



# The Fibroblast Growth Factor signaling pathway

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The signaling component of the mammalian Fibroblast Growth Factor (FGF) family is comprised of eighteen secreted proteins that interact with four signaling tyrosine kinase FGF receptors (FGFRs). Interaction of FGF ligands with their signaling receptors is regulated by protein or proteoglycan cofactors and by extracellular binding proteins. Activated FGFRs phosphorylate specific tyrosine residues that mediate interaction with cytosolic adaptor proteins and the RAS-MAPK, PI3K-AKT, PLC $\gamma$ , and STAT intracellular signaling pathways. Four structurally related intracellular non-signaling FGFs interact with and regulate the family of voltage gated sodium channels. Members of the FGF family function in the earliest stages of embryonic development and during organogenesis to maintain progenitor cells and mediate their growth, differentiation, survival, and patterning. FGFs also have roles in adult tissues where they mediate metabolic functions, tissue repair, and regeneration, often by reactivating developmental signaling pathways. Consistent with the presence of FGFs in almost all tissues and organs, aberrant activity of the pathway is associated with developmental defects that disrupt organogenesis, impair the response to injury, and result in metabolic disorders, and cancer. © 2015 Wiley Periodicals, Inc.

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## INTRODUCTION

The Fibroblast Growth Factor (FGF) family is comprised of secreted signaling proteins (secreted FGFs) that signal to receptor tyrosine kinases and intracellular non-signaling proteins (intracellular FGFs (iFGFs)) that serve as cofactors for voltage gated sodium channels and other molecules (Table 1(a) and Figure 1(a)). Additionally, secreted FGFs and iFGFs may have direct functions in the nucleus and functional interactions with other cellular proteins. Members of both branches of the FGF family are related by core sequence conservation and structure and are found in vertebrates and invertebrates.<sup>1,2</sup> Secreted FGFs are expressed in nearly all tissues and they serve essential roles in the earliest stages of

embryonic development, during organogenesis, and in the adult, where they function as homeostatic factors that are important for tissue maintenance, repair, regeneration, and metabolism (Table 2(a)). In general, secreted FGFs function as autocrine or paracrine factors (canonical FGFs; also called paracrine FGFs), however, three members of the secreted FGFs have evolved to function as endocrine factors (endocrine FGFs) with essential roles in the adult where they regulate phosphate, bile acid, carbohydrate and lipid metabolism in addition to the canonical FGF functions that control cell proliferation, differentiation and survival.<sup>75–77,98,149–163</sup>

At the cellular level, secreted FGFs regulate fundamental cellular processes that include positive and negative regulation of proliferation, survival, migration, differentiation, and metabolism.

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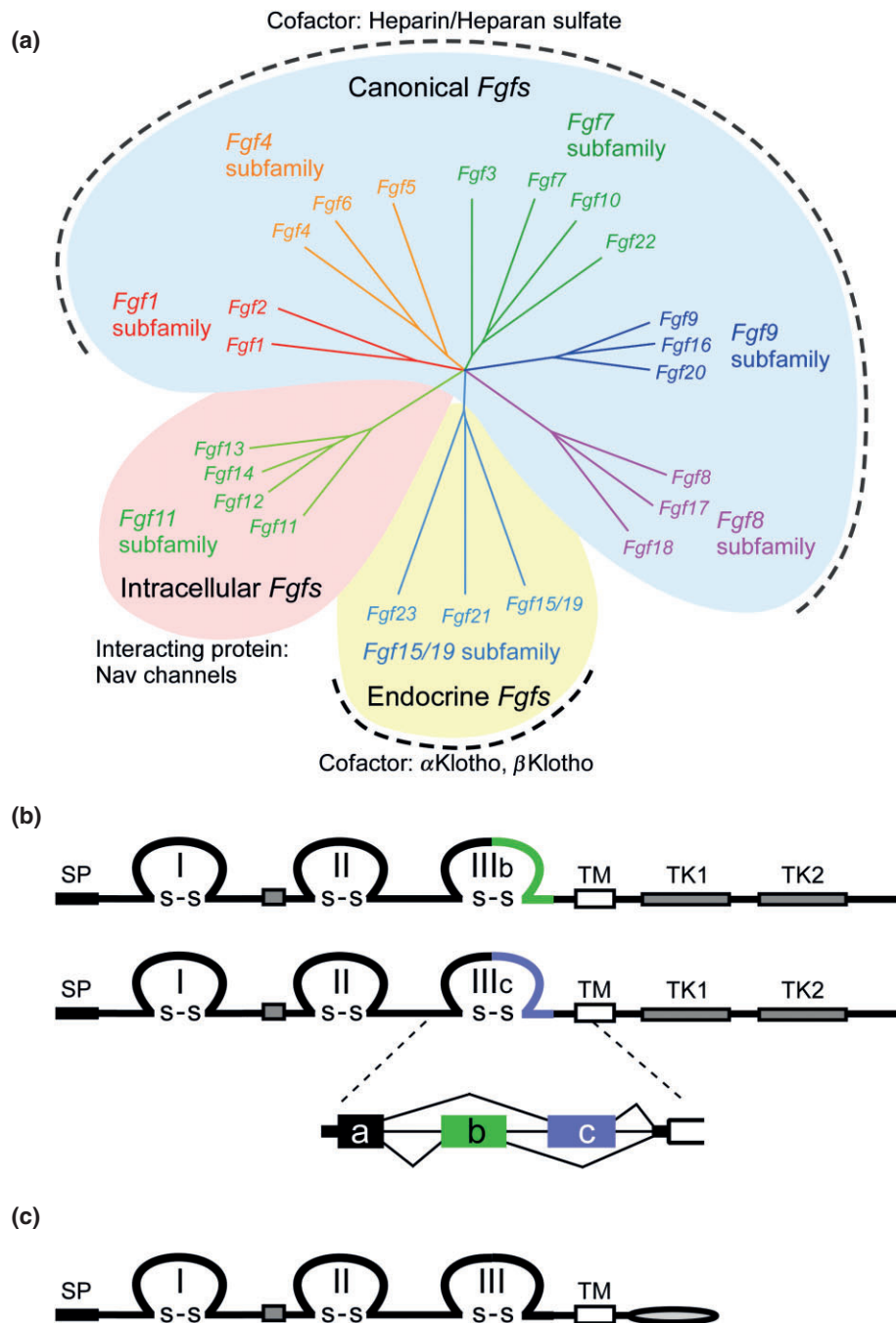
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**TABLE 1** | Nomenclature of the Mammalian *Fgf* and *Fgfr* family

HUGO/MGI Symbol	Name	Alternative Symbol	Name, Comments
<b>(a) <i>Fgf</i></b>			
<i>FGF1/Fgf1</i>	Fibroblast Growth Factor 1	<i>aFgf</i> <i>Hbgf1</i> <i>Ecgr</i>	Acidic Fgf Heparin-binding growth factor 1 Endothelial cell growth factor
<i>FGF2/Fgf2</i>	Fibroblast Growth Factor 2	<i>bFgf</i> <i>Hbgf2</i>	Basic Fgf Heparin-binding growth factor 2
<i>FGF3/Fgf3</i>	Fibroblast Growth Factor 3	<i>Int-2</i> <i>V-Int-2</i>	Int-2 oncogene MMTV integration site 2
<i>FGF4/Fgf4</i>	Fibroblast Growth Factor 4	<i>Hst1</i> <i>Hstf1</i> <i>K-Fgf, Kfgf</i>	Human stomach tumor oncogene Heparin secretory transforming protein 1 Kaposi sarcoma Fgf
<i>FGF5/Fgf5</i>	Fibroblast Growth Factor 5		
<i>FGF6/Fgf6</i>	Fibroblast Growth Factor 6	<i>Hst2</i>	Hst2 oncogene
<i>FGF7/Fgf7</i>	Fibroblast Growth Factor 7	<i>Kgf</i>	Keratinocyte growth factor
<i>FGF8/Fgf8</i>	Fibroblast Growth Factor 8	<i>Aigf</i> <i>Kal6</i>	Androgen induced growth factor
<i>FGF9/Fgf9</i>	Fibroblast Growth Factor 9	<i>Gaf</i> <i>Eks</i>	Glia activating factor Elbow knee synostosis
<i>FGF10/Fgf10</i>	Fibroblast Growth Factor 10	<i>Kgf-2</i>	Keratinocyte growth factor 2
<i>FGF11/Fgf11</i>	Fibroblast Growth Factor 11	<i>Fhf3</i>	Fibroblast Growth Factor homologous factor 3
<i>FGF12/Fgf12</i>	Fibroblast Growth Factor 12	<i>Fhf1</i>	Fibroblast Growth Factor homologous factor 1
<i>FGF13/Fgf13</i>	Fibroblast Growth Factor 13	<i>Fhf2</i>	Fibroblast Growth Factor homologous factor 2
<i>FGF14/Fgf14</i>	Fibroblast Growth Factor 14	<i>Fhf4</i> <i>Sca27</i>	Fibroblast Growth Factor homologous factor 4 spinocerebellar ataxia 27
<i>Fgf15</i>	Fibroblast Growth Factor 15		Rodent ortholog of vertebrate <i>Fgf19</i>
<i>FGF16/Fgf16</i>	Fibroblast Growth Factor 16		
<i>FGF17/Fgf17</i>	Fibroblast Growth Factor 17		Called FGF-13 in some older literature
<i>FGF18/Fgf18</i>	Fibroblast Growth Factor 18		
<i>FGF19</i>	Fibroblast Growth Factor 19		Human ortholog of rodent <i>Fgf15</i>
<i>FGF20/Fgf20</i>	Fibroblast Growth Factor 20		
<i>FGF21/Fgf21</i>	Fibroblast Growth Factor 21		
<i>FGF22/Fgf22</i>	Fibroblast Growth Factor 22		
<i>FGF23/Fgf23</i>	Fibroblast Growth Factor 23		
<b>(b) <i>Fgfr</i></b>			
<i>FGFR1/Fgfr1</i>	Fgf receptor 1	<i>Flg</i> <i>Flt2</i> <i>Cek</i> <i>KAL2</i> <i>K-sam</i>	Fms-like gene Fms-like tyrosine kinase 2 Chicken embryo kinase 1 Kallman syndrome 2 KATO-III cell-derived stomach cancer amplified gene
<i>FGFR2/Fgfr2</i>	Fgf Receptor 2	<i>Bek</i> <i>Cek3</i> <i>Kgfr</i>	Bacterial expressed kinase Chicken embryo kinase 3 KGF receptor
<i>FGFR3/Fgfr3</i>	Fgf Receptor 3	<i>Cek2</i> <i>Ach</i>	Chicken embryo kinases 2 Achondroplasia
<i>FGFR4/Fgfr4</i>	Fgf Receptor 4	<i>Tkf</i>	Tyrosine kinase related to Fibroblast Growth Factor receptor
<i>FGFRL1/Fgfrl1</i>	Fgf receptor like 1	<i>Fgfr5</i>	Fgf receptor 5



**FIGURE 1** | FGF and FGFR families. (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. The *Fgf1*, *Fgf4*, *Fgf7*, *Fgf8*, and *Fgf9* subfamily genes encode secreted canonical FGFs, which bind to and activate FGFRs with heparin/HS as a cofactor. The *Fgf15/19* subfamily members encode endocrine FGFs, which bind to and activate FGFRs with the Klotho family protein as a cofactor. The *Fgf11* subfamily genes encode intracellular FGFs, which are non-signaling proteins serving as cofactors for voltage gated sodium channels and other molecules. (b) Schematic representations of FGFR protein structures are shown. FGFR is a receptor tyrosine kinase of ~800 amino acids with several domains including three extracellular immunoglobulin-like domains (I, II, and III), a transmembrane domain (TM), and two intracellular tyrosine kinase domains (TK1 and TK2). SP indicates a cleavable secreted signal sequence. The *Fgfr* gene family is comprised of four members, *Fgfr1*–*Fgfr4*. Among them, *Fgfr1*–*Fgfr3* generate two major splice variants of immunoglobulin-like domain III, referred to as IIIb and IIIc, which are essential determinants of ligand-binding specificity. (c) The schematic representation of FGFR5 protein structure is shown. FGFR5, with structural similarity to FGFRs, is a membrane protein of ~500 amino acids with three extracellular immunoglobulin-like domains (I, II, and III), a transmembrane domain (TM), and a short intracellular tail with no tyrosine kinase domain. SP indicates a cleavable secreted signal sequence.

**TABLE 2** | Phenotypes of Null and Tissue-Specific *Fgf* Mutations

Gene Name	Viability /Age at Death of Null Mutant	Null Phenotype (Organ, Structure, or Cell Type Affected)	Tissue-Specific (Conditional) Phenotypes, Redundant Phenotypes, Phenotypes Induced by Physiological Challenge	Selected References
<b>(a) Phenotypes of germline and conditional loss-of-function <i>Fgf</i> mutations in mice</b>				
<i>Fgf1</i>	Viable	No apparent phenotype	An aggressive diabetic phenotype with white adipocyte remodeling on high-fat diet	3,4
<i>Fgf2</i>	Viable	Cortical neuron, vascular smooth muscle, blood pressure, skeletal development, and wound healing	Decreased cardiac hypertrophy induced by ischemic injury and delayed wound healing; Increased bone mineralization in high molecular weight isoform knockout	5–11
<i>Fgf3</i>	Viable	Inner ear and skeletal development	Heart development (redundant with <i>Fgf10</i> )	12,13
<i>Fgf4</i>	E4-5	Blastocyst inner cell mass	Limb bud development (redundant with <i>Fgf8</i> )	14–17
<i>Fgf5</i>	Viable	Hair follicle development		18
<i>Fgf6</i>	Viable	Muscle development	Muscle regeneration	19–21
<i>Fgf7</i>	Viable	Hair follicle and ureteric bud development and synaptogenesis	Thymus regeneration (radiation injury) and wound healing	22–26
<i>Fgf8</i>	E7	Gastrulation	Heart field, limb, somitogenesis, kidney, CNS, inner ear development, spermatogenesis	27–39
<i>Fgf9</i>	P0	Lung, heart, skeletal, gonad, inner ear, and intestine development	Migration of cerebellar granule neurons and kidney agenesis (redundant with <i>Fgf20</i> )	40–53
<i>Fgf10</i>	P0	Limb bud, lung bud, trachea, thymus, pancreas, pituitary, palate, tongue epithelium, cecum, kidney, submandibular, salivary, lacrimal, and mammary gland, heart, stomach, and white adipose tissue	Lung branching morphogenesis and inner ear development (redundant with <i>Fgf3</i> )	54–68
<i>Fgf11</i>	Viable	No identified phenotype		(unpublished)
<i>Fgf12</i>	Viable	No identified phenotype	Severe ataxia and motor weakness (redundant with <i>Fgf14</i> )	69
<i>Fgf13</i>	Viable	Neuronal migration, learning and memory deficits, and microtubule binding		69–73
<i>Fgf14</i>	Viable	Ataxia, motor weakness, learning and memory deficits, and impaired neuronal excitability	Severe ataxia and motor weakness (redundant with <i>Fgf12</i> )	69,74
<i>Fgf15</i>	E13.5-P7	Cardiac outflow tract development, neurogenesis, and bile acid metabolism	Liver regeneration	75–80
<i>Fgf16</i>	Viable	Heart development		81–83
<i>Fgf17</i>	Viable	Cerebellum and frontal cortex development	Promotes cardiac remodeling induced by angiotensin II	31,84
<i>Fgf18</i>	P0	CNS, skeletal, palate, and lung development		40,85–89
<i>Fgf20</i>	Viable	Guards hair, teeth, cochlea, and kidney development	Kidney agenesis (redundant with <i>Fgf9</i> )	40,90–92
<i>Fgf21</i>	Viable	Energy/lipid metabolism		75,93,94

