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Review

A review of FGF18: Its expression, signaling pathways and possible functions during embryogenesis and post-natal development

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Summary. FGF18 is a novel growth factor first reported in 1998. Current evidence suggests that FGF18 may play a prominent role in chondrogenesis and osteogenesis during skeletal development and growth. However, its function extends to many other biological processes. Although there remains much to be discovered and investigated on the functions and mechanisms of FGF18, it may play a role as a useful therapeutic target for various applications. The following review summarizes the current knowledge on FGF18 with special emphasis on its skeletal functions and highlights its potential areas for future research.

Key words: FGF18, FGF2, Chondrogenesis, Skeletal development

Background on FGFs and discovery of FGF18

Fibroblastic growth factors (FGF) are a family of polypeptides that are involved in cell growth, differentiation, morphogenesis, tissue repair, inflammation, angiogenesis, tumor growth and numerous developmental processes including embryonic and skeletal development (Canalis et al., 1991; Hu et al., 1998; Barnes et al., 1999; Liu et al., 2002; Dailey et al., 2005; Antoine et al., 2005). The significance of FGFs and their signaling pathways became evident from genetic studies which revealed that achondroplasia (ACH), the most common form of skeletal dysplasia, is caused by a point mutation in FGFR3 (Ornitz et al., 2002). Since this finding, several other human skeletal dysplasias including at least 14 congenital bone diseases were found to be caused by specific mutations in FGFR 1, 2 and 3 (Ornitz, 2005; Chen et al., 2005). There are 23 members of the FGF family (FGF1-22) in human and mice which signal by activating one or several of 4 distinct cell surface receptors (FGFR1-4) (Liu et al., 2002; Ornitz et al., 2002; Chen et al., 2005; Dailey et al., 2005). Although some of these ligands are expressed only during embryonic development such as FGF 3, 4, 8, 15, 17 and 19, several FGFs including FGF 1, 2, 9, 18 and 22 are found to be expressed throughout lifespan (Chen et al., 2005). FGF signaling is involved in both intramembranous and endochondral bone formation (Ohbayashi et al., 2002) but its function is not limited to skeletal development and can extend to numerous other cell processes (Kato et al., 1998; Kawaguchi et al., 2001).

Of the 23 FGFs so far identified, FGF 1, 2 and 18 seem to be the most important ones in bone development and repair (Hurley et al., 2001; Marie, 2003). FGF1 (also known as acidic) and FGF2 (also referred to as basic) were the first members of the FGF family to be characterized (Hu et al., 1998; Solheim, 1998).

FGF18 is a recently investigated member of the FGF family which has been shown to play a key role in skeletal growth and development (Marie, 2003; Moore et al., 2005). Shimoaka reported that the mitogenic action of FGF18 on osteoblasts and chondrocytes are as strong as FGF2 and may therefore potentially compensate for the role of FGF2 in skeletal development (Shimoaka et al., 2002). However, FGF18 expression is not limited to just skeletal development but is also involved in several other tissues (Hu et al., 1998; Ohuchi et al., 2000b; Ellsworth et al., 2002; Dichmann et al., 2003; Kawano et al., 2005). Previous observations from in-vitro and in vivo studies all demonstrate that FGF18 plays a key role in morphogenesis, angiogenesis and development of a variety of cells (Hu et al., 1998; Shimoaka et al., 2002; Ishibe et al., 2005).

FGF18 structure

Structurally, FGF18 is most similar to FGF8 and FGF17 (Hu et al., 1998; Ohbayashi et al., 1998). It contains two potential N-linked glycosylation which categorizes it as a glycoprotein (Katoh et al., 2005). The

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relevance of FGF18 being a glycoprotein on its function however remains elusive. FGF18 isolated from both mouse and humans revealed that amongst the two species, amino acid sequence is 99% identical while the nucleotide sequence is 90% conserved. The human FGF18 gene is localized to chromosome 5q34 and it encodes a 207 amino acid protein sequence (Whitmore et al., 2000; Cormier et al., 2005). The first 26 amino acids of the FGF18 protein are hydrophobic residues which may act as signal peptides for secretion. FGF1 and 2 as well as 9 lack this secretory sequence (Hu et al., 1998).

