs have yet been directly assigned to FGF loci in musculoskeletal tissues, the regulatory landscapes of key FGF genes are highly enriched in tissue-specific enhancers: integrated “holo-enhancer” units have been identified around the Fgf8 locus that drive expression in limb apical ectodermal ridge and craniofacial domains, and multiple cis-regulatory elements have been mapped for Fgf10 in limb bud, craniofacial mesenchyme, and other organs (Marinić et al., 2013; Kawakami et al., 2018; Jin et al., 2019; Hörnblad et al., 2021). Fgf18 expression in perichondrium and periosteum is also tightly controlled by upstream transcription factors such as RUNX2 and Wnt/β-catenin (Liu et al., 2002; Su et al., 2014). Given that many active enhancers elsewhere in the genome are now known to produce eRNAs, it is reasonable to hypothesize that enhancer clusters surrounding Fgf8, Fgf10, and Fgf18 may generate eRNAs that participate in rapid, context-specific modulation of FGF transcription during limb growth, craniofacial morphogenesis, and skeletal repair, even though such eRNAs have not yet been experimentally characterized.

Beyond linear RNAs, circular RNAs originating from FGF receptor loci have emerged as additional post-transcriptional regulators that intersect with FGF-connected signaling. In skeletal muscle, circFgfr2, generated from exons of the Fgfr2 gene, is upregulated during development and

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regeneration and promotes myogenesis by sponging miR-133, thereby relieving repression of the MAP3K20–JNK/MAPK cascade (Yan et al., 2022). In rat dental follicle cells, circFgfr2 similarly enhances osteogenic differentiation through a circFgfr2/miR-133/BMP6 axis, increasing the expression of RUNX2, DLX3 and other osteogenic markers (Pan et al., 2021; Du et al., 2022). Although circFgfr2 has not yet been shown to regulate FGFR2 mRNA itself, its genomic origin at the Fgfr2 locus and its control of MAPK and BMP pathways highlight circular RNAs as FGF-linked post-transcriptional regulators in muscle and tooth–bone interfaces.

Despite the speculative nature of some of these mechanisms in the FGF context, they represent important frontiers for investigation (see examples summary in Table 4). The convergence of transcriptional and post-transcriptional control at enhancer-associated loci, the influence of m^{6}A and m^{7}G methylation on mRNA turnover and translational competence, and the context-specific activity of RBPs and epitranscriptomic readers all suggest that FGF signaling is likely subject to a broader and more plastic RNA-level regulatory architecture than is currently appreciated. Recent work further adds a biophysical dimension to this view: nuclear FGF2 has been shown to form phase-separated condensates with rDNA and associated RNAs in BMSCs, reorganizing rDNA chromatin and biasing lineage choice between osteogenic and adipogenic fates, underscoring how FGF-dependent protein–RNA condensates can influence musculoskeletal cell identity (Zhang et al., 2025a). Elucidating these mechanisms, particularly how RBPs such as IGF2BP1 and Lin28, RNA modifications such as METTL1-mediated m^{7}G on Fgfr2, and putative eRNAs at FGF loci intersect with classic miRNA/lncRNA networks, could enhance our understanding of tissue regeneration and disease, and may offer new molecular targets for therapeutic modulation of FGF signaling in musculoskeletal disorders.

Table 4. Other emerging post-transcriptional mechanisms regulating FGF signaling in musculoskeletal systems.

Regulatory element	FGF target(s)	Tissue / cell type	Species	Mechanism affected	References
METTL1- m^{7}G	Fgfr2	Limb mesenchymal stem cells (bone/cartilage progenitors)	Mouse	m^{7}G stabilizes Fgfr2; Osteo/chondrogenesis & limb growth	Li et al., 2025
METTL3- m^{6}A on pri-miR-7212-5p	FGFR3 (via miR-7212-5p)	Osteoblasts; femoral fracture callus	Mouse	↑miR-7212-5p, ↓FGFR3, restrains osteoblast differentiation & fracture healing	Mi et al., 2020
IGF2BP1 m^{6}A reader complex	FGFR1	Primary skeletal myoblasts	Mouse	Binds m^{6}A-FGFR1, ↑mRNA stability/translation, sustains ERK signaling, delays differentiation	Liu et al., 2024
ALKBH5–YTHDF2 m^{6}A axis	FGF21	Bone marrow MSCs (diabetic bone model)	Human	ALKBH5 stabilizes FGF21; YTHDF2 promotes decay of m^{6}A-FGF21, shifting osteogenic program	Wang et al., 2025
IRES + p54nrb/hnRNPM	FGF1	C2C12 myoblasts during differentiation	Mouse	IRES drives cap-independent FGF1 translation in myoblasts, promoting myotube formation	Ainaoui et al., 2015
IRES / RNA G-quadruplex	FGF2 (HMW & LMW isoforms)	Mammalian cells; FGF2 isoforms act in osteoblasts/BMSCs	Human / mouse	G-quadruplex-IRES controls CUG/AUG initiation and HMW:LMW FGF2 ratio, influencing bone mass	Bonnal et al., 2003; Xiao et al., 2009
circFgfr2	FGF–MAPK effector branch	Skeletal muscle satellite cells / myofibers	Mouse	Sponges miR-133, ↑MAP3K20–JNK/MAPK, supporting myogenesis & MAPK output	Yan et al., 2022