**TABLE 2** | Continued

Gene Name	Viability /Age at Death of Null Mutant	Null Phenotype (Organ, Structure, or Cell Type Affected)	Tissue-Specific (Conditional) Phenotypes, Redundant Phenotypes, Phenotypes Induced by Physiological Challenge	Selected References
<i>Fgf22</i>	Viable	Synaptogenesis	Decreased skin papillomas formation following carcinogenesis challenge	22,95–97
<i>Fgf23</i>	PW4-13	Phosphate and vitamin D homeostasis, deafness, middle ear development		98–102
<b>(b) Phenotypes of germline and conditional loss-of-function <i>Fgfr</i> mutations in mice</b>				
<i>Fgfr1</i>	E7.5-9.5	Gastrulation, Blastocyst inner cell mass	Hematopoietic cell engraftment Osteoblast maturation Limb bud development Hippocampal progenitor cell proliferation Inner ear sensory epithelium Deletion of Ig domain 1 (defect in node regression) Adipocyte metabolism Endothelial <i>Tgfb<math>\beta</math></i> expression and endothelial-mesenchymal transition; Endothelial regulation of CXCR4 in liver regeneration and fibrosis Spermatogenesis	39,103–114
<i>Fgfr2</i>	E10-11	Placenta, no limb buds	Skeletal, lung, limb bud, CNS, GI tract, skin, and adrenal cortex development in <i>Fgfr2b</i> null mice	115–119
<i>Fgfr1/2</i>			Myelin sheath thickness in oligodendrocyte Kidney, metanephric mesenchyme, ureteric bud, ocular gland development	120–126
<i>Fgfr3</i>	Viable	Skeletal overgrowth, inner ear, brain, articular cartilage, oligodendrocyte differentiation, pancreatic growth, intestinal crypt cell growth arrest	Angiogenesis, vascular integrity Hepato-cytoprotective through regulation of cytochrome P450 enzymes	10,127–139
<i>Fgfr4</i>	Viable	Cholesterol metabolism and bile acid synthesis	Alveolar septation and elastogenesis (redundant with <i>Fgfr4</i> ) Increased liver injury and fibrosis induced by carbon tetrachloride Alveolar septation and elastogenesis (redundant with <i>Fgfr3</i> ) Vitamin D homeostasis (redundant with <i>Fgfr3</i> ) Phosphate homeostasis (redundant with <i>Fgfr1</i> )	131,139–146
<i>Fgfr1</i>	P0	Kidney, diaphragm, skeleton		147,148

During early development, FGFs regulate differentiation of the inner cell mass into epiblast and primitive endoderm lineages.<sup>164–167</sup> Later in development, FGFs have key roles in organogenesis, for example in the regulation of the anterior and secondary heart fields,<sup>168,169</sup> induction of limb buds<sup>54,55,170</sup> and lung buds,<sup>54,55</sup> ventral liver and pancreas,<sup>171,172</sup> kidney development,<sup>27,40,120,121,147,</sup> inner ear development,<sup>12,28,41,56,90,103,104,127,173</sup> and brain development.<sup>174,175</sup>

In the adult, FGFs have important roles in response to injury and tissue repair.<sup>176</sup> FGF signaling is cardioprotective following ischemic injury to the heart,<sup>177–179</sup> and is important for epithelial repair in the lung and in wound healing.<sup>180–182</sup> FGF signaling, however, may also increase or decrease tissue fibrosis.<sup>81,183–185</sup> Endocrine FGFs mediate mineral, metabolic, energy, and bile acid homeostasis.<sup>75,98,186,187</sup> *FGF receptor (Fgfr)* mutation, amplification, and gene fusions can drive abnormal morphogenesis, the progression of several types of cancer, and provide escape pathways for drugs that target other oncogenic tyrosine kinase receptors.<sup>152,188–196</sup>

Given the ubiquitous roles for FGF signals in development, homeostasis, and disease, tight regulation of the pathway is essential. Canonical FGFs are tightly bound to heparin/heparan sulfate (HS) proteoglycans (*HSPGs*), which function to limit diffusion through the extracellular matrix (ECM) and serve as cofactors that regulate specificity and affinity for signaling FGFRs.<sup>153,197–201</sup> The endocrine FGFs, evolved with reduced affinity for heparin/HS and the requirement for a protein cofactor,  $\alpha$ Klotho,  $\beta$ Klotho, or KLPH for receptor binding.<sup>75,202</sup> Additional regulation is provided by a fifth non-tyrosine kinase FGFR (FGFRL1) which can bind FGF ligands and possibly function as a decoy receptor, dimerization-induced inhibitor of tyrosine kinase FGFRs, or modulator of receptor turnover or signaling.<sup>203</sup> Downstream of the signaling tyrosine kinase FGFRs, intracellular signaling cascades are also tightly regulated by specialized adaptor proteins such as FGFR substrate 2 $\alpha$  (FRS2 $\alpha$ ) and regulators of the RAS-MAPK and PI3K-AKT pathways such as Sprouty (SPRY) proteins<sup>151,204–207</sup> (Figure 3(a)).

iFGFs (also known as FGF homologous factors (FHF)) are essential regulators of neuronal and myocardial excitability. However, whether iFGFs are required during normal embryonic development is currently not known. Several proteins are known to directly interact with iFGFs. These include members of the voltage gated sodium channel family,<sup>154</sup> IB2 (MAPK8IP2, Mitogen-activated protein

kinase 8-interacting protein 2),<sup>208</sup>  $\beta$ -tubulin,<sup>70</sup> and NEMO<sup>209</sup> (NF- $\kappa$ B essential modulator). Analysis of evolutionary relationships in the FGF family suggests that iFGFs may be the first members of the family to evolve, followed by the acquisition of a signal peptide for secretion, and affinity for heparin/HS to limit diffusion and regulate receptor binding.<sup>210</sup> The most recent evolutionary event led to the endocrine branch of the FGF family, which has reduced affinity for heparin/HS and a requirement for Klotho family cofactors for receptor binding.

In this review we will focus on the roles and regulation of FGF signaling pathways that function during vertebrate organogenesis and on how gain and loss-of-function mutations in the FGF pathway result in developmental or metabolic disease and cancer.

## PATHWAY COMPONENTS

### Fibroblast Growth Factors

#### *Historical Perspective*

Embryo extracts and brain extracts were shown to promote the growth of chicken periosteal fibroblast as early as 1939.<sup>211</sup> A proteinaceous ‘Fibroblast Growth Factor’ activity was first identified in an extract from bovine pituitary in 1973.<sup>212</sup> This activity was shown to be protease sensitive and thermolabile and could stimulate the proliferation of 3T3 fibroblasts at low (ng/ml) concentrations. This activity was partially purified in 1975<sup>213</sup> and purified to homogeneity in 1983<sup>214</sup> and would later be referred to as basic FGF (bFGF or FGF2) due the overall basic composition of amino acids and high isoelectric point. Purification of a factor with similar mitogenic activity from bovine brain that was free of myelin basic protein fragments identified a second Fibroblast Growth Factor-like activity with a low isoelectric point that was eventually referred to as acidic FGF<sup>215–220</sup> (aFGF or FGF1). This factor was also found to be identical to an activity called endothelial cell growth factor<sup>221</sup> (ECGF) and related to FGF2.<sup>217</sup> In addition to stimulation of 3T3 cell proliferation, these growth factors were found to promote proliferation of a wide variety of mesoderm-derived cells such as endothelial cells.<sup>217,220–222</sup> cDNA clones for *FGF1* were first isolated from a human brain cDNA library in 1986.<sup>223</sup> cDNA clones for *Fgf1* and *Fgf2* were also isolated from bovine pituitary cDNA libraries in 1986.<sup>224</sup> Additional members of the FGF family were identified as growth factors for cultured cells, as oncogenes tagged by retroviral insertions, as genes responsible for hereditary diseases, or by homology-based PCR or homology-based searches of DNA databases.<sup>152,153,99</sup>

The mammalian *Fgf* family contains 22 genes, 18 of which encode molecules known to signal through FGF tyrosine kinase receptors (Table 1(a)). The secreted signaling FGFs can be grouped into subfamilies based on biochemical function, sequence similarities, and evolutionary relationships. The current consensus is that there are 5 subfamilies of paracrine FGFs, one subfamily of endocrine FGFs, and one subfamily of intracellular FGFs<sup>150,153,157,158,210,225,226</sup> (Figure 1(a)). *Fgf15* and *Fgf19* are likely to be orthologs in vertebrates. The orthologs were named *Fgf15* in rodents and *Fgf19* in other vertebrates. In this review, we refer to these as *Fgf15/19*.

### Canonical (Secreted) FGFs

#### FGF1 Subfamily

The FGF1 subfamily is comprised of FGF1 and FGF2 (Figure 1(a)). These FGFs lack classical secretory signal peptides but are nevertheless readily exported from cells by direct translocation across the cell membrane.<sup>227</sup> The mechanism of translocation is thought to involve a chaperone complex that includes synaptotagmin-1 and the calcium binding protein S100A13.<sup>228,229</sup> FGF1 and FGF2 have also been found in the nucleus of some cells. The mechanisms by which FGFs transit through the cell are poorly understood, but are thought to require binding to and activating cell surface tyrosine kinase FGFRs with heparin/HS as a cofactor and interaction with HSP90.<sup>230,231</sup> Several studies have shown that extracellular FGF1 passes through the plasma membrane, moves through the cytosol, and enters the nucleus.<sup>232,233</sup> Potential functions of nuclear FGF1 include regulation of the cell cycle, cell differentiation, survival, and apoptosis.<sup>234,235</sup> FGF1 is the only FGF that can activate all FGFR splice variants (Figure 2; see below).

#### FGF4 Subfamily

Phylogenetic analysis suggests that the FGF4 family is comprised of FGF4, FGF5 and FGF6<sup>236</sup> (Figure 1(a)). However, there is some controversy as to whether FGF5 should be included in this subfamily, because synteny relationships could be used to place FGF5 in the FGF1 subfamily.<sup>210</sup> All members of this subfamily are secreted proteins with cleavable N-terminal signal peptides that mediate biological responses as extracellular proteins by binding to and activating FGFRs.<sup>158</sup> These FGFs activate IIIc splice variants of FGFRs 1–3 and FGFR4<sup>237,238</sup> (Figure 2; see below).

#### FGF7 Subfamily

Phylogenetic analysis suggests that the FGF7 family is comprised of FGF3, FGF7, FGF10 and FGF22<sup>236</sup> (Figure 1(a)). However, there is some controversy as

to whether FGF3 should be included in this subfamily. Sequence homology and biochemical properties support inclusion in the FGF7 subfamily, while chromosomal localization supports inclusion with FGF4 and FGF6.<sup>210</sup> One recent study proposed an eighth subfamily composed of only FGF3.<sup>226</sup> FGFs, 3, 7, 10, and 22 preferentially activate the IIIb splice variant of FGFR2 and FGF3 and FGF10 also activate the IIIb splice variant of FGFR1<sup>237,238</sup> (Figure 2; see below).

#### FGF8 Subfamily

The FGF8 subfamily is comprised of FGF8, FGF17, and FGF18<sup>236</sup> (Figure 1(a)). Members of this subfamily contain an N-terminal cleaved signal peptide. These FGFs activate IIIc splice variants of FGFRs 1–3 and FGFR4<sup>237,238</sup> (Figure 2; see below).

#### FGF9 Subfamily

The FGF9 subfamily is comprised of FGF9, FGF16, and FGF20 (Figure 1(a)). This subfamily does not have a classical N-terminal signal peptide but does have an internal hydrophobic sequence that functions as a non-cleaved signal for transport into the endoplasmic reticulum and secretion from cells.<sup>239–241</sup> This subfamily has the unique properties of activation of the IIIb splice variant of FGFR3 in addition to FGFR4 and the IIIc splice variants of FGFRs 1, 2 and 3<sup>237,238</sup> (Figure 2; see below).

#### FGF15/19 Subfamily (Endocrine FGFs)

The FGF15/19 subfamily is comprised of FGF15/19, FGF21, and FGF23<sup>75,242</sup> (Figure 1(a)). These FGFs are unique in that they primarily function as endocrine factors and are referred to as endocrine FGFs. In contrast to canonical FGFs, endocrine FGFs bind to heparin/HS with very low affinity.<sup>243</sup> The reduced heparin-binding affinity facilitates release from ECM and allows these FGFs to function as endocrine factors. However, endocrine FGFs still mediate their biological responses in an FGFR-dependent manner, but instead of heparin/HS as cofactors for receptor binding and activation, endocrine FGFs require members of the Klotho family,  $\alpha$ Klotho (Klotho),  $\beta$ Klotho, and Klotho-LPH related protein (KLPH), which has also been called Lactase-like Klotho (Lctl) or  $\gamma$ Klotho.  $\alpha$ Klotho and  $\beta$ Klotho are structurally related single-pass transmembrane proteins of ~1000 amino acids with a short cytoplasmic domain. FGF15/19 and FGF21 signaling requires  $\beta$ Klotho<sup>1,75,156,244–246</sup> (see below). *In vitro* assays for receptor activation using BaF3 cells or L6 myoblasts that co-express FGFR splice variants and  $\beta$ Klotho shows that FGF19 can activate FGFR1c, FGFR2c, FGFR3c, and FGFR4, while FGF21 only activates

FGF subfamily	FGF	Cofactor	Receptor specificity
FGF1 subfamily	FGF1 FGF2		[ All FGFRs [ FGFR 1c, 3c > 2c, 1b, 4Δ
FGF4 subfamily	FGF4 FGF5 FGF6		[ FGFR 1c, 2c > 3c, 4Δ
FGF7 subfamily	FGF3 FGF7 FGF10 FGF22	+ Heparin or Heparan sulfate	[ FGFR 2b > 1b
FGF8 subfamily	FGF8 FGF17 FGF18		[ FGFR 3c > 4Δ > 2c > 1c >> 3b
FGF9 subfamily	FGF9 FGF16 FGF20		[ FGFR 3c > 2c > 1c, 3b >> 4Δ
FGF15/19 subfamily	FGF15/19 FGF21 FGF23	+βKlotho +αKlotho	[ FGFR 1c, 2c, 3c, 4Δ [ FGFR 1c, 3c [ FGFR 1c, 3c, 4

**FIGURE 2** | Receptor specificity of canonical and endocrine FGFs. The six subfamilies of signaling FGFs use either heparin-like molecules or Klotho molecules as cofactors for receptor binding. Data is derived from receptor activation assays using BaF3 cells, L6 myoblasts, or HEK293 cells transfected with individual splice variants of FGFRs or by direct binding studies.<sup>140,141,162,237,238,246–254</sup> FGFR4Δ is a two immunoglobulin-like domain form of FGFR4.

FGFR1c and FGFR3c<sup>162,246</sup> (Figure 2). *In vivo* studies show that FGF21 directly regulates hepatocyte and adipocyte metabolism through interactions with FGFR1 and βKlotho.<sup>162,245,255</sup> By contrast, FGF19, but not FGF21, activates FGFR4, which functions in hepatocytes as a proliferative signal and as a regulator of bile acid synthesis, and has been implicated in the etiology or progression of hepatocellular carcinoma.<sup>143,162,256,257</sup> KLPH has been shown to enhance signaling of FGF19 in HEK293 cells,<sup>160</sup> however, the *in vivo* function of KLPH is not known. FGF23 signaling is mediated through the activation of FGFR1c, FGFR3c, and FGFR4, together with the cofactor, αKlotho<sup>140,141,247,248,258</sup> (Figure 2; see below).

### Intracellular FGFs

#### FGF11 Subfamily

The FGF11 subfamily (FGF11, FGF12, FGF13, FGF14) is also known as iFGFs<sup>259</sup> (Figure 1(a)). iFGFs are not secreted and have no identified interaction with signaling FGFRs.<sup>260</sup> iFGFs interact with the cytosolic carboxy terminal tail of voltage gated sodium (Nav) channels. This interaction may help to regulate the subcellular localization of Nav channels at the axon initial segment during development and the ion-gating properties of the channel in mature neurons and other excitable cells such as cardiomyocytes.<sup>69,261,262,263,264</sup> Additional interacting proteins have been identified for some iFGFs. For example, FGF12 (FHF1) was shown to interact with the MAP kinase scaffolding

protein, IB2 (MAPK8IP2),<sup>265</sup> and FGF13 (FHF2) was shown to interact with microtubules.<sup>70</sup>