FGF18 during embryonic development

The expression of FGF18 is apparent in several areas during embryonic development. In vitro as well as in vivo studies on mice, rats and chick embryos have shown that FGF18 is expressed during the embryonic development of various organs including the midbrain (Maruoka et al., 1998; Ohuchi et al., 2000a,b; Ellsworth et al., 2003; Sato et al., 2004), lungs (Usui et al., 2004), pancreas (Dichmann et al., 2003), muscles (Maruoka et al., 1998; Ohuchi et al., 2000b) and intestinal tract (Hu et al., 1998). FGF18 was also found to be involved in cortical neuron activity (Hasegawa et al., 2004), regulating hair growth and skin maintenance in mice (Kawano et al., 2005), as well as play a role in the survival, differentiation and proliferation of adenohypophyseal progenitor cells which are involved in pituitary development (Herzog et al., 2004). FGF18 was reported to be present in cephalic and mandibular mesenchyme, and in the heart of human embryos (Cormier et al., 2005). Previous observations in embryonic development and in-vitro studies all imply that FGF18 plays a key role in morphogenesis, angiogenesis and development of a variety of cells (Hu et al., 1998; Shimoaka et al., 2002; Ishibe et al., 2005).

Role of FGF18 in skeletal development

FGF18 plays an important mediator for skeletal development. Numerous in vitro and in vivo studies have demonstrated the requirement for FGF18 during bone development (Ellsworth et al., 2002; Liu et al., 2002; Ohbayashi et al., 2002; Ozasa et al., 2005). FGF18 expression is apparent in the perichondrium during long bone development and in mesenchymal cells and osteoblasts during calvarial bone development (Marie, 2003). The role of FGF18 in skeletal development is summarized in Table 1. FGF18 is involved in both chondrogensis in the growth plate and osteogenesis in cortical and trabecular bone (Liu et al., 2002). Mice lacking FGF18 were also found to develop defects in

Table 1. Summary of the role of FGF18 in chondrogenesis and osteogenesis.

RESEARCH MODEL	CHONDROGENESIS	OSTEOGENESIS
Embryonic/Growth Plate of Mice		
FGF18 Knockout	Increased chondroctye proliferation Increased hypertrophic zones in growth plate (Liu et al. 2002)	Delayed ossification Defects in joint development Delayed calvarial suture closure (Moore et al. 2005, Ohbayashi et al.2002)
Exogenous Application	Decreased chondrocyte proliferation (Liu et al. 2002, Ohbayashi et al. 2002)	No reports found
Adult Mice		
FGF18 Knockout	N/A (premature death)	N/A (premature death)
Exogenous Application	Stimulated cell proliferation and repair of damaged cartilage (Ellsworth at al. 2002) Stimulated in rats cartilage depots including rat sernum junction, trachea, spine, articular cartilage within 2 weeks (Moore et al. 2005).	No reports found
In vitro (cell culture)		
Exogenous Application	Stimulated cell proliferation Decreased differentiation and matrix synthesis (Davidson et al. 2005)	Stimulated osteoblast and osteoclast formation Decreased differentiation and matrix synthesis (Shimoaka et al. 2002)
In vitro (embryonic cell cultures)		
Exogenous Application	Reduced chondrocyte cell size and number (Osaza et al. 2005) Decreased production of proteoglycan and type II collagen (Davidson et al. 2005)	No reports found

joint development (Liu et al., 2002; Ohbayashi et al., 2002)

Extensive studies have been conducted on FGF18 knockout mice embryos, however, it is important to note that although FGF18 knockout mice survive embryonic development, they die early during neonatal period (within 30 minutes after birth) due to cyanosis. All FGF18-/- mice expressed skeletal abnormalities including curved radius and tibia and some mice showed incomplete development of the fibula. Embryos were approximately 10-15% smaller than the wild type. The ribs of all FGF18 knockout mice were deformed causing a reduction in the thoracic cavity volume. This may have triggered respiratory failure which was the suspected reason for early death of FGF18 knockout mice (Liu et al., 2002).

