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-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; 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).

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Fig. 1. Action mechanisms of Fgfs. Fgfs act on target cells in a paracrine, endocrine, or intracrine manner.
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$\gamma$ (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). $\alpha$Klotho is a single-pass transmembrane protein of ~1,000 amino acids with a short cytoplasmic domain. The phenotypes of $\alpha$Klotho knockout mice are very similar to those of Fgf23 knockout mice (Shimada et al., 2004), indicating that FGF23 and $\alpha$Klotho may function in a common signal transduction pathway. $\alpha$Klotho most efficiently binds to and activates FGFR1c among several isoforms of FGFRs in cultured cells, suggesting that FGFR1c can transduce an FGF23/$\alpha$Klotho signal (Urakawa et al., 2006).

$\beta$Klotho is a protein that shares structural similarity and characteristics with $\alpha$Klotho. The phenotypes of $\beta$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 $\beta$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/$\beta$Klotho signal. $\beta$Klotho is also essential for FGF21 signaling in cultured cells (Kharitonenkov et al., 2008). However, Fgf21 knockout mouse phenotypes are distinct from $\beta$Klotho knockout mouse phenotypes (Ito et al., 2005; Hotta et al., 2009). In addition, the administration of recombinant human FGF21 to $\beta$Klotho knockout mice demonstrated that FGF21 signals can be transduced in the absence of $\beta$Klotho (Tomiyama et al., 2010). These results indicate the existence of a $\beta$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 & 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 microodontia (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).
$\textit{Fgf20}$ 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 $\textit{Fgf14}$                         |
| 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 $\textit{Fgf}$ knockout mice Phenotypes of most $\textit{Fgf}$ knockout mice have been published. Phenotypes of $\textit{Fgf11}, \textit{Fgf13}$, and $\textit{Fgf20}$ knockout mice have not been published. *$\textit{Fgf15}$ is referred to as $\textit{Fg15/19}$.

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 $\textit{Fgf}$ 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 hypothyroid 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; Shakottai 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 ethyl nitrosourea, 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 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 lipatrophy, 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 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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