## Fibroblast Growth Factor Receptors

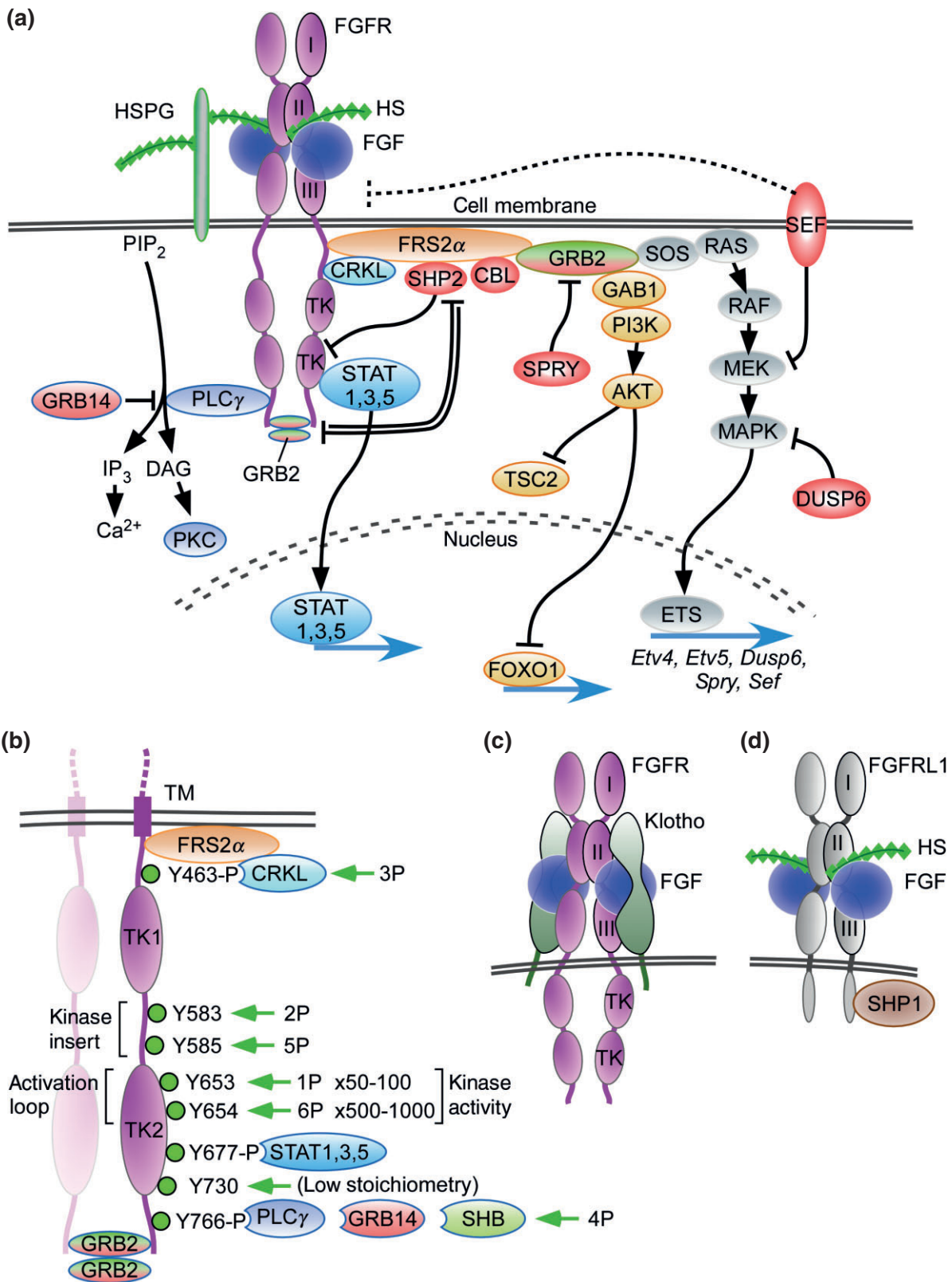
### Historical Perspective

Tyrosine kinase activity was first associated with signaling by brain-derived growth factor, an activity with similar properties to FGF1.<sup>266</sup> Subsequently, purified FGF1 and FGF2 were shown to cause phosphorylation of a 90 kDa protein in Swiss 3 T3 cells.<sup>267</sup> Crosslinking of <sup>125</sup>I-FGF2 was used to tag and purify a receptor protein from chicken embryo membrane fractions. Sequence of tryptic peptides from the chicken FGF receptor, were found to match a partial human cDNA clone called *FLG* (*Fms-like gene*),<sup>268</sup> now referred to as FGF receptor 1 (FGFR1) (Table 1(b)). This information was used to clone a full-length cDNA from a chicken library. The cDNA encoded a 91.7 kDa protein with an N-terminal hydrophobic signal sequence, three extracellular immunoglobulin-like domains, and an intracellular tyrosine kinase domain (Figures 1(b) and 3). The chicken cDNA showed high homology to a cDNA isolated from a human library (90–100% in the tyrosine kinase domain) and the partial *FLG* cDNA clone, and 84% sequence identity to a mouse partial cDNA called *Bek* (bacterial expressed kinase).<sup>269</sup> *Bek* is now referred to as FGF receptor 2 (FGFR2) (Table 1(b)). Homology based cloning was used to identify *Fgfr3* and *Fgfr4*.<sup>270–273</sup> A receptor for FGF7/KGF was isolated by functional cloning in NIH3T3 cells that expressed FGF7.<sup>274</sup> Sequencing revealed a two immunoglobulin-like domain variant with identity to BEK in the tyrosine kinase domain.

### Determinants of Ligand Binding Affinity and Specificity of FGFRs

Immunoglobulin-like domains II and III, and the linker region between these domains regulates the ligand binding specificity of the four FGFR proteins.<sup>275–277</sup> Immunoglobulin-like domain I and the acidic amino acid sequence (acidic box) located between immunoglobulin-like domains I and II are thought to inhibit ligand binding.<sup>278</sup> Consistent with this, an alternative splicing event that results in receptor variants lacking immunoglobulin-like domain I and the I-II linker have increased affinity for FGF ligands.<sup>279,280</sup> *Fgfr1–Fgfr3* generate two additional major splice variants of immunoglobulin-like domain III, referred to as IIIb and IIIc<sup>281–283</sup> (Figure 1(b)). The FGFRb and FGFRc splice variants are essential determinants of ligand-binding specificity (Figure 2).<sup>237,238,275,281,282</sup> Alternative splicing of *Fgfrs* is critical to pathway function as evidenced by the highly conserved intronic control elements





**FIGURE 3** | legend on the next page.

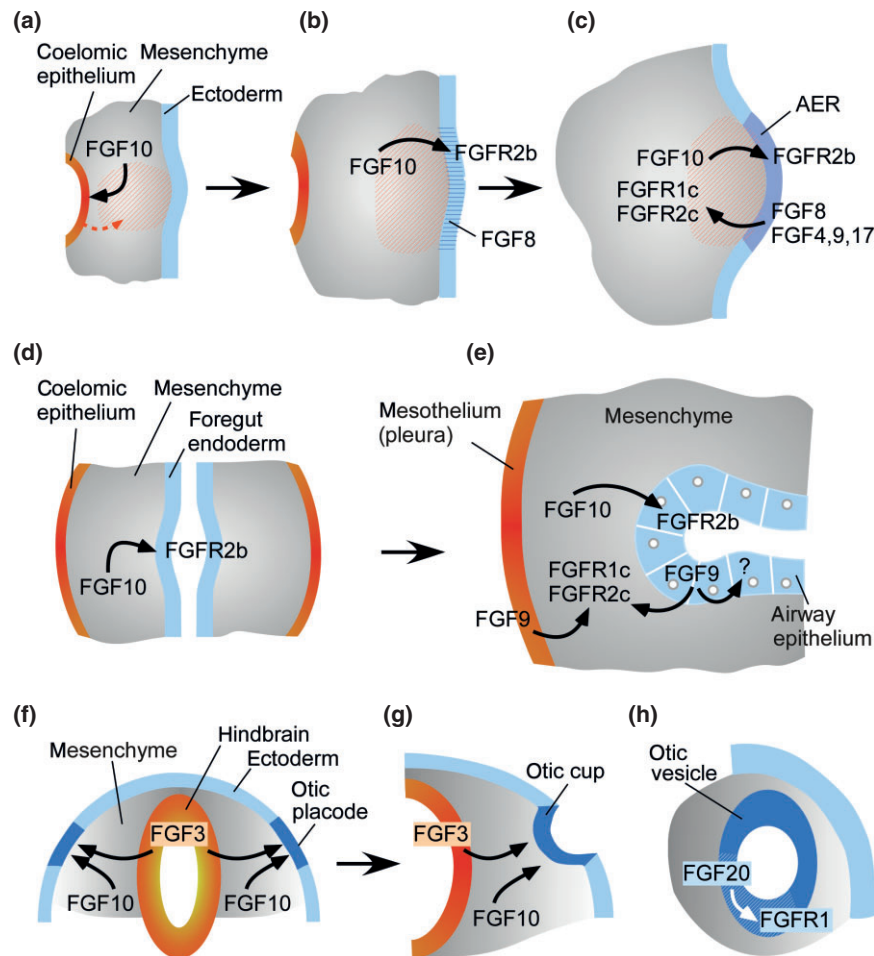
in species ranging from sea urchin to mammals.<sup>284</sup> Immunoglobulin-like domain III of *Fgfr4* is not alternatively spliced.<sup>271</sup> Among the other three *Fgfrs*, alternative splicing of *Fgfr2* is functionally the most important. *Fgfr1* splicing and ligand binding properties parallels that of *Fgfr2*, and these two receptors often show functional redundancy during development. Other splice variants of *Fgfrs* have also been identified. For example, an *Fgfr1* cDNA encoding immunoglobulin-like domains II and III generates a secreted FGFR binding domain that can functionally inhibit FGFR signaling.<sup>285</sup> An *Fgfr3* splice variant in which exons 8–10, which encode the transmembrane domain, are skipped has been identified in both normal epithelial cells and some cancer cell lines. This splice variant produces a secreted protein that can bind FGF ligands and functionally inhibit FGFR signaling.<sup>286,287</sup>

Ligand binding specificity of the 18 secreted FGFs have been compared using various mitogenic assays and by directly measuring affinity for FGFRs. The BaF3 cell line and L6 myoblasts have been particularly useful, as they have little or no endogenous *Fgfr* expression. Studies in BaF3 cells identified strong mitogenic response to FGFR1 and FGFR2 and weak responses to FGFR3 and FGFR4, suggesting that the strength or the specific downstream signaling pathways activated by FGFRs may be

unique.<sup>238,249,288</sup> Using BaF3 cells or L6 myoblasts that express unique extracellular splice variants of *Fgfrs* (*Fgfr1b*, *1c*, *2b*, *2c*, *3b*, *3c*, *4*) fused to either the FGFR1 or FGFR2 cytoplasmic domain, the mitogenic activity of all secreted FGFs were compared in the presence of heparin.<sup>162,237,238,249–254</sup> Additionally, the mitogenic activity of FGF15/19 and FGF21 were assayed on BaF3 cells or L6 myoblasts that also co-expressed  $\beta$ *Klotho* and FGF23 was assayed on HEK293 cells that co-expressed  $\alpha$ *Klotho*.<sup>162,246,248</sup> This analysis showed that FGF1 was the only ligand that could activate all receptor splice variants (Figure 2). This analysis also showed that members of FGF subfamilies have very similar receptor specificities. Direct binding, using iodinated FGFs and using surface plasmon resonance has also been used to evaluate FGF binding specificity.<sup>281,282,289,290</sup> The binding studies are qualitatively in agreement with mitogenic assays.

Expression of alternative splice variants of *Fgfr1* and *Fgfr2* are regulated in a tissue-specific manner. Mesenchymal tissue expresses IIIc splice variants of *Fgfr1* and *Fgfr2* and often are activated by FGF ligands that are expressed in epithelial cells, such as members of the *Fgf4* and *Fgf8* subfamilies.<sup>54,55,291,292</sup> By contrast, epithelial tissues express IIIb splice variants of *Fgfr1* and *Fgfr2* and bind ligands that are normally expressed in mesenchymal tissues, such as members of

**FIGURE 3** | FGF signaling pathways. (a) Binding of canonical FGFs to FGFR with HS (or HSPG) as a cofactor induces the formation of ternary FGF-FGFR-HS complex, which activates the FGFR intracellular tyrosine kinase domain by phosphorylation of specific tyrosine residues. The activated receptor is coupled to intracellular signaling pathways including the RAS-MAPK, PI3K-AKT, PLC $\gamma$ , and STAT pathways. The RAS-MAPK pathway: The major FGFR kinase substrate, FRS2 $\alpha$ , which is constitutively associated with the juxtamembrane region of FGFR (peptide: MAVHKLAKSIPLRRQVTSADS), interacts with CRKL bound to pY463 and is phosphorylated by the activated FGFR kinase. Phosphorylated FRS2 $\alpha$  recruits the adaptor protein GRB2, which then recruits the guanine nucleotide exchange factor SOS. The recruited SOS activates the RAS GTPase, which then activates the MAPK pathway. MAPK activates members of the Ets transcription factor family such as Etv4 (Pea3) and Etv5 (Erm) and negative regulators of the FGF signaling pathways such as SHP2, CBL, SPRY, SEF, and DUSP6. The PI3-AKT pathway: The recruited GRB2 also recruits the adaptor protein GAB1, which then activates the enzyme PI3K, which then phosphorylates the enzyme AKT. AKT has multiple activities including activation of the mTOR complex 1 through inhibition of TSC2 and phosphorylation of the FOXO1 transcription factor causing it to exit the nucleus. The PLC $\gamma$  pathway: Activated FGFR kinase recruits and activates the enzyme PLC $\gamma$ , which produces IP $_3$  and DAG by the hydrolysis of PIP $_2$ . IP $_3$  induces calcium ion release from intracellular stores and the activation of downstream signaling pathways. DAG activates the enzyme PKC and its downstream signaling pathways. GRB14 inhibits activation of PLC $\gamma$ . The STAT pathway: FGFR kinase also activates STAT1, 3, and 5. STAT3 interacts with phosphorylated tyrosine 677 (pYxxQ motif). These activated signaling pathways mostly regulate gene expression in the nucleus. SPRY interacts with GRB2 to inhibit the RAS-MAPK pathway and to regulate the PI3K-AKT pathway. GRB2 dimers are docked at the c-terminus of FGFR2 where they inhibit SHP2, allowing low-level receptor kinase activity. Molecules shaded red generally function to inhibit FGFR signaling. (b) Dimerization of the FGFR1 kinase domain leads to sequential phosphorylation of tyrosine residues (1P–6P) leading to increasing activity of the FGFR kinase and phosphorylation of tyrosine substrates for CRKL, STAT, GRB14, and PLC $\gamma$  binding. In the first phase of activation, Y653 (1P), in the activation loop, is phosphorylated, resulting in a 50- to 100-fold increase in kinase activity. In the third phase of activation, Y654 (6P), in the activation loop, is phosphorylated, resulting in an overall 500–1000 fold increase in kinase activity. Y730 is weakly phosphorylated. Phosphorylation of Y677 allows docking of STAT3 and phosphorylation of Y766 allows docking of either GRB14 or PLC $\gamma$ . Ligand-induced receptor activation phosphorylates GRB2, leading to its dissociation from the receptor. Tyrosine residues correspond to human FGFR1 (accession NP\_075598). (c) Binding of endocrine FGF to FGFR with Klotho as a cofactor induces the formation of ternary FGF-FGFR-Klotho complex, which leads to activation of the FGFR tyrosine kinase. (d) FGFR1 is a protein containing three extracellular immunoglobulin-like domains with similarity to FGFRs. FGFR1 has a single transmembrane domain, and a short intracellular tail with no tyrosine kinase domain. The short cytoplasmic domain contains an SH2 binding motif that interacts with SHP1. FGFR1 is not simply a decoy receptor, but rather a non-tyrosine kinase signaling molecule.



**FIGURE 4** | Mechanisms of FGF signaling during organogenesis. (a–c) Limb bud development uses a classical reciprocal epithelial-mesenchymal FGF signal. The earliest identified event in limb bud development involves an FGF10 signal to coelomic epithelium (a). This induces an epithelial to mesenchymal transition (orange arrow) that increases the amount of mesenchyme (orange hash) at the forming limb bud, resulting in a bulge. As development progresses (b), FGF10 signals to ectoderm to induce the formation of the apical ectodermal ridge (AER). Initially FGF8 (blue hash) is expressed throughout its length of the AER (b) and later FGF4, FGF9, and FGF17 are also expressed in the posterior half of the AER. AER FGFs signal to FGFR1 and FGFR2 in distal mesenchyme. (d, e) Lung development uses a modified reciprocal mesothelial/epithelial-mesenchymal FGF signal. The lung bud is initiated with an FGF10 signal from foregut mesenchyme to FGFR2b in foregut epithelium. Continued FGF10 expression is required for epithelial branching. Reciprocal signals from mesothelial FGF9 regulates mesenchymal proliferation through FGFR1 and FGFR2, while epithelial FGF9 functions as an autocrine factor to regulate epithelial branching through an as yet unidentified receptor. (f–h) Induction of the otic placode and differentiation of the otic vesicle. (f, g) FGF3, derived from the hindbrain and FGF10 derived from head mesenchyme, together, induce formation of the otic placode and its progression to the otic cup and otic vesicle. (h) After formation of the otic vesicle, FGF20 signals to FGFR1 within the prosensory epithelium (white hash) as a permissive autocrine factor required for differentiation of outer hair cells and outer supporting cells in the organ of Corti.

the *Fgf7* subfamily.<sup>293,294</sup> This epithelial/mesenchymal expression of alternative splice variants of FGFRs and reciprocal expression of interacting FGF ligands is essential for the development of many organs, particularly those that undergo branching morphogenesis such as the lung or salivary gland, and structures such as the limb bud, and skin (Figure 4).