FGF18 and Ooteogenesis

Studies on FGF18-/- mice embryos revealed that FGF18 is a perichondrial regulator of endochondral bone growth (Liu et al., 2002; Ohbayashi et al., 2002). FGF18 expression was observed around developing bones and in the cerebral cortex of the developing brain in 15.5 day old mouse embryos (Hu et al., 1998). Its role in osteogenesis is further confirmed by a study reporting delayed cranial suture closure and long bone ossification in FGF18 deficient mice (Ohbayashi et al., 2002; Marie, 2003).

It has been reported that mice lacking FGF18 have delayed ossification and decreased expression of the osteogenic markers, osteopontin and osteocalcin. This was not observed in FGFR3-/- mice, therefore, FGF18 most likely acts through other mediators apart from FGFR3 during osteogenesis and intramembranous bone formation (Liu et al., 2002). This is further confirmed by another study on the FGFR3 and Stat1 signaling pathways. Stat1 is an important factor during intramembranous bone formation in adult mice. Stat1-/- mice revealed higher bone mineral density as well as lower expression of FGFR3. Interestingly though, a high expression of FGF18 was observed. The study concluded that the higher bone mass observed may be attributed to FGF18. This suggests that FGF18 may be an important modulator for both endochondral and intramembranous bone formation in adult mice. The decreased expression of FGFR3 observed also implies that FGF18 may function independently of FGFR3 (Xiao et al., 2004)

FGF18 and chondrogenesis

FGF18 knockout mice embryos showed a decrease in proliferation of osteogenic mesenchymal cells. However an increase in the number of proliferating chondrocytes was observed (Ohbayashi et al., 2002). Therefore, during embryonic development, FGF18 most likely positively promotes osteogenesis and negatively controls chondrogenesis (Liu et al., 2002; Ohbayashi et al., 2002). Inhibition of chondrocyte proliferation and differentiation by FGF18 stimulation in embryos has been previously reported (Kapadia et al., 2005; Ozasa et al., 2005). FGF18-/- mice had enlarged growth plates due to expanded proliferating and hypertophic chondrocyte regions as well an expanded domain of type X collagen (Liu et al., 2002). However, the overall long bone length remained nearly normal even though the height of the distal femoral proliferating zone was increased. Although the size of the hypertrophic zone is modulated by the rate of chondrocyte differentiation and apoptosis, in this study, apoptosis was not the cause of hypertrophic zone elongation. Organ cultures of fetal mouse tibias that were treated with FGF18 showed a decrease in the total length of tibial explants. Similarly, a reduction in cell size and number of hypertrophic chondrocytes was observed following treatment with FGF18 (Ozasa et al., 2005).

Interestingly, on the contrary, FGF18 has been shown to have positive effects on chondrocytes in other cartilaginous tissues apart from the growth plate (Moore et al., 2005). Its localization in the periosteum during embryonic development suggests that it may promote cartilage repair by enhancing the differentiation of pre chondrogenic cells to cartilage producing chondrocytes (Davidson et al., 2005). Ellsworth reported that the adenovirus mediated transfer of FGF18 to mice pinnae stimulated cell proliferation and resulted in increased number of chondrocytes and expression of proteoglycans as well as type II collagen (Ellsworth et al., 2002). The study concluded that FGF18 could potentially promote the repair of damaged cartilages (Ellsworth et al., 2002) and it has recently been shown that intra articular injection of FGF18 can stimulate the repair of damaged cartilage in a rat model of osteoarthirits (Moore et al., 2005). Interestingly, the latter study reported that the anabolic effect of FGF18 in chondrocyte proliferation may be a specific outcome of tissue injury and is enhanced by additional growth factors and cytokines that are expressed post injury (Moore et al., 2005).

