
Review

Roles of the fibroblast growth factor signal transduction system in tissue injury repair

Keyang Chen^{1,3,4,†}, Zhiheng Rao^{1,3,4,†}, Siyang Dong^{1,2}, Yajing Chen¹, Xulan Wang¹, Yongde Luo^{1,2,4,*}, Fanghua Gong^{1,4,*} and Xiaokun Li^{1,4,*}

¹School of Pharmaceutical Sciences, Wenzhou Medical University, Wenzhou, Zhejiang 325000, China, ²Department of breast surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325000, China, ³Department of neurology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325000, China and ⁴Research Units of Clinical Translation of Cell Growth Factors and Diseases Research, Chinese Academy of Medical Science, Wenzhou Medical University, Wenzhou, Zhejiang 325000, China

*Correspondence. Xiaokun Li, Email: xiaokunli@wzmc.edu.cn; Fanghua Gong, Email: gongwenheng@163.com; Yongde Luo, Email: yongdeluo08@wmu.edu.cn

[†]These authors contributed equally to this work.

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Abstract

Following injury, tissue autonomously initiates a complex repair process, resulting in either partial recovery or regeneration of tissue architecture and function in most organisms. Both the repair and regeneration processes are highly coordinated by a hierarchy of interplay among signal transduction pathways initiated by different growth factors, cytokines and other signaling molecules under normal conditions. However, under chronic traumatic or pathological conditions, the reparative or regenerative process of most tissues in different organs can lose control to different extents, leading to random, incomplete or even flawed cell and tissue reconstitution and thus often partial restoration of the original structure and function, accompanied by the development of fibrosis, scarring or even pathogenesis that could cause organ failure and death of the organism. Ample evidence suggests that the various combinatorial fibroblast growth factor (FGF) and receptor signal transduction systems play prominent roles in injury repair and the remodeling of adult tissues in addition to embryonic development and regulation of metabolic homeostasis. In this review, we attempt to provide a brief update on our current understanding of the roles, the underlying mechanisms and clinical application of FGFs in tissue injury repair.

Key words: Tissue injury, Repair, Regeneration, Cell growth, Fibroblast growth factor, Signal transduction

Highlights

- A total of 18 FGFs in humans activate four prototypes of membrane-spanning receptor tyrosine kinases, FGFRs.
- FGFs play pleiotropic roles in embryonic development and adult tissue homeostasis including injury repair.
- Aberrations in FGF signal pathways contribute to an array of diseases.
- Agonists or antagonists of FGFs are potential agents to treat wounds and injuries.

Background

In all life forms ranging from a single-cell organism to multicellular prokaryotic and eukaryotic species, remodeling, damage or injury always occur at the cellular, tissue and organ levels in adults as a result of either a normal, intrinsic biological process, a pathological insult or an external traumatic incident. The impacts of the damage or injury are immediately followed by responses at the cellular, tissue and organismal levels, e.g. the activation and initiation of the reparative or regenerative processes that antagonize the progression of injury and collateral damage, preventing them from developing into failure or death of the cell, tissue, organ or organism [1]. It is known that although many organisms have remarkable regenerative ability to restore the original architecture and function following injury, mammals have rather limited ability or even lose the potential to regenerate their tissues and the associated organs. Instead, they often adopt a complex wound healing process, resulting in only partial restoration to the original structure and function, and more often, with the prominent formation of scar, a non-functional or partially functioning mass of fibrotic tissue that can lead to organ malfunction and even failure [2]. Hence, effective tissue repair and remodeling are critical for the survival of all living organisms [3], and practically, restoring injured tissues and organs is a long-standing aspiration of all humans but a highly challenging goal for clinicians, researchers and engineers.

In mammals, the repair or regeneration of injured tissues and whole organs is a rather complex biological process that can be roughly divided into four overlapping phases, including maintenance of homeostasis, an inflammatory response, a proliferative phase and remodeling. In the initial response, clotting and isolation of the damaged region(s) occur to prevent worsening and to maintain overall tissue and organ homeostasis. This is followed by the activation of an inflammatory response that facilitates the clearance of necrotic debris and prevents infection at the damage site. Then, competent cells or progenitor cells within the damaged area or from adjacent tissues proliferate or migrate to the wound site, giving rise to new cells, from which new tissue with extracellular matrix that supports subsequent tissue repair is laid down. Finally, this newly produced filling tissue is altered or remodeled to resemble the original or the surrounding, mature functional tissues. These injury-responsive and reparative processes are multifactorial, tissue-autonomous and seamlessly cooperative; however, under many conditions, these highly coordinated processes are often interrupted, leading to chronic wounds, malformation of non-functional tissue or the development of fibrosis. Most often, an improper inflammatory response can lead to the activation of a fibrotic response and scar formation [4].

The repair and regeneration processes are controlled by a variety of cytokines, growth factors, differentiation factors and other molecules with distinct functions that are often in complex association [5]. Fibroblast growth factors (FGFs) as

master regulators of cell growth and proliferation, organogenesis and tissue homeostasis represent a typical class of factors critical for tissue repair, remodeling and regeneration. In this review, we attempt to briefly update current progress in our understanding of the role, the therapeutic potential and the underlying mechanism of the FGF signaling system in tissue injury repair.

Review

FGF family

The FGF family is a group of structurally conserved extracellular signaling molecules that range in size from 15 to 38 kDa and act on a family of transmembrane receptor tyrosine kinases, the FGFRs [6–8]. The human FGF family is known to contain 22 members, of which 18 polypeptides [9] are grouped into six subfamilies based on the similarity of their primary sequence structure and receptor binding functionality (Table 1) [10]. Five of the paracrine subfamilies are the FGF1 subfamily including FGF1 and FGF2, the FGF4 subfamily including FGF4, FGF5 and FGF6, the FGF7 subfamily including FGF3, FGF7, FGF10 and FGF22, the FGF8 subfamily including FGF8, FGF17 and FGF18, and the FGF9 subfamily including FGF9, FGF16 and FGF20. The remaining three FGFs including FGF19 (FGF15 in mice), FGF21 and FGF23 constitute the so-called endocrine subfamily [11–13]. The other four non-signaling FGF-homologous proteins, including FGF11–FGF14 are called intracellular or intracrine FGFs, serving as co-factors for the regulation of the voltage-gated sodium channels important for neuronal and myocardial excitability [14].

All FGFs share a core domain of ~120 amino acids with varied homology, which folds into an interleukin 1 β (IL-1 β)-like β -trefoil barrel structure in three dimensions, while both the N-terminus and C-terminus protrude from the barrel core, being mostly flexible [15,16]. All five subfamilies of autocrine and paracrine FGFs present typical surface domains that bind heparin or heparan sulfate (HS) with high yet varied affinity that can be defined on the basis of the concentration of sodium chloride used to dissociate the binding. The binding to a HS chain that extends from the transmembrane core proteins as one type of glycosylation in the extracellular matrix traps the HS-binding FGFs in the vicinity of the secretion cells, bestowing on these FGFs HS-dependent, enhanced activities and autocrine and paracrine modes of action. In contrast, all three endocrine FGFs lose the Arg and Lys-rich composition and surface topology compatible with a linear heparin chain for high-affinity binding as a result of lacking the β 11 strand structure in the homologous HS-binding domain [9], which ensures their free circulation in blood and to distal tissues or areas of the tissues.

Except for the four intracrine FGF homologs, all the autocrine/paracrine and endocrine FGFs take effect by binding to the extracellular domains and activating the intracellular kinase domain of the transmembrane FGFR tyrosine kinases. The HS motifs as co-factors are required

Table 1. The FGF family, tissue expression pattern and functions

FGF subfamily	Alternative name	Main expression sites	Function
FGF1 subfamily			
FGF1	aFGF; HBGF1	Brain, pituitary, nerve tissue, retina, adrenal gland, heart and bone	Promoting mitosis, wound healing, angiogenesis, hematopoiesis, tumorigenesis and neurogenesis.
FGF2	bFGF; HBGF2	Various tissues and organs derived from mesoderm, neuroectoderm and tumor tissues	Promoting mitosis, vascular remodeling, bone formation, pulmonary fibrosis, neural development and tumor metabolism.
FGF4 subfamily			
FGF4	HST1; HSTF1; K-FGF	Posterior part of the limb buds	Limb and internal organs development.
FGF5	-	Brain	Hair follicle development, a brain resident FGF for regulating neuron differentiation and survival, regulating GFAP expression.
FGF6	HST2	Developing skeletal muscle	Myogenesis and muscle regeneration.
FGF7 subfamily			
FGF3	Int-2; V-Int-2	Mammary tumors	Controlling the inner ear plan.
FGF7	KGF	Fetal lung mesenchymal tissue	Preventing lung branch formation and lung inflammation.
FGF10	KGF-2	First observed in the limb bud	Lung development, injury and repair.
FGF22		Mammalian brain, skin wound	Presynaptic molecule, repairing and stimulating the formation of inhibitory presynaptic terminal, alleviating depression and vesicle clustering, skin development
FGF8 subfamily			
FGF8	AIGF; KAL6	Regulate the growth and differentiation of progenitor cells, produce ultimate structure of midbrain and hindbrain	AIGF, establishment and maintenