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JB Review

Fibroblast growth factors: from molecular evolution to roles in development, metabolism and disease

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Fibroblast growth factors (FGFs) are a family of structurally related polypeptides that are essential for embryonic development and that function postnatally as homoeostatic factors, in the response to injury, in the regulation of electrical excitability of cells and as hormones that regulate metabolism. In humans, FGF signalling is involved in developmental, neoplastic, metabolic and neurological diseases. *Fgf*s have been identified in metazoans but not in unicellular organisms. In vertebrates, FGFs can be classified as having intracrine, paracrine and endocrine functions. Paracrine and endocrine FGFs act via cell-surface FGF receptors (FGFRs); while, intracrine FGFs act independent of FGFRs. The evolutionary history of the *Fgf* family indicates that an intracrine *Fgf* is the likely ancestor of the *Fgf* family. During metazoan evolution, the *Fgf* family expanded in two phases, after the separation of protostomes and deuterostomes and in the evolution of early vertebrates. These expansions enabled FGFs to acquire diverse actions and functions.

Keywords: Development/disease/evolution/FGF/metabolism.

Abbreviations: BMP, bone morphogenetic protein; FGF, fibroblast growth factor; FGFR, FGF receptor; MAPK, mitogen-activated protein kinase; PCR, polymerase chain reaction; PI3K, phosphatidylinositol 3-kinase; PLCγ, phospholipase Cγ; STAT, signal transducer and activator of transcription.

Various signalling pathways are activated in a highly coordinated manner to ensure proper development and morphogenesis in vertebrates. Secreted signalling molecules such as fibroblast growth factors (FGFs), bone morphogenetic proteins (BMPs), WNTs and Hedgehogs play crucial roles in development and morphogenesis by acting over variable distances to influence intracellular signalling events in neighbouring cells. FGFs are polypeptide growth factors with diverse biological activities. The mammalian FGF family comprises 22 members. These FGFs can be classified as intracellular FGFs (iFGFs), canonical FGFs and hormone-like FGFs (hFGFs) by their mechanisms of action (*1*). In this review, we refer to intracellular, canonical and hFGFs as intracrine, paracirne and endocrine FGFs, respectively. Paracrine FGFs mediate biological responses by binding to and activating cell surface tyrosine kinase FGFRs. They act as local paracrine signalling molecules and function in multiple developmental processes including differentiation, cell proliferation and migration (*1*, *2*). Endocrine FGFs are thought to mediate biological responses in an FGFR-dependent manner. However, they function over long distances as endocrine hormones (*3*, *4*). In contrast, intracrine FGFs act as FGFR-independent intracellular molecules that regulate the function of voltage gated sodium channels (*5*, *6*).

The mouse is a widely used mammalian model for studying gene function. Targeted mutagenesis of *Fgf* genes in mice has elucidated their functions in development and metabolism. In addition, evidence for the involvement of FGF signalling in hereditary, paraneoplastic and metabolic diseases has also accumulated. FGF-signalling disorders contribute to pathological conditions. Several comprehensive reviews on FGFs and FGFRs have been published (*1*, *2*, *7–9*). In this article, we provide a succinct review of the FGF family, focusing on its evolutionary history, physiological roles in mice and pathophysiological roles in humans.

The FGF family

'Invention is often the mother of necessity, rather than vice versa.' (Jared Diamond, 1937∼).

The prototypic FGFs, FGF1 and FGF2, were originally isolated from the brain and pituitary as mitogens for cultured fibroblasts (*10*, *11*). Several FGFs have since been isolated as growth factors for cultured cells. In addition, several *Fgf* genes have been identified by homology-based PCR or searches in DNA databases. A few *Fgf* genes also have been identified as genes responsible for hereditary diseases or cancer (*1*, *2*, *7–9*).

The human *Fgf* gene family comprises 22 members including *Fgf1*-*Fgf23*. *Fgf15* has not been identified in humans. No other *Fgf* genes have been identified in the complete human genome sequence. Human FGFs contain ∼150–300 amino acids and have a conserved core of ∼120 amino acids with ∼30–60% identity (*12*). The mouse *Fgf* family also comprises 22 members including *Fgf1*–*Fgf23* (*1*). *Fgf19* has not been identified in the mouse and rat. *Fgf15* and *Fgf19* are likely to be orthologous genes in vertebrates. Except for mouse and rat, the *Fgf15/19* orthologues were named *Fgf19* in other vertebrates. In this review, we refer to these genes as *Fgf15/19*.

The FGF subfamilies and their mechanisms of action

Phylogenetic analysis of the human *Fgf* gene family identify seven subfamilies; *Fgf1/2*, *Fgf4/5/6*, *Fgf3/7/10/22*, *Fgf8/17/18*, *Fgf9/16/20*, *Fgf11/12/13/14* and *Fgf15/19/21/23* (Fig. 1A). Phylogenetic analysis indicates potential evolutionary relationships in the gene family. However, it alone is not sufficient to determine these relationships. Analysis of gene loci on chromosomes indicates more precise evolutionary relationships in a gene family. Their conserved chromosomal locations (synteny) identify 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*. *Fgf* subfamilies indicated by phylogenetic analysis and gene-location analysis are similar to each other, but not identical. For example, gene location analysis indicates that *Fgf3* and *Fgf5* should be members of an *Fgf3/4/6* and *Fgf1/2/5* subfamily, respectively (Fig. 1B). The mouse *Fgf* gene subfamiles are identical to the human *Fgf* gene subfamilies (*1*, *12*).