In another study it was found that FGF18 can enhance BMP function and stimulate chondrogenesis in earlier stages of cartilage formation by suppressing noggin expression (Reinhold et al., 2004). Noggin is an extracellular binding protein that inhibits the function of BMP. We have previously shown in our laboratory that the expression of noggin is upregulated in a rabbit model of distraction osteogenesis following local application of exogenous BMP7. Therefore, reducing noggin may promote BMP function and lead to accelerated bone formation. Thus, FGF18 can potentially be used for blocking noggin as treatment modality to increase or accelerate bone formation in DO.

FGF18 and FGF2

Extensive research has been conducted on FGF2 (or basic) which is known for its significance in embryonic development (Dailey et al., 2005) as well as its

involvement in modulating bone and cartilage functions (Shimoaka et al., 2002). FGF2 was first isolated from growth plate chondrocytes and was subsequently observed in periosteal cells and osteoblasts (Hurley et al., 1999; Sabbieti et al., 1999; Montero et al., 2000). Several studies reported the potential therapeutic roles of FGF2 which include increasing bone volume in segmental bone defects in rabbits (Kato et al., 1998), accelerating fracture healing (Radomsky et al., 1998; Radomsky et al., 1999; Kawaguchi et al., 2001)and enhancing bone ingrowth from bone implants (Schnettler et al., 2003). However, disruption in the FGF2 gene in mice revealed only a mild decrease in ostebolast replication and no defects in chondrogenesis were observed post targeted deletion of FGF2 (Montero et al., 2000). Although these studies reported FGF2 deficient mice to result in moderate abnormalities in bone and cartilage development, FGF18 deficient mice revealed severe developmental delays in ossification and in long bone formation (Liu et al., 2002; Shimoaka et al., 2002). Therefore, mice lacking FGF18 were associated with defects in chondrogenesis and osteogenesis (Ohbayashi et al., 2002). Shimoaka reported that the mitogenic action of FGF18 on osteoblasts and chondrocytes are as strong as FGF2 (Shimoaka et al., 2002) and may be more specific to bone and cartilage cells. It is therefore suggested that FGF18 may potentially compensate for the role of FGF2 in skeletal development and formation, however the role of FGF18 cannot be replaced by FGF2 (Shimoaka et al., 2002).

Mechanism of action

FGF18 and receptors

The function of FGFs is dependent on the spatial and temporal expression of FGF receptors (Marie, 2003). Since there are 4 known FGF receptors, receptor to ligand binding is not unique and one receptor can be activated by several FGFs (Dailey et al., 2005; L'Hote et al., 2005; Minina et al., 2005). FGF signaling is transmited via tyrosine phosphorylation mediated by FGFRs and other intermediate molecules (Chen et al., 2005). The binding of FGF to its receptors requires the presence of heparin sulfate proteolglycans (HSPG) (Dailey et al., 2005). HSPG is a structurally complex glycosaminoglycan related to heparin which can functions to either activate or inhibit different FGFs. (Turnbull et al., 1992; Hu et al., 1998). FGFs, FGF receptors and HSPG form a trimolecular complex on the plasma membrane which is essential for FGFR activation and signaling (Schlessinger et al., 2000; Ibrahimi et al., 2004; Ornitz, 2005). However, one study found that the addition of heparin to cultures did not appear to affect the mitogenic effect of FGF18 on osteoblasts (Shimoaka et al., 2002). FGFRs contain a hydrophobic leader sequence, three immunoglobulin (Ig) like domains, an acidic box, a transmembrane domain and a tyrosine kinase domain. FGFR 1,2 and 3 have two major isoforms, referred to as IIIb and IIIc, which form through alternative splicing (Chen et al., 2005). It has been reported that FGF18 binds with high affinity to FGFR3 and modestly with FGFR2 (Ohbayashi et al., 2002). FGF18 activates the IIIc splice variants of FGFR2 and FGFR3 which are positive regulators of bone formation (Eswarakumar et al., 2002; Moore et al., 2005).

