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The FGF Family in Humans, Mice, and Zebrafish: Development, Physiology, and Pathophysiology

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1. Introduction

In vertebrates, various signaling pathways are activated in a highly coordinated manner to ensure proper development and morphogenesis. Secreted signaling molecules such as FGFs (Fibroblast growth factors), BMPs (Bone morphogenetic factors), WNTs (Wingless/int), and Hedgehogs play crucial roles in development and morphogenesis by acting over variable distances to influence intracellular signaling events in neighboring cells. FGFs are polypeptide growth factors with diverse biological functions. The human FGF family comprises twenty-two members. The mouse and zebrafish are widely used vertebrate models for studying gene function *in vivo*. The mouse and zebrafish FGF families comprise twenty-two and twenty-eight members, respectively. These FGFs can be classified as paracrine, endocrine, and intracrine FGFs by their mechanisms of action (Itoh & Ornitz, 2008). Paracrine FGFs (canonical FGFs) mediate biological responses by binding to and activating cell surface tyrosine kinase FGFRs. They act as local paracrine signaling molecules and function in multiple developmental processes including differentiation, cell proliferation, and migration (Itoh & Ornitz, 2008; Beenken & Mohammadi, 2009). Endocrine FGFs are thought to mediate biological responses in an FGFR-dependent manner. However, they function over long distances as endocrine hormones (Kharitonenkov, 2009; Itoh, 2010). In contrast, intracrine FGFs act as FGFR-independent intracellular molecules that regulate the function of voltage-gated sodium channels (Goldfarb et al., 2007; Laezza et al., 2009).
Targeted mutagenesis of *Fgf* genes in mice has elucidated their functions in development and metabolism. Studies with zebrafish *Fgf* mutant and knockdown embryos also have revealed their functions in development. In addition, evidence for the involvement of FGF signaling in hereditary, paraneoplastic, and metabolic diseases has also accumulated. FGF signaling disorders contribute to pathological conditions. In this article, we provide a succinct review of the FGF family in humans, mice, and zebrafish and their developmental physiological and pathophysiological roles.

2. The human/mouse FGF family

FGF1 and FGF2 are prototypic FGFs originally isolated from the brain and pituitary as mitogens for cultured fibroblasts (Gospodarowicz, 1975; Gospodarowicz, et al., 1978). New

FGF proteins have since been isolated as growth factors for cultured cells or been identified as oncogene products. In addition, new *Fgf* genes have been identified by homology-based PCR/DNA database searching and as genes responsible for hereditary diseases or cancer (Itoh & Ornitz, 2008; Beenken & Mohammadi, 2009; Itoh, 2007; Krejci et al., 2009; Turner & Grose, 2010). The human/mouse *Fgf* family comprises twenty-two members, *Fgf1*-*Fgf*23. No other *Fgf* genes have been identified in the human/mouse genome.

Human/mouse FGFs are proteins of ~150-300 amino acids and have a conserved core of ~120-amino acids with ~30-60% identity. *Fgf15* has not been identified in humans. *Fgf19* has not been identified in mice. *Fgf15* and *Fgf19* are likely to be orthologous genes in vertebrates. Except for rodents, the orthologs are named *Fgf19* in vertebrates (Itoh & Ornitz, 2004; Itoh & Ornitz, 2008). In this review, we refer to these genes as *Fgf15/19*. Phylogenetic analysis indicates potential evolutionary relationships in the gene family. However, this alone is not sufficient to determine the relationships. Analyzing gene loci on chromosomes gives a more precise indication of the evolutionary relationships in a gene family. The gene location analysis of the human/mouse *Fgf* family has identified seven subfamilies; *Fgf/1/2/5*, *Fgf3/4/6*, *Fgf7/10/22*, *Fgf8/17/18*, *Fgf9/16/20*, *Fgf11/12/13/14*, and *Fgf15/19/21/23* (Itoh & Ornitz, 2004; Itoh & Ornitz, 2008). FGFs can also be classified as paracrine, endocrine, and intracrine FGFs based on their mechanisms of action (Fig. 1). Paracrine FGFs comprise members of the FGF/1/2/5, FGF3/4/6, FGF7/10/22, FGF8/17/18, and FGF9/16/20 subfamilies. They are secreted proteins, which mediate biological responses in a paracrine manner. Endocrine FGFs, FGF15/19, FGF21, and FGF23, are also secreted proteins. However, they mediate biological responses in an endocrine manner. Intracrine FGFs, FGF11-FGF14, are intracellular proteins, which mediate biological responses in an intracrine manner (Fig. 2).

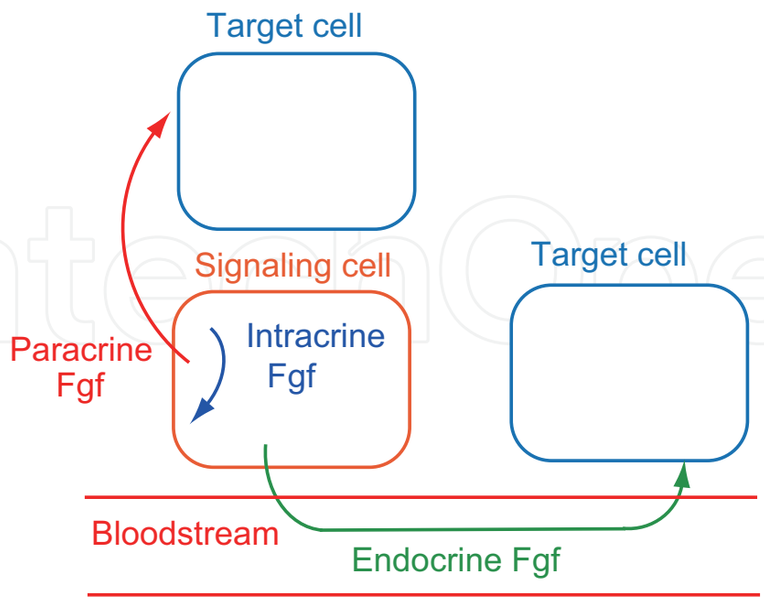

Fig. 1. Action mechanisms of Fgfs. Fgfs act on target cells in a paracrine, endocrine , or intracrine manner.

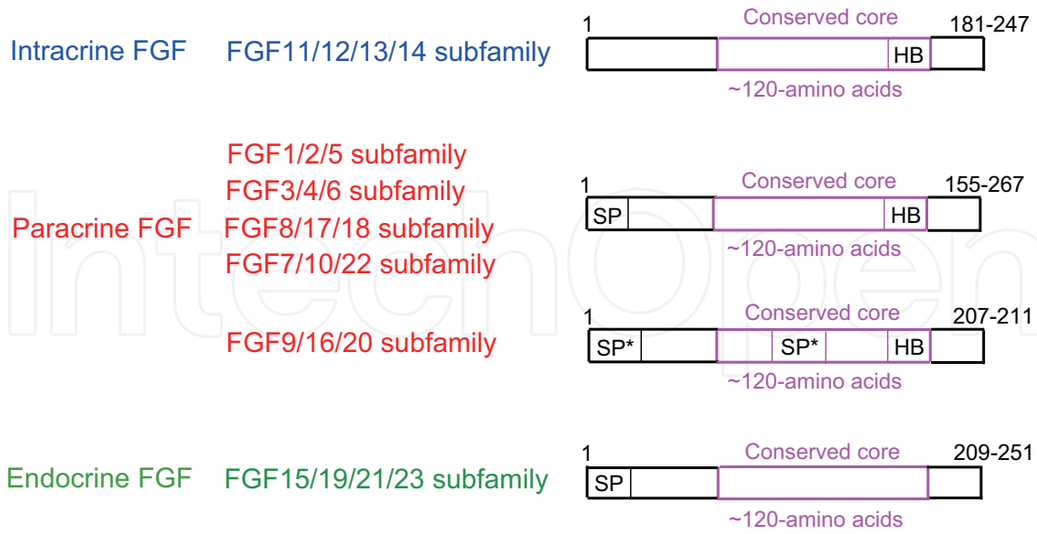

Fig. 2. Schematic representations of structure. Schematic diagrams of intracrine, paracrine, and endocrine FGFs are shown. SP, SP* and HB indicate a cleavable secreted signal sequence, an uncleaved bipartite secreted signal sequence, and a heparin-binding site, respectively.

3. Mechanisms of action

3.1 Paracrine FGFs

Most paracrine FGFs are secreted proteins with cleavable N-terminal secreted signal peptides. However, FGF9, FGF16, and FGF20 have uncleaved bipartite secreted signal sequences (Revest et al., 2000). By contrast, FGF1 and FGF2 without N-terminal signal sequences are not typical secreted proteins. They might be released from damaged cells or by an exocytotic mechanism that is independent of the endoplasmic reticulum-Golgi pathway (Mohan et al., 2010; Nickel, 2010). Paracrine FGFs mediate biological responses as extracellular proteins by binding to and activating cell surface tyrosine kinase FGFR receptors (FGFRs) with heparin/heparan sulfate as a cofactor.

The human/mouse *Fgfr* gene family comprises four *Fgfr* genes, *Fgfr1–Fgfr4* (Beenken & Mohammadi, 2009; Turner & Grose, 2010). All FGFR proteins are receptor tyrosine kinases of ~800 amino acids with an extracellular ligand-binding domain with three immunoglobulin-like domains (I, II, and III). *Fgfr1–Fgfr3* encode two major versions of immunoglobin-like domain III (IIIb and IIIc) generated by alternative splicing that utilizes one of two unique exons. The immunoglobulin-like domain III is an essential determinant of ligand-binding specificity (Zhang et al., 2006). Thus, seven major FGFR proteins (FGFRs 1b, 1c, 2b, 2c, 3b, 3c, and 4) with differing ligand-binding specificity are generated from four *Fgfr* genes.

Paracrine FGFs have a heparin-binding site and interaction with heparin-like molecules is necessary for their stable interaction with FGFRs and local signaling (Goetz et al., 2007). Paracrine FGFs function in development by influencing the intracellular signaling events of neighboring cells from a distance. The range of FGF signaling is regulated in part by affinity for extracellular matrix heparan sulfate proteoglycans (Kalinina et al., 2009) and in part by

the dimerization of some FGFs (Kalinina et al., 2009; Harada et al., 2009). The binding of FGFs to FGFRs induces functional dimerization, receptor transphosphorylation, and the activation of four key downstream signaling pathways: RAS-RAF-MAPK, PI3K-AKT, STAT, and PLCγ (Beenken & Mohammadi, 2009; Turner & Grose, 2010).

3.2 Endocrine FGFs

Endocrine FGFs are also thought to mediate biological responses in an FGFR-dependent manner. However, they bind to FGFRs and heparin/heparan sulfate with very low affinity. The reduced heparin-binding affinity enables endocrine FGFs to function in an endocrine manner (Zhang et al., 2006; Goetz et al., 2007). αKlotho is a single-pass transmembrane protein of ~1,000 amino acids with a short cytoplasmic domain. The phenotypes of *αKlotho* knockout mice are very similar to those of *Fgf23* knockout mice (Shimada et al., 2004), indicating that FGF23 and αKlotho may function in a common signal transduction pathway. αKlotho most efficiently binds to and activates FGFR1c among several isoforms of FGFRs in cultured cells, suggesting that FGFR1c can transduce an FGF23/αKlotho signal(Urakawa et al., 2006).

βKlotho is a protein that shares structural similarity and characteristics with αKlotho. The phenotypes of *βKlotho* knockout mice overlap those of *Fgfr4* knockout mice and *Fgf15/19* knockout mice (Ito et al., 2005; Inagaki et al., 2005). FGF15/19 can bind to a βKlotho-FGFR4 complex in cultured cells. FGF15/19 also activates FGF signaling in hepatocytes that primarily express *Fgfr4* (Kurosu et al., 2007). These results indicate FGFR4 to be the primary receptor for transduction of an FGF15/19/βKlotho signal. βKlotho is also essential for FGF21 signaling in cultured cells (Kharitonenkov et al., 2008). However, *Fgf21* knockout mouse phenotypes are distinct from *βKlotho* knockout mouse phenotypes (Ito et al., 2005; Hotta et al., 2009). In addition, the administration of recombinant human FGF21 to *βKlotho* knockout mice demonstrated that FGF21 signals can be transduced in the absence of βKlotho (Tomiyama et al., 2010). These results indicate the existence of a βKlotho-independent FGF21 signaling pathway in which undefined cofactors might be involved.

3.3 Intracrine FGFs

Intracrine FGFs interact with intracellular domains of voltage-gated sodium channels and with a neuronal MAPK scaffold protein, islet-brain-2 (Schoorlemmer & Goldfarb, 2002; Goldfarb et al., 2007). The only known role for intracrine FGFs is in regulating the electrical excitability of neurons and possibly other cell types (Goldfarb et al., 2007; Xiao et al., 2007; Shakkottai et al., 2009; Dover et al., 2010).

4. Evolutionary history of the human/mouse *Fgf* gene family

The FGF signaling system has been conserved throughout metazoan evolution. Two *Fgf-like* genes have been identified in the nematode, *C. elegans* (Huang & Stern, 2005). Six *Fgf-like* genes, which are potential ancestral genes of the human/mouse *Fgf* subfamilies, have been identified in the ascidian, *C. intestinalis* (Satou et al., 2002). Ascidians belong to the Subphylum Urochordata, the earliest branch in the Phylum Chordata. These results indicate that most ancestral genes of the human/mouse *Fgf* subfamilies were generated by gene duplication after the diversion of protostomes and deuterostomes. The evolutionary history of the mouse *Fgf* family has been proposed (Fig. 3) (Itoh & Ornitz, 2008). The ancestral gene

of the *Fgf* family is an ancestral intracrine *Fgf* gene, *Fgf13-like*, with a heparin-binding site but no secreted signal sequence. An ancestral gene of paracrine *Fgf*s, *Fgf4-like*, was generated from *Fgf13-like* by gene duplication during the early stages of metazoan evolution. During this evolution, *Fgf4-like* acquired a secreted signal sequence, thus allowing it to function as a paracrine *Fgf*. Ancestral genes, *Fgf5-like, Fgf8-like, Fgf9-like*, and *Fgf10-like*, of paracrine *Fgf* subfamilies were also generated from *Fgf4-like* by gene duplication after the separation of protostomes and deuterostomes. Secreted signal sequences were conserved in *Fgf5-like*, *Fgf8-like*, and *Fgf10-like*. A cleavable secreted signal sequence also evolved into an uncleaved bipartite signal sequence in *Fgf9-like*. These FGFs with heparin-binding sites function in a paracrine manner. In contrast, no ancestral gene of endocrine *Fgf*s has been identified in *Ciona intestinalis*. The ancestral gene of endocrine *Fgf*s, *Fgf15/19-like*, appears to have arisen from *Fgf4-like* by local gene duplication early in vertebrate evolution. During this evolution, *Fgf15/19-like* lost its high affinity heparin-binding capacity, thus allowing it to function in an endocrine manner. Conserved gene orders are observed among members of each *Fgf* subfamily, indicating that each subfamily further expanded into three or four members via two large-scale genome duplication events (R1 and R2) during the evolution of early vertebrates.

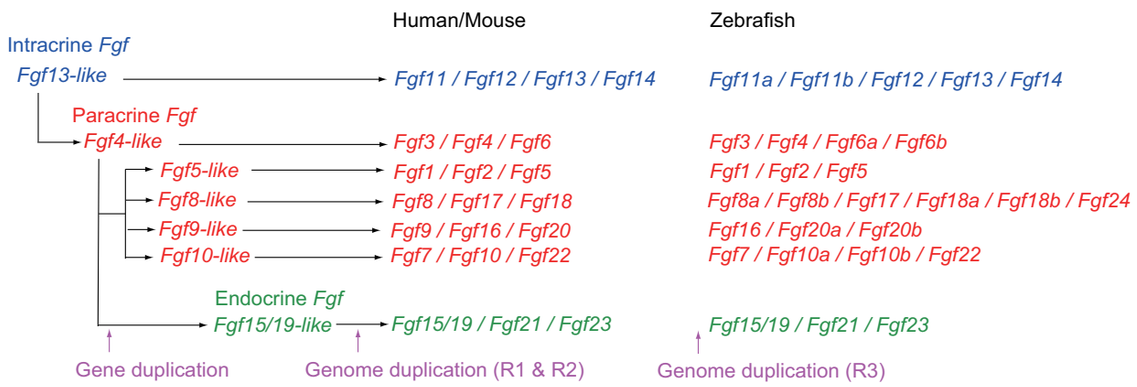

Fig. 3. The functional evolutionary history of the human/mouse/zebrafish *Fgf* gene family. *Fgf13-like* is the ancestral gene of the *Fgf* family. *Fgf4-like* was generated from *Fgf13-like* by gene duplication during the early stages of metazoan evolution. *Fgf5-like*, *Fgf8-like*, *Fgf9-like*, and *Fgf10-like* were generated from *Fgf4-like* by gene duplication. *Fgf15/19-like* was also generated from *Fgf4-like* by local gene duplication. Each subfamily further expanded into three or four members via two genome duplication events (R1 &R2) during the evolution of early vertebrates. The zebrafish *Fgf* family further expanded via an additional genome duplication event (R3) shortly after the teleost radiation.

5. The zebrafish FGF family

Almost all zebrafish orthologs of human/mouse *Fgf* genes except for *Fgf9* have been identified. In addition, *Fgf24* has been identified in zebrafish as well as all teleosts examined including the stickleback, medaka, and puffer fish. However, *Fgf24* has not been identified in all tetrapods examined. These results indicate that *Fgf9* and *Fgf24* were lost in the teleost lineage and tetrapod lineage during evolution, respectively. Zebrafish also has six additional *Fgf* genes including *Fgf6b*, *Fgf8b*, *fgf10b*, *fgf13b*, *fgf18b*, and *fgf20b*. The zebrafish *Fgf* family comprises twenty-eight members. Analysis of the location of the additional genes

indicates that they are paralogs (Fig. 3) (Itoh & Konsihi, 2007). Comparisons of mammalian genes with genes of teleost fish have shown that in teleosts, including zebrafish, there are often two homologs of the mammalian equivalent. This suggests that there has been an additional genome duplication event (R3) shortly after the teleost radiation. This duplication must have been either a partial or a whole genome duplication followed by rapid gene loss because gene duplications account for only ~20% of the zebrafish genes examined (Nusslein-Volhard et al., 2002). Zebrafish *Fgf* paralogs were also generated by genome duplication.

6. Physiological roles of FGFs indicated by *Fgf* knockout mouse phenotypes

The mouse is a widely used mammalian model for studying functions of genes. Gene functions can be effectively blocked in mice by targeted disruption of genes. Gene knockout mouse phenotypes have indicated their physiological functions. Most *Fgf* genes have been disrupted in mice. Phenotypes range from early embryonic lethality to changes in adult physiology (Table 1). Paracrine, endocrine, and intracrine FGFs mostly play roles in development, and metabolism, and neuronal functions, respectively.