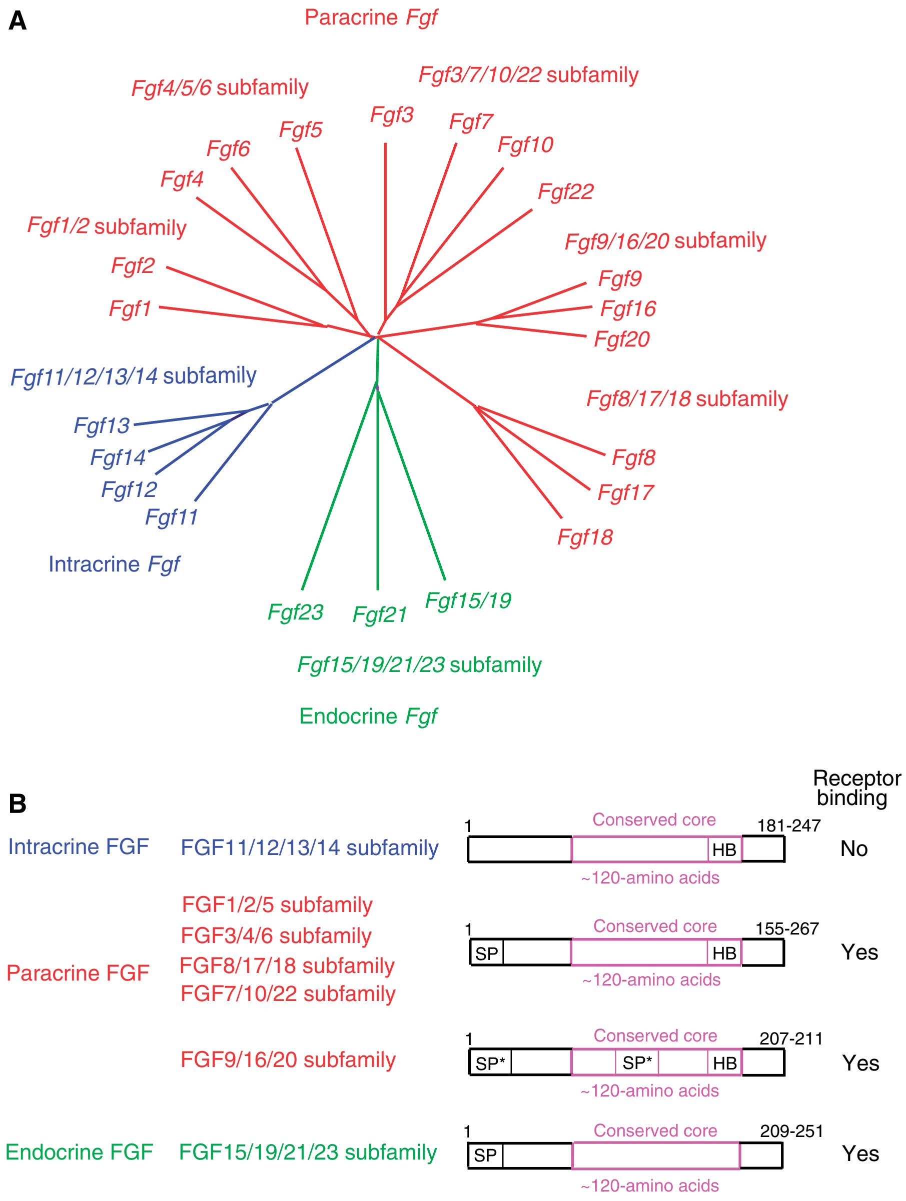

Fig. 1 Evolutionary relationships within the human *Fgf* gene family and schematic representations of FGF structures. (A) Phylogenetic analysis suggests that 22 *Fgf* genes can be arranged into seven subfamilies containing two to four members each. Branch lengths are proportional to the evolutionary distance between each gene. (B) Gene-location analysis suggests that the *Fgf* genes can be arranged into seven subfamilies containing three to four members each. FGFs act on target cells in an intracrine, paracrine or endocrine manner. Schematic representations of intracrine, paracrine and endocrine FGF structures are shown. SP, SP* and HB indicate a cleavable secreted signal sequence, an uncleaved bipartite secreted signal sequence and a heparin-binding site, respectively.

FGFs also can be classified as intracrine, paracrine and endocrine FGFs by their mechanisms of action (Fig. 1B). Intracrine FGFs, FGF11-FGF14, are not secreted extracellulary. They act as intracellular molecules in an FGFR-independent manner. They interact with intracellular domains of voltage gated sodium channels and with a neuronal MAPK scaffold protein, islet-brain-2 (*5*, *13*). The only known role for intracrine FGFs is in regulating the electrical excitability of neurons and possibly other cell types (*5*, *14–16*).

Paracrine FGFs comprise members of the FGF/1/2/5, FGF3/4/6, FGF7/10/22, FGF8/17/18 and FGF9/16/20 subfamilies (Fig. 1B). Most are secreted proteins with cleavable N-terminal secreted signal peptides, however FGF9, FGF16 and FGF20 have uncleaved bipartite secreted signal sequences (*17*). In contrast, FGF1 and FGF2, which have no N-terminal hydrophobic sequences, are not typical secreted proteins. FGF1 and FGF2 might be released from damaged cells or by an exocytotic mechanism that is independent of the endoplasmic reticulum-Golgi pathway (*18*, *19*). All paracrine FGFs mediate biological responses as extracellular proteins by binding to and activating cell surface tyrosine kinase FGFRs with heparin/heparan sulphate as a cofactor. However, it has also been reported that FGF1, FGF2 and FGF3 can directly translocated to the nucleus and act in an intracrine manner (*20*).

Four *Fgfr* genes, *Fgfr1–Fgfr4*, have been identified in humans and mice (*2*, *9*, *12*). These genes encode receptor tyrosine kinases (~800 amino acids) that contain an extracellular ligand-binding domain with three immunoglobulin-like domains (I, II and III), a transmembrane domain and a split intracellular tyrosine kinase domain. *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 (*21*). 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 the stable interaction with FGFRs and local signalling (*22*). Paracrine FGFs function in development by influencing the intracellular signalling events of neighbouring cells from a distance. The range of FGF signalling is regulated in part by its affinity for extracellular matrix heparan sulphate proteoglycans (*23*) and in part by dimerization of some FGFs (*24*, *25*). FGF binding to FGFRs induces functional dimerization, receptor transphosphorylation and activation of four key downstream signalling pathways: RAS-RAF-MAPK, PI3K-AKT, STAT and PLCγ (*2*, *9*).