In comparison to FGF1 and FGF2, FGF18 has a greater receptor selectivity (Xu et al., 2000; Ellsworth et al., 2002; Ellsworth et al., 2003). Several studies imply that FGF18 is a ligand for FGFR3 (Ellsworth et al., 2002, 2005; Ornitz et al., 2002; Xiao et al., 2004; Barnard et al., 2005; Davidson et al., 2005). FGF18 also interacts with FGFR1 in the prehypertrophic and hypertrophic zones (Ornitz, 2005). In developing bone, FGFR1 expression is found in prehypertrophic and hypertrophic chondroctyes whereas FGFR3 is expressed in proliferating chondroctyes (Barnard et al., 2005; Minina et al., 2005). The different spatial expression suggests that FGFR3 is involved in regulating chondrocyte proliferation and FGFR1 in cell survival, differentiation and apoptosis (Barnard et al., 2005). The activation of FGFR3 has in fact been reported to inhibit the proliferation and differentiation of growth plate chondroctyes (Naski et al., 1998b). The interaction of FGF18 with FGFR3 further confirms studies that indicate FGF18 positively regulates osteogenesis and negatively regulates chondrogenesis. Previous studies indicated that FGF18 acts on chondrocytes via FGFR3 (Ohbayashi et al., 2002). Both FGFR3 and FGF18 knockout mice reveal the same phenotype of long bones during embryonic development. The length of the long bone however is considerably smaller in FGF18-/- mice in comparison to the wildtype than for FGFR3-/- mice. This difference implies that other signaling pathways such as FGF18s interaction with FGFR2 may be involved in osteogenesis of developing long bone (Ohbayashi et al., 2002; Marie, 2003).

FGF18 and other proteins

Cell response to FGF signaling is partially mediated by indirect activation or repression of other signaling pathways (Ornitz et al., 2002; Barnard et al., 2005; Dailey et al., 2005; Mukherjee et al., 2005). Fig. 1 illustrates possible signaling pathways of FGF18 in the growth plate during chondrogenesis. FGFs are known to upregulate TGFB, IGF-I and VEGF as well as interact with hedgehog and BMP signaling pathways (Marie, 2003; Dailey et al., 2005; Ornitz, 2005). Ihh signaling is involved in endochondral skeletal development including the proliferation of chondrocytes and development of osteoblasts (Hilton et al., 2005). Ihh modulates cartilage development by regulating PTHrP (parathyroid hormone related protein) and interacts with the patched and smoothened receptors (Kobayashi et al., 2005). It has been reported that FGFR3 negatively regulates chondrocyte proliferation and differentiation,

in part, by regulating the expression of the IHH/PTHrP and BMP pathways in the developing growth plate (Naski et al., 1998a; Minina et al., 2002; Dailey et al., 2003; Kronenberg, 2003).

The expression of Ihh, Patched and BMP4 is decreased in mice overexpressing FGFR3 and increased in mice lacking FGFR3 (Ornitz, 2005). FGF18 knockout mice show similar results where Ihh and Patched expression is increased which supports the theory that FGF18 is a physiological ligand for FGFR3 (Liu et al., 2002). One study revealed that in the growth plate of mice lacking FGF18, the expression of the receptor patched was significantly increased, however in the perichondrium and the interface between cartilage and bone, no change in patched expression was observed. Therefore, FGF18 may in part regulate chondrogenesis by inhibiting IHH signaling in the prehypertrophic chondrocytes (Liu et al., 2002). However, FGF18-/- mice display other additional growth complications including delayed ossification. This may be attributed to FGF18s role in modulating osteoblasts (Ohbayashi et al., 2002; Liu et al., 2002; Dailey et al., 2003; Ornitz, 2005).

The molecular mechanism by which FGF18 controls osteogenesis is still under investigation. It has been reported that the osteogenic markers osteopontin (Op) and osteocalcin (Oc) are decreased in FGF18-/- mice (Liu et al., 2002). The expression of Cbfa1, an early osteogenic marker, did not vary in the perichondrium, however was significantly reduced in the trabecular bone. The results suggested that FGF18 may be involved in the process of osteoblasts maturation and proliferation or function to modulate the transfer of osteoblasts to the trabecular region (Ohbayashi et al., 2002; Liu et al., 2002). FGF18 knockout mice did not show any changes in the expression of VEGF (Liu et al., 2002).