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circFgfr2	FGF–BMP osteogenic network	Dental follicle–derived osteogenic cells	Rat	Sponges miR-133, ↑BMP6, enhancing osteogenesis & intersecting with FGF–BMP crosstalk	Du et al., 2019; Pan et al., 2021
PCBP2–FGF2 ribonucleoprotein complex	FGF2	Human bone marrow MSCs (replicative aging)	Human	PCBP2 level tunes FGF2 expression and ROS–FGF2 signaling; high PCBP2/FGF2 promotes hBMSC senescence, knockdown lowers FGF2	Chen et al., 2025

Together, these findings suggest that the pathway-specific RNA regulome of FGF signaling extends well beyond the miRNA and lncRNA layers characterized in previous sections, encompassing a broader and more plastic set of regulatory inputs, whose full integration into a coherent regulatory model remains a major challenge and opportunity in the field.

7. Translational Perspectives: Tissue-Specific Regulation and Therapeutic Implications

The post-transcriptional regulation of FGF signaling in musculoskeletal tissues reveals a multifaceted system of control that varies not only across molecular mechanisms but also between tissue types (Ornitz and Marie, 2015; Xie et al., 2020; Loh et al., 2023). Bone, cartilage, muscle, and tooth each exhibit distinct transcriptomic environments in which microRNAs, long non-coding RNAs, and alternative splicing events modulate FGF ligand availability, receptor isoform usage, and downstream signaling outcomes (Li et al., 2014; Mirzamohammadi et al., 2014; Horak et al., 2016; Huynh et al., 2017). More recently, circular RNAs and epitranscriptomic marks such as m^6A and m^7G have added further layers of tissue- and lineage-specific regulation to this FGF "RNA regulome" (Su et al., 2014; Yan et al., 2022; Xu et al., 2024; Pashay Ahi, 2025). These differences are shaped by developmental timing, biomechanical inputs, injury responses, and cell-type composition (Su et al., 2014; Huynh et al., 2017). Recognizing these distinctions is essential for identifying tissue-specific regulatory vulnerabilities and guiding the design of targeted therapeutic interventions (Su et al., 2014; Ornitz and Marie, 2015; Xie et al., 2020; Loh et al., 2023).

In bone, the most extensively studied mechanisms include miRNA-mediated repression of FGF2 and FGF18 and the isoform-dependent activity of FGFR1 and FGFR2 during osteoblast differentiation (Su et al., 2014; Ornitz and Marie, 2015; Wang et al., 2017; Douglas Coffin et al., 2018; Qi et al., 2020). Yang et al. provided specific evidence for FGFR1 regulation by miR-214, reinforcing the role of miRNAs in modulating FGFR activity during osteoblast differentiation. Luciferase reporter assays confirmed FGFR1 as a direct miR-214 target, and miR-214 overexpression suppressed osteoblast differentiation and mineralization through inhibition of FGFR1-mediated FGF signaling in MSCs. This outcome is significant as it directly links miR-214 to FGFR1 repression, offering strong mechanistic support for miRNA-mediated regulation of FGF/FGFR signaling in bone (Yang et al., 2016).

Similarly, miR-16/miR-16a and miR-195 family members directly target FGF2 and FGF18 in osteogenic and periodontal ligament cells, while m^6A-dependent miR-7212-5p–FGFR3 regulation modulates osteoblast and chondrocyte differentiation as well as fracture healing (Chang et al., 2017; Wang et al., 2017; Mi et al., 2020; Qi et al., 2020). These findings establish miRNA-mediated control of FGF/FGFR signaling as a central mechanism in bone biology. Li et al., provides general support for miRNA involvement in osteoblast differentiation (Li et al., 2009), while Sun et al., offer secondary evidence of FGF2 regulation in cancer biology, together reinforcing the FGF2/FGF18 and FGFR3 regulation (Sun et al., 2015).