Endocrine FGFs, FGF15/19, FGF21 and FGF23, are thought to mediate their biological responses in an FGFR-dependent manner. However, they bind to FGFRs and heparin/heparan sulphate with very low affinity. The reduced heparin-binding affinity enables endocrine FGFs to function in an endocrine manner (Fig. 1C) (*21*, *22*). 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 (*26*). These results indicate 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 (*27*), suggesting the FGFR1c can transduce an FGF23/αKlotho signal.

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 (*28*, *29*). FGF15/19 can bind to a βKlotho–FGFR4 complex in cultured cells. FGF15/19 also activates FGF signalling in hepatocytes that primarily express *Fgfr4* (*30*). These results indicate that FGFR4 may be the primary receptor for transduction for an FGF15/19/βKlotho signal.

βKlotho is also essential for FGF21 signalling in cultured cells (*31*). However, *Fgf21* knockout mouse phenotypes are distinct from *βKlotho* knockout mouse phenotypes (*28*, *32*). In addition, the administration of recombinant human FGF21 to *βKlotho* knockout mice demonstrated that FGF21 signals can be transduced in the absence of βKlotho (*33*). These results indicate the existence of a βKlotho-independent FGF21-signalling pathway in which undefined cofactors might be involved.

Evolutionary history of the *Fgf* family

'Nothing in biology makes sense except in the light of evolution.' (Theodosius Dobzhansky, 1900–1975).

The FGF-signalling system has been conserved throughout metazoan evolution. Two *Fgf-like* genes, *egl-17* and *let-756*, have been identified in the nematode, *Caenorhabditis elegans* (*34*). Six *Fgf-like* genes, *Fgf4-like*, *Fgf5-like*, *Fgf8-like*, *Fgf9-like*, *Fgf10-like* and *Fgf13-like*, which are potential ancestral genes of the human/mouse *Fgf* subfamilies, have been identified in the ascidian, *Ciona intestinalis* (*35*). 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 (Fig. 2A).

The evolutionary history of the mouse *Fgf* family has been proposed (Fig. 2B) (*1*). 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 (Figs 1B and 2B). 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* (Figs 1B and 2B). 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

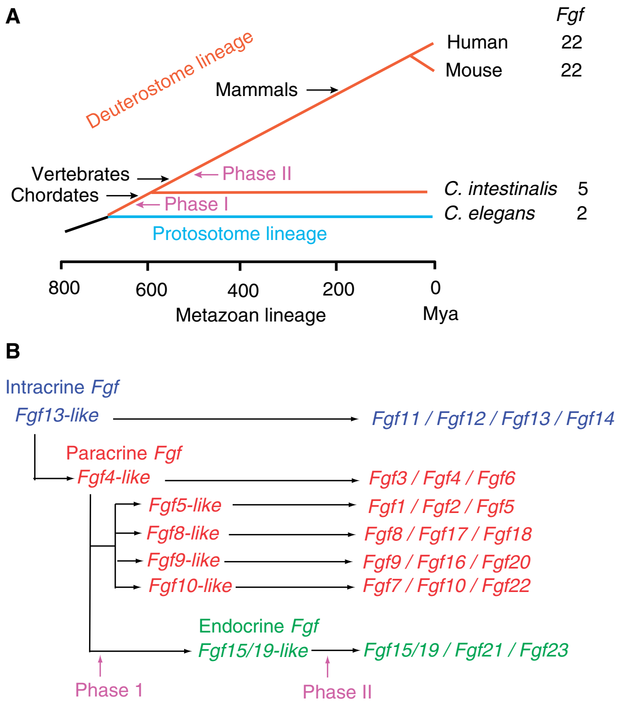

Fig. 2 The evolutionary lineage of metazoan organisms and functional evolutionary history of the *Fgf* gene family. (A) The entire *C. elegans*, *C. intestinalis*, mouse and human genomes have been sequenced. The *Fgf* gene family expanded in two major phases (I and II) during metazoan evolution. Phase I occurred after the separation of protostomes and deutrostomes. Phase II occurred at the early emergence of vertebrates. Mya, million years ago. (B) *Fgf13-like* is the ancestral gene of the *Fgf* gene 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* in phase I 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 large-scale genome duplication events in phase II.