6.1 Paracrine Fgfs

Paracrine FGFs are a major FGF group, canonical FGFs, including FGF1-FGF10, FGF16-FGF18, FGF20, and FGF22. Knockout mouse phenotypes mostly indicate roles as growth/differentiation factors. *Fgf1* knockout mice are viable and normal (Miller, et al., 2000). *Fgf2* knockout mice are also viable, but have decreased vascular tone and reduced numbers of neurons in deep cortical layers (Raballo et al., 2000; Zhou et al., 1998; Dono et al., 1998). In addition, *Fgf2* knockout mice show impaired recovery from ischemic injury to the heart (House et al., 2003; Virag et al., 2007). *Fgf3* knockout mice are viable, but have phenotypes that include inner ear agenesis and dysgenesis, microtia, and microdontia (Mansour et al., 1993; Alvarez et al., 2003; Tekin et al., 2007)). *Fgf4* and *Fgf8* knockout mice die at early embryonic stages. *Fgf4* and *Fgf8* have essential roles in blastocyst formation and gastrulation, respectively (Feldman et al., 1995; Sun et al., 1999). Conditional inactivation of *Fgf8* has identified additional roles in limb bud development and organogenesis. *Fgf5*, *Fgf6*, and *Fgf7* knockout mice are viable. Abnormal long hair is observed in *Fgf5* knockout mice (Hébert et al., 1994). *Fgf6* knockout mice have defects in muscle regeneration (Floss et al., 1997). *Fgf7* knockout mice have impaired hair and kidney development (Guo et al., 1996; Qiao et al., 1999). *Fgf9, Fgf10,* and *Fgf18* knockout mice die shortly after birth. *Fgf10* is critical for epithelial-mesenchymal interactions necessary for the development of epithelial components of multiple organs (Min et al., 1998; Sekine et al., 1999; Ohuchi et al., 2000; Sakaue et al., 2002). *Fgf9* and *Fgf18* have essential roles in the development of mesenchymal components of multiple organs (Colvin et al., 2001a,b; Colvin et al., 2001; Ohbayashi et al., 2002; Liu et ,al. 2002; Usui et al., 2004; Hung et al., 2007). *Fgf16* knockout mice on a C57BL/6 genetic background are viable, but have impaired embryonic cardiomyocyte proliferation (Hotta et al., 2008). *Fgf16* knockout phenotypes may be more severe on a Black Swiss genetic background where they die at embryonic day (E) 10.5 with severely impaired cardiac and facial development (Lu et al., 2008; Lu et al., 2010). *Fgf17* and *Fgf22* knockout mice are viable, but show impaired hindbrain development and impaired synaptic differentiation, respectively (Xu et al., 2000; Terauchi et al., 2010). In addition, *Fgf22* knockout mice also show a clear delay in weight gain upon sexual maturity (Grose et al., unpublished data).

Fgf20 knockout mice are viable but have profound hearing loss (Ornitz et al., unpublished data).

FGF	Physiological roles
FGF1	None identified
FGF2	Loss of vascular tone, slight loss of cortical neurons, defects in heart repair
FGF3	Inner ear agenesis, microtia, microdontia
FGF4	Defects in blastocyst formation
FGF5	Abnormal long hair
FGF6	Defective muscle regeneration
FGF7	Impaired hair and kidney development
FGF8	Defects in gastrulation, limb development, organogenesis
FGF9	Impaired multiple organ development
FGF10	Impaired multiple organ development
FGF11	–
FGF12	None identified, functional redundancy with *Fgf14*
FGF13	–
FGF14	Ataxia, paraoxysmal hyperkinetic movement disorder
FGF15/19 *	Impaired cardiac outflow tract morphogenesis and bile acid metabolism
FGF16	Impaired cardiac and facial development Impaired embryonic cardiomyocte proliferation
FGF17	Impaired hindbrain development
FGF18	Impaired multiple organ development
FGF20	Impaired inner ear development
FGF21	Impaired lipid metabolism
FGF22	Impaired synapse differentiation and delay in weight gain
FGF23	Impaired phosphate and vitamin D metabolism

Table 1. Physiological roles of FGFs indicated by *Fgf* knockout mice Phenotypes of most *Fgf* knockout mice have been published. Phenotypes of *Fgf11*, *Fgf13*, and *Fgf20* knockout mice have not been published. **Fgf15* is referred to as *Fg15/19*.

Although roles of paracrine FGFs in embryogenesis have been revealed from knockout mouse phenotypes, their contributions to adult physiology remain relatively unexplored. The widespread expression of paracrine *Fgf* genes in adult tissues suggests multiple roles in tissue homeostasis and repair (Fon Tacer et al., 2010). Emerging reports indicate homeostatic and regenerative roles for paracrine FGF signaling (Böhm et al., 2010; Yang et al., 2010).

6.2 Endocrine Fgfs

Endocrine FGFs, FGF15/19, FGF21, and FGF23, are hormone-like FGFs. Hormones are usually responsible for communication between tissues in an endocrine manner. However, several hormones are produced in developing tissues that are unrelated to the endocrine gland of origin in adults. These hormones are synthesized locally, and serve as differentiation factors in embryos (Sanders & Harvey, 2008). Endocrine FGFs also act as differentiation factors in embryos and as hormones in adults (Itoh, 2010).

Fgf15/19 knockout mice develop normally until E10.5, but then gradually die. The phenotype indicates that FGF15/19 is required for proper morphogenesis of the cardiac outflow tract at embryonic stages (Vincentz et al., 2005). Although most *Fgf15/19* knockout mice die by postnatal day (P) 7, a few survive and appear phenotypically normal. However, fecal bile acid excretion was found to be increased in surviving *Fgf15/19* knockout mice, indicating that intestinal FGF15/19 plays a crucial role in regulating hepatic bile acid synthesis (Inagaki et al., 2005). *Fgf21* knockout mice are seemingly normal, but show hypertrophy and decreased lipolysis in adipocytes. In contrast, *Fgf21* knockout mice fasted for 24 h show increased lipolysis in adipocytes and increased serum nonesterified fatty acid levels. Their phenotypes indicate that *Fgf21* is important for the metabolic regulation of lipolysis in white adipose tissue (Hotta et al., 2009). *Fgf21* knockout mice fed a ketogenic diet show partial impairments in ketogenesis (Badman et al., 2009). However, we have observed that ketogenesis is not impaired in *Fgf21* knockout mice fed a ketogenic diet (Itoh et al., unpublished data). *Fgf23* knockout mice survive until birth, but then gradually die, usually by 12 weeks of age (Shimada et al., 2004). The mice show hyperphosphatemia and increased active vitamin D levels. *Fgf23,* which is expressed in osteocytes, signals to the kidney where it regulates serum phosphate and active vitamin D levels. FGF23 may have other targets including the parathyroid gland and osteoblasts (Ben-Dov et al., 2007; Tang et al., 2010).

6.3 Intracrine Fgfs

Intracrine FGFs, FGF11-FGF14, are intracellular proteins. *Fgf14* knockout mice are viable. However, they develop ataxia and a paraoxysmal hyperkinetic movement disorder (Goldfarb et al., 2007; Xiao et al., 2007; Shakkottai et al., 2009). In contrast, *Fgf12* knockout mice are apparently normal. *Fgf12/Fgf14* double knockout mice show severe ataxia and other neurological deficits (Goldfarb et al., 2007). Phenotypes of *Fgf11* and *Fgf13* knockout mice have not been reported.

7. Roles of FGFs indicated by *Fgf* mutated or knockdown zebrafish phenotypes

The zebrafish is also a widely used vertebrate model for studying functions of genes. Because zebrafish embryos are small, the fertilization and subsequent embryonic development occur externally, and the development is rapid (Nusslein-Volhard et al., 2002), phenotypes of zebrafish embryos in which the functions of genes are blocked–the knockout of which is lethal at early embryonic stages in mice–can be potentially analyzed. In a large-scale screening, many zebrafish mutants, which were mutagenized with ethylnitrosourea, displaying distinct phenotypes in embryos were generated (Haffter et al., 1996). Furthermore, antisense morpholino oligonucleotides can easily block the functions of multiple genes in zebrafish embryos (Nasevicius & Ekker, 2000). Therefore the zebrafish is

expected to be a useful vertebrate model for studying physiological functions of *Fgf* genes *in vivo*.

7.1 Paracrine FGFs

Several zebrafish paracrine *Fgf* mutants have been generated by mutagenesis with ethylnitrosourea. *acerebellar* is a mutation of *Fgf8*. *acerebellar* embryos lack a cerebellum and the midbrain-hindbrain boundary organizer (Reifers et al., 1998). *ikarus* is a mutation of *Fgf24*. *ikarus* embryos lack pectoral fin buds (Fischer et al., 2003). *daedalus* is a mutation of *Fgf10*. *Daedalus* embryos have no pectoral fin buds either and a severely dysmorphic hepatopancreatic ductal system (Norton et al., 2005; Dong et al., 2007). *devoid of blastema* is a mutation of *Fgf20a*. *devoid of blastema* embryos have no pectoral fin buds (Whitehead et al., 2005). These results indicate that zebrafish fgfs also play crucial roles in development.

Several paracrine *Fgf* knockdown zebrafish embryos were generated using antisense morpholino oligonucleotides. Phenotypes of these embryos indicate roles of Fgfs in zebrafish. FGF1 is required for normal differentiation of erythrocytes (Songhet et al., 2007). FGF3 and FGF8 are required together for formation of the otic placode and vesicle (Maroon et al., 2002). FGF4 is required for left-right patterning of visceral organs (Yamauchi et al., 2009). In addition, FGF16 is also required for the fin buds to form (Nomura et al., 2006).

7.2 Endocrine FGFs

Fgf15/19 and *Fgf21* knockdown zebrafish embryos were generated using antisense morpholino oligonucleotides. FGF15/19 and FGF21 are required for the forebrain and eye to develop (Miyake et al., 2005; Nakayama et al., 2008), and hematopoiesis (Yamauchi et al., 2006).

8. FGF signaling disorders in human diseases

As described above, FGF signaling is crucial to development, metabolism, and neuronal functions as paracrine, endocrine, and intracrine factors. In addition, FGF signaling disorders also result in human hereditary, paraneoplastic, and metabolic diseases.