Although this pattern of reciprocal signaling is essential for the development of some organs, it is not universal. For example, the tissue-specific regulation of alternative splicing is less stringent for *Fgfr3*, where

both splice variants have been found in epithelial cell types.<sup>295,296</sup> The FGF9 subfamily, though primarily expressed in epithelial cells, has the unique ability to activate FGFR3b in addition to IIIc splice variants of FGFRs 1–3<sup>237,253</sup> (Figure 2). *Fgf10* expression can be found in some epithelial cell types, such as the developing inner ear where it likely signals in an autocrine manner to epithelial cells.<sup>237</sup> During somitogenesis, *Fgf4* and *Fgf8* are expressed and signal within presomitic mesenchyme and nascent somites where they suppress differentiation.<sup>29</sup>

## PATHWAY REGULATION

### Extracellular FGF Associated Cofactors and Binding Proteins

#### *Heparan Sulfate Proteoglycans*

HS is now recognized to function as a potent cofactor for canonical FGF signaling as well as a wide range of other signaling pathways including bone morphogenetic proteins (BMPs), WNTs, and Hedgehogs<sup>197,297–299</sup> (Figure 3(a)). Heparin was found to potentiate the biological activity of FGF1 in 1985<sup>220–222</sup> and was first shown to directly enhance FGFR binding and activity in 1991.<sup>200,201,254</sup> Using a cell line (BaF3) that lacks cell surface HS, or through inhibition of HS sulfation (with chlorate), the signaling ability of all canonical FGFs were shown to require heparin/HS<sup>200,237,238,254,300</sup> (Figure 2).

HS is a long linear carbohydrate chain of repeating sulfated disaccharides, glucuronic acid linked to N-acetylglucosamine. The HS chains are covalently linked to specific core proteins such as syndecan, perlecan, glypican, and agrin. These HS proteoglycans (HSPGs) are cell surface transmembrane type proteins (e.g. syndecans), cell surface glycerophosphatidylinositide-anchored type proteins (e.g. glypicans), or diffusible proteins localized in the ECM<sup>198,298,301–304</sup> (e.g. perlecan and agrin). HS independently can interact with both FGFs and FGFRs and is proposed to cooperatively increase the affinity of a 1:1 FGF-FGFR dimer by binding to a cleft formed between the HS binding sites on FGFs and the N-terminal region of immunoglobulin-like domain<sup>230,305</sup> (Figure 3(a)). This 1:1:1 FGF-HS-FGFR complex leads to conformational changes that stabilize a symmetric 2:2:2 dimer. FGFR dimerization then directs the juxtaposition and activation of the intracellular tyrosine kinase domains, followed by the activation of intracellular signaling pathways.<sup>198,301</sup> As a component of the ECM, HS also functions to sequester FGFs and modulate their diffusion through tissue to effectively regulate the shape of a gradient. For example, differences in binding affinity of FGF7 and FGF10 for HS, underlie differences in epithelial branching patterns during glandular organogenesis.<sup>306</sup>

The structure of HS is complex and heterogeneous; with variations in chain length, and patterns of sulfation and acetylation along the length of the glycosaminoglycan (GAG) chain.<sup>307–309</sup> Synthesis of the HS chain is catalyzed by the glycosyltransferases, EXT1 and EXT2.<sup>310</sup> The HS molecule consists of repeating disaccharide units of N-acetylglucosamine and glucuronic acid. The HS chain matures in the

Golgi where N-acetylglucosamine residues are partially N-deacetylated and N-sulfated by a family of four N-deacetylase/N-sulfotransferase enzymes<sup>311</sup> (NDST1-4). Subsequently, 2-O-sulfotransferases, 6-O-sulfotransferases, and 3-O-sulfotransferases add O linked sulfate groups.<sup>309</sup> The pattern and density of deacetylation and sulfation varies along the length of the GAG chain. In the extracellular environment, the 6-O-endosulfatases, SULF1 and SULF2, can also selectively desulfate HS.

The sulfation pattern and length of HS chains regulate FGF signaling.<sup>198,312</sup> In the embryo, specific HS chains can regulate the cell-specific patterns of FGF and FGFR binding to the extracellular matrix, the direct interactions between FGFs and FGFRs, and activation of FGFR signaling.<sup>313–315</sup> In general, higher levels of sulfation of HS chains facilitate FGF signaling and the formation of ternary complexes with FGFs and FGFRs.<sup>316,317</sup> Furthermore, oligosaccharides with eight or more sugar residues are most active, but shorter HS chains can also facilitate the formation of ternary complexes with FGFs and FGFRs.<sup>254,316,318,319</sup> Cleavage of the HSPG core protein also modulates FGF signaling.<sup>198</sup> The cleavage by serine proteinases possibly facilitates FGF signaling by releasing FGFs that were sequestered at the cell-surface.<sup>315</sup> In addition, the cleavage by endoglycosidases such as heparanase possibly modulates FGF signaling.<sup>198</sup> For example, FGF10 in the basement membrane, that is released by heparanase, promotes FGF signaling in branching morphogenesis.<sup>320</sup>

#### *Klotho Family Proteins*

The  $\alpha$ Klotho gene was originally identified as a candidate gene responsible for a premature aging syndrome.<sup>321</sup> Based on the phenotypic similarity of  $\alpha$ Klotho and *Fgf23* knockout mice,  $\alpha$ Klotho was identified as a cofactor for FGF23 signaling through FGFR1c, FGFR3c and FGFR4<sup>140,141,247,248,322</sup> (Figure 2). The  $\alpha$ Klotho gene is highly expressed in the distal convoluted tubules in the kidney and choroid plexus in the brain.<sup>321</sup> A major function of FGF23- $\alpha$ Klotho-FGFR signaling in the kidney is to regulate phosphate and calcium homeostasis. Mice lacking *Fgf23* or  $\alpha$ Klotho develop hyperphosphatemia and hypercalcemia by two weeks of age.<sup>258,323</sup>

The Klotho family is comprised of three members including  $\alpha$ Klotho,  $\beta$ Klotho, and KLPH.<sup>98,324</sup>  $\alpha$ Klotho contains ~1000 amino acid, a single transmembrane domain, and a short cytoplasmic domain (Figure 3(c)). There are no known functions of the cytoplasmic domains of Klotho proteins. The large extracellular part of the Klotho molecule has two repeated internal domains, KL1 and KL2, which

are structurally similar to  $\beta$ -glucosidases. However, there is no evidence for glucosidase activity of  $\alpha$ Klotho.  $\beta$ Klotho is also a single-pass transmembrane protein similar to  $\alpha$ Klotho. The  $\beta$ Klotho gene is predominantly expressed in the liver and white adipose tissue.<sup>325</sup>  $\beta$ Klotho is a cofactor for FGF15/19 and FGF21 signaling through FGFR4 and FGFR1c, respectively (Figure 3(b)).<sup>322</sup> KLPH is also a single-pass transmembrane protein similar to  $\alpha$ Klotho.<sup>326</sup> The *KLPH* gene is expressed in the eye and brown adipose tissue. KLPH efficiently interacts with FGFR1b, FGFR1c, FGFR2c, and FGFR4. In *KLPH*-transfected HEK293 cells, FGF19, but not FGF21 and FGF23, causes ERK phosphorylation.<sup>160</sup> However, the physiological function of KLPH remains unclear. Although Klotho proteins act as cofactors for the endocrine FGFs through formation of an FGF-FGFR-Klotho ternary complex, they also directly compete with a receptor docking site for canonical FGF8 family ligands, and thus may actively suppress these canonical FGFs while activating endocrine FGFs.<sup>327</sup>

### FGF Binding Proteins

#### FGFBP1 (FGF Binding Protein 1)

FGFBP1 (HBP17) was originally isolated as a heparin-binding protein that co-eluted with FGF2 from a heparin affinity column.<sup>328</sup> The *Fgfbp1* cDNA encodes a secreted 234 amino acid polypeptide ( $M_r$  17,000) that binds both heparin and FGF1 and FGF2.<sup>328</sup> In these initial studies, FGFBP1 was shown to inhibit the biological activity of these FGFs by inhibiting receptor binding. However, in later studies, FGFBP1 was shown to mobilize FGF from HS binding sites in the extracellular matrix and function to present FGF to the FGFR.<sup>329</sup>

*FGFBP1* is expressed in several human tumors, including breast and colon cancer, and FGFBP1 can be rate-limiting for tumor growth, but pro-angiogenic, thus acting to facilitate tumor invasion.<sup>330</sup> In mice, *Fgfbp1* is abundantly expressed in the colon, stomach, ileum, and eye.<sup>160</sup> FGFBP1 also binds to and activates FGF7, FGF10 and FGF22, and functions to enhance wound healing.<sup>331,332</sup>

#### FGFRL1/FGFR5

FGFRL1 was identified as a protein structurally similar to FGFRs<sup>203,333</sup> (Figure 1(c)). The *Fgfr1l* cDNA, originally cloned from human cartilage, encodes a ~500 amino acid protein containing three extracellular immunoglobulin-like domains with similarity to FGFRs, a single transmembrane domain, and a short intracellular tail with no tyrosine kinase domain.<sup>333,334</sup> *Fgfr1l* (termed *Fgfr5*) was also cloned

from human and mouse cDNA libraries.<sup>335,336</sup> A soluble form of FGFRL1 binds to heparin and to FGF2, 3, 4, 8, 10, 22, and ectopic expression antagonized FGF signaling during *Xenopus* development and inhibited cell proliferation *in vitro*.<sup>334,337</sup> Interestingly, the short cytoplasmic domain of FGFRL1 contains an SH2 binding motif that interacts with the tyrosine phosphatase SHP1<sup>338</sup> (Figure 3(d)). Overexpression of *Fgfr1l* results in increased ERK1/2 signaling.<sup>338</sup> This result suggests that FGFRL1 is not a decoy receptor, but rather a non-tyrosine kinase signaling molecule.

*Fgfr1l* knockout mice die immediately after birth from respiratory failure due to a hypoplastic diaphragm.<sup>148</sup> Analysis of these mice reveals agenesis of slow muscle fibers.<sup>339</sup> These mice also show kidney agenesis due to a reduction in mesenchymal nephron progenitors (cap mesenchyme), arrested branching of the urogenic epithelium, failure to form functional nephrons, and a hypoplastic collecting duct system<sup>147</sup> (Table 2(b)). Interestingly, mice that lack the intracellular domain of FGFRL1 are viable, fertile, and phenotypically normal, suggesting that the extracellular domain of FGFRL1 mediates most of its activity (Box 1).<sup>340</sup>

### Intracellular Signal Transduction

#### Cytosolic Signaling Pathways

FGF binding activates the FGFR tyrosine kinase by inducing receptor dimerization and trans-autophosphorylation of the kinase domain<sup>1</sup> (Figure 3(a)). For FGFR1, six tyrosine residues are sequentially phosphorylated to fully activate the kinase domain<sup>341,342</sup> (Figure 3(b)). In the first phase of activation, Y653 is phosphorylated, resulting in a 50- to 100-fold increase in tyrosine kinase activity. In the second phase of activation, Y583, and then Y463, Y766, and Y585 are phosphorylated. In the third phase of activation, Y654 is phosphorylated, resulting in a further 10 fold (overall 500- to 1000-fold) increase in tyrosine kinase activity. Phosphorylation of two additional tyrosine residues, 677 and 766, is required, respectively, for STAT3 and phospholipase  $C\gamma$  (PLC $\gamma$ ) binding.<sup>343-345</sup> The adaptor protein, FGFR substrate 2 $\alpha$  (FRS2 $\alpha$ ) is constitutively docked to its binding site in the juxtamembrane region of FGFRs and anchored to the cell membrane through myristoylation<sup>207,346,347</sup> (Figure 3(b)).

The activated FGFR phosphorylates adaptor proteins for four major intracellular signaling pathways, RAS-MAPK, PI3K-AKT, PLC $\gamma$ , and signal transducer and activator of transcription (STAT)<sup>1,151-153,344</sup> (Figure 3(a) and (b)). Activation of the RAS-MAPK and PI3K-AKT pathway is initiated

## BOX 1

## INHIBITORY MECHANISMS THAT REGULATE FGFR SIGNALING

Inhibition of FGFR signaling is important for the precise control of cellular functions. Several mechanisms have evolved to regulate FGF signaling. These range from internalization and degradation of the receptor to modulation of receptor kinase activity by phosphatases and regulation of accessibility to downstream signaling pathways.

In recent studies,<sup>389,749</sup> a dimeric form of GRB2, the adaptor protein that couples FRS2 to the RAS-MAPK and PI3K-AKT pathways (Figure 3(a)), was found to interact directly with the FGFR2 C-terminal 10 amino acid residues, where it stabilized a FGFR dimer which could autophosphorylate a limited number of tyrosine residues including Y653 and Y654 in the activation loop (Figure 3(b)). However, additional C-terminal phosphorylation and recruitment of signaling proteins was sterically hindered by the bound GRB2 dimer. Following ligand mediated receptor activation, phosphorylation of GRB2 caused GRB2 to dissociate from the FGFR C-terminus permitting full receptor activation.<sup>749</sup> Additionally, high levels of GRB2 inhibited phosphorylation-independent binding of PLC $\gamma$  (through its SH3 domain) to the very C-terminus of the FGFR. Lower levels of GRB2 allowed PLC $\gamma$  binding and increased phospholipase activity, resulting in increased cell motility, an activity that can promote metastatic behavior of melanoma cells.<sup>750</sup>

The RAS-MAPK pathway can also exert direct negative feedback inhibition of FGFRs. ERK1 and ERK2, which are activated by FGFR and other receptor tyrosine kinases, can phosphorylate the C-terminus of FGFR2 at Ser777 to functionally inhibit FGFR2 tyrosine kinase activity.<sup>751</sup> This provides a negative feedback pathway for FGF signaling and a means for other receptor tyrosine kinases that use the RAS-MAPK pathways to communicate with FGFRs.

by phosphorylation of FRS2 $\alpha$ . FRS2 $\alpha$  phosphorylation and ERK1/2 activation is partially dependent on phosphorylation of Y463 and the presence of CRKL.<sup>348,349</sup> pY463 directly interacts with the adapter protein CRKL and with much lower affinity to the related protein, CRK.<sup>348–350</sup> Downstream of RAS and PI3K, FGFR signaling has been shown to regulate several distinct MAP kinases including ERK1/2, JNK and p38.<sup>178,179,351–353</sup>

Activated (phosphorylated) FRS2 $\alpha$  binds the membrane anchored adaptor protein, growth factor receptor-bound 2 (GRB2) and the tyrosine phosphatase SHP2.<sup>207,354</sup> GRB2 further activates the RAS-MAPK pathway through recruitment of SOS, and the PI3K-AKT pathway through recruitment of GAB1 to the signaling complex (Figure 3(a)).<sup>207,355</sup> The RAS-MAPK pathway regulates the expression of diverse target genes through activation of E26 transformation-specific (ETS) transcription factors. Ets4 (Pea3) and Ets5 (Erm) are ETS transcription factors that are often transcriptionally induced by FGF signaling.<sup>356–359</sup> Phosphorylation of ETS transcription factors by activated MAPK allows interaction with DNA and regulation of target gene expression.<sup>352</sup>

In contrast to the RAS-MAPK pathway, the PI3K-AKT pathway functions to inhibit the activity of target molecules such as the forkhead box class transcription factor, FOXO1, and the cytosolic tuberous sclerosis complex 2, TSC2. FOXO1, a pro-apoptotic effector, is inactivated by AKT phosphorylation, causing it to exit the nucleus and promote cell survival.<sup>360</sup> AKT also activates the mTOR complex 1 through phosphorylation and inhibition of TSC2, ultimately stimulating cell growth and proliferation.<sup>360</sup> Phosphorylation of PLC $\gamma$  by the activated FGFR tyrosine kinase leads to the hydrolysis of phosphatidylinositol 4,5-bisphosphate to produce inositol triphosphate (IP $_3$ ) and diacylglycerol (DAG) (Figure 3(a)). IP $_3$  increases intracellular calcium ion levels and DAG activates protein kinase C (PKC). The adaptor protein, GRB14, also interacts with the activated FGFR1 at multiple sites, including pY766<sup>361</sup> (and possibly pY776). Binding of GRB14 to pY766 inhibits tyrosine phosphorylation and activation of PLC $\gamma$ <sup>362</sup> (Figure 3(a) and (b)). Additionally, the SRC homology-2 protein, SHB, interacts with pY766 and acts to enhance phosphorylation of FRS2 $\alpha$  and the mitogenic response to FGFs in an immortalized brain endothelial cell line.<sup>363</sup>

The activated FGFR also phosphorylates and activates STAT1, STAT3, and STAT5, to regulate STAT pathway target gene expression<sup>343,364–367</sup> (Figure 3(a) and (b)). STAT1 was activated in chondrocytes derived from Thanatophoric dysplasia patients with a constitutively active mutant of FGFR3,<sup>364</sup> and STAT1 activation in response to FGF1 in primary growth plate chondrocytes was necessary to suppress proliferation.<sup>368</sup> However, using a rat chondrosarcoma cell line that stops growing in response to FGF1, it has been controversial as to whether STAT1 or MAPK signaling mediates the observed growth arrest.<sup>368,369</sup> In cancer cells, under conditions of gene amplification or overexpression of *FGFR3*,

STAT3 was phosphorylated resulting in activation of downstream target genes.<sup>343</sup> In brain microvascular endothelial cells, FGF signaling was found to activate STAT5, which was necessary for migration, invasion, and tube formation.<sup>370</sup>

To the best of our knowledge, quantitative similarities and differences in the signaling output of the four FGFR kinase domains have not been assessed. However, activation of downstream signaling pathways are thought to be qualitatively similar for *Fgfr1* and *Fgfr2* and different from *Fgfr3* and *Fgfr4*.<sup>238,249,288</sup> Similarities and differences in signaling of the four FGFRs could be mediated by differential rates of endocytosis,<sup>371</sup> by differential subcellular trafficking after ligand activation,<sup>372,373</sup> or by differences in the affinity or specificity for adaptor proteins that couple to downstream signaling cascades.<sup>374</sup>

### ***Inhibitors of FGFR Signaling***

Sprouty (SPRY) is an intracellular negative regulator of receptor tyrosine kinases including FGFR, vascular-endothelial growth factor receptor, platelet-derived growth factor receptor, and nerve growth factor receptor.<sup>375,376</sup> The human/mouse SPRY family is composed of four members, SPRY1-SPRY4. Most *Spry* genes are ubiquitously expressed in both embryos and adult tissues. In FGF signaling, SPRY interacts with GRB2 to inhibit the RAS-MAPK pathway and to regulate the PI3K-AKT pathway<sup>206,377</sup> (Figure 3(a)). The phenotypes of *Spry* knockout mice indicate that SPRYs are essential for development and growth. The deregulation of SPRY function often results in human cancers and autoimmune diseases.<sup>375,376</sup>

SEF (similar expression to *Fgf*) is a transmembrane protein that functions as an antagonist of FGF signaling through the Ras-MAPK pathway<sup>378,379</sup> (Figure 3(a)). SEF functions by binding to activated MEK to inhibit dissociation of the MEK-MAPK (ERK1/2) complex, thus blocking nuclear translocation of activated MAPK.<sup>377,380</sup> The extracellular domain of SEF may also interact directly with the FGFR to inhibit receptor phosphorylation.<sup>381</sup>

*Dusp6* (Dual-specificity phosphatase 6) encodes an ERK-specific MAPK phosphatase (MKP3)<sup>382</sup> *Dusp6* expression is transcriptionally upregulated by FGFR signaling and *Dusp6* expression patterns closely resemble those of *Fgfs*.<sup>383-386</sup> DUSP6 serves *in vivo* as a negative feedback regulator of FGFR signaling by directly dephosphorylating MAPK (ERK1 and ERK2) on phosphotyrosine and phosphothreonine residues<sup>382</sup> (Figure 3(a)).