Signal transduction of FGF18

Studies on FGF18 induced phosphorylation of various proteins in cell culture revealed that FGF18

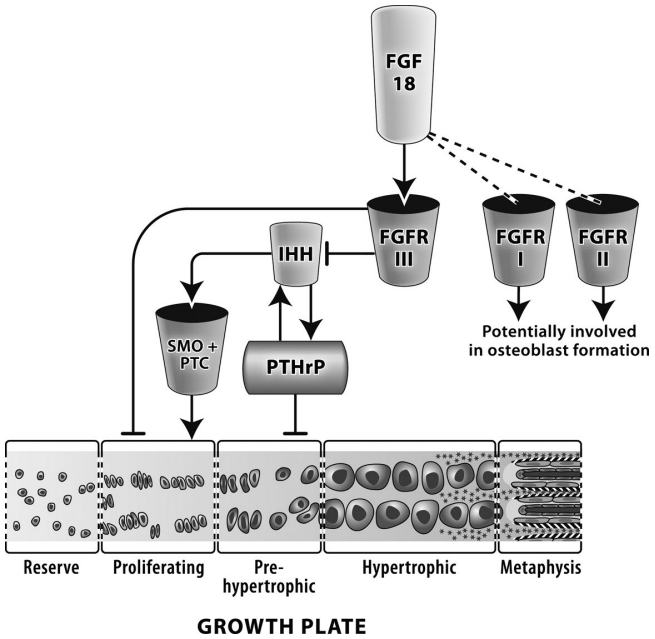

Fig. 1. Regulation of chondrocyte proliferation and differentiation in the growth plate. FGF18 interacts with FGFR3 to directly regulate chondrogenesis. FGF18 indirectly modulates chondrogenesis by interacting and inhibiting the hedgehog signaling pathway. IHH functions via a negative feedback mechanism with PTHrP and signals using the smoothened (Smo) and patched (Ptc) receptors for regulating chondrocyte proliferation. FGF18 may also interact with FGFR1 (in the hypertrophic zone of chondrocytes) and FGFR2 (the perichondrium and trabecular bone).