8.1 Paracrine FGFs

Michel aplasia is a unique autosomal recessive syndrome characterized by type I microtia, microdontia, and profound congenital deafness associated with a complete absence of inner ear structures. Michel aplasia is caused by mutations in *Fgf3* (Tekin et al., 2007). Nonsense mutations in *Fgf8* are found in familial isolated hypogonadotropic hypogonadism with variable degrees of gonadotropin-releasing hormone deficiency and olfactory phenotypes. These findings confirm that loss-of-function mutations in *Fgf8* cause human gonadotropin-releasing hormone deficiency (Trarbach et al., 2010). Cleft lip and/or palate (CLP) appear when the two halves of the palatal shelves fail to fuse completely. A missense mutation in *Fgf8* was found in a patient with CLP. This mutation is predicted to cause loss-of-function by destabilizing the N-terminal conformation, which is important for FGFR binding affinity and specificity (Riley et al., 2007). Aplasia of lacrimal and salivary glands (ALSG) is an autosomal dominant congenital anomaly characterized by aplasia, atresia, or hypoplasia of the lacrimal and salivary systems. Lacrimo-auriculo-dento-digital syndrome (LADD) is an autosomal-dominant multiple congenital anomaly disorder characterized by aplasia, atresia, or hypoplasia of the lacrimal and salivary systems, cup-shaped ears, hearing loss, and

dental and digital anomalies. Both ALSG and LADD are caused by *Fgf10* mutations (Entesarian et al., 2007; Rohmann et al., 2006). *Fgf20* was originally identified as a neurotrophic factor preferentially expressed in dopaminergic neurons within the substantia nigra pars compacta of rat brain (Ohmachi et al., 2003). Parkinson disease (PD) is caused by a pathogenic process responsible for the loss of dopaminergic neurons within the substantia nigra pars compacta. A pedigree disequilibrium test and a case-control association study indicated that *Fgf20* is potentially a risk factor for PD (Gao et al., 2008).

8.2 Endocrine FGFs

Serum FGF15/19 levels are markedly increased in patients with extrahepatic cholestasis caused by a pancreatic tumor. FGF15/19 is abundantly expressed in the liver of cholestatic patients, but not in the normal liver. FGF15/19 signaling may be involved in some of the adaptations that protect the liver against bile salt toxicity (Schaap et al., 2009). Serum FGF15/19 levels are also significantly increased in patients on chronic hemodialysis (Reiche et al., 2010). Nonalcoholic fatty liver disease (NAFLD) is a hepatic manifestation of metabolic syndrome, and ranges from simple fatty liver to nonalcoholic steatohepatitis. Its prevalence has increased dramatically over recent years in developed countries (Morris-Stiff & Feldstein, 2010). The pathophysiological hallmark of NAFLD is insulin resistance. NAFLD may increase the risk of type 2 diabetes and atheroclerosis (Bugianesi et al., 2010). Hepatic lipid metabolism is disturbed in patients with NAFLD. The hepatic response to FGF15/19 is impaired in NAFLD patients with insulin resistance. This impaired response may contribute to the disturbance of lipid homeostasis in NAFLD (Schreuder et al., 2010).

Serum FGF21 levels are significantly increased in NAFLD (Yilmaz et al., 2010; Dushay et al., 2010; Li et al., 2010). Serum FGF21 levels are positively correlated with intrahepatic triglyceride levels (Li et al., 2010). As NAFLD is now recognized as a major public health problem, reliable biomarkers for NEFLD are needed. Serum FGF21 levels might be useful as a biomarker for NEFLD (Morris-Stiff & Feldstein, 2010). Type 2 diabetes connected with visceral obesity and insulin resistance has become a global health concern. Serum FGF21 levels are increased in patients with type 2 diabetes, gestational diabetes, and obesity, indicating FGF21 to be a potential new marker in patients with type 2 diabetes (Table 1) (Chen et al., 2008; Zhang et al., 2008; Chavez et al., 2009; Mraz et al., 2009; Stein et al., 2010; Matuszek et al., 2010). Serum FGF21 levels are independently associated with markers of insulin resistance and an adverse lipid profile (Chen et al., 2008; Stein et al., 2010). The up-regulation of serum FGF21 levels might be a compensatory mechanism to improve glucose metabolism when insulin resistance is present. Impaired glucose tolerance (IGT) is an important category of prediabetes. Serum FGF21 levels were also increased in Chinese subjects with IGT, however, they did not correlate with insulin resistance (Li et al., 2009). Cushing's syndrome is a hormone disorder caused by high levels of cortisol (hypercortisolism) in the blood. Patients with Cushing's syndrome frequently suffer from visceral obesity, insulin resistance/diabetes, and other abnormalities similarly to patients with metabolic syndrome. Serum FGF21 levels are also increased in patients with Cushing's syndrome. The increased FGF21 levels are due to excessive fat accumulation and related metabolic abnormalities rather than a direct effect of cortical on FGF21 production (Durovcová et al., 2010). Lipodystrophy is a common alteration in HIV-1-infected patients under anti-retroviral treatment. This syndrome is usually associated with peripheral lipoatrophy, central adiposity, and, in some cases, lipomatosis, as well as systemic insulin resistance and hyperlipidemia (Villarroya et al., 2007). Serum FGF21 levels are increased in

HIV-1-infected patients with lipodystrophy. This increase is closely associated with insulin resistance, metabolic syndrome, and markers of liver damage. FGF21 might be a biomarker of altered metabolism in HIV-1-infected, antiretroviral-treated patients (Domingo et al., 2010). Serum FGF21 levels correlate with renal function and are markedly increased in chronic kidney disease patients receiving hemodialysis, suggesting a possible link between their FGF21 levels and renal function (Stein et al., 2009). Patients with end-stage renal disease (ESRD) show insulin resistance. Serum FGF21 levels are also markedly increased in patients with ESRD, suggesting FGF21 to play a role in insulin resistance in these patients (Han et al., 2010).

Autosomal dominant hypophosphatemic rickets (AHDR) is caused by gain-of-function mutations of *Fgf23* (ADHR Consortium, 2000). FGF23 is partially cleaved by intracellular proteolysis. The cleaved forms lose their biological activity. *Fgf23* mutations in ADHR result in impaired proteolysis of FGF23 and increased serum levels of active FGF23 (White et al., 2001). Reduced FGF23 signaling also causes human hereditary diseases. Familial tumoral calcinosis (FTC) is characterized by ectopic calcification and hyperphosphatemia. Loss-of-function mutations of *Fgf23* result in FTC. These mutations destabilize the tertiary structure of FGF23 and increase its susceptibility to degradation (Benet-Pagès et al., 2005). Tumors that over-produce FGF23 also cause tumor-induced osteomalacia, which is a paraneoplasitc disease characterized by hypophosphatemia caused by renal phosphate wasting (Shimada et al., 2001). Serum FGF23 levels are also greatly increased in patients with renal failure, partly owing to decreased renal clearance. These results suggest that FGF23 has a compensatory role in the disease (Larsson et al., 2003).

8.3 Intracrine FGFs

Börjeson-Forssman-Lehmann syndrome (BFLS) is a syndromic X-linked mental retardation disease. *Fgf13* is a candidate causative gene for BFLS (Gecz et al., 1999). Hereditary spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group of neurodegenerative disorders. One SCA with early-onset tremors, dyskinesia, and slowly progressive cerebellar ataxia is caused by *Fgf14* mutations (van Swieten et al., 2003; Brusse et al., 2006; Misceo et al., 2009).

9. Conclusion

The human/mouse FGF family comprises twenty-two members, which were generated by gene duplication after the diversion of protostomes and deuterostomes and two genome duplication events (R1 and R2) during the evolution of early vertebrates. In contrast, the zebrafish FGF family comprises twenty-eight members including several paralogs, which were generated by an additional genome duplication event (R3) in the teleost lineage during evolution. FGFs are now recognized as proteins with diverse biological functions and act as extracellular signaling molecules in a paracrine or endocrine manner or as intracellular signaling molecules. Experiments with *Fgf* knockout mice indicate that FGFs play vital roles in development, metabolism, and neuronal functions. Studies with *Fgf* mutated or knockdown zebrafish also indicate that FGFs are crucial to development. In addition, research on human diseases indicates that FGF signaling disorders contribute to pathological conditions. Secreted signaling molecules such as BMPs, WNTs, and Hedgehogs also play crucial roles in development by influencing the intracellular signaling events of their neighbors from a distance. FGFs, along with these signaling molecules, have roles in

diverse biological processes in multicellular organisms. However, the interaction/cooperation of FGFs with BMPs, WNTs, and Hedgehogs mostly remain unclear. Further understanding of the roles of FGFs will provide clues to their mechanisms of interaction/cooperation.

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11. References

ADHR Consortium (2000). Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. *Nature Genetics*, Vol. 26, No. 3, pp. 345-348

Alvarez, Y.; Alonso, M.T.; Vendrell V.; Zelarayan, L.C.; Chamero, P.; Theil, T.; Bösl, M.R.; Kato, S.; Maconochie, M.; Riethmacher, D. & Schimmang, T. (2003). Requirements for FGF3 and FGF10 during inner ear formation. *Development,* Vol. 130, No. 25, pp. 6329-6338

Badman, M.K.; Koester, A.; Flier, J.S.; Kharitonenkov, A. & Maratos-Flier, E. (2009). Fibroblast growth factor 21-deficient mice demonstrate impaired adaptation to ketosis. *Endocrinology,* Vol. 150, No. 11, pp. 4931-4940

Beenken, A. & Mohammadi, M. (2009). The FGF family: biology, pathophysiology and therapy. *Nature Review Drug Discovery,* Vol. 8, No. 3, pp. 235-253

Ben-Dov, I.Z.; Galitzer, H.; Lavi-Moshayoff, V.; Goetz, R.; Kuro-o, M.; Mohammadi, M.; Sirkis, R.; Naveh-Many, T. & Silver, J. (2007). The parathyroid is a target organ for FGF23 in rats. *Journal of Clinical Investigation,* Vol. 117, No. 12, pp. 4003-4008

Benet-Pagès, A.; Orlik, P.; Strom, T.M. & Lorenz-Depiereux, B. (2005). An FGF23 missense mutation causes familial tumoral calcinosis with hyperphosphatemia. *Human Molecular Genetics*, Vol. 14, No. 3, pp. 385-390