CBL, an E3 ubiquitin ligase, forms a ternary complex with phosphorylated FRS2 $\alpha$  and GRB2, resulting in the ubiquitination and degradation of

FGFR and FRS2 in response to FGF stimulation<sup>387</sup> (Figure 3(a)). FGFR2 activation can also increase CBL-PI3K interactions, leading to PI3K degradation and attenuated signaling.<sup>388</sup>

SHP2 binds to phosphorylated FRS2 following ligand activation of the FGFR.<sup>354</sup> SHP2 functions to dephosphorylate FGFR2 and GRB2 (Figure 3(a)). However, activation of SHP2 (by phosphorylation) and access to the FGFR are also inhibited by receptor-bound GRB2.<sup>389,390</sup>

### ***Regulation of the Cellular Response to FGFR Activation***

The cellular response to FGFR signaling is regulated by differences in the intrinsic signaling properties of FGFRs and by the dynamics of subcellular FGFR trafficking in response to ligand binding. Cytosolic signaling pathways can be differentially activated by cell surface FGFRs and internalized FGFRs. Furthermore, regulating synthesis and degradation of FGFRs can modulate the strength of the FGFR signal. Differential cellular response can also result from differences in signal output from multiple FGFRs. For example, FGF1 stimulates lung epithelial cells to form buds resulting in branching, while FGF7 stimulates lung epithelial cells to form cyst-like structures.<sup>391,393</sup> This could be due to activation of FGFR2 and FGFR4 by FGF1 and only activation of FGFR2b in response to FGF7. Two FGFs that are even more similar, FGF7 and FGF10, still can elicit different cellular responses. FGF10 specifically induced the formation of a Y734-phosphorylated FGFR2b-PI3K-SH3BP4 complex that targets FGFR2b to recycling endosomes and controls cell migration and epithelial branching, whereas FGF7 leads to cell proliferation and degradation of FGFR2b.<sup>373,392,393</sup>

### ***Function of FGFs and FGFRs in the Nucleus***

Both FGF ligands and receptors can localize to the cell nucleus where they carry out signaling functions that can be independent of receptor tyrosine kinase activity.<sup>394,395</sup> FGF1 localization in the nucleus was found to stimulate DNA synthesis independent of FGFRs, and FGF2 nuclear localization was associated with glioma cell proliferation.<sup>396,397</sup> It is not clear whether FGFs have direct transcriptional functions or exert their activity in the nucleus through interactions with other molecules.

Following ligand-mediated internalization, FGFR1 can be transported to the nucleus by interactions with importin  $\beta$ . Nuclear FGFR1 is required for neuronal differentiation and functions by activating transcription in cooperation with cyclic AMP response element-binding protein (CREB).<sup>398,399</sup>

Nuclear translocation of FGFR1, along with its ligand, FGF2, promoted pancreatic stellate cell proliferation and changes in the elaborated ECM, making it more permissive for pancreatic cancer cell invasion.<sup>400</sup> In breast cancer cells, activation of FGFR1b by FGF10 activated granzyme B cleavage of FGFR1. Transport of the resulting C-terminal fragment of FGFR1 to the nucleus was required for cell migration.<sup>401</sup>

## MICRORNA REGULATION OF FGF AND FGFR EXPRESSION AND SIGNALING

MicroRNAs (miRNAs) are small (approximately 21–24 nucleotides) non-coding RNAs, which are post-transcriptional regulators of gene expression.<sup>402</sup> miRNAs participate in diverse biological processes including development, differentiation, cell proliferation, metabolism, as well as in human diseases including metabolic disorders and cancers.<sup>403,404</sup> FGF pathway activity during development or regeneration can be regulated by miRNAs and loss of miRNA regulation of FGF signaling can result in disease progression or cancer.

During development, miRNAs can affect cell differentiation by directly regulating *Fgf* or *Fgfr* expression. For example, in the osteoblast, miR-338 was found to directly regulate the 3' untranslated region (UTR) of *Fgfr2* to suppress *Fgfr2* expression. Decreased miR-338 increased *Fgfr2* expression resulting in enhanced osteoblast differentiation.<sup>405</sup> miRNAs can also affect FGF signaling during development by regulating downstream effectors of the pathway. For example, the miR-17 family directly targets *Stat3* and *Mapk14* in lung epithelium to modulate the response to FGF10-FGFR2b signaling.<sup>406</sup>

In disease pathogenesis, such as in pulmonary arterial hypertension (PAH), hyperproliferation of pulmonary artery endothelial and smooth-muscle cells leads to destruction of the pulmonary vascular plexus. miR-424 and miR-503 directly regulate (suppress) *Fgf2* and *Fgfr1* expression in pulmonary artery endothelial cells. Decreased expression of miR-424 and miR-503 in PAH leads to increased FGF2 and FGFR1 and consequent vascular hyperproliferation.<sup>407</sup> In a model for tissue repair, inhibition of miR-710, a direct regulator of *Fgf15* expression in myofibroblasts, increased FGF15 in conditioned media and enhanced *in vitro* intestinal epithelial wound repair.<sup>408</sup>

The metabolic functions of endocrine FGFs can be regulated by miRNAs. miR-34a is highly elevated in adipose tissue in obese mice and in liver in patients with steatosis. Elevated miR-34a in obesity attenuates hepatic FGF19 signaling and

adipose FGF21 signaling by directly targeting the 3' UTR of  $\beta$ -*Klotho* and *Fgfr1*.<sup>409,410</sup> Downregulation of miR-34a increases the levels of the FGF21 receptor components, FGFR1 and  $\beta$ Klotho (and also SIRT1), resulting in FGF21/SIRT1-dependent induction of genes that favor brown fat and improved hepatic FGF21 signaling and lipid oxidation.<sup>410</sup>

In several cancers, decreased expression of miRNAs that normally suppress *FGF* expression have been identified as a potential mechanism for promoting cancer progression. For example, in non-small-cell lung cancer (NSCLC) miR-152 and miR-198 are downregulated, and *FGF2*, a direct target of miR-152, and *Fgfr1*, a direct target of miR-198, are overexpressed, leading to decreased apoptosis and increased proliferation and invasion.<sup>411,412</sup> In a breast cancer cell line, miR-503 expression is suppressed by HBXIP (hepatitis B X-interacting protein). Reduced expression of miR-503, which directly targets the 3' UTR of *FGF8*, results in increased FGF8 and consequent increased angiogenesis and proliferation of the breast cancer cells.<sup>413</sup> In gastric cancer and hepatocellular carcinoma, miR-26a and miR-140-5p, respectively, are strongly downregulated, and *FGF9*, a direct target of both of these miRNAs is increased.<sup>414,415</sup> Interestingly, decreased miR-140-5p and miR-99b expression has also been observed in NSCLC tissue.<sup>416,417</sup> High *FGF9* expression observed in 10% of human NSCLC specimens,<sup>418</sup> suggests an additional pathogenic relationship between miR-140-5p and FGF9 in lung cancer. Increased expression of *FGFR3*, a direct target of miR-99b, was observed in human NSCLC tissue.<sup>417</sup> Of relevance to this mechanism, FGFR3 is the obligate FGFR mediating FGF9 induced adenocarcinoma in a mouse model for lung cancer.<sup>419</sup>

## DEVELOPMENTAL, GENETIC, AND PATHOLOGICAL FUNCTIONS

### FGF Signaling during Peri-implantation Development

The earliest requirement for FGF signaling is in the preimplantation embryo, where *Fgf4* is first expressed in the morula and later in the epiblast cells of the inner cell mass (ICM).<sup>420</sup> *Fgf4* gene inactivation in mice shows that FGF4 is required for ICM proliferation and for formation of the primitive ectoderm.<sup>167,14</sup> The receptor for FGF4 in the ICM is more controversial. Campbell et al. detected *Fgfr1* (*Flg*) but not *Fgfr2* (*Bek*) transcripts in mouse blastocysts,<sup>421</sup> Orr-Urtreger et al. concluded that both *Fgfr1* and *Fgfr2* are expressed in the ICM and *Fgfr2* is expressed in the embryonic ectoderm,<sup>422</sup> while



Guo et al. concluded that *Fgfr2* is not expressed in the epiblast lineage but is highly expressed in embryonic ectoderm.<sup>423</sup> *Fgfr* knockout studies are also controversial (Table 2(b)). Arman et al. generated a mutant allele of *Fgfr2* and found defects in the outgrowth, differentiation, and maintenance of the inner cell mass<sup>424</sup>; however, it is possible that this allele functions as a dominant negative that partially interferes with *Fgfr1* signaling, as mice homozygous for two other engineered null alleles of *Fgfr2* survived until embryonic day 10–11<sup>115,116</sup> (Table 2(b)). Inactivation of *Fgfr1* or *Fgf8*, which are also expressed in the blastocyst, indicates a function slightly later in development, with phenotypes affecting axis formation and mesoderm specification<sup>105,425,426</sup> (Table 2(a) and (b)). We are not aware of studies in which both *Fgfr1* and *Fgfr2* have been conditionally inactivated in the ICM.

### FGF Signaling in Organogenesis

FGF signaling is involved almost ubiquitously throughout organogenesis.<sup>161</sup> A key function of FGF signaling is to regulate interactions between epithelial (and mesothelial) cells and mesenchyme. A general principle that applies to branched organs (lung, salivary gland, lacrimal gland), intestine, liver, and limb bud development involves mesenchymal expressed FGFs, such as FGF10 signaling to the epithelial IIIb splice variant of FGFR1 and FGFR2.<sup>171,117,427</sup> Reciprocal signaling, from epithelium to mesenchyme is mediated by FGFs expressed in epithelia, such as FGF8 and FGF9, which signal to mesenchymal IIIc splice variants of FGFR1 and FGFR2.<sup>428,429</sup> However, this general principle does not apply to all tissues. For example, in the developing central nervous system, FGF8 signals as an autocrine/paracrine factor in the anterior neural primordium<sup>430</sup> and during development of the inner ear, autocrine/paracrine FGF signaling regulates differentiation of the cochlear sensory epithelium.<sup>90,103,104</sup>

#### *Epithelial-Mesenchymal Signaling in Limb, Lung, and Neurogenic Placode Development*

FGF signaling is essential for initiation and proximal-distal growth of the limb bud (Figure 4(a)–(c)). *Fgf10* is expressed diffusely in the lateral plate mesoderm.<sup>54</sup> FGF10 was recently shown to signal to coelomic epithelium where it induces an epithelial-mesenchymal transition to generate mesenchyme in the presumptive limb fields.<sup>431</sup> Later, FGF10 signals to overlying ectoderm to initiate formation of the apical ectodermal ridge (AER), a specialized thickening of epithelium at the tip of the

growing limb that is required for proximal-distal limb growth. Inactivation of FGFR2 in the AER at different times during development results in blunt truncations of the limb<sup>117,427</sup> (Table 2(b)). FGF10 signaling to the AER activates expression of *Wnt3a* and expression of the downstream transcription factors SP6 and SP8, which are required for *Fgf8* expression.<sup>432–434</sup> *Fgf8* is first expressed as the lateral ectoderm begins to swell and then throughout the AER. *Fgf4*, *Fgf9*, and *Fgf17* are subsequently expressed in the posterior AER.<sup>15,30,435,436</sup> AER FGFs signal to distal limb mesenchyme through FGFR1 and FGFR2 to activate ETV1 and EWSR1, which are required to maintain *Fgf10* expression<sup>117,437</sup> (Table 2(b)).

FGF signaling in lung development follows similar principles to that in limb development (Figure 4(d) and (e)). *Fgf10* expression in mesenchyme adjacent to the sites of lung bud formation is regulated by the transcription factor Tbx4.<sup>293,438,439</sup> FGF10 signals to FGFR2 in foregut endoderm to induce expression of Nkx2.1, a transcription factor that demarcates the lung field in the foregut.<sup>118,393,439</sup> In the absence of FGF10, primary lung buds fail to form.<sup>54,55,440</sup> Conditional inactivation of FGF10 or FGFR2, after initial lung bud formation, results in reduced epithelial branching.<sup>57,441</sup> FGF10 signaling in lung epithelium is inhibited by *Spry1*, *Spry2*, and *Spry4*, which are expressed in the distal ductal epithelium proximal to sites of *Fgf10* expression in mesenchyme.<sup>442,443</sup> Inactivation of *Spry1* and *Spry2* results in increased epithelial proliferation, branching, and differentiation toward distal airway cell-types.<sup>444,445</sup> Inactivation of *Spry2* and *Spry4* results in epithelial dilation and reduced branching.<sup>446</sup> Interestingly, *Fgf10* appears to be expressed in a lung mesenchymal progenitor that can give rise to parabronchial cells, vascular smooth muscle cells and lipofibroblasts.<sup>447</sup>

FGF9 has a complementary role to that of FGF10. *Fgf9* is expressed in the mesothelium and epithelium.<sup>448,449</sup> Mice lacking *Fgf9* have severely hypoplastic lung development, characterized by reduced distal mesenchyme and decreased epithelial branching.<sup>42,43</sup> The primary target of FGF9 in lung mesenchyme is FGFR1 and FGFR2.<sup>43</sup> Most of the mesenchymal proliferation can be accounted for by FGF9 derived from the mesothelium, whereas epithelial-derived FGF9 is important for branching.<sup>44</sup> In lung mesenchyme, an interaction with FGFR and canonical WNT signaling is essential for development. FGFR activation is required for the expression of *Wnt2a* and WNT/ $\beta$ -catenin signaling is required to maintain mesenchymal *Fgfr1* and *Fgfr2* expression.<sup>450</sup> Thus WNT/ $\beta$ -catenin signaling functions to modulate the tissue responsiveness to FGF signals.

