Effect of FGF/FGFR Signal in Fluid Shear Stress and Estrogen Regulating Bone Metabolism

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Abstract

Estrogen and fluid shear stress (FSS) play an important role in bone metabolism, displaying a synergistic effect. Fibroblast growth factors (FGFs) are also of great importance in bone development before and after birth. FGFs regulate downstream signaling pathway by activating FGF receptors (FGFRs) to control the expression of bone tissue cells. This paper conducts a brief discussion of the effect of FGF/FGFR as well as fluid shear stress and estrogen in bone metabolism regulation.

Keywords: FGF; FGFR; Estrogen; Fluid shear stress; Bone metabolism

Introduction

Bone is a kind of tissue that is always in constant dynamic development. Bone metabolism depends upon balanced osteoblast osteogenesis ability and osteoclast bone resorption ability, which are subject to the influence of many factors, such as cytokines, mechanical load and hormone [1]. Estrogen can enhance osteogenesis [2], because it has the dual effect of hindering osteoclast bone resorption and promoting osteoblast osteogenesis [3,4]. Mechanical stress serves as another important factor influencing bone remodeling, for suitable mechanical stress can promote the growth of bone tissues. Cells are more sensitive to FSS than to pressure and stretch stress [5]. Flowing fluid forms FSS on the surface of bone tissue cells, such as osteocytes and osteoblasts. At present, the mechanism of FSS being turned into biochemical signal and introduced into nucleus through the surface of cytomembrane is regarded as stress transduction mechanism [6]. FGFs fall into the family of polypeptides, which control several crucial cellular processes. In bones, FGF/FGFR signals are important regulators for prenatal and postnatal bone development [7,8]. This paper mainly discusses the influence of the separate and joint effect of FGF/FGFR signals, estrogen and FSS upon bone metabolism as well as the effect of FGF/FGFR signals in FSS and estrogen regulating bone metabolism. Starting from the intracellular signal paths induced by FGF/FGFR signals, estrogen and FSS, this paper explores their interaction at molecular level, presenting a new approach for following explorations into bone regeneration in clinics and research.

Introduction of the Structures of FGF/FGFR, Estrogen and Estrogen Receptor

There are two types of FGFs, namely secretion type and intracellular type. Secretion type FGFs can be further divided into canonical type and endocrine type, in which the former contains five subfamilies, namely FGF1, FGF4, FGF7, FGF8 and FGF9, while the latter contains three members, namely FGF15/19, FGF21 and FGF23 (Table 1).

Secretion type FGFs mainly combine with FGFR as signal protein to transmit signals and activate multiple cellular pathways. Intracellular FGF is a kind of non-signal protein, mainly used as voltage-gated sodium channel and the cofactor of other molecules [9-11] (Figure 1).

| FGFR Subfamily | FGF1 Subfamily | FGF4 Subfamily | FGF7 Subfamily | FGF8 Subfamily | FGF9 Subfamily | FGF15/19 Subfamily |
|----------------|----------------|----------------|----------------|----------------|----------------|-------------------|
| FGF            | FGF1           | FGF4           | FGF3           | FGF8           | FGF9           | FGF15/19          |
| FGF2           | FGF5           | FGF7           | FGF17          | FGF16          | FGF21          |                   |
| FGF6           | FGF10          | FGF18          | FGF20          | FGF23          |                |                   |

Table 1: The subfamilies of FGF.
FGFR is a kind of tyrosine kinase receptor, and shares similar structure with other types of tyrosine kinase receptors, mainly consisting of ligand-binding domain, transmembrane domain and cytoplasmic domain [12-14]. FGFR family includes FGFR1, FGFR2, FGFR3 and FGFR4. Fgfr1-Fgfr3 generates two additional major splice variants of immunoglobulin-like domain III, referred to as IIIb and IIIc. Data is derived from receptor activation assays using BaF3 cells, L6 myoblasts or HEK293 cells transfected with individual splice variants of FGFRs or by direct binding studies [9] (Table 2).