Fgf5-like, *Fgf8-like* and *Fgf10-like*. A cleavable secreted signal sequence also evolved into an uncleaved bipartite signal sequence in *Fgf9-like* (*36–38*). These FGFs with heparin-binding sites function in a paracrine manner. In contrast, no ancestral gene of endocrine *Fgf*s has been identified in *C 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 (Figs 1B and 2B). 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 during the evolution of early vertebrates (Fig. 2B).

Physiological roles of FGFs in mice

Most *Fgf* genes have been disrupted by homologous recombination in mice. Phenotypes range from early embryonic lethality to changes in adult physiology (Table I).

Roles of intracrine Fgfs in neuronal functions

Fgf14 knockout mice are viable. However, they develop ataxia and a paraoxysmal hyperkinetic movement disorder (*5*, *14*, *15*). In contrast, *Fgf12* knockout mice are apparently normal. *Fgf12*/*Fgf14* double knockout mice show severe ataxia and other neurological deficits (*5*). Phenotypes of *Fgf11* and *Fgf13* knockout mice have not been reported.

Roles of paracrine Fgfs in development

Paracrine FGFs are expected to act as growth/differentiation factors in developing embryos. *Fgf* knockout mouse phenotypes mostly indicate roles as growth/differentiation factors.

Fgf1 knockout mice are viable and normal (*39*). *Fgf2* knockout mice are also viable, but have decreased vascular tone and reduced numbers of neurons in deep cortical layers (*40–42*). *Fgf2* knockout mice show impaired recovery from ischaemic injury to the heart (*43*, *44*). *Fgf3* knockout mice are viable, but have phenotypes that include inner ear malformation and microdontia (*45–48*). *Fgf4* and *Fgf8* knockout mice die at early embryonic stages. *Fgf4* and *Fgf8* have essential roles in blastocyst formation and gastrulation, respectively (*49*, *50*). 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 (*51*). *Fgf6* knockout mice have defects in muscle regeneration (*52*). *Fgf7* knockout mice have impaired hair and kidney development (*53*, *54*). *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 (*55–58*). *Fgf9* and *Fgf18* have essential roles in the development of mesenchymal components of multiple organs (*59–64*). *Fgf16* knockout mice on a C57BL/6 genetic background are viable, but have impaired embryonic cardiomyocyte proliferation (*65*). *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 (*66*, *67*). *Fgf17* and *Fgf22* knockout mice are viable, but show impaired hindbrain development and impaired synaptic differentiation, respectively (*68*, *69*). In addition, *Fgf22* knockout mice also show a clear delay in weight gain upon sexual maturity (R. Grose *et al.*, unpublished data). *Fgf20* knockout mice are viable but have profound hearing loss (D.M. Ornitz *et al.*, ARO abstract 423, 2009).

Roles of endocrine Fgfs in development and metabolism

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 (*70*). Endocrine FGFs also act as differentiation factors in embryos and as hormones in adults (*4*).

Table I. Phenotypes in *Fgf* knockout mice.