FGF signaling is required for the induction of neurogenic placodes.<sup>451</sup> For example, the otic placode, which gives rise to the entire inner ear including sensory hair cells, specialized supporting cells and the innervating sensory neurons, requires direct signaling from FGF3 and FGF10 (Figure 4(f) and (g)). FGF3 is derived from the hindbrain and FGF10 is expressed in head mesenchyme. Both of these FGFs signal to pre-otic ectoderm to induce the otic placode.<sup>452,453</sup> The size of the otic placode is initially regulated by FGF-induced proliferation and expression of the FGF pathway inhibitors, *Spry1* and *Spry2*.<sup>454,455</sup> FGF8 is also necessary for otic placode development; however, FGF8 functions indirectly, signaling from cranial endoderm to regulate *Fgf10* expression in adjacent head mesenchyme.<sup>28</sup>

### Canonical FGF Signaling within the Nervous System

Canonical FGF signaling within an epithelial or mesenchymal compartment is used in an autocrine, paracrine, or juxtacrine manner during the development of some neuronal tissues. For example, in the developing central nervous system, *Fgf8* is expressed in localized organizing centers such as the anterior neural primordium (neuroepithelium) where it signals as a paracrine factor to regulate anterior–posterior patterning of the telencephalon<sup>430</sup> and maintain the survival of telencephalic progenitors.<sup>456</sup> Similarly, FGF signaling is important for patterning around the midbrain–hindbrain junction and around rhombomere 4.<sup>31,457–464</sup>

During development of the cochlear duct in the inner ear, *Fgf20* is expressed in the prosensory epithelium and signals as an autocrine/paracrine factor to FGFR1 to regulate differentiation of the cochlear sensory epithelium<sup>103,90</sup> (Figure 4(h)). FGF signaling is also required for neuronal migration in the cortical ventricular zone and for the translocation of astroglial cells from the ventricular zone to the cortical surface.<sup>465,466</sup> In myelinating nerves, FGFs expressed in neurons, signal to FGFR1 and FGFR2 in oligodendrocytes to regulate myelination<sup>122</sup> and in synaptogenesis, FGF7 and FGF22, expressed in specific neuronal populations, are required for the induction of inhibitory and excitatory synapses, respectively, in the neurons that they innervate.<sup>22,467</sup>

### Canonical FGF Diffusion Controlled by ECM Interactions Regulates Development

Interactions of FGF ligands and the ECM affect receptor affinity and their diffusion through tissue.<sup>197,468</sup> Receptor binding and diffusion through tissue can have synergistic or antagonistic effects on overall

FGF signaling. An example of this is the elbow knee synostosis (EKS) mutation and multiple synostosis syndrome, both of which result from missense mutations in *Fgf9*<sup>469,470</sup> (discussed under Heritable disease mutations below). The *Fgf9*<sup>EKS</sup> mutation reduces its affinity for heparan sulfate proteoglycan and increases diffusion of FGF9 through developing joint tissue. This increases FGF9 signaling distally in the presumptive joint space and results in failure to form a joint cavity. In lacrimal gland development, *Fgf10* is expressed in periocular mesenchyme. Lacrimal gland development was impaired in mice in which the mesenchymal biosynthetic enzyme for glycosaminoglycans, UDP-glucose dehydrogenase, or enzymes required for heparan sulfation, NDST1 and NDST2, were inactivated.<sup>471</sup> Phenotypic analysis indicated that these mutations resulted in increased FGF10 diffusion, decreased local concentrations, and defective epithelial branching into the FGF10-deficient mesenchyme.

### Loss-of-Function *Fgf* and *Fgfr* Mutations in Mice

#### *Fgf1* Subfamily

FGF1 and FGF2 appear to have relatively minor roles in embryonic development but are important regulators of the injury response.<sup>3,5,6,181,472–475</sup> *Fgf1* expression in adipose tissue is induced in response to a high fat diet and mice lacking *Fgf1* develop a diabetes phenotype when placed on a high fat diet<sup>4</sup> (Table 2(a)). Mice lacking *Fgf2* also develop normally, but show reduced vascular tone, impaired cardiac hypertrophy, reduced cortical neuron density, and defects in response to cutaneous, pulmonary, or cardiac injury<sup>3,5,7,181,473,476–478</sup> (Table 2(a)).

#### *Fgf4* Subfamily

*Fgf4* knockout mice die at early embryonic stages due to impaired proliferation of the blastocyst inner cell mass<sup>14</sup> (Table 2(a)). Conditional inactivation of *Fgf4* in limb bud apical ectodermal ridge cells identified redundancy with *Fgf8* for survival of cells located distal to the apical ectodermal ridge.<sup>292</sup> Similarly, *Fgf4* and *Fgf8* show redundancy in somitogenesis and conditional loss of both genes results in loss of presomitic mesoderm and its premature differentiation.<sup>29</sup> Genetic analysis in domestic dog breeds identified a retrovirus-mediated duplication of *Fgf4* associated with a short-legged phenotype resembling chondrodysplasia.<sup>16</sup> *Fgf5* and *Fgf6* knockout mice are viable. Inactivation of the *Fgf5* gene results in a long hair phenotype in angora mice and in engineered knockouts<sup>18</sup> (Table 2(a)). *Fgf6* knockout mice have defects in muscle regeneration<sup>19</sup> and

the combined loss of *Fgf2*, *Fgf6* and the *Mdx* gene leads to severe dystrophic changes with reduced formation of new myotubes in regenerating muscle<sup>20</sup> (Table 2(a)).

### *Fgf7* Subfamily

*Fgf3* knockout mice are viable, but have phenotypes that include inner ear agenesis and dysgenesis, microtia, and microdontia<sup>12,56,479</sup> (Table 2(a)). *Fgf7* knockout mice, which are also viable, have impaired hair and kidney development<sup>23,24</sup> and defects in the formation of neuronal synapses<sup>22</sup> (Table 2(a)). *Fgf10* knockout mice die shortly after birth. *Fgf10* is critical for epithelial-mesenchymal interactions necessary for the development of epithelial components of multiple organs including the limb, lung, salivary glands kidney, and white adipose tissue<sup>54,55,58,480</sup> (Table 2(a)). *Fgf22* knockout mice are viable, but like *Fgf7* have defects in synaptogenesis.<sup>467</sup> Interestingly, *Fgf22* knockout mice have defects in the formation of excitatory synapses, while *Fgf7* knockout mice have defects in inhibitory synapses. Consistent with this, *Fgf7* and *Fgf22* knockout mice are either resistant to or prone to epileptic seizures, respectively<sup>22,95</sup> (Table 2(a)).

### *Fgf8* Subfamily

*Fgf8* knockout mice lack all embryonic mesoderm and endoderm-derived structures and die by embryonic day 9.5.<sup>426</sup> Subsequent analysis revealed that FGF8 is required for *Fgf4* expression in the primitive streak resulting in impaired migration away from the primitive streak.<sup>32</sup> Conditional inactivation of *Fgf8* identified additional roles in limb bud development and organogenesis<sup>15</sup> (Table 2(a)). *Fgf17* knockout mice are viable, but show impaired hindbrain development and a selective reduction in the size of the dorsal frontal cortex<sup>31,84</sup> (Table 2(a)). *Fgf18* knockout mice die shortly after birth. *Fgf18* has essential roles in the development of mesenchymal components of multiple organs including the skeleton, lung, and brain.<sup>85–88,481</sup> Late in embryonic development FGF18 is involved in lung alveolar development<sup>88</sup> (Table 2(a)).

### *Fgf9* Subfamily

Mice lacking *Fgf9* have hypoplastic lungs, sex reversal and impaired survival of male germ cells, impaired skeletal growth, impaired cardiomyocyte growth, impaired growth of the small intestine and cecum, and defects in inner ear development<sup>41,42,45–49,482</sup> (Table 2(a)). Mice lacking *Fgf16* are viable but have decreased proliferation of cardiomyocytes in embryos and neonatal mice<sup>82,83</sup> and enhanced cardiac hypertrophy and fibrosis in response to angiotensin II as adults<sup>81</sup> (Table 2(a)). Mice lacking *Fgf20* are viable

but lack guard hairs, have impaired differentiation of sensory cells in the cochlea, small kidneys, and defects in tooth development.<sup>40,90–92</sup> *Fgf9* and *Fgf20* show redundancy in their requirement for kidney development, where they function to maintain the stemness of cap mesenchyme progenitor cells<sup>40</sup> (Table 2(a)).

### *Fgf15/19* Subfamily

Mice lacking *Fgf15* develop normally until E10.5, but then gradually die due to variably penetrant defects in morphogenesis of the cardiac outflow tract.<sup>76,483</sup> At postnatal stages, intestinal FGF15/19 functions to regulate hepatic bile acid synthesis<sup>78</sup> (Table 2(a)). Following partial hepatectomy, mice lacking *Fgf15* have severe defects in regeneration; showing reduced or delayed expression of early response genes and transcription factors that regulate the cell cycle.<sup>79,484</sup> Mice lacking *Fgf21* are phenotypically normal under homeostatic conditions. However, when fasted, *Fgf21* expression is rapidly upregulated in the liver,<sup>485–487</sup> and in response to fasting, mice lacking *Fgf21* showed increased lipolysis<sup>93</sup> and an impaired adaptation to a ketogenic diet.<sup>488</sup> Subsequent studies showed that FGF21 is an upstream effector of adiponectin in white adipocytes and that adiponectin mediates many of the systemic effects of FGF21 on energy metabolism and insulin sensitivity in liver and skeletal muscle<sup>489,490</sup> (Table 2(a)). *Fgf23* knockout mice survive until birth, but then gradually die.<sup>100</sup> *Fgf23* knockout mice and mice in which FGF23 is inhibited with antibodies show hyperphosphatemia and increased levels of the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D). *Fgf23*, which is expressed in osteocytes, signals to the kidney where it induces the vitamin D activating enzyme Cyp27b1 and inhibits Cyp24, which inactivates vitamin D. Injection of recombinant FGF23 rapidly reduces circulating parathyroid hormone (PTH) and levels of the sodium-dependent phosphate co-transporters, NPT2a and NPT2c, in the kidney, resulting in phosphaturia.<sup>491,492</sup> FGF23 has also been shown to signal directly to cardiomyocytes to induce hypertrophy,<sup>493</sup> and increase myocyte Ca<sup>2+</sup> levels and cardiac contractility<sup>494</sup> (Table 2(a)).

### *Fgf11* Subfamily

Mice lacking *Fgf13*, though viable, have defects in neuronal migration and deficits in learning and memory<sup>70</sup> (Table 2(a)). Mice lacking *Fgf14* have paroxysmal dyskinesia, movement disorders, and impaired spatial learning<sup>71,72,74</sup> (Table 2(a)). FGF14 and other members of the iFGF family interact with the cytoplasmic carboxy terminal tail of voltage gated sodium channel (Nav)  $\alpha$  subunits<sup>69,263,264,495–498</sup>.

FGF13 was also found to interact directly with and stabilize microtubules<sup>70</sup> and bind junctophilin-2, a protein that regulates L-type Ca<sup>2+</sup> channels.<sup>499</sup>

Mice lacking *Fgf14* have defective neuronal firing due to altered Nav channel physiology<sup>69,72,73,500</sup> (Table 2(a)). Inactivation of *Fgf14* in adult mouse Purkinje neurons results in loss of spontaneous firing and deficits in coordination,<sup>501</sup> suggesting that FGF14 functions as a physiological regulator of Nav channels *in vivo*. Interestingly, FGF14 interactions with Nav channels may be regulated downstream of glycogen synthase kinase 3 providing a pathway that could link intercellular signaling and neuronal excitability.<sup>498,502–504</sup> Consistent with phenotypes seen in *Fgf14* deficient mice, mutations in *Fgf14* in humans result in a progressive spinocerebellar ataxia syndrome (SCA27)<sup>505,506</sup> (see below).

### *Fgfr* Family

Most embryos lacking both alleles of *Fgfr1* do not survive past embryonic day 8.5. Analysis of earlier stages of development shows that *Fgfr1*-null embryos are smaller, but do initiate gastrulation (mesoderm formation), have impaired mesoderm migration, but fail to initiate somitogenesis<sup>105,425</sup> (Table 2(b)). Mice lacking *Fgfr2* survive until embryonic day 10–11. These embryos fail to form a functional placenta and do not form limb buds<sup>115,116</sup> (Table 2(b)). As discussed above, another presumed null allele of *Fgfr2* that dies earlier in development may have dominant negative effects on other *Fgfrs*, uncovering potential redundancies and resulting in earlier and more severe phenotypes.<sup>424</sup> At later stages of development, several studies have demonstrated redundant function of *Fgfr1* and *Fgfr2* in organogenesis.<sup>43,49,121,507</sup>

Mice lacking *Fgfr3* are viable. In the absence of *Fgfr3*, the most prominent phenotype is skeletal overgrowth<sup>127,128</sup> (Table 2(b)). However, close examination of *Fgfr3* null mice revealed defects in inner ear development resulting in sensorineural hearing loss,<sup>127,129,508</sup> decreased growth of the cerebral cortex and telencephalon,<sup>509</sup> reduced numbers of differentiated oligodendrocytes,<sup>130</sup> and fewer intestinal crypts with impaired paneth cell differentiation.<sup>510</sup>

Mice lacking *Fgfr4* are viable and overtly healthy.<sup>131</sup> Although, they have normal liver histology and regenerative response to partial hepatectomy, mice lacking *Fgfr4* exhibit depleted gallbladders, elevated bile acid reserves, elevated bile acid excretion, increased mass of white adipose tissue, hyperlipidemia, glucose intolerance, insulin resistance, and hypercholesterolemia<sup>143,511</sup> (Table 2(b)). The role of FGFR4 in tumorigenesis is controversial. In one study, mice lacking *Fgfr4* have increased susceptibility

to chemically induced hepatocellular carcinoma, indicating that FGFR4 may function as a tumor suppressor in the liver.<sup>512</sup> However, in a second study, FGFR4 was found to be required for FGF15/19 induced hepatocellular carcinoma and mice lacking *Fgf15* are resistant to chemically induced hepatocellular carcinogenesis.<sup>257,513</sup> FGFR3 and FGFR4 show redundant function in the regulation of vitamin D levels and in regulating alveolar septation<sup>131,140,142</sup> (Table 2(b)). FGFR1 and FGFR4 show redundant function in phosphate homeostasis<sup>141</sup> (Table 2(b)).

## Heritable Disease Mutations in *FGFs* and *FGFRs* in Humans and Other Mammals

### *FGF4* Subfamily

Chondrodysplasia is a short-legged phenotype that defines at least 19 dog breeds. The expression of a recently acquired expressed retrogene encoding *Fgf4* is strongly associated with the chondrodysplasia phenotype<sup>16</sup> (Table 3(a)). Genome-wide association studies (GWAS) in dogs identified a mutation in *Fgf5* that is associated with hair length<sup>518</sup> (Table 3(a)). A missense mutation in *Fgf5* was also found in longhaired cats and the Angora mouse mutant<sup>18,519</sup> (Table 3(a)).

### *FGF7* Subfamily

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*<sup>514</sup> (Table 3(a)). Human chronic obstructive pulmonary disease (COPD) is a type of obstructive lung disease characterized by chronically poor airflow. Genome wide association studies identified single nucleotide polymorphisms in *FGF7* significantly associated with COPD<sup>522</sup> (Table 3(a)). Aplasia of the 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 (LADD) syndrome 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 syndromes are caused by *FGF10* mutations<sup>530,531</sup> (Table 3(a)). Severe myopia (nearsightedness) is associated with a single nucleotide polymorphism in *FGF10*<sup>532</sup> (Table 3(a)). In strong support of an FGF10-FGFR2b signal, loss-of-function mutations in *FGFR2* are also a cause of LADD syndrome (see below).