| FGFR   | FGFR subfamily | FGF       | FGF subfamily |
|--------|----------------|-----------|---------------|
| FGFR1b | FGFR1 subfamily | FGF12     | FGF1 subfamily |
|        |                | FGF371022 | FGF7 subfamily |
| FGFR1c | FGFR1 subfamily | FGF12     | FGF1 subfamily |
|        |                | FGF456    | FGF4 subfamily |
|        |                | FGF81718  | FGF8 subfamily |
| FGFR2b | FGFR2 subfamily | FGF91620  | FGF9 subfamily |
|        |                | FGF15/19  | FGF15/19 subfamily |
| FGFR2c | FGFR2 subfamily | FGF371022 | FGF7 subfamily |
|        |                | FGF12     | FGF1 subfamily |

Table 2: Receptor specificity of canonical and endocrine FGFs. (Data is derived from receptor activation assays using BaF3 cells, L6 myoblasts or HEK293 cells transfected with individual splice variants of FGFRs or by direct binding studies [9]).

There are three important processes for FGFR activation, i.e., ligand binding, receptor ligand dimerization and intracellular phosphorylation of receptors [15]. The binding of FGF and FGFR also needs the participation of cofactors to enhance the bioactivity of FGF. Heparan sulfate (HS) and heparan sulfate proteoglycan (HSPG) are currently regarded as potent cofactors for canonical FGF signaling pathways [9,16-18]. The cofactor of endocrine FGFs is a kind of Klotho protein used to form FGF-FGFR-Klotho trimer [19,20] (Figure 1).

Estrogen is an important type of endogenous hormones in human physiology, including estrone (E), 17-estriol (E1), estriol (E3), etc. They are mainly produced in ovary and testis and scattered in all cells [21]. Estrogen features extremely important biological functions, including its significant regulatory effect on the metabolism of multiple organs like reproductive system, bone and cartilage system, and cardiocerebral vascular system [21,22].

There are two subtypes of estrogen receptor (ER), namely ERα and ERβ, both of which fall into nuclear receptor hormone superfamily receptor and share common structural framework, i.e., N terminal (I region), DNA binding region (II region) and C terminal ligand binding region (III region) [23-27]. Canonical ER pathway is the binding between estrogen and ER, inducing conformational changes of receptors and ultimately leading to homodimerization or heterodimerization (ERα-ERβ, ERβ-ERβ or ERα-ERβ). The
homodimerization or heterodimerization generated are further to be transferred to nucleus to make receptor and chromatin in high affinity combined, thereby regulating the transcription of target genes [28-30] (Figure 2).

There is ER expression in many cells, mainly distributed in uterus, ovary, mammary gland, bone tissue, urinary organs, neurocyte and immunocyte, liver and fat, etc. [23]. ER activation is mainly related to phosphorylation [31], in which there are many types of enzyme involved, including tyrosine kinase (TK), casin kinase (CK), etc. [32]. In addition, other signal systems like commonly-seen cell phosphorylases (PKA, PKC), intracellular signals like polypeptide growth factor, kinase, neurotransmitter and regulatory factor can also realize ER phosphorylation [31]. ER serves as an operation node for receptor in GSS-induced osteogenesis [57]. Lrp5/Wnt/b-catenin pathway and IGF-ER signal were cross-linked through GSK-3b [61-65]. Many studies have demonstrated the importance of estrogen receptor in GSS-induced osteogenesis [57,61-65]. The increased number of ER could enhance stress or estrogen-related signaling pathway transduction, and all these responses could be prevented by ER antagonists ICI 182,780, hence proving that these pathways were interlinked through GSK-3b.

Estrogen and FSS Regulating Bone Metabolism

Estrogen is one type of steroids with wide biological activity that balance the osteoblast osteogenesis ability and osteoclast bone resorption ability [22]. Lack of estrogen is prone to cause postmenopausal osteoporosis (OP) [36,37]. In 1941, Albright first adopted estrogen substitution therapy to treat OP [38]. Lack of estrogen may promote the resorption of experimental periodontitis alveolar bone. Estrogen substitution therapy can effectively prevent decreased alveolar bone height and lower the risk of agomphiasis [39]. Research has demonstrated that the icaricin separated from epimedium can prevent loss of bone mass, for it can enhance the activity of ERK and JNK in MC3T3-E1 osteoblast yet without obvious influence upon P38. After estrogen receptor antagonist ICI182780 is applied, the division and mineralization abilities of MC3T3-E1 osteoblasts significantly drop, and the phosphorylation of ERK and JNK is also hindered. Therefore, it is deducted that estrogen-ER-ERK/JNK pathway can promote the division and mineralization of osteoblasts and ultimately osteogenesis [40]. Research has proved it is by estrogen-ER-ERK-Target pathway that estrogen promotes the autophagy of osteoblasts to hinder its apoptosis and ultimately facilitate osteogenesis [41].