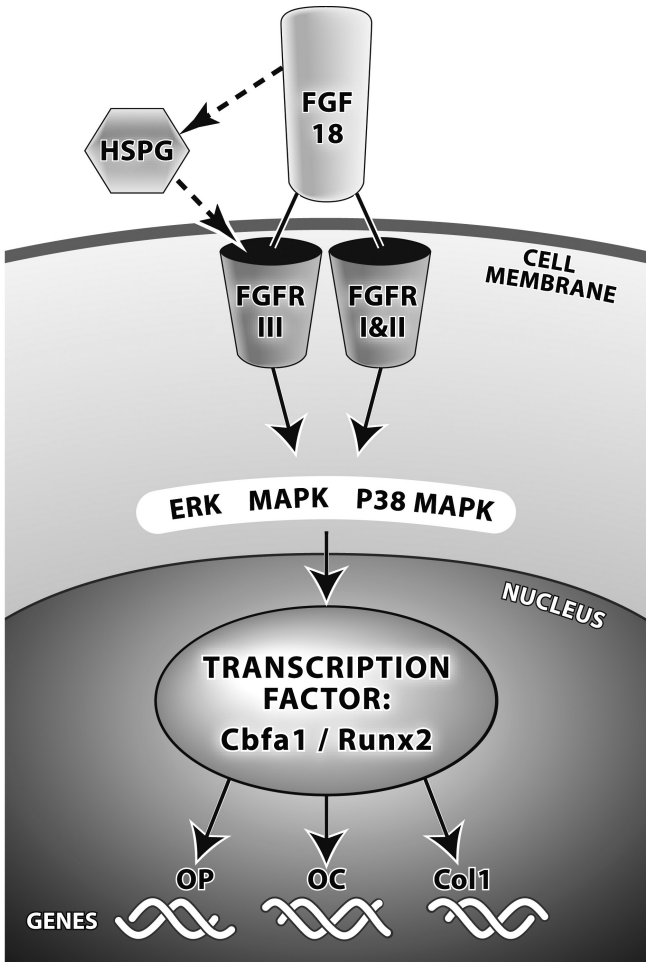

Fig. 2. FGF18 signaling pathway in regulating osteoblasts and osteoclasts. FGF18 binds with receptors FGFR3 (as well as FGFR 1 and 2). Receptor dimerization activates the MAP kinases and ERKs (extracellular signal-regulated kinases). The activation triggers the expression of transcription factors Runx2 (also known as Cbfa1) which leads to the downstream expression of the osteoblast differentiation genes, osteopontin (Op), Osteocalcin (Oc) and Collagen 1 (Col1).

stimulates osteoblast proliferation via ERK activation and stimulates osteoclasts via RANKL and cyclooxygenase-2. ERK and p38 MAPK activation was also involved in FGF18 mediated stimulation of chondroctyes (Shimoaka et al., 2002). Fig. 2 summarized the current knowledge on the mechanism of action of FGF18 druing osteogenesis

The role of FGF18 in endochondral bone development has also been suggested to be mediated by glycogen synthase kinase 3 (GSK3). GSK3 regulates developmental pathways including the Wnt and hedgehog signaling and is essential for endochondral bone formation. The repression of GSK3 was found to induce FGF18 expression which in turn reduced chondrocyte and osteoblast differentiation in mouse embryonic cultures. The study suggested that FGF18 expression is controlled by GSK3 via upregulation of B-catenin (Kapadia et al., 2005).

Non-Skeletal Functions of FGF18

Digestive System

FGF18 is found in a variety of cell types and its function is not limited to just skeletal development. The biological effects of recombinant murine FGF18 was investigated by injection into normal mice and by using transgenic mice overexpressing FGF18 (Hu et al., 1998). FGF18 was found to be a pleiotropic growth factor which stimulated the proliferation of numerous mesenchymal and epithelial cells and tissues including the lungs, kidneys, heart, testes, spleen, skeletal muscles and the brain. Within a week of FGF18 administration, histological results showed the liver and small intestine to have high proliferation as well as significant weight gains. Ectopic overexpression of FGF18 in transgenic mice also showed similar results in the liver but not the small intestine. The study concluded that FGF18 is a potent mitogen for a wide variety of cells and seem to play a significant role in the liver and small intestine (Hu et al., 1998). Expression of FGF18 is also evident in embryonic pancreas, however its role in the pancreas is not yet understood (Dichmann et al., 2003). The relevance of FGF18 balance in the digestive system is further highlighted by Shimokawa who reports that elevated expression of FGF18 may result in colorectal tumorigenesis (Shimokawa et al., 2003)

Respiratory system

FGF18 is also abundantly expressed in embryonic and postnatal lungs (Hu et al., 1998; Whitsett et al., 2002; Usui et al., 2004). Although, FGF9 and FGF10 are known to be crucial FGFs for embryonic lung

Table 2. Summary of overall FGF18 research and functions in biological processess.