**TABLE 3** | Heritable Mutations in FGFs Associated with Disease in Humans (and Mice)

Gene Name	Mutation	Associated Disease	Selected References
(a) Heritable mutations in FGFs associated with disease in humans (and other mammals)			
<i>FGF1</i>			
<i>FGF2</i>			
<i>FGF3</i>	Haploinsufficiency	Oto-dental syndrome	479,514–517
	Missense/frameshift mutation	Michel aplasia (inner ear agenesis, microtia, and microdontia), LAMM syndrome (labyrinthine aplasia, microtia, and microdontia)	
<i>FGF4</i>	Retroviral overexpression	Chondrodysplasia (dogs)	16
<i>FGF5</i>	Deletion mutation	Angora mutation (mice)	18,518–521
	Missense/splice-site mutation	Coat variability (pure bred dogs)	
	Missense/insertion/deletion mutation	Long-hair (cats)	
<i>FGF6</i>			
<i>FGF7</i>	Polymorphism	Chronic obstructive pulmonary disease risk	522
<i>FGF8</i>	Nonsense mutation	Hypogonadotropic hypogonadism	523–528
	Missense mutation	Cleft lip and palate, Holoprosencephaly, craniofacial defects, Hypothalamo-pituitary dysfunction, Kallman syndrome type 6	
	Hypomorphic allele	Lack of hypothalamic GnRH neurons	
<i>FGF9</i>	Missense mutation	Multiple synostoses syndrome, Elbow knee synostosis (mice)	469,470,529
	Promoter polymorphism	Sertoli cell-only syndrome	
<i>FGF10</i>	Nonsense mutation	Aplasia of lacrimal and salivary glands, LADD syndrome	530–534
	Polymorphism	Extreme myopia	
<i>FGF11</i>			
<i>FGF12</i>	Missense mutation	Brugada syndrome (candidate gene)	535
<i>FGF13</i>	Nonsense mutation	Börjeson-Forssman-Lehmann syndrome (BFLS) (candidate gene)	536,537
	Position effect	X-linked congenital generalized hypertrichosis	
<i>FGF14</i>	Missense mutation/translocation/deletion	Spinocerebellar ataxia 27 (SCA27)	505,538,539
<i>FGF15/19</i>			
<i>FGF16</i>	Nonsense mutation	Metacarpal 4–5 fusion	540,541
<i>FGF17</i>	Missense mutation	Hypogonadotropic hypogonadism	542
<i>FGF18</i>	Polymorphism	Nonsyndromic cleft lip and palate	524
<i>FGF20</i>	Polymorphism	Parkinson disease risk	40,543–545
	Missense mutation	Kidney agenesis (human)	
<i>FGF21</i>	Polymorphism	Macronutrient intake, obesity, and type-2 diabetes risk	546–548
<i>FGF22</i>			
<i>FGF23</i>	Missense mutation	Autosomal dominant hypophosphataemic rickets, Familial hyperphosphatemic tumoral calcinosis	242,549–555
	Polymorphism	Cardiac abnormality risk in Kawasaki syndrome (increased serum FGF23)	
(b) Heritable mutations in FGFRs associated with disease in humans (and other mammals)			
<i>FGFR1</i>	Missense mutation	Pfeifer syndrome, Kallman syndrome 2, Normosmic idiopathic hypogonadotropic hypogonadism, Split hand/foot malformation, Osteoglophonic dysplasia, Harstfield syndrome	556–566
	Missense or frameshift mutation	Jackson-Weiss syndrome	

TABLE 3 | Continued

Gene Name	Mutation	Associated Disease	Selected References
<i>FGFR2</i>	Missense mutation	Apert syndrome, Crouzon syndrome, Jackson-Weiss syndrome, Pfeifer syndrome, Non syndromic craniosynostosis, Bent bone dysplasia	567–579
	Deletion	Saethre-Chotzen-syndrome	
<i>FGFR3</i>	Missense mutation	Hypochondroplasia, Achondroplasia, Thanatophoric dysplasia, Coronal craniosynostosis, Crouzon syndrome with acanthosis nigricans, Platyspondylic lethal skeletal dysplasia, Achondroplasia with developmental delay, and acanthosis nigricans (SADDAN), Muenke syndrome, Saethre-Chotzen-syndrome, CATSHL syndrome, Mouse models for aberrant osteogenesis, Achondroplasia, Muenke syndrome	288,574,580–611
<i>FGFR4</i>	Overexpression	Facioscapulohumeral muscular dystrophy	612–614
	Missense mutation	Gallstone disease	
	Polymorphism	Bronchopulmonary dysplasia, Neonatal respiratory distress syndrome	
<i>FGFRL1</i>	Frameshift mutation	Craniosynostosis, Antley–Bixler-like syndrome	615–617
	Deletion	Wolf-Hirschhorn syndrome	

### *FGF8* Subfamily

Nonsense mutations in *FGF8* and destabilizing missense mutations in *FGF17* were found in familial hypogonadotropic hypogonadism with variable degrees of gonadotropin-releasing hormone deficiency and olfactory phenotypes<sup>523,542</sup> (Table 3(a)). Cleft lip and/or palate (CLP) appear when the two halves of the palatal shelves fail to fuse completely. A missense mutation in *FGF8* which is predicted to cause loss-of-function by destabilizing the N-terminal structure of the protein (important for FGFR binding affinity and specificity) was found in a patient with CLP<sup>524</sup> (Table 3(a)).

### *FGF9* Subfamily

An autosomal dominant missense mutation in *FGF9* was found in patients with multiple synostosis syndrome (SYNS). The mutation leads to significantly impaired FGF9 receptor binding, reduced chondrocyte proliferation, increased osteoblast differentiation, and matrix mineralization resulting in joint fusions (synostosis)<sup>470</sup> (Table 3(a)). An autosomal dominant missense mutation in *Fgf9* is also responsible for the mouse mutant, elbow knee synostosis (EKS), showing elbow and knee joint synostosis, and premature fusion of cranial sutures. The mutation prevents homodimerization of the FGF9 protein, resulting in reduced affinity for heparin. Even though receptor binding affinity is decreased by this mutation, the EKS phenotype resembles that of a gain-of-function mutation. The reduced affinity for heparan sulfate results in increased diffusion of FGF9 through tissue,

leading to ectopic FGF9 signaling and repression of joint and suture development<sup>469</sup> (Table 3(a)). Overexpression of an activated form of FGFR1 in developing chondrocytes results in a similar joint fusion phenotype.<sup>618</sup>

Sertoli cell–only syndrome (SCOS) patients commonly have atrophic testes, azoospermia, and hypogonadism. *FGF9* is expressed in the Leydig cells of the testis and *FGF9* expression is significantly decreased in patients with SCOS. A promoter mutation in *FGF9* results in weak promoter activity and the resulting low expression of testicular *FGF9*<sup>529</sup> (Table 3(a)). Metacarpal 4–5 fusion is a rare congenital malformation of the hand characterized by the partial or complete fusion of the fourth and fifth metacarpals in humans. Nonsense mutations in *FGF16* are associated with X-linked recessive metacarpal 4–5 fusion, indicating the involvement of FGF16 in the fine tuning of skeletal development<sup>540,619</sup> (Table 3(a)). Parkinson disease is a common neurodegenerative disorder resulting in the inability to control movement. The disease has been attributed to the severe loss of dopaminergic neurons within the substantia nigra. The significant correlation of Parkinson disease with single nucleotide polymorphisms in *FGF20* indicates that the genetic variability of *FGF20* may be a risk factor for Parkinson disease<sup>543–545</sup> (Table 3(a)). A frameshift mutation in *FGF20* also results in bilateral renal agenesis in humans, indicating that FGF20 is essential for metanephric kidney development<sup>40</sup> (Table 3(a)).

### ***FGF15/19 Subfamily***

Dietary intake of macronutrients has been associated with risk of obesity and type 2 diabetes. Polymorphisms in *FGF21* are potentially associated with macronutrient consumption and risk of obesity and type 2 diabetes in humans<sup>546–548</sup> (Table 3(a)). Mutations resulting in either gain- or loss-of-function of *FGF23* result in human disease<sup>620</sup> (Table 3(a)). Autosomal dominant hypophosphatemic rickets (AHDR) is caused by gain-of-function mutations in *FGF23*.<sup>242</sup> Tumors that over-produce FGF23 also cause tumor-induced osteomalacia (TIO), which is a paraneoplastic disease characterized by renal phosphate wasting and resulting hypophosphatemia.<sup>621</sup> Reduced FGF23 signaling also causes familial tumoral calcinosis (FTC); a disease characterized by ectopic calcification and hyperphosphatemia<sup>549,550</sup> (Table 3(a)). Kawasaki syndrome (KS) is a childhood vascular inflammatory disease with an increased risk of developing subsequent cardiac abnormalities. Thirty three percent of patients examined were found to have a polymorphism in *FGF23* and elevated serum levels of FGF23.<sup>551,552</sup> *FGF23* polymorphisms were significantly associated with cardiac abnormalities (Table 3(a)).

### ***FGF11 Subfamily***

Brugada syndrome (BrS) is a potentially life-threatening inherited cardiac arrhythmia. *FGF12* (*FHF1*) is the major intracellular *FGF* expressed in the human ventricle. A single missense mutation in *FGF12* in Brugada syndrome patients reduces binding to the voltage gated sodium channel (Nav1.5) C-terminus, resulting in reduced Na<sup>+</sup> channel current density and availability without affecting Ca<sup>2+</sup> channel function<sup>535</sup> (Table 3(a)). Börjeson–Forssman–Lehmann syndrome (BFLS) is an X-linked mental retardation syndrome. A duplication breakpoint identified in a patient with BFLS maps near the *FGF13* (*FHF2*) gene at Xq26.3. This disease association and the high expression of *FGF13* in brain and skeletal muscle makes it a good candidate gene for BFLS<sup>536</sup> (Table 3(a)). X-linked congenital generalized hypertrichosis is an extremely rare condition of hair overgrowth on different body sites. This disease maps to Xq24–27 and a large interchromosomal insertion at Xq27.1 co-segregates with the disease. In patients with this disease, *FGF13* expression is significantly decreased throughout the outer root sheath of affected hair follicles, suggesting a role for FGF13 in hair follicle growth and in the hair cycle<sup>537</sup> (Table 3(a)). Spinocerebellar ataxias (SCAs) are neurodegenerative disorders with multiple genetic etiologies. SCA27 is characterized by early onset tremor, dyskinesia, and

slowly progressive cerebellar ataxia. SCA27 is caused by missense, translocation, or deletion mutations in *FGF14*<sup>506,622,623</sup> (Table 3(a)). Loss of binding of the mutant FGF14 protein to Nav channel  $\alpha$  subunits and instability of the mutant protein are thought to be the primary factors leading to this disease<sup>505,624</sup> (Table 3(a)).

### ***FGFR1***

Gain-of-function missense mutations in *FGFR1* are found in several craniosynostosis syndromes including Pfeiffer syndrome, Jackson-Weiss syndrome, Muenke syndrome, and osteoglophonic dysplasia<sup>556,557,567,625,626</sup> (Table 3(a)). These are autosomal dominant syndromes that affect cranial suture closure and have various additional skeletal and soft tissue phenotypes. Interestingly, Pfeiffer syndrome, Jackson-Weiss syndrome, and Muenke syndrome phenotypes also can be caused by activating mutations in *FGFR2* (Pfeiffer) or *FGFR3* (Pfeiffer, Muenke), suggesting possible redundant or parallel function of these FGFRs in skeletal development.<sup>568,626</sup>

Loss-of-function missense mutations have also been identified in *FGFR1* as a cause of Kallmann syndrome 2 (hypogonadotropic hypogonadism 2) with or without anosmia<sup>558,559</sup> (Table 3(a)). Dominant or recessive mutations in *FGFR1* that are likely loss-of-function are found in Harstfield syndrome (holoprosencephaly and ectrodactyly, with or without cleft lip and palate)<sup>560</sup> (Table 3(a)).

### ***FGFR2***

Autosomal dominant gain-of-function missense mutations, deletions, and insertions in *FGFR2* result in Apert syndrome, Crouzon syndrome, non syndromic craniosynostosis syndrome, Saetho-Chatzen syndrome, Pfeiffer syndrome, and Jackson-Weiss syndrome<sup>567–574,627,628</sup> (Table 3(b)). Pfeiffer and Jackson-Weiss syndromes also result from mutations in *FGFR1*, as described above. All of these syndromes have in common synostosis of at least one cranial suture; many of these syndromes also affect the appendicular skeleton and other organs. For example, the Crouzon syndrome mutation, *FGFR2*<sup>C342Y</sup>, affects the shape of the brain, but not its overall volume.<sup>629</sup>

The biochemical consequences of the classic Apert syndrome mutations (*FGFR2*<sup>S252W</sup> and *FGFR2*<sup>P253R</sup>) and a relatively rare Alu element insertion, or deletion of an intronic splicing element in the intron between exon 8 (IIIb) and exon 9 (IIIc) of *FGFR2* is to change the ligand binding affinity to an extent that mesenchymal ligands such as FGF10 are able to activate mesenchymal splice variants of *FGFR2*<sup>575,630</sup> (Figure 5(b)). Importantly, the Apert

mutations all remain ligand dependent. The Alu element insertion acts by disrupting splicing to exon 9, encoding the IIIc splice variant (Figure 1(b)), leading to alternative mesenchymal misexpression of exon 8, encoding the IIIb splice variant. The missense mutations directly affect ligand affinity for the mutant receptor.<sup>575,576,631–638</sup>

Bent bone dysplasia, which is a perinatal lethal skeletal dysplasia characterized by osteopenia, craniofacial dysmorphology and bent bones, results from mutations in *FGFR2* that decrease plasma membrane signaling without affecting nuclear localization of the mutant receptor<sup>577</sup> (Table 3(b)). The consequence of this mutation is enhanced nucleolar occupancy of the receptor at the ribosomal DNA promoter where it activates rDNA transcription.<sup>639</sup>

Loss-of-function mutations in *FGFR2* are seen in lacrimo-auriculo-dento-digital (LADD) syndrome, which is characterized by lacrimal-duct aplasia, dysplastic ears, hearing loss, small teeth, and digital malformations<sup>531</sup> (Table 3(b)). Mutations in *FGFR2* disrupt the catalytic pocket of the tyrosine kinase domain resulting in reduced substrate binding and reduced tyrosine kinase activity.<sup>640,641</sup> Other individuals with LADD syndrome have inactivating mutations in *FGF10* (see above), a ligand for *FGFR2b*,<sup>533</sup> or a missense mutation in *FGFR3*<sup>531</sup> (Box 2).

### FGFR3

Hypochondroplasia, Achondroplasia, Thanatophoric dysplasia, and Platyspondylic lethal skeletal dysplasia are autosomal dominant disorders characterized by short-limbed dwarfism.<sup>580,581</sup> These syndromes are caused by gain-of-function missense mutations in *FGFR3*. Among the mutations, the G380R mutation in the transmembrane domain of *FGFR3* activates the receptor in a ligand dependent manner resulting in Achondroplasia, the most common form of skeletal dwarfism in humans (Figure 5(c)). By contrast, in the lethal skeletal dysplasia syndrome, Thanatophoric dysplasia, type I or type II, the R248C mutation in the extracellular domain or the K650E mutation in the

or indirect inhibition of the *FGFR3* signaling pathway could form the basis of a therapy for Achondroplasia.<sup>738</sup> The direct inhibition of the *FGFR3* kinase has thus far not succeeded *in vivo*, possibly because of difficulties in achieving therapeutic levels of *FGFR3* kinase inhibitors in the avascular growth plate. However, over the past 20 years, other therapies have been aimed at indirectly augmenting skeletal growth or indirectly suppressing *FGFR3* signaling. One of the first therapies to be evaluated was the use of human growth hormone; however, no long-term benefit was observed.<sup>581,739</sup> More recently, it was discovered that C-type natriuretic peptide (CNP) signaling through its receptor, natriuretic peptide receptor 2 (guanylate cyclase B) in chondrocytes, inhibits the MAPK signaling pathway at the level of RAF1, to regulate skeletal growth. Overexpression of *CNP* in mice or humans results in skeletal overgrowth through attenuation of *FGFR3* signaling.<sup>740,741</sup> BMN-111, a CNP agonist with an extended half-life, was found to normalize skeletal growth in a mouse model for Achondroplasia<sup>604,742,743</sup> and this drug is currently being evaluated in a clinical trial for the treatment of Achondroplasia.

Other indirect strategies involve the use of a soluble *FGFR3* extracellular domain (s*FGFR3*) to interfere with endogenous *FGFR3* signaling by binding FGF ligands (FGF9 and FGF18) that normally are required to activate the receptor during postnatal skeletal development.<sup>47,85–87,744</sup> In a mouse model for Achondroplasia,<sup>132</sup> subcutaneous injections of recombinant s*FGFR3* throughout the growth period normalized skeletal growth and decreased mortality without having any apparent toxic side effects. Several inhibitory antibodies have also been developed to target the *FGFR3* extracellular domain for potential cancer therapeutics, but these have not yet been evaluated for treatment of Achondroplasia.<sup>745–747</sup>

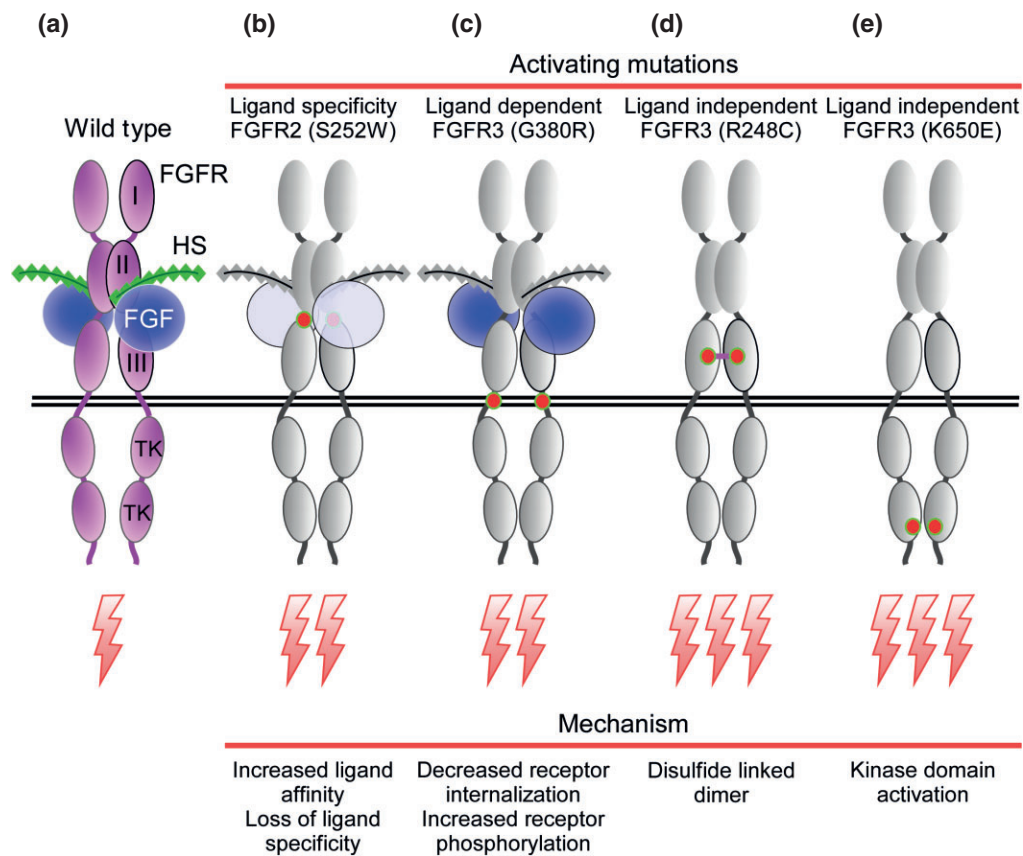
Statins (drugs that inhibit cholesterol biosynthesis) were recently identified through a screen for drugs that could improve chondrogenic differentiation of induce pluripotent stem cells (iPSCs) derived from patients with Thanatophoric dysplasia.<sup>748</sup> Treatment of a mouse model for Achondroplasia<sup>132</sup> with Rosuvastatin, which is one of the statin drugs, increased anteroposterior skull length and the lengths of the ulnas, femurs and tibiae.<sup>748</sup> Although the mechanism is poorly defined, statin treatment was found to increase degradation of the mutant *FGFR3*.