Gene	Phenotype	
Fgf1	Viable	None identified
Fgf2	Viable	Loss of vascular tone, slight loss of cortical neurons, defects in heart repair
Fgf3	Viable	Inner ear malformations, microdontia
Fgf4	Lethal, E4-5	Defects in blastocyst formation
Fgf5	Viable	Abnormal long hair
Fgf6	Viable	Defective muscle regeneration
Fgf7	Viable	Impaired hair and kidney development
Fgf8	Lethal, E8	Defects in gastrulation, limb development, organogenesis
Fgf9	Lethal, PD0	Impaired multiple organ development
Fgf10	Lethal, PD0	Impaired multiple organ development
Fgf11	–	–
Fgf12	Viable	None identified, functional redundancy with *Fgf14*
Fgf13	–	–
Fgf14	Viable	Ataxia, paraoxysmal hyperkinetic movement disorder
Fgf15/19[a]	Lethal, E13.5-P7	Impaired cardiac outflow tract morphogenesis and bile acid metabolism
Fgf16	Lethal, E11.5	Impaired cardiac and facial development
	Viable	Impaired embryonic cardiomyocte proliferation
Fgf17	Viable	Impaired hindbrain development
Fgf18	Lethal, PD0	Impaired multiple organ development
Fgf20	Viable	Impaired inner ear development
Fgf21	Viable	Impaired lipid metabolism
Fgf22	Viable	Impaired synapse differentiation and delay in weight gain
Fgf23	Lethal, PW4-13	Impaired phosphate and vitamin D metabolism

Phenotypes of *Fgf11*, *Fgf13* and *Fgf20* knockout mice have not been published. [a]*Fgf15* is referred to as *Fg15/19*. E, embryonic day; PD, postnatal day; PW, postnatal week.

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 (*71*). Although most *Fgf15/19* knockout mice die by post-natal 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 (*29*). *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 non-esterified fatty acid levels. Their phenotypes indicate that *Fgf21* is important for the metabolic regulation of lipolysis in white adipose tissue (*32*). *Fgf21* knockout mice fed a ketogenic diet show partial impairments in ketogenesis (*72*). However, we have observed that ketogenesis is not impaired in *Fgf21* knockout mice fed a ketogenic diet (N. Itoh *et al.*, unpublished data). *Fgf23* knockout mice survive until birth, but then gradually die, usually by 12 weeks of age (*26*). The mice show hyperphosphataemia 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 target organs including parathyroid gland and osteoblasts (*73*, *74*).

Although roles of FGFs in embryogenesis have been revealed from *Fgf* knockout mouse phenotypes, their contributions to adult physiology remain relatively unexplored. The widespread expression of *Fgf* genes in the adult tissues suggests multiple roles in tissue homeostasis and repair (*75*). In addition to endocrine FGFs, which have well defined endocrine roles in the adult (*4*), emerging reports indicate homoeostatic and regenerative roles for canonical paracrine FGF signalling (*76–78*).

FGF-signalling disorders in human diseases

As described earlier, FGF-signalling is crucial to development and metabolism. In addition, FGF-signalling disorders also result in human hereditary, paraneoplastic and metabolic diseases (Tables II and III).

Intracrine FGF-signalling disorders

Börjeson–Forssman–Lehmann syndrome (BFLS) is a syndromic X-linked mental retardation disease. *Fgf13* is a candidate causative gene for BFLS (*79*). Hereditary spinocerebellar ataxias (SCAs) are a clinically and genetically heterogeneous group of neurodegenerative disorders. One SCA with early onset tremour, dyskinesia and slowly progressive cerebellar ataxia is caused by *Fgf14* mutations (*80–82*).

Paracrine FGF-signalling disorders

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* (*47*).

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

Table II. Human hereditary diseases caused by *Fgf* mutations.

Gene	Disease	Gene mutation
Fgf3	Michel aplasia	Lost-of-function
Fgf8	Familial isolated hypogonadotropic hypogonadism	Lost-of-function
	Cleft lip and/or plate	Lost-of-function
Fgf10	Aplasia of lacrimal and salivary glands	Lost-of-function
	Lacrimo-auriculo-dento-digital syndrome	Lost-of-function
Fgf13	BFLS	Lost-of-function
Fgf14	Hereditary spinocerebellar ataxias	Lost-of-function
Fgf20	A potential risk factor for Parkinson disease	Lost-of-function
Fgf23	Autosomal dominant hypophosphataemic rickets	Gain-of-function
	Familial tumoural calcinosis	Lost-of-function

Table III. Human paraneoplastic or metabolic diseases caused by endocrine FGF-signalling disorders.