ORGAN	MODELS STUDIED	OBSERVATIONS	FUNCTION	REFERENCES
Midbrain	Embryonic, Mice, Embryonic chicks, Adult rats	Expression in midbrain and cerebellar region embryos and adults	Involved in organizing midbrain during development Stimulates glial cells. Improved recovery post cerebral ischemia	Ellsworth, Hoshikawa, Maruka, Ohuchi, Sako.
Lungs	Embryonic FGF18 knockout mice	Reduced cell proliferation and alveolar space Overexpression of FGF18. Enlargement of bronchial cartilage	Involved in lung alveolar development during late embryonic development	Moore, Usui, Whitest.
Skin	Adult mice, in vitro cultures	Hair growth observed post subcutaneous administration. Stimulated DNA synthesis in human dermal fibroblasts, dermal papilla cells and endothelial cells	Involved in regulating hair growth and skin maintenance	Kawani
Smooth Muscles	Embryonic Mice and Chicks	Expression observed in the developing limb bud	Suggested role in muscle and tendon development	Mauoka, Ohuchi.
Pancreas	Embryonic Mice	Expression observed in the pancreas	undetermined	Dichman
Bone	Embryonic Chicks, Embryonic FGF18 knockout mice, Adult mice, in vitro cultures	Thicker humerus, distorted radius and ulna reduced post FGF18 implantation in chicks Knockout mice embryos result in increased cell chondrocytes, and decreased osteogenic cell proliferation. Application of FGF18 can have postitive effects on chondrogenesis in adult mice and cell cultures	Modulates osteoblast and chondrocyte differentiation during skeletal development and bone formation. May promote repair of damaged cartilages	Cormier, Ellsworth, Hajihusseini, Liu, Marie, Moore, Ohbayashi, Ohuchi.
Liver and Intestine	Embryonic and Adult Mice, In vitro cultures	Injection of FGF18 resulted in higher proliferation in the liver and small intestine	FGF18 may be a pleiotropic growth factor whose main target are the liver and small intestine	Hu

development, FGF18 seems to play a key role in the later embryonic lung development stages. FGF18 knockout mice showed reduced alveolar space, thicker interstitial mesenchymal compartments and many embedded capillaries. Cell proliferation was reduced but the expression marker gene for lung epithelial cells was not impaired. Overexpressing FGF18 in developing lungs resulted in increased size of conducting airways and diminished number of peripheral lung tubules. The study concluded that FGF18 plays a role in lung alveolar development during late embryonic lung development stages but not in lung branching morphogenesis. FGF18 also functions distinctly from FGF10 and 9 which are crucial primarily during the earlier stages of development and which signal via FGFR2b. FGF18, in this context, may be mediated by activating FGFR2c. (Ohbayashi et al., 2002; Whitsett et al., 2002; Usui et al., 2004).

Brain and midbrain

FGF18 is expressed in the mid brain and cerebellar region during development and it also functions to stimulate glial cells (Maruoka et al., 1998; Ohuchi et al., 2000a,b; Hoshikawa et al., 2002; Sato et al., 2004). Although FGF18 mutant mice results in no abnormal phenotype in the midbrain or cerebellum, it is involved in organizing the midbrain by collaborating with other growth factors (Xu et al., 2000; Ornitz et al., 2002; Ellsworth et al., 2003; Sato et al., 2004) Ellsworth reported that FGF18 is expressed within brain tissues both during development and adulthood (Maruoka et al., 1998; Ellsworth et al., 2003; Sato et al., 2004). In a study of cerebral ischemia in rats, infusion of FGF18 within 15 minutes post onset of ischemia was found to increase cerebral blood flow, reduce infarct volumes and improve behaviour in terms of memory and motor skills. FGF18 seemed to be more efficient than FGF2. The study concluded that FGF18 is a potent tissue protectant for short term cerebral ischemia in a rat model (Ellsworth et al., 2003, 2004).

FGF18s role in the brain was also investigated in a study comparing the expression profiles of FGF8 and FGF18 in the brain and limb development in chick embryos. It has been found that both growth factors are closely associated. Ectopic application of FGF18 beads in limb mesenchyme inhibits bone growth and reduces specific skeletal components. FGF18 expression is induced in the chick brain in response to FGF8 (Ohuchi et al., 2000b). FGF18 expression was found in the anterior neural fold, branchial arches, and domains associated with gastrulation. FGF18 is also involved in specifying left-right asymmetry (Ohuchi et al., 2000a).

Conclusion

FGF18 is a recently investigated member of the FGF family. It has a wide variety of expression and is involved in many cellular processes. However, most research to date revealed that it is a significant growth factor in skeletal growth and development. FGF18 may therefore potentially have various therapeutic uses. However, further research needs to be conducted to define its specific functions and mechanisms of action.

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