In muscle, regulatory emphasis has been placed on FGFR1 and FGFR4 expression in satellite cells, modulated by myomiRs such as miR-1, miR-133, and miR-206 and by FGF1/FGF2 IRES-dependent translation (Chen et al., 2005; Sweetman et al., 2006; Feng et al., 2013; Ainaoui et al., 2015;

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Pawlikowski et al., 2017). The circRNA circFgfr2 adds an additional feedback loop by sponging miR-133 to tune MAP3K20–JNK/MAPK activity during myogenesis and regeneration (Yan et al., 2022).

Cartilage-specific regulation remains less well-characterized, though miR-140, lncRNA-CIR, and FGFR3 gain-of-function or isoform changes have been associated with chondrocyte proliferation, hypertrophy, and matrix remodeling (Miyaki et al., 2010; Liu et al., 2014; Mirzamohammadi et al., 2014; Ornitz and Legeai-Mallet, 2017; Chaudhry et al., 2022).

In dental mesenchyme and epithelium, the role of FGF ligands such as FGF8 and FGF10 in cusp patterning and root elongation has been demonstrated (Kettunen and Thesleff; Li et al., 2014; Du et al., 2018). Early work on lncRNAs such as H19 and MALAT1, as well as circFgfr2 in dental follicle–derived cells, suggests that post-transcriptional control of FGF-coupled pathways in tooth-supporting tissues is likely more extensive than currently appreciated (Li et al., 2019b; Sufianov et al., 2023; Xu et al., 2024).

Therapeutically, these insights raise the possibility of live cell-specific detection and modulation of FGF signaling at the RNA level to correct dysregulated tissue growth or repair (Douglas Coffin et al., 2018; Xie et al., 2020; Zhu et al., 2022; Loh et al., 2023; Ahi and Khorshid, 2025; Mancino et al., 2025; Pashay Ahi, 2025). In skeletal diseases characterized by excessive FGF activity, such as craniosynostosis or FGFR3-related chondrodysplasias, RNA-based ligands and oligonucleotides that blunt FGF signaling are under active development. A prominent example is the anti-FGF2 RNA aptamer RBM-007 (umedaptanib pegol), which neutralizes FGF2, reduces aberrant FGFR3 activation in growth plate chondrocytes, and restores bone growth in achondroplasia mouse models and human iPSC-derived cartilage xenografts (Kimura et al., 2021; Nakamura, 2021).

Aptamer engineering and delivery strategies specific for bone disease are being explored as a route to translate such FGF-directed RNA agents into the clinic (Liu et al., 2023). Conversely, in disorders marked by insufficient FGF expression or impaired FGF responsiveness, such as osteoporosis or disuse-associated bone loss and muscle wasting, stabilizing FGF mRNA transcripts through RNA-binding protein modulation or inhibition of degrading miRNAs may enhance regenerative capacity (Douglas Coffin et al., 2018; Zhu et al., 2022; Frank et al., 2025; Pashay Ahi, 2025; Khorshid and Ahi, 2026). Proof-of-concept studies using miRNA mimics or antagomirs delivered in bone-targeted scaffolds or nanoparticles, such as miRNA modulators to accelerate fracture healing and improve bone mass, illustrate how RNA-based control of growth factor networks (including FGF, BMP, and Wnt) can be harnessed to enhance skeletal repair (Douglas Coffin et al., 2018; Zhu et al., 2022; Ahi and Khorshid, 2025; Frank et al., 2025).

Non-coding RNAs also offer potential as biomarkers for musculoskeletal conditions (Mirzamohammadi et al., 2014; Horak et al., 2016; Huynh et al., 2017; Siracusa et al., 2018; Frank et al., 2025). Circulating miRNAs targeting FGF pathway components or their downstream effectors have been detected in serum during fracture healing and bone loss, and several groups have proposed miRNA signatures that distinguish normal from delayed or non-union healing (Zhu et al., 2022; Frank et al., 2025). In parallel, muscle-enriched myomiRs such as miR-1, miR-133, and miR-206 increase in circulation after acute muscle injury or exercise and are being developed as biomarkers of muscle damage and disease progression, with potential to report on FGF-dependent satellite-cell activation and myofiber turnover (Chen et al., 2005; Siracusa et al., 2018).

LncRNAs, due to their tissue specificity and longer half-life, could be harnessed to monitor disease progression or response to RNA-based therapies, as suggested by emerging data on MALAT1, H19, and NEAT1 in osteoporotic bone and osteoarthritic cartilage (Huynh et al., 2017; Li et al., 2019b; Sufianov et al., 2023).

In agricultural and veterinary contexts, FGF-related loci and their RNA regulators have been implicated in growth and carcass traits in poultry and livestock, indicating cross-species relevance for applied science and breeding strategies, even though FGF-specific post-transcriptional mechanisms remain less systematically explored in these species (Xie et al., 2020; Zhu et al., 2022).