Böhm, F.; Speicher, T.; Hellerbrand, C.; Dickson, C.; Partanen, J.M.; Ornitz, D.M. & Werner, S. (2010). FGF Receptors 1 and 2 Control Chemically Induced Injury and Compound Detoxification in Regenerating Livers of Mice. *Gastroenterology*, Vol. 139, No. 4, pp. 1385-1396

Brusse, E.; de Koning, I.; Maat-Kievit, A.; Oostra, B.A.; Heutink, P. & van Swieten, J.C. (2006). Spinocerebellar ataxia associated with a mutation in the fibroblast growth factor 14 gene (SCA27): A new phenotype. *Movement Disorders*, Vol. 21, No. 3, pp. 396-401

Bugianesi, E.; Moscatiello, S.; Ciaravella, M.F. & Marchesini, G. (2010). Insulin resistance in nonalcoholic fatty liver disease. *Current Pharmaceutical Design*, Vol. 16, No. 17, pp. 1941-1951

Chen, W.W.; Li, L.; Yang, G.Y.; Li, K.; Qi, X.Y.; Zhu, W.; Tang, Y.; Liu, H. & Boden, G. (2008). Circulating FGF-21 levels in normal subjects and in newly diagnose patients with Type 2 diabetes mellitus. *Experimental and Clinical Endocrinology Diabetes*, Vol. 116, No. 1, pp. 65-68

Chavez, A.O.; Molina-Carrion, M.; Abdul-Ghani, M.A.; Folli, F.; Defronzo, R.A. & Tripathy, D. (2009). Circulating fibroblast growth factor-21 is elevated in impaired glucose tolerance and type 2 diabetes and correlates with muscle and hepatic insulin resistance. *Diabetes Care*, Vol. 32, No. 8, pp. 1542-1546

Colvin, J.S.; Green, R.P.; Schmahl, J.; Capel, B. & Ornitz, D.M. (2001a). Male-to-female sex reversal in mice lacking fibroblast growth factor 9. *Cell*, Vol. 104, No. 6, pp. 875-889

Colvin, J.S.; White, A.C.; Pratt, S.J. & Ornitz, D.M. (2001b). Lung hypoplasia and neonatal death in Fgf9-null mice identify this gene as an essential regulator of lung mesenchyme. *Development*, Vol. 128, No. 11, pp. 2095-2106

Domingo, P.; Gallego-Escuredo, J.M.; Domingo, J.C.; Gutiérrez Mdel, M.; Mateo, M.G.; Fernández, I.; Vidal, F.; Giralt, M. & Villarroya, F. (2010). Serum FGF21 levels are elevated in association with lipodystrophy, insulin resistance and biomarkers of liver injury in HIV-1-infected patients. *AIDS*, Vol. 24, No. 17, pp. 2629-2637

Dong, P.D.; Munson, C.A.; Norton, W.; Crosnier, C.; Pan, X.; Gong, Z.; Neumann, C.J. & Stainier, D.Y. (2007). Fgf10 regulates hepatopancreatic ductal system patterning and differentiation. *Nature Genetics*, Vol. 39, No. 3, pp. 397-402

Dono, R.; Texido, G.; Dussel, R.; Ehmke, H. & Zeller, R. (1998). Impaired cerebral cortex development and blood pressure regulation in FGF-2-deficient mice. *EMBO Journal*, Vol. 17, No. 15, pp. 4213-4225

Dover, K.; Solinas, S.; D'Angelo, E. & Goldfarb, M. (2010). Long-term inactivation particle for voltage-gated sodium channels. *Journal of Physiology*, Vol. 588, No. 19, pp. 3695-3711

Durovcová, V.; Marek, J.; Hána, V.; Matoulek, M.; Zikán, V.; Haluzíková, D.; Kaválková, P.; Lacinová, Z.; Krsek, M. & Haluzík, M. (2010). Plasma concentrations of fibroblast growth factors 21 and 19 in patients with Cushing's syndrome. *Physiological Research*, Vol. 59, No. 3, pp. 415-422

Dushay, J.; Chui, P.C.; Gopalakrishnan, G.S.; Varela-Rey, M.; Crawley, M.; Fisher, F.M.; Badman, M.K.; Martinez-Chantar, M.L. & Maratos-Flier, E. (2010). Increased fibroblast growth factor 21 in obesity and nonalcoholic fatty liver disease. *Gastroenterology*, Vol. 139, No. 2, pp. 456-463

Entesarian, M.; Dahlqvist, J.; Shashi, V.; Stanley, C.S.; Falahat, B.; Reardon, W. & Dahl, N. (2007). FGF10 missense mutations in aplasia of lacrimal and salivary glands (ALSG). *European Journal of Human Genetics*, Vol. 15, No. 3, pp. 379-382

Feldman, B.; Poueymirou, W.; Papaioannou, V.E.; DeChiara, T.M. & Goldfarb, M. (1995). Requirement of FGF-4 for postimplantation mouse development. *Science*, Vol. 267, No. 5195, pp. 246-249

Fischer, S.; Draper, B.W. & Neumann, C.J. (2003). The zebrafish fgf24 mutant identifies an additional level of Fgf signaling involved in vertebrate forelimb initiation. *Development*, Vol. 130, No. 15, pp. 3515-3524

Floss, T.; Arnold, H.H. & Braun, T. (1997). A role for FGF-6 in skeletal muscle regeneration. *Genes & Development*, Vol. 11, No. 16, pp. 2040-2051

Fon Tacer, K.; Bookout, A.L.; Ding, X.; Kurosu, H.; John, G.B.; Wang, L.; Goetz, R.; Mohammadi, M.; Kuro-o, M.; Mangelsdorf, D.J. & Kliewer, S.A. (2010). Research Resource: Comprehensive Expression Atlas of the Fibroblast Growth Factor System in Adult Mouse. *Molecular Endocrinology*, Vol. 24, No. 10, pp. 2050-2064

Gao, X.; Scott, W.K.; Wang, G.; Mayhew, G.; Li, Y.J.; Vance, J.M. & Martin, E.R. (2008). Gene-gene interaction between FGF20 and MAOB in Parkinson disease. *Annals of Human Genetics*, Vol. 72, No. 2, pp. 157-162

Goetz, R.; Beenken, A.; Ibrahimi, O.A.; Kalinina, J.; Olsen, S.K.; Eliseenkova, A.V.; Xu, C.; Neubert, T.A.; Zhang, F.; Linhardt, R.J.; Yu, X.; White, K.E.; Inagaki, T.; Kliewer, S.A.; Yamamoto, M.; Kurosu, H.; Ogawa, Y.; Kuro-o, M.; Lanske, B.; Razzaque, M.S. & Mohammadi, M. (2007). Molecular insights into the klotho-dependent, endocrine mode of action of fibroblast growth factor 19 subfamily members. *Molecular and Cellular Biology*, Vol. 27, No. 9, pp. 3417-3428

Gecz, J.; Baker, E.; Donnelly, A.; Ming, J.E.; McDonald-McGinn, D.M.; Spinner, N.B.; Zackai, E.H.; Sutherland, G.R. & Mulley, J.C. (1999). Fibroblast growth factor homologous factor 2 (FHF2): gene structure, expression and mapping to the Börjeson-Forssman-Lehmann syndrome region in Xq26 delineated by a duplication breakpoint in a BFLS-like patient. *Human Genetics*, Vol. 104, No. 1, pp. 56-63

Goldfarb, M.; Schoorlemmer, J.; Williams, A.; Diwakar, S.; Wang, Q.; Huang, X.; Giza, J.; Tchetchik, D.; Kelley, K.; Vega, A.; Matthews, G.; Rossi, P.; Ornitz, D.M. & D'Angelo, E. (2007). Fibroblast growth factor homologous factors control neuronal excitability through modulation of voltage-gated sodium channels. *Neuron*, Vol. 55, No. 3, pp. 449-463

Gospodarowicz, D. (1975). Purification of a fibroblast growth factor from bovine pituitary. *Journal of Biological Chemistry*, Vol. 250, No. 7, pp. 2515-2520

Gospodarowicz, D.; Bialecki, H. & Greenburg, G. (1978). Purification of fibroblast growth factor activity from bovine brain. *Journal of Biological Chemistry*, Vol. 253, No. 10, pp. 3736-3743

Guo, L.; Degenstein, L. & Fuchs, E. (1996). Keratinocyte growth factor is required for hair development but not for wound healing. *Genes & Development*, Vol. 10, No. 2, pp. 165-175

Haffter, P.; Granato, M.; Brand, M.; Mullins, M.C.; Hammerschmidt, M.; Kane, D.A.; Odenthal, J.; van Eeden, F.J.; Jiang, Y.J.; Heisenberg, C.P.; Kelsh, R.N.; Furutani-Seiki, M.; Vogelsang, E.; Beuchle, D.; Schach, U.; Fabian, C. & Nüsslein-Volhard, C. (1996). The identification of genes with unique and essential functions in the development of the zebrafish, Danio rerio. *Development*, Vol. 123, No. 1, pp. 1-36

Han, S.H.; Choi, S.H.; Cho, B.J.; Lee, Y.; Lim, S.; Park, Y.J.; Moon, M.K.; Lee, H.K.; Kang, S.W.; Han, D.S.; Kim, Y.B.; Jang, H.C. & Park, K.S. (2010). Serum fibroblast growth factor-21 concentration is associated with residual renal function and insulin resistance in end-stage renal disease patients receiving long-term peritoneal dialysis. *Metabolism*, Vol. 59, No. 11, pp. 1656-1562