#### BOX 2

##### DEVELOPING A PHARMACOLOGICAL TREATMENT FOR ACHONDROPLASIA

Achondroplasia is caused by a ligand dependent autosomal dominant mutation in *FGFR3*. Because the disease phenotypes form during the prepubertal years when bones are actively growing, it was anticipated that direct





**FIGURE 5 |** Activating mutations in FGFRs in heritable and acquired disease. (a) Wild type FGFR-FGF-HS complex. (b) Missense mutations in the linker between immunoglobulin-like domain II and III affect the affinity and specificity of the receptor. The Apert syndrome mutation, S252W, allows FGF10 to activate the IIIc splice variant of FGFR2. (c) Missense mutations in the transmembrane domain, as seen in the G380R Achondroplasia mutation, weakly activates the receptor in a ligand dependent manner by impeding receptor internalization. (d) The strongly activating ligand independent mutation, R248C, in Thanatophoric dysplasia, type I, causes constitutively active disulfide linked receptor dimers. (e) Mutations in the tyrosine kinase domain, as seen in the K640E Thanatophoric dysplasia, type II mutation, are often ligand independent and result in receptor autophosphorylation and signaling from intracellular sites such as the endoplasmic reticulum.

intracellular domain activates FGFR3 in a ligand independent manner<sup>288,582–595,642,643</sup> (Figure 5(d) and (e)). Muenke syndrome (Muenke nonsyndromic coronal craniosynostosis) is an autosomal dominant disorder characterized by synostosis, macrocephaly, midfacial hypoplasia, and hearing loss caused by gain-of-function missense mutations in *FGFR3*<sup>596–602,644</sup> (Table 3(b)). Mouse models for aberrant osteogenesis, Achondroplasia, and Muenke syndrome have been developed<sup>603–606</sup> (Table 3(b)). Two craniosynostosis syndromes, Crouzon syndrome and Saetho-Chotzen syndrome, can result from mutations in *FGFR2* or *FGFR3*, suggesting overlapping or redundant functions of these FGFRs.<sup>592,607,608</sup>

Loss-of-function missense mutations, that likely function through a dominant negative mechanism, have been identified in *FGFR3* as the cause of CAT-SHL syndrome (autosomal dominant syndrome characterized by camptodactyly, tall stature, and hearing

loss)<sup>609</sup> (Table 3(b)). A recessive loss-of-function mutations in *FGFR3* has also been identified in two siblings with tall stature, severe skeletal abnormalities, camptodactyly, arachnodactyly, scoliosis and hearing impairment.<sup>610</sup> A similar disease, spider-lamp syndrome in sheep, is characterized by abnormally long limbs, kyphoscoliosis, malformed ribs and sternebrae, hooked or ‘Roman’ nose, lack of body fat, and muscular atrophy.<sup>645,646</sup> This disease is associated with a missense mutation in the FGFR3 tyrosine kinase domain coupled with poorly described interactions with other genetic and environmental factors.

A mutation in *FGFR3* has also been associated with LADD syndrome (Table 3(b)). Although the function of the mutation, localized to the conserved proximal tyrosine kinase domain (TK1, Figure 1(b)), is not known, the phenotypes of affected individuals are distinct from both known gain-of-function mutations causing chondrodysplasia syndromes and

loss-of-function mutations resulting in skeletal overgrowth and hearing loss.<sup>531,581,609</sup>

### **FGFR4**

Facioscapulohumeral muscular dystrophy is an autosomal dominant disorder, ranging from mild dysfunction to severe respiratory failure. Overexpression of *FGFR4* in muscle and surrounding connective tissue and overexpression of *FGF1* and *FGF2* on the sarcolemma may be associated with this disease.<sup>612</sup> Bronchopulmonary dysplasia, characterized by impaired alveolar development and inflammation is the most common chronic lung disease resulting from premature birth. Neonatal respiratory distress syndrome is a pulmonary disease affecting preterm neonates. A single nucleotide polymorphism (I>V) in exon 10 of *FGFR4* is a potential risk factor for these diseases<sup>613</sup> (Table 3(b)). The common allelic variant (G388R) in *FGFR4* is associated with breast cancer progression and increased insulin secretion and risk of diabetes.<sup>647</sup>

### **FGFRL1/FGFR5**

Antley–Bixler syndrome is a disorder characterized by craniosynostosis, radio-ulnar synostosis, and genital abnormalities. A C-terminal frameshift mutation in *FGFRL1* was found in one patient with this disease. The mutation results in preferential localization of the mutant protein to the plasma membrane, compared to the localization of wild-type *FGFRL1* to vesicular structures and the Golgi complex<sup>615</sup> (Table 3(b)). Wolf-Hirschhorn syndrome (WHS) is a disease resulting in growth delay, craniofacial dysgenesis, developmental delay, and epilepsy. Micro deletions containing *FGFRL1*, but not the *WHSC1* gene have craniofacial features resembling that seen in WHS patients, suggesting that *FGFRL1* could be a possible candidate gene<sup>616</sup> (Table 3(b)). Analysis of a new null allele for *Fgfr11* in mice revealed skeletal and other defects that resemble WHS.<sup>617</sup>

## **FGFs and FGFRs: Mutations and Expression in Cancer**

Deregulation of FGF signaling pathways have been implicated in many types of human and animal cancers. Deregulation can occur at the level of gene/protein expression of ligands or receptors, which can result from changes in transcriptional activity or gene amplification. Deregulation can also result from mutations in FGF ligands, receptors, or downstream signaling pathways. A more detailed discussion of FGF signaling in cancer can be found in a review by Turner and Grose.<sup>152</sup>

### **FGF Family**

Mechanisms of FGF ligand activation involve aberrant expression, gene amplification leading to overexpression, or mutations that increase diffusion through tissue or increase affinity for FGFRs (Table 4(a)). Aberrant expression and mutations in FGFs have been observed in many human cancers.<sup>163,418,649–653,656–662,664,665,667–669,671,672</sup> Gene amplification of *FGFs* has also been observed.<sup>648,654</sup> Overexpression and gene amplification leads to excessive FGF signaling, which can result in cancer initiation or progression. In contrast to the oncogenic properties of many FGF ligands, in some human colon and endometrial cancers that lack  $\beta$ -catenin activation, homozygosity for loss-of-function somatic mutations in *FGF9* have been observed. Additionally, mice lacking *Fgf22* have normal skin, but show increased papilloma formation in a DMBA/TPA induced tumorigenesis model<sup>96</sup> (Table 4(a)). These examples show that in at least some cases, FGF signaling can also function to suppress tumorigenesis, possibly by promoting cell differentiation.<sup>664</sup> Single nucleotide polymorphisms in *FGF23* have been associated with an increased risk of prostate cancer, although it remains unclear whether polymorphisms result in gain- or loss-of-function.<sup>673</sup>

### **FGFR Family**

FGFRs can be activated by gene amplification leading to receptor overexpression, by activating mutations (Figure 5), or by translocations resulting in activating gene fusions.<sup>720,721</sup> *FGFR1* gene amplification has been identified in 20% of lobular breast cancer, in 3% of lung adenocarcinomas and 21% of squamous cell lung cancer.<sup>192,674,722,723</sup> *FGFR1* or *FGFR2* was amplified in 47% of hormone resistant prostate cancers.<sup>724</sup> *FGFR3* was amplified in 3% of bladder cancers.<sup>725</sup> *FGFR4* overexpression (65% of cases) and amplification (30% of adult tumors) were observed in adrenocortical tumors and amplification was associated with worse prognosis.<sup>726</sup> *FGFR4* amplification was also found in 10% of primary breast tumors.<sup>727</sup> Thus, *FGFR* gene amplification may be pathogenic in a large fraction of some of the major cancer subtypes (Table 4(b)).

Oncogenic gene fusions that activate the FGFR tyrosine kinase domain is a relatively common occurrence in myeloproliferative syndrome, glioblastoma, bladder, lung, breast, thyroid, oral, and prostate cancers.<sup>193,684</sup> In the 8p11 myeloproliferative syndrome (myeloid and lymphoid neoplasms with *FGFR1* abnormalities), *FGFR1* translocations result in at least 10 fusion proteins with N-terminal dimer forming partners fused to the C-terminal

**TABLE 4** | Acquired and Heritable Mutations in FGFs and FGFRs in Malignancy

Gene Name	Mutation	Type of Cancer	Selected References
<b>(a) Contributions of FGFs to malignancy (<i>in vivo</i>)</b>			
<i>FGF1</i>	Amplification	Ovarian cancer	648
<i>FGF2</i>	Over expression	Bladder cancer, Prostate cancer, Small cell lung carcinoma, Melanoma, Hepatocellular carcinoma	649–653
<i>FGF3</i>	Amplification	Breast cancer	654
<i>FGF4</i>	Amplification	Breast cancer	655
<i>FGF5</i>	Over expression	Glioblastoma	656
<i>FGF6</i>	Over expression	Prostate cancer	657
<i>FGF7</i>	Over expression	Lung adenocarcinoma	658
<i>FGF8</i>	Over expression	Breast cancer, Prostate cancer, Hepatocellular carcinoma, Colorectal cancer	659–663
<i>Fgf9</i>	Frameshift/missense/nonsense mutation	Colorectal and endometrial carcinomas	418,664–666
	Over expression	Non small cell lung cancer	
<i>FGF10</i>	Over expression	Breast carcinomas, Prostate cancer	667,668
<i>FGF15/19</i>	Over expression	Prostate cancer, Hepatocellular carcinoma	162,163,513,669,670
<i>FGF16</i>	Over expression	Ovarian cancer	671
<i>FGF17</i>	Over expression	Prostate cancer, Hepatocellular carcinoma	660,672
<i>FGF18</i>	Over expression	Hepatocellular carcinoma	660
<i>FGF22</i>	Knockout	Suppresses skin papilloma (in mice)	96
<i>FGF23</i>	Polymorphism	Increased risk of prostate cancer	673
<b>(b) Contributions of FGFRs to malignancy (<i>in vivo</i>)</b>			
<i>FGFR1</i>	Amplification	Small cell lung cancer, Squamous cell lung cancer, Breast cancer, Ovarian cancer, Pancreatic ductal adenocarcinoma, Tongue squamous cell carcinoma	191,192,674–682
	Missense mutation	Melanoma, Pilocytic astrocytoma	683
	Translocation	Leukemia, Lymphoma, Alveolar rhabdomyosarcoma, Glioblastoma, Myeloproliferative syndrome (fusion with CUX1, FGFR2, FIM, RANBP2/NUP358, SQSTM1, TRP, ZNF198)	681,684–692
	Over expression	Glioblastoma	656
<i>FGFR2</i>	Amplification	Gastric cancer, Breast cancer	693–697
	Missense mutation	Endometrial carcinoma, Gastric cancer	693,698
	Translocation	Cholangiocarcinoma	699–702
<i>FGFR3</i>	Missense mutation	Gastric cancer, Colorectal cancer, Breast cancer, Endometrial carcinoma, Urothelial carcinoma, Bladder tumor, Skin tumor, Myeloma	608,693,703–706
	Mis-localization	Brest cancer	707
	Translocation	Myeloma, Squamous cell lung cancer, Bladder cancer, Glioblastoma, Lymphoma	708–712
	Over expression	Breast cancer, Colon cancer (FGFR3c)	713,714
<i>FGFR4</i>	Missense mutation	Rhabdomyosarcoma, Adenoid cystic carcinoma, Breast Cancer (resistance to adjuvant therapy)	715–717
	Over expression	Ovarian cancer, hepatocellular carcinoma	256,718,719

FGFR1 tyrosine kinase domain<sup>684</sup> (Table 4(b)). *FGFR1–FGFR3* are also closely linked to the transforming, acidic coiled-coil containing protein 1–3 genes (*TACC1–TACC3*).<sup>236</sup> *FGFR1* and *TACC1* or *FGFR3* and *TACC3* gene fusions have been identified in glioblastoma, non-small cell lung cancers (NSCLC), bladder cancer, multiple myeloma, and lung squamous cell carcinoma<sup>685,708,728–730</sup> (Table 4(b)). These gene fusions can generate constitutively active FGFR kinase domains that are localized to the mitotic spindle. *FGFR2* translocations resulting in gene fusions with *AHCYL1*, *BICC1*, *MGEA5*, *AFF3*, and *TACC3* have been identified in subtypes of cholangiocarcinoma.<sup>699–701</sup> Gene fusions can also result in 3' UTR deletion, allowing escape from regulation by microRNAs, as seen in an *FGFR3–TACC3* fusion in multiple myeloma<sup>729</sup> (Table 4(b)).

Activation of *FGFR3* in multiple myeloma can occur through several mechanisms and is thought to contribute to the neoplastic transformation. A common translocation between the immunoglobulin heavy chain locus on chromosome 14q32 and the *FGFR3* and *MMSET* (*multiple myeloma set domain*) region of chromosome 4 is found in 15–20% of multiple myeloma cases and many of these result in increased expression of *FGFR3*<sup>731,732</sup> (Table 4(b)). However, although this translocation is associated with poor survival, survival does not correlate with *FGFR3* expression.<sup>733,734</sup>

Activation of FGFRs by somatic acquisition of missense mutations is another common tumorigenic mechanism. Missense mutations in *FGFR2* have been found in gastric and endometrial cancer.<sup>693,698,735</sup> (Table 4(b)). Missense mutations in *FGFR3* have been observed in 25% of cervical carcinomas and 35% of bladder carcinomas<sup>736</sup> (Table 4(b)). Interestingly, these mutations are identical to the activating mutations that cause Thanatophoric dysplasia. Tyrosine kinase domain mutations were found in 7.5% of rhabdomyosarcomas.<sup>715</sup> In gastric cancer, at least one allele of the common G388R variant of *FGFR4* was present in 57% of patients, and expression of this allele was associated with worse prognosis<sup>737</sup> (Table 4(b)).

## CONCLUSION

Since the purification of the first FGF over thirty years ago, an amazing amount of research has uncovered biochemical and biological functions of FGFs, FGFRs, and other interacting molecules that are essential for almost all aspects of life through the regulation of developmental, physiological, and pathological processes, from the earliest stages of embryonic development, to organogenesis, tissue maturation, homeostasis, response to injury, and cancer. Biochemical studies have identified mechanisms that regulate the expression of FGFs, their bioavailability, and their ability to activate cellular responses through interaction with cell surface receptors. Within the cell, signal transduction mechanisms have been identified that reveal interactions with multiple cellular signaling pathways, complex feedback mechanisms, and regulatory molecules that control FGF signaling, both extracellularly and intracellularly. Developmental studies have uncovered redundant functions of FGFs and FGFRs, and interactions with most of the other major signaling pathways, including BMP, WNT, Notch and Hedgehog. The discovery of endocrine FGFs has uncovered new mechanisms that regulate metabolism, lipid, and mineral homeostasis, and has provided potential therapeutic targets for a variety of common diseases, including type 2 diabetes, chronic kidney disease, and obesity. Understanding pathogenic mechanisms resulting from mutations, gene fusions, and gene amplifications in FGFs and FGFRs has led to therapeutic approaches for chondrodysplasia and craniosynostosis syndromes, as well as a variety of cancers. Future directions will be aimed at acquiring a deeper mechanistic understanding of the roles of FGF signaling in development and in adult tissues with a goal of understanding how these pathways become reactivated during injury response and cancer. The development of highly selective pharmacological agonists and antagonists that function at all levels of FGF signaling should provide new tools to protect tissues from injury, enhance cell and tissue repair, treat a variety of metabolic diseases, and inhibit cancer.

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