Gene	Disease	FGF signalling
Paraneoplastic disease		
Fgf15/19[a]	Extrahepatic cholestasis caused by a pancreatic tumour	Increase
Fgf23	Tumour-induced osteomalacia	Increase
Metabolic disease		
Fgf15/19[a]	Chronic hemodialysis	Increase
	Non-alcoholic fatty liver disease (NAFLD)	Impaired response
Fgf21	Type 2 diabetes	Increase
	Obesity	Increase
	Cushing's syndrome	Increase
	NAFLD	Increase
	Anorexia nervosa	Decrease
Fgf23	Renal failure	Increase

[a] *Fgf19* is referred to as *Fg15/19*.

human gonadotropin-releasing hormone deficiency (*83*). 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 (*84*).

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 (*85*, *86*).

Fgf20 was originally identified as a neurotrophic factor preferentially expressed in dopaminergic neurons within the substantia nigra pars compacta of rat brain (*87*). 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 (*88*).

Endocrine FGF signalling disorders

Serum FGF15/19 levels are markedly increased in patients with extrahepatic cholestasis caused by a pancreatic tumour. FGF15/19 is abundantly expressed in the liver of cholestatic patients, but not in the normal liver. FGF15/19 signalling may be involved in some of the adaptations that protect the liver against bile salt toxicity (*89*). Serum FGF15/19 levels are also significantly increased in patients on chronic hemodialysis (*90*). 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 (*91*).

Serum FGF21 levels are increased in patients with type 2 diabetes and obesity, Cushing's syndrome or NAFLD (*92–94*). In contrast, serum FGF21 levels are decreased in patients with anorexia nervosa (*95*).

FGF23-signalling disorders also result in diseases (*96*). Autosomal dominant hypophosphatemic rickets (AHDR) is caused by gain-of-function mutations of *Fgf23* (*97*). FGF23 is partially cleaved by intracellular proteolysis. The cleaved FGF23 forms lose their biological activity. *Fgf23* mutations in ADHR result in impaired proteolysis of FGF23 and increased serum levels of active FGF23 (*98*). Reduced FGF23 signalling also causes human hereditary diseases. Familial tumoural calcinosis (FTC) is characterized by ectopic calcification and hyperphosphataemia. Loss-of-function mutations of *Fgf23* result in FTC. These mutations destabilize the tertiary structure of FGF23 and increase its susceptibility to degradation (*99*). Tumours that over produce FGF23 also cause tumour-induced osteomalacia, which is a paraneoplasitc disease characterized by hypophosphataemia caused by renal phosphate wasting (*100*). In addition, 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 (*101*).

Conclusion

The prototypic FGFs, FGF1 and FGF2, were originally isolated as mitogens for fibroblasts from the brain and pituitary >20 years ago. Many FGF proteins or *Fgf* genes have since been isolated as growth factors for cultured cells or identified by homology-based PCR and/or homology-based searches in DNA databases, respectively. The human/mouse *Fgf* family comprises 22 members. FGFs are now recognized as polypeptide growth factors with diverse biological activities and act as intracellular or extracellular signalling molecules in an intracrine, paracrine or endocrine manner. *Fgf* knockout mice indicate that FGFs play crucial roles in development and metabolism. In addition, the roles of FGFs in human diseases indicate that FGF-signalling disorders contribute to pathological conditions. Although *Fgf1* and *Fgf2* are genes for prototypic FGFs, they are not ancestral genes of the *Fgf* family in evolution. The ancestral gene of the *Fgf* family is an ancestral gene of the intracrine *Fgf* subfamily, *Fgf13-like*. The evolutional history of the *Fgf* gene family indicates that *Fgf* genes acquired a diversity of roles and functions with the expansion of the *Fgf* gene family by gene duplication after the diversion of protostomes and deuterostomes and by two genome-duplication events during the evolution of early vertebrates. Secreted signalling molecules such as BMPs, WNTs and Hedgehogs also play crucial roles in development by influencing the intracellular signalling events of their neighbours from a distance. FGFs, along with these signalling molecules, have roles in diverse biological processes of 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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Conflict of interest

None declared.

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