Harada, M.; Murakami, H.; Okawa, A.; Okimoto, N.; Hiraoka, S.; Nakahara, T.; Akasaka, R.; Shiraishi, Y.; Futatsugi, N.; Mizutani-Koseki, Y.; Kuroiwa, A.; Shirouzu, M.; Yokoyama, S.; Taiji, M.; Iseki, S.; Ornitz, D.M. & Koseki, H. (2009). FGF9 monomer-dimer equilibrium regulates extracellular matrix affinity and tissue diffusion. *Nature Genetics*, Vol. 41, No. 3, pp. 289-298

Hébert, J.M.; Rosenquist, T.; Götz, J. & Martin, G.R. (1994). FGF5 as a regulator of the hair growth cycle: evidence from targeted and spontaneous mutations. *Cell*, Vol. 78, No. 6, pp. 1017-1025

Hotta,Y.; Sasaki, S.; Konishi, M.; Kinoshita, H.; Kuwahara, K.; Nakao, K. & Itoh, N. (2008). Fgf16 is required for cardiomyocyte proliferation in the mouse embryonic heart. *Developmental Dynamics*, Vol. 237, No. 10, pp. 2947-2954

Hotta, Y.; Nakamura, H.; Konishi, M.; Murata, Y.; Takagi, H.; Matsumura, S.; Inoue, K.; Fushiki, T. & Itoh, N. (2009). Fibroblast growth factor 21 regulates lipolysis in white adipose tissue but is not required for ketogenesis and triglyceride clearance in liver. *Endocrinology*, Vol. 150, No. 10, pp. 4625-4633

House, S.L.; Bolte, C.; Zhou, M.; Doetschman, T.; Klevitsky, R.; Newman, G. & Schultz Jel, J. (2003). Cardiac-specific overexpression of fibroblast growth factor-2 protects against myocardial dysfunction and infarction in a murine model of low-flow ischemia. *Circulation*, Vol. 108, No. 25, pp. 3140-3148

Huang, P. & Stern, M.J. (2005). FGF signaling in flies and worms: more and more relevant to vertebrate biology. *Cytokine & Growth Factor Reviews*, Vol. 16, No. 2, pp. 151-158

Hung, I.H.; Yu, K.; Lavine, K.J. & Ornitz, D.M. (2007). FGF9 regulates early hypertrophic chondrocyte differentiation and skeletal vascularization in the developing stylopod. *Developmental Biology*, Vol. 307, No. 2, pp. 300-313

Inagaki, T.; Choi, M.; Moschetta, A.; Peng, L.; Cummins, C.L.; McDonald, J.G.; Luo, G.; Jones, S.A.; Goodwin, B.; Richardson, J.A.; Gerard, R.D.; Repa, J.J.; Mangelsdorf, D.J. & Kliewer, S.A. (2005). Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. *Cell Metabolism*, Vol. 2, No. 4, pp. 217-225

Ito, S.; Fujimori, T.; Furuya, A.; Satoh, J.; Nabeshima, Y. & Nabeshima, Y. (2005). Impaired negative feedback suppression of bile acid synthesis in mice lacking betaKlotho. *Journal of Clinical Investigation*, Vol. 115, No. 8, pp. 2202-2208

Itoh, N. & Ornitz, D.M. (2004). Evolution of the Fgf and Fgfr gene families. *Trends in Genetics*, Vol. 20, No. 11, pp. 563-569

Itoh, N. (2007). The Fgf families in humans, mice, and zebrafish: their evolutional processes and roles in development, metabolism, and disease. *Biological & Pharmaceutical Bulletin*, Vol. 30, No. 10, pp. 1819-1825

Itoh, N. & Konishi, M. (2007). The zebrafish fgf family. *Zebrafish*, Vol. 4, No. 3, pp. 179-186

Itoh, N. & Ornitz, D.M. (2008). Functional evolutionary history of the mouse Fgf gene family. *Developmental Dynamics*, Vol. 237, No. 1, pp. 18-27

Itoh, N. (2010). Hormone-like (endocrine) Fgfs: their evolutionary history and roles in development, metabolism, and disease. *Cell and Tissue Research*, Vol. 342, No. 1, pp. 1-11

Kalinina, J.; Byron, S.A.; Makarenkova, H.P.; Olsen, S.K.; Eliseenkova, A.V.; Larochelle, W.J.; Dhanabal, M.; Blais, S.; Ornitz, D.M.; Day, L.A.; Neubert, T.A.; Pollock, P.M. & Mohammadi, M. (2009). Homodimerization controls the fibroblast growth factor 9 subfamily's receptor binding and heparan sulfate-dependent diffusion in the extracellular matrix. *Molecular and Cellular Biology*, Vol. 29, No. 17, pp. 4663-4678

Kharitonenkov, A. (2009). FGFs and metabolism. *Current Opinion in Pharmacology*, Vol. 9, No. 6, pp. 805-810

Kharitonenkov, A.; Dunbar, J.D.; Bina, H.A.; Bright, S.; Moyers, J.S.; Zhang, C.; Ding, L.; Micanovic, R.; Mehrbod, S.F.; Knierman, M.D.; Hale, J.E.; Coskun, T. & Shanafelt, A.B. (2008). FGF-21/FGF-21 receptor interaction and activation is determined by betaKlotho. *Journal of Cellular Physiology*, Vol. 215, No. 1, pp. 1-7

Kurosu, H.; Choi, M.; Ogawa, Y.; Dickson, A.S.; Goetz, R.; Eliseenkova, A.V.; Mohammadi, M.; Rosenblatt, K.P.; Kliewer, S.A. & Kuro-o, M. (2007). Tissue-specific expression of betaKlotho and fibroblast growth factor (FGF) receptor isoforms determines metabolic activity of FGF19 and FGF21. *Journal of Biological Chemistry*, Vol. 282, No. 37, pp. 26687-2695

Krejci, P.; Prochazkova, J.; Bryja, V.; Kozubik, A. & Wilcox, W.R. (2009). Molecular pathology of the fibroblast growth factor family. *Human Mutation*, Vol. 30, No. 9, pp. 1245-1255

Laezza, F.; Lampert, A.; Kozel, M.A.; Gerber, B.R.; Rush, A.M.; Nerbonne, J.M.; Waxman, S.G.; Dib-Hajj, S.D. & Ornitz, D.M. (2009). FGF14 N-terminal splice variants differentially modulate Nav1.2 and Nav1.6-encoded sodium channels. *Molecular and Cellular Neuroscience*, Vol. 42, No. 2, pp. 90-101

Larsson, T.; Nisbeth, U.; Ljunggren, O.; Jüppner, H. & Jonsson, K.B. (2003). Circulating concentration of FGF-23 increases as renal function declines in patients with chronic kidney disease, but does not change in response to variation in phosphate intake in healthy volunteers. *Kidney International*, Vol. 64, No. 6, pp. 2272-2279

Li, H.; Bao, Y.; Xu, A.; Pan, X.; Lu, J.; Wu, H.; Lu, H.; Xiang, K. & Jia, W. (2009). Serum fibroblast growth factor 21 is associated with adverse lipid profiles and gamma-glutamyltransferase but not insulin sensitivity in Chinese subjects. *Journal of Clinical Endocrinology and Metabolism*, Vol. 94, No. 6, pp. 2151-2156

Li, H.; Fang, Q.; Gao, F.; Fan, J.; Zhou, J.; Wang, X.; Zhang, H.; Pan, X.; Bao, Y.; Xiang, K.; Xu, A. & Jia, W. (2010). Fibroblast growth factor 21 levels are increased in nonalcoholic fatty liver disease patients and are correlated with hepatic triglyceride. *Journal of Hepatology*, Vol. 53, No. 5, pp. 934-940

Liu, Z.; Xu, J.; Colvin, J.S. & Ornitz, D.M. (2002). Coordination of chondrogenesis and osteogenesis by fibroblast growth factor 18. *Genes & Development*, Vol. 16, No. 7, pp. 859-869

Lu, S.Y.; Sheikh, F.; Sheppard, P.C.; Fresnoza, A.; Duckworth, M.L.; Detillieux, K.A. & Cattini, P.A. (2008). FGF-16 is required for embryonic heart development. *Biochemical and Biophysical Research Communication*, Vol. 373, No. 2, pp. 270-274

Lu, S.Y.; Jin, Y.; Li, X.; Sheppard, P.; Bock, M.E.; Sheikh, F.; Duckworth, M.L. & Cattini, P.A. (2010). Embryonic survival and severity of cardiac and craniofacial defects are affected by genetic background in fibroblast growth factor-16 null mice. *DNA and Cell Biology*, Vol. 29, No. 8, pp. 407-415

Mansour, S.L.; Goddard, J.M. & Capecchi, M.R. (1993). Mice homozygous for a targeted disruption of the proto-oncogene int-2 have developmental defects in the tail and inner ear. *Development*, Vol. 117, No. 1, pp. 13-28

Maroon, H.; Walshe, J.; Mahmood, R.; Kiefer, P.; Dickson, C. & Mason, I. (2002). Fgf3 and Fgf8 are required together for formation of the otic placode and vesicle. *Development*, Vol. 129, No. 9, pp. 2099-2108

Matuszek, B.; Lenart-Lipińska, M.; Duma, D.; Solski, J. & Nowakowski, A. (2010). Evaluation of concentrations of FGF-21 - a new adipocytokine in type 2 diabetes. *Endokrynolgia Polska*, Vol. 61, No. 1, pp. 50-54

Miller, D.L.; Ortega, S.; Bashayan, O.; Basch, R. & Basilico, C. (2000). Compensation by fibroblast growth factor 1 (FGF1) does not account for the mild phenotypic defects observed in FGF2 null mice. *Molecular and Cellular Biology*, Vol. 20, No. 6, pp. 2260-2268

Min, H.; Danilenko, D.M.; Scully, S.A.; Bolon, B.; Ring, B.D.; Tarpley, J.E.; DeRose, M. & Simonet, W.S. (1998). Fgf-10 is required for both limb and lung development and exhibits striking functional similarity to Drosophila branchless. *Genes & Development*, Vol. 12, No. 20, pp. 3156-3161