FSS stimulated osteoblast proliferation and differentiated stress transduction mechanism involve multiple cell-dependent and independent signaling pathways, such as intracellular and extracellular Ca current [42,43], NOS-NO [44], Cox-PGI2-PGE2, PTX-Gi/o, etc. [6]. Many of them are involved activating one or more members of the MAPK family, including ERK1/2, JNK, P38 and/or interaction with integrin signaling pathway [6]. Integrin, an ECM-cell surface receptor, is connected with cytoskeleton and extracellular matrix, serving as an important mechanical transducer for FSS stimulation and being able to act as mechanoreceptors [45]. ERK1/2 can be activated through integrin/FAK pathway [46]. Research has shown that ERK5 participates in the early reaction of osteoblast against FSS and annular FSS promotes MC3T3-E1 osteoblast proliferation through ERK5/ AP-1/cyclin D1 pathway [46,47]. Zhao et al. [48] in the experiment of adding FSS into MC3T3-E1 cells obtained the conclusion that MEK5/ ERK5 pathway could regulate FSS induced osteoblast differentiation. It was reported that FSS working on human osteogenesis sample MG63 cells and MG63 cells could enhance the phosphorylation level of ERK and JNK [49]. Li et al. [50] also proved that FSS could uplift the phosphorylation level of ERK, JNK and P38. Moreover, much research found out that mechanical stimulation could enhance the expression of insulin-like growth factor (IGF), a reaction factor regulating osteogenesis with mechanical load [51,52]. Kahlert et al. [53] further proposed that IGF-ER signaling pathway needed the participation of ERK signal; ERα signal was at the upper stream and downstream of ERK and JNK [54]. There was a series of research highlighting the importance of Lrp5/Wnt/b-catenin pathway in loading osteogenesis reaction [55,56], the process of which needs ER [57-59]. Lrp5/Wnt/b-catenin pathway and IGF-ER signal were cross-linked through GSK-3b [44,60].

Many studies have demonstrated the importance of estrogen receptor in GSS-induced osteogenesis [57,61-65]. The increased number of ER could enhance stress or estrogen-related signaling pathway transduction, and all these responses could be prevented by ER antagonists ICI 182,780, hence proving that these pathways were ER mediated [61]. Research by Lee et al. [62] showed that when mechanical stress was imposed upon the ulna of mice after ERα knockout, the formation amount of was only 1/3 of the newborn mice at the same litter where ERα existed; and the osteoblast extracted from mice after ERα knockout had a weak response to mechanical stress [57]. Damien et al. [63] pointed out that among males and females, mechanical stress could promote osteoblast proliferation through ER. If ROS 17/2.8 cell lineage is exposed to estrogen for 5 min or monocyclic dynamic strain force was imposed for 5 min, it can be observed that both ERα phosphorylation and ERK1 activation increase, which however can be hindered by MAPK inhibitor U0126 and protein kinase A (PKA) inhibitor PKI. That is to say, osteocyte can...
respond to estrogen or FSS through Estrogen/FSS-ERα-ERK1 pathways [64,65].

Joldersma et al. [66] found that estrogen could enhance the generation of E2 (PGE2) in postmenopausal non-osteoporosis female osteoblasts induced by FSS. Bakker et al. [67] demonstrated the adhesion of estrogen and FSS against the PGE2 and NO in osteocytes among females with osteoporosis (age 62-90). Yeh et al. [68] proved that estrogen could enhance FSS, strengthening the phosphorylation of human osteogenesis sample cells (MG63 cells), primary osteoblasts ERK and P38 and increasing the expression of c-fos and Cox-2. This process was realized by estrogen receptor increasing β1 integrin. These results suggest that estrogen may influence the response function of osteocytes to FSS and there is a synergistic effect between estrogen and FSS in osteogenesis. Li et al. [50] discovered that estrogen and FSS both had the effect of promoting osteoblast proliferation differentiation and their synergistic effect superseded the independent effect of individual, so they had the synergistic effect (Figure 3).