The therapeutic translation of these mechanisms, however, is not without challenges. Delivery of RNA-based agents to dense or avascular musculoskeletal tissues remains technically complex, and

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unintended off-target effects on global FGF signaling must be carefully managed (Elangovan et al., 2020; Paunovska et al., 2022; Zhu et al., 2022; Sparmann and Vogel, 2023; Mancino et al., 2025). For bone and cartilage, limited vascularity and dense extracellular matrix impede diffusion of oligonucleotides and nanoparticles, necessitating localized delivery (e.g., intra-articular injections, bone-targeting peptides, calcium-based or bisphosphonate-modified nanocarriers) and raising questions about dosing, durability, and immunogenicity (Elangovan et al., 2020; Paunovska et al., 2022; Zhu et al., 2022).

In skeletal muscle, systemic delivery of antisense or siRNA drugs is already being deployed clinically for exon-skipping therapies, but translation to FGF-focused or myomiR-based interventions will require careful evaluation of long-term safety and potential interactions with other anabolic pathways (Sparmann and Vogel, 2023).

Furthermore, the redundancy among FGF ligands and receptors, together with extensive crosstalk with other signaling pathways, complicates single-target approaches. Combinatorial strategies that integrate upstream RNA regulators (miRNAs, lncRNAs, circRNAs, RBPs) with downstream signaling convergence nodes (e.g., MAPK, PI3K–AKT, STAT) may therefore offer greater specificity and therapeutic effectiveness (Xie et al., 2020; Zhu et al., 2022; Loh et al., 2023; Pashay Ahi, 2025).

In summary, post-transcriptional control of FGF signaling holds significant promise as both a diagnostic and therapeutic entry point in musculoskeletal biology (Ornitz and Marie, 2015; Douglas Coffin et al., 2018; Xie et al., 2020; Zhu et al., 2022; Loh et al., 2023; Mancino et al., 2025; Pashay Ahi, 2025). Understanding how RNA-based regulatory mechanisms operate in a tissue-specific manner may inform the development of interventions that restore proper signaling balance in developmental disorders, injury, and degenerative diseases (Su et al., 2014; Ornitz and Marie, 2015; Horak et al., 2016; Huynh et al., 2017).

Future work will benefit from *in vivo* functional validation of candidate RNA–FGF interactions, systematic multi-omics profiling of pathway-specific "RNA regulomes" in bone, cartilage, muscle, and tooth, and continued advances in delivery platforms, from bone-targeted nanoparticles and biomaterial scaffolds to clinically validated oligonucleotide chemistries and RNA aptamers, to facilitate the translation of FGF-directed RNA therapeutics from bench to bedside (Paunovska et al., 2022; Zhu et al., 2022; Sparmann and Vogel, 2023; Mancino et al., 2025; Pashay Ahi, 2025).

8. Conclusions

Post-transcriptional regulators of fibroblast growth factor (FGF) signaling in musculoskeletal development and regeneration, spanning miRNA-mediated repression, lncRNA-dependent nuclear organization, alternative splicing, epitranscriptomic modification, and RNA-binding protein activity, act collectively and constitute a pathway-specific RNA regulome, with an integrated activity modulating FGF signaling output in tissue- and context-dependent manner.

These mechanisms provide an additional layer of specificity, allowing cells to fine-tune FGF activity in response to developmental cues, environmental changes, and tissue damage. Across bone, cartilage, muscle, and tooth, the influence of RNA-level regulation is context-dependent and regulatory mechanisms at the pathway level appear to be conserved across vertebrate species. Functional interactions between non-coding RNAs and FGF pathway components have been observed in diverse vertebrate species, reinforcing the relevance of these findings beyond a single model organism and motivating cross-species validation as the field evolves. While many post-transcriptional modulators have been identified, the field remains in its early stages, with several regulatory axes lacking direct validation or mechanistic clarity. Importantly, the potential translational impact of these findings extends to diagnostic, therapeutic, and regenerative applications. By targeting RNA-mediated control points within the pathway specific RNA regulome, it may be possible to modulate FGF signaling with greater precision and specificity than with traditional receptor-targeted approaches. Continued research into tissue-specific RNA regulation of the FGF pathway is likely to uncover novel strategies for managing musculoskeletal disorders and

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enhancing endogenous repair mechanisms. Systematic mapping of the pathway-specific RNA regulome across musculoskeletal tissue types, disease states, and developmental windows represents both the immediate experimental priority and the conceptual foundation on which precision post-transcriptional therapeutics for skeletal and muscle disorders will ultimately be built.

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