Miyake, A.; Nakayama, Y.; Konishi, M. & Itoh, N. (2005). Fgf19 regulated by Hh signaling is required for zebrafish forebrain development. *Developmental Biology*, Vol. 288, No. 1, pp. 259-275

Misceo, D.; Fannemel, M.; Barøy, T.; Roberto, R.; Tvedt, B.; Jaeger, T.; Bryn, V.; Strømme, P. & Frengen, E. (2009). SCA27 caused by a chromosome translocation: further delineation of the phenotype. *Neurogenetics*, Vol. 10, No. 4, pp. 371-374

Mohan, S.K.; Rani, S.G. & Yu, C. (2010). The heterohexameric complex structure, a component in the non-classical pathway for fibroblast growth factor 1 (FGF1) secretion. *Journal of Biological Chemistry*, Vol. 285, No. 20, pp. 15464-15475

Morris-Stiff, G. & Feldstein, A.E. (2010). Fibroblast growth factor 21 as a biomarker for NAFLD: integrating pathobiology into clinical practice. *Journal of Hepatology*, Vol. 53, No. 5, pp. 795-796

Mraz, M.; Bartlova, M.; Lacinova, Z.; Michalsky, D.; Kasalicky, M.; Haluzikova, D.; Matoulek, M.; Dostalova, I.; Humenanska, V. & Haluzik, M. (2009). Serum

concentrations and tissue expression of a novel endocrine regulator fibroblast growth factor-21 in patients with type 2 diabetes and obesity. *Clinical Endocrinology*, Vol. 71, No. 3, pp. 369-375

Nakayama, Y.; Miyake, A.; Nakagawa, Y.; Mido, T.; Yoshikawa, M.; Konishi, M. & Itoh, N. (2008). Fgf19 is required for zebrafish lens and retina development. *Developmental Biology*, Vol. 313, No. 2, pp. 752-766

Nasevicius, A. & Ekker, S.C. (2000). Effective targeted gene 'knockdown' in zebrafish. *Nature Genetics*, Vol. 26, No. 2, pp. 216-220

Nickel, W. (2010). Pathways of unconventional protein secretion. *Current Opinion in Biotechnology*, Vol. 21, No. 5, pp. 621-626

Nomura, R.; Kamei, E.; Hotta, Y.; Konishi, M.; Miyake, A. & Itoh, N. (2006). Fgf16 is essential for pectoral fin bud formation in zebrafish. *Biochemical and Biophysical Research Communications*, Vol. 347, No. 1, pp. 340-346

Norton, W.H.; Ledin, J.; Grandel, H. & Neumann, C.J. (2005). HSPG synthesis by zebrafish Ext2 and Extl3 is required for Fgf10 signalling during limb development. *Development*, Vol. 132, No. 22, pp. 4963-4973

Nusslein-Volhard, C.; Gilmour, D.T. & Dahm, R. (2002). Zebrafish eds. Nusslein-Volhard, C. & Dahm, R., *Oxford University Press*, London, pp. 1–6

Ohbayashi, N.; Shibayama, M.; Kurotaki, Y.; Imanishi, M.; Fujimori, T.; Itoh, N. & Takada, S. (2002). FGF18 is required for normal cell proliferation and differentiation during osteogenesis and chondrogenesis. *Genes & Development*, Vol. 16, No. 7, pp. 870-879

Ohmachi, S.; Mikami, T.; Konishi, M.; Miyake, A. & Itoh, N. (2003). Preferential neurotrophic activity of fibroblast growth factor-20 for dopaminergic neurons through fibroblast growth factor receptor-1c. *Journal of Neuroscience Research*, Vol. 72, No. 4, pp. 436-443

Ohuchi, H.; Hori, Y.; Yamasaki, M.; Harada, H.; Sekine, K.; Kato, S. & Itoh, N. (2000). FGF10 acts as a major ligand for FGF receptor 2 IIIb in mouse multi-organ development. *Biochemical and Biophysical Research Communication*, Vol. 277, No. 3, pp. 643-649

Qiao, J.; Uzzo, R.; Obara-Ishihara, T.; Degenstein, L.; Fuchs, E. & Herzlinger, D. (1999). FGF-7 modulates ureteric bud growth and nephron number in the developing kidney. *Development*, Vol. 126, No. 3, pp. 547-554

Raballo, R.; Rhee, J.; Lyn-Cook, R.; Leckman, J.F.; Schwartz, M.L. & Vaccarino, F.M. (2000). Basic fibroblast growth factor (Fgf2) is necessary for cell proliferation and neurogenesis in the developing cerebral cortex. *Journal of Neuroscience*, Vol. 20, No. 13, pp. 5012-5023

Reiche, M.; Bachmann, A.; Lössner, U.; Blüher, M.; Stumvoll, M. & Fasshauer, M. (2010). Fibroblast growth factor 19 serum levels: relation to renal function and metabolic parameters. *Hormone and Metabolic Research*, Vol. 42, No. 3, pp. 178-181

Reifers, F.; Böhli, H.; Walsh, E.C.; Crossley, P.H.; Stainier, D.Y. & Brand, M. (1998). Fgf8 is mutated in zebrafish acerebellar (ace) mutants and is required for maintenance of midbrain-hindbrain boundary development and somitogenesis. *Development*, Vol. 125, No. 13, pp. 2381-2395

Revest, J.M.; DeMoerlooze, L. & Dickson, C. (2000). Fibroblast growth factor 9 secretion is mediated by a non-cleaved amino-terminal signal sequence. *Journal of Biological Chemistry*, Vol. 275, No. 11, pp. 8083-8090

Riley, B.M.; Mansilla, M.A.; Ma, J.; Daack-Hirsch, S.; Maher, B.S.; Raffensperger, L.M.; Russo, E.T.; Vieira, A.R.; Dodé, C.; Mohammadi, M.; Marazita, M.L. & Murray, J.C. (2007). Impaired FGF signaling contributes to cleft lip and palate. *Proceedings of*

Natural Academy Sciences of the United State of America, Vol. 104, No. 11, pp. 4512-4517

Rohmann, E.; Brunner, H.G.; Kayserili, H.; Uyguner, O.; Nürnberg, G.; Lew, E.D.; Dobbie, A.; Eswarakumar, V.P.; Uzumcu, A.; Ulubil-Emeroglu, M.; Leroy, J.G.; Li, Y.; Becker, C.; Lehnerdt, K.; Cremers, C.W.; Yüksel-Apak, M.; Nürnberg, P.; Kubisch, C.; Schlessinger, J.; van Bokhoven, H. & Wollnik, B. (2006). Mutations in different components of FGF signaling in LADD syndrome. *Nature Genetics*, Vol. 38, No. 4, pp. 414-417

Sakaue, H.; Konishi, M.; Ogawa, W.; Asaki, T.; Mori, T.; Yamasaki, M.; Takata, M.; Ueno, H.; Kato, S.; Kasuga, M. & Itoh, N. (2002). Requirement of fibroblast growth factor 10 in development of white adipose tissue. *Genes & Development*, Vol. 16, No. 8, pp. 908-912

Satou, Y.; Imai, K.S. & Satoh, N. (2002). Fgf genes in the basal chordate Ciona intestinalis. *Development Genes and Evolution*, Vol. 212, No. 9, pp. 432-438

Sanders, E.J. & Harvey, S. (2008). Peptide hormones as developmental growth and differentiation factors. *Developmental Dynamics*, Vol. 237, No. 6, pp. 1537-1552

Schaap, F.G.; van der Gaag, N.A.; Gouma, D.J. & Jansen, P.L. (2009). High expression of the bile salt-homeostatic hormone fibroblast growth factor 19 in the liver of patients with extrahepatic cholestasis. *Hepatology,* Vol. 49, No. 4, pp. 1228-1235

Schreuder, T.C.; Marsman, H.A.; Lenicek, M.; van Werven, J.R.; Nederveen, A.J.; Jansen, P.L. & Schaap, F.G. (2010). The hepatic response to FGF19 is impaired in patients with nonalcoholic fatty liver disease and insulin resistance. *Americal Journal of Physiology. Gastrointestinal and Liver Physiology*, Vol. 298, No. 3, pp. 440-445

Schoorlemmer, J. & Goldfarb, M. (2002). Fibroblast growth factor homologous factors and the islet brain-2 scaffold protein regulate activation of a stress-activated protein kinase. *Journal of Biological Chemistry*, Vol. 277, No. 51, pp. 49111-49119

Sekine, K.; Ohuchi, H.; Fujiwara, M.; Yamasaki, M.; Yoshizawa, T.; Sato, T.; Yagishita, N.; Matsui, D.; Koga, Y.; Itoh, N. & Kato, S. (1999). Fgf10 is essential for limb and lung formation. *Nature Genetics*, Vol. 21, No. 1, pp. 138-141

Shakkottai, V.G.; Xiao, M.; Xu, L.; Wong, M.; Nerbonne, J.M.; Ornitz, D.M. & Yamada, K.A. (2009). FGF14 regulates the intrinsic excitability of cerebellar Purkinje neurons. *Neurobiology of Disease*, Vol. 33, No. 1, pp. 81-88

Shimada, T.; Mizutani, S.; Muto, T.; Yoneya, T.; Hino, R.; Takeda, S.; Takeuchi, Y.; Fujita, T.; Fukumoto, S. & Yamashita, T. (2001). Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. *Proceedings of Natural Academy Sciences of the United State of America*, Vol. 98, No. 11, pp. 6500-6505

Shimada, T.; Kakitani, M.; Yamazaki, Y.; Hasegawa, H.; Takeuchi, Y.; Fujita, T.; Fukumoto, S.; Tomizuka, K. & Yamashita, T. (2004). Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. *Journal of Clinical Investigation*, Vol. 113, No. 4, pp. 561-568

Songhet, P.; Adzic, D.; Reibe, S. & Rohr, K.B. (2007). fgf1 is required for normal differentiation of erythrocytes in zebrafish primitive hematopoiesis. *Developmental Dynamics*, Vol. 236, No. 3, pp. 633-643