**Figure 3:** Cross-linking of FSS, estrogen, FGF-FGFR, Wnt-β-catenin signaling pathways. (1: FGF/FGFR, Estrogen+ER, FSS+ER can directly induce the activation of Ras/Raf-MAPK-ERK1/2 pathway [40,41,46,68,70,71]. 2: The activation of IGF-1+IGF-IR+ER induced downstream factors also needs the participation of ERK1/2 signals [51,53]. 3: The effect of ERα and LIF/LEF-1R can also be realized by down-regulating the GSKbeta activity through PI3K-AKT [44,51]. 4: FGF/FGFR signal can be transduced to frs2-grb2-gab1-P13K-AKT signal cascade, and down-regulate GSK3beta activity under the condition of being accompanied by Ser 9 phosphorylation [60]. 5: Wnt signal transduces through frizzled receptor and lrp5/6 co-receptor to down-regulate the activity of GSK-β(GSK3B) [60]. 6: ERK1/2 and P13K-AKT signals at the downstream of FGF/FGFR also participate in the release of NO [9,44]. 1.2: Realize expression by E-ER binding target gene after entering nucleus. 3,4,5: Influence the β-catenin-ER nuclear accumulation through regulating the activity of β-catenin and ultimately regulate the expression of target gene [28-30,51,58-60,65]).

**FGF/FGFR Signal Regulating Bone Metabolism**

FGF/FGFR signaling pathways have an important effect upon regulating osteogenesis. Much research has proved that FGF/FGFR can promote the division and differentiation of osteoblasts. There are three important processes in FGFR activation, namely ligand binding, receptor ligand dimerization and receptor intracellular domain phosphorylation [13,67]. FGF/FGFR signaling pathways start from the extracellular binding of FGF and FGFR and take HS/HSPGs/Klotho as the co-factor to form FGF-HS/HSPGs/Klotho-FGFR 1:1:1 compound; and its dimerization induces juxtaposition and activation of tyrosine kinase structural domain inside FGFR (TK1, TK2) and ultimately activates four types of main intracellular signaling pathways, including RAS-MAPK [12,69-71], PI3K-AKT [70,72,73], PLCγ [69] and STAT [74]. The most familiar MAPKs are ERK1/2, JNK, P38, which can be divided into different subfamilies according to genetic coding, namely ERK (1/2), JNK (1/3) and P38 (α, β, γ and δ) [75-78]. After activation, FRS2α binds with cytomembrane anchor adaptor protein GRB2 and tyrosine phosphatase SHP2 and then GRB2 collects SOS to activate RAS-MAPK signaling pathway, and collects GAB1 to activate PI3K-AKT signaling pathway. FGF/FGFR tyrosine kinase activation promotes PLCγ phosphorylation, hence causing PI45-HEDP hydrolyzation into IP3 and DAG. IP3 can uplift the level of intracellular Ca ions while DAG can activate PKC protein kinase C [9]).

Recent data showed that FGF2 activated PKC could activate the activity of Runx2 in mesenchymal stem cells and osteoblasts [79,80]. ERK1/2 signals induced by FGF2 were found to promote the proliferation of osteoblast precursor cells and induce FGFR2 induced osteoblast differentiation [70,71]. PLC/PKC activation was also involved in FGF2 or FGFR2 activated osteoblast differentiation [79]. PI3K is another FGF mediated signal cascade reaction controlled by osteoblast cytoposis. For example, FGF or FGFR4 activated PI3K-Akt pathway promoted the proliferation of osteoblast precursor cells [81]. FGF18-FGFR1/FGFR4 mediated signaling pathways could regulate the differentiation of osteogenesis [82,83]. Delayed ossification has been described in FGF18-deficient mice [84], suggesting that FGF18 controls osteogenesis. Recent data indicated that FGF18 played an important role in osteogenesis of mice [85]. The mice mesenchymal stem cells osteoblast differentiation mediated by FGF18 and induced
by FGFR1/FGFR2 was also involved in PI3K and ERK1/2 signals [83] and the Akt activity increase caused by FGFR2 mutation could promote osteocyte differentiation [73,84,85]. FGFR23/FGFR1 signaling pathways were related to bone mass and bone mineralization [86,87].

