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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 (Kharitonov, 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-Fgf23*. 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; *Fgf1/2/5*, *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 *FGF1/2/5*, *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 immunoglobulin-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 PLC γ (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). α Klotho is a single-pass transmembrane protein of ~1,000 amino acids with a short cytoplasmic domain. The phenotypes of α Klotho knockout mice are very similar to those of *Fgf23* knockout mice (Shimada et al., 2004), indicating that FGF23 and α Klotho may function in a common signal transduction pathway. α Klotho most efficiently binds to and activates FGFR1c among several isoforms of FGFRs in cultured cells, suggesting that FGFR1c can transduce an FGF23/ α Klotho signal (Urakawa et al., 2006).

β Klotho is a protein that shares structural similarity and characteristics with α Klotho. The phenotypes of β Klotho 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 β Klotho-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/ β Klotho signal. β Klotho is also essential for FGF21 signaling in cultured cells (Kharitonov et al., 2008). However, *Fgf21* knockout mouse phenotypes are distinct from β Klotho knockout mouse phenotypes (Ito et al., 2005; Hotta et al., 2009). In addition, the administration of recombinant human FGF21 to β Klotho knockout mice demonstrated that FGF21 signals can be transduced in the absence of β Klotho (Tomiya et al., 2010). These results indicate the existence of a β Klotho-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 *Fgfs*, *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 *Fgfs* has been identified in *Ciona intestinalis*. The ancestral gene of endocrine *Fgfs*, *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 & Kónsihi, 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 <i>Fgf14</i>
FGF13	-
FGF14	Ataxia, paroxysmal hyperkinetic movement disorder
FGF15/19 *	Impaired cardiac outflow tract morphogenesis and bile acid metabolism
FGF16	Impaired cardiac and facial development Impaired embryonic cardiomyocyte 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 paroxysmal 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 atherosclerosis (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 cortisol 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 (ADHR) 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 paraneoplastic 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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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 “genetic approach” 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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