Stein, S.; Bachmann, A.; Lössner, U.; Kratzsch, J.; Blüher, M.; Stumvoll, M. & Fasshauer, M. (2009). Serum levels of the adipokine FGF21 depend on renal function. *Diabetes Care*, Vol. 32, No. 1, pp. 126-128

Stein, S.; Stepan, H.; Kratzsch, J.; Verlohren, M.; Verlohren, H.J.; Drynda, K.; Lössner, U.; Blüher, M.; Stumvoll, M. & Fasshauer, M. (2010). Serum fibroblast growth factor 21

levels in gestational diabetes mellitus in relation to insulin resistance and dyslipidemia. *Metabolism*, Vol. 59, No. 1, pp. 33-37

Sun, X.; Meyers, E.N.; Lewandoski, M. & Martin, G.R. (1999). Targeted disruption of Fgf8 causes failure of cell migration in the gastrulating mouse embryo. *Genes & Development*, Vol. 13, No. 14, pp. 1834-1846

Tang, W.J.; Wang, L.F.; Xu, X.Y.; Zhou, Y.; Jin, W.F.; Wang, H.F. & Gao, J. (2010). Autocrine/paracrine action of vitamin D on FGF23 expression in cultured rat osteoblasts. *Calcified Tissue International*, Vol. 86, No. 5, pp. 404-410

Tekin, M.; Hişmi, B.O.; Fitoz, S.; Ozdağ, H.; Cengiz, F.B.; Sirmaci, A.; Aslan, I.; Inceoğlu, B.; Yüksel-Konuk, E.B.; Yilmaz, S.T.; Yasun, O. & Akar, N. (2007). Homozygous mutations in fibroblast growth factor 3 are associated with a new form of syndromic deafness characterized by inner ear agenesis, microtia, and microdontia. *American Journal of Human Genetics*, Vol. 80, No. 2, pp. 338-344

Terauchi, A.; Johnson-Venkatesh, E.M.; Toth, A.B.; Javed, D.; Sutton, M.A. & Umemori, H. (2010). Distinct FGFs promote differentiation of excitatory and inhibitory synapses. *Nature*, Vol. 465, No. 7299, pp. 783-737

Tomiyama, K.; Maeda, R.; Urakawa, I.; Yamazaki, Y.; Tanaka, T.; Ito, S.; Nabeshima, Y.; Tomita, T.; Odori, S.; Hosoda, K.; Nakao, K.; Imura, A. & Nabeshima, Y. (2010). Relevant use of Klotho in FGF19 subfamily signaling system in vivo. *Proceedings of Natural Academy Sciences of the United State of America*, Vol. 107, No. 4, pp. 1666-1671

Trarbach, E.B.; Abreu, A.P.; Silveira, L.F.; Garmes, H.M.; Baptista, M.T.; Teles, M.G.; Costa, E.M.; Mohammadi, M.; Pitteloud, N.; Mendonca, B.B. & Latronico, A.C. (2010). Nonsense mutations in FGF8 gene causing different degrees of human gonadotropin-releasing deficiency. *Journal of Clinical Endocrinology and Metabolism*, Vol. 95, No. 7, pp. 3491-3496

Turner, N. & Grose, R. (2010). Fibroblast growth factor signalling: from development to cancer. *Nature Reviews Cancer*, Vol. 10, No. 2, pp. 116-129

Usui, H.; Shibayama, M.; Ohbayashi, N.; Konishi, M.; Takada, S. & Itoh, N. (2004). Fgf18 is required for embryonic lung alveolar development. *Biochemical and Biophysical Research Communication*, Vol. 322, No. 3, pp. 887-892

Urakawa, I.; Yamazaki, Y.; Shimada, T.; Iijima, K.; Hasegawa, H.; Okawa, K.; Fujita, T.; Fukumoto, S. & Yamashita, T. (2006). Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature*, Vol. 444, No. 7120, pp. 770-774

van Swieten, J.C.; Brusse, E.; de Graaf, B.M.; Krieger, E.; van de Graaf, R.; de Koning, I.; Maat-Kievit, A.; Leegwater, P.; Dooijes, D.; Oostra, B.A. & Heutink, P. (2003). A mutation in the fibroblast growth factor 14 gene is associated with autosomal dominant cerebellar ataxia. *American Journal of Human Genetics*, Vol. 72, No. 1, pp. 191-199

Villarroya, F.; Domingo, P. & Giralt, M. (2007). Lipodystrophy in HIV 1-infected patients: lessons for obesity research. *International Journal of Obesity*, Vol. 31, No. 12, pp. 1763-1776

Vincentz, J.W.; McWhirter, J.R.; Murre, C.; Baldini, A. & Furuta, Y. (2005). Fgf15 is required for proper morphogenesis of the mouse cardiac outflow tract. *Genesis*, Vol. 41, No. 4, pp. 192-201

Virag, J.A.; Rolle, M.L.; Reece, J.; Hardouin, S.; Feigl, E.O. & Murry, C.E. (2007). Fibroblast growth factor-2 regulates myocardial infarct repair: effects on cell proliferation, scar contraction, and ventricular function. *American Journal of Pathology*, Vol. 171, No. 5, pp. 1431-1440

White, K.E.; Carn, G.; Lorenz-Depiereux, B.; Benet-Pages, A.; Strom, T.M. & Econs, M.J. (2001). Autosomal-dominant hypophosphatemic rickets (ADHR) mutations stabilize FGF-23. *Kidney International*, Vol. 60, No. 6, pp. 2079-2086

Whitehead, G.G.; Makino, S.; Lien, C.L. & Keating, M.T. (2005). fgf20 is essential for initiating zebrafish fin regeneration. *Science*, Vol. 310, No. 5756, pp. 1957-1960

Xiao, M.; Xu, L.; Laezza, F.; Yamada, K.; Feng, S. & Ornitz, D.M. (2007). Impaired hippocampal synaptic transmission and plasticity in mice lacking fibroblast growth factor 14. *Molecular and Cellular Neurosciences*, Vol. 34, No. 3, pp. 366-377

Xu, J.; Liu, Z. & Ornitz, D.M. (2000). Temporal and spatial gradients of Fgf8 and Fgf17 regulate proliferation and differentiation of midline cerebellar structures. *Development*, Vol. 127, No. 9, pp. 1833-1843

Yamauchi, H.; Miyakawa, N.; Miyake, A. & Itoh, N. (2009). Fgf4 is required for left-right patterning of visceral organs in zebrafish. *Developmental Biology*, Vol. 332, No. 1, pp. 177-185

Yamauchi, H.; Hotta, Y.; Konishi, M.; Miyake, A.; Kawahara, A. & Itoh, N. (2006). Fgf21 is essential for haematopoiesis in zebrafish. *EMBO Reports*, Vol. 7, No. 6, pp. 649-654

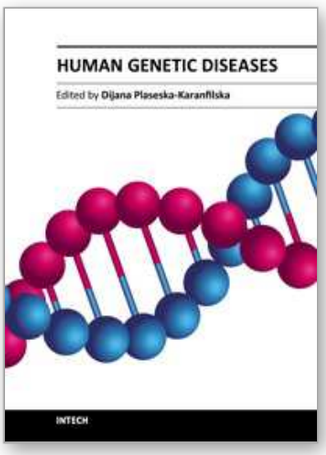
Yang, J.; Meyer, M.; Müller, A.K.; Böhm, F.; Grose, R.; Dauwalder, T.; Verrey, F.; Kopf, M.; Partanen, J.; Bloch, W.; Ornitz, D.M. & Werner, S. (2010). Fibroblast growth factor receptors 1 and 2 in keratinocytes control the epidermal barrier and cutaneous homeostasis. *Journal of Cell Biology*, Vol. 188, No. 6, pp. 935-952

Yilmaz, Y.; Eren, F.; Yonal, O.; Kurt, R.; Aktas, B.; Celikel, C.A.; Ozdogan, O.; Imeryuz, N.; Kalayci, C. & Avsar, E. (2010). Increased serum FGF21 levels in patients with nonalcoholic fatty liver disease. *European Journal of Clinical Investigation*, Vol. 40, No. 10, pp. 887-892

Zhang, X.; Ibrahimi, O.A.; Olsen, S.K.; Umemori, H.; Mohammadi, M. & Ornitz, D.M. (2006). Receptor specificity of the fibroblast growth factor family. The complete mammalian FGF family. *Journal of Biological Chemistry*, Vol. 281, No. 23, pp. 15694-15700

Zhang, X.; Yeung, D.C.; Karpisek, M.; Stejskal, D.; Zhou, Z.G.; Liu, F.; Wong, R.L.; Chow, W.S.; Tso, A.W.; Lam, K.S. & Xu, A. (2008). Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. *Diabetes*, Vol. 57, No. 5, pp. 1246-1253

Zhou, M.; Sutliff, R.L.; Paul, R.J.; Lorenz, J.N.; Hoying, J.B.; Haudenschild, C.C.; Yin, M.; Coffin, J.D.; Kong, L.; Kranias, E.G.; Luo, W.; Boivin, G.P.; Duffy, J.J.; Pawlowski, S.A. & Doetschman, T. (1998). Fibroblast growth factor 2 control of vascular tone. *Nature Medicine*, Vol. 4, No. 2, pp. 201-207



Human Genetic Diseases

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The genetics science is less than 150 years old, but its accomplishments have been astonishing. Genetics has become an indispensable component of almost all research in modern biology and medicine. Human genetic variation is associated with many, if not all, human diseases and disabilities. Nowadays, studies investigating any biological process, from the molecular level to the population level, use the â€œgenetic approachâ€ to gain understanding of that process. This book contains many diverse chapters, dealing with human genetic diseases, methods to diagnose them, novel approaches to treat them and molecular approaches and concepts to understand them. Although this book does not give a comprehensive overview of human genetic diseases, I believe that the sixteen book chapters will be a valuable resource for researchers and students in different life and medical sciences.

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