FGFRs mutation could cause two types of skeleton diseases, namely skeletal dysplasia and craniosynostosis. FGFR1 expression went throughout the bone development and postnatal bone reconstruction, fracture healing and osteogenesis in embryo. Missense mutation of FGFR1 (P252R) could cause Pfeiffer Syndrome [88]. Mice with important fragmentary mutation of FGFR2 scarcity or FGFR2 displayed bone hyperplasia drop and bone mineral density drop. And the absence of FGFR2 in mice could lead to dysfunction of mature osteoblasts [89,90]. Research showed that activated FGFR2 mutation could promote osteoblast differentiation and ultimately cause human craniofacial disease through increasing Runx2 expression and osteogenic marker genes [91]. Through activated FGFR2 mutation, activated ERK-MAPK could increase Runx2 transcription activity and osteogenic marker gene expression [81]. Therefore, activated FGFR2 mutation could promote osteoblast differentiation of mesenchymal stem cells [80]. FGFR3 failure and FGFR3 activation both could lead to osteoporosis [92,93]. In mouse model with achondroplasia, chondrocyte specific FGFR3 activation was related to the increase of osteogenesis around cartilage, indicating partial osteogenesis increase [94], which might be indirectly mediated through BMP.

FGF/FGFR signal controlling osteogenesis involved multiple signaling pathway activation. FGF/FGFR signal and canonical Wnt/β-catenin pathway had complicated interaction. The loss of efficiency of Wnt inhibitor Axin2 could lead to craniosynostosis of mice [95,96]. Experiments of Liu et al. [97] showed that lack of Axin2 could promote β-catenin signal and ultimately cause ossification of periosteum. The interaction between Wnt and FGF signals activated Wnt signals, mesenchymal stem cell osteoblast differentiation and osteogenesis [97]. Runx2 and Sox2 also played an important role in FGF and Wnt signaling pathway crosstalk [23,98]. FGFR1, FGFR4, FGFR18 and FGFR20 were direct target factors of Wnt [97-101].

Wnt-dependent BMP signals could guide intracellular β-catenin distribution, featuring an important positive feedback regulation effect upon β-catenin [96]. FGFR signal and BMP signal, apart from the Wnt/β-catenin mediated indirect relations, also shared certain direct relations. FGFR2 could lower the resistance of BMP to noggin and thereby promote BMP signal transduction in skull development [102]. In addition, FGFR18 hindered the expression of noggin, hence increasing the BMP signals in cytoskeletons [103]. Endogenous FGF signals up-regulated BMP2 in osteoblasts and skull, and upfitted BMP2 induced ectopia osteogenesis in mice [104-106]. These studies highlighted the positive interaction of FGF and BMP signals in controlling osteogenesis.

**Interaction of FGF/FGFR Signals with FSS and Estrogen Regulating Bone Metabolism**

Li et al. [50] after imposing estrogen, FSS or two stimulation factors upon MC3T3-E1 cells, found out that there was obvious change in FGFR1 expression, suggesting that FGFR1 played an important role in regulating the process of estrogen and FSS promoting osteocyte proliferation and differentiation. Further experiments, after intervention of estrogen and FSS upon MC3T3-E1 osteoblasts, saw significant increase of FGFR1 expression. Applying FGFR1 inhibitor PD166866+estrogen+FSS and comparing with control group, the division and differentiation abilities of osteoblasts were hindered, indicating that FGFR1 played a core role in osteoblast response to estrogen and FSS. When estrogen and FSS independently or jointly worked on osteoblasts, the phosphorylation level of ERK, JNK and P38 significantly improved. After applying FGFR1 inhibitor PD166866, the phosphorylation level of ERK was hindered, i.e., FGFR1-ERK signals played a key role in osteogenesis induced by estrogen and FSS. This process was the result of the intracellular signal cascading of FGFR, estrogen and FSS. It remains to be further studied whether estrogen and FSS directly work on FGFR.

It could be obtained from the above discussions of intracellular signaling pathways induced by FGF/FGFR signals, estrogen and FSS that MAPKs-ERK1/2 signaling pathway, Wnt/β-catenin signaling pathway, PI3K-AKT signaling pathway and TGFβ-Smads-BMP signaling pathway were cross-linked pathway of the three (Figure 3).

**ERK1/2 pathway**

FGF/FGFR, Estrogen/ER and FSS+ER could directly transduce Ras/Raf-MAPK-ERK1/2 pathway activation [40,41,64,68,71,72]. FSS induced NO release [44] and IGF-1+IGF-IR+ER induced downstream factor activation also needed the participation of ERK1/2 signals [51,53].

**Wnt/β-catenin signaling pathway**

Wnt signals could conduct transduction through frizzled receptor and I rp 5/6 co-receptor to down-regulate GSK3β (GSK3B) activity. FGF/FGFR signals, after transduced to frs2-grb2-gabl-PI3K-AKT signal cascading, also down-regulated GSK3beta activity under the condition of being accompanied by Ser 9 phosphorylation [60]. ERα and LEF/LEF-1R could also down-regulate GSK3beta activity through PI3K-AKT [51,52]. GSK3beta downregulation caused β-catenin accumulation [60]. FSS could work upon the Wnt/Irp5 on cytomebrane, causing Wnt/β-catenin signaling pathway activation; but in this process β-catenin nuclear accumulation needed ERα mediation [56,65,68,107]. The activity and number of ERα changed with the level of estrogen [36], i.e., estrogen could indirectly participate in Wnt/β-catenin signaling pathways.

FGF/FGFR signal scan could promote Runx2 activity, while Runx2 could induce FGFR mutation, leading to increased expression of Sox2. The interaction between Sox2 and β-catenin hindered the activity of Wnt responsive plasmids and led to the downregulated expression of Wnt target genes [98]. And Wnt signals could also hinder Runx2 activity through P38 and ERK signals [23]. In addition, FGF genes are also the direct target genes of Wnt signals [96,99-101].

**TGFβ-Smad-BMP signaling pathway**

TGFβ-Smad-BMP signaling pathway and Wnt/β-catenin signaling pathway had a synergistic effect, so that those which could work on Wnt signals could indirectly work on TGFβ-Smad-BMP signals [96]. In addition, FGF/FGFR also had a direct effect on TGFβ-Smad-BMP signaling pathway, and Noggin had a negative feedback regulation effect on BMP signaling pathways. FGFR18 hindered the expression of noggin, hence increasing the BMP signals in cytoskeletons [102,103]. Meanwhile, Smads could also be activated by P38 and ERK signaling pathways [108] and P38 and ERK were also downstream factors of FGF/FGFR [9].
PI3K-AKT signaling pathway

PI3K-AKT pathway was one of the four canonical pathways for FGF/FGFR signals [9]. FSS worked upon cells to produce NO needed for PI3K-AKT signals and ER participation [44]. FSS-IGF-1/IGF-IR/ER [51,53] pathways and FGF/FGFR-PI3K-AKT [60] downstream could down-regulate GSK3-β (GSK3B) activity, thereby interacting with Wnt/β-catenin signaling pathways.

Based on the above, a great deal of research has demonstrated that the independent effect of FGF/FGFR, estrogen and FSS and the joint effect of estrogen and FSS play an important role in bone development. In addition, this paper also discusses at the level of molecule that MAPKs-ERK1/2 signaling pathway, Wnt/β-catenin pathway, PI3K-AKT signaling pathway and TGFβ-Smads-BMP signaling pathway are the cross-linked pathways of FGF/FGFR, estrogen and FSS. There is also research shown that FGFR1-ERK signals play a key role in FSS and estrogen induced osteogenesis. In addition, it remains to be studied whether there are other direct or indirect relations between FGF/FGFR, estrogen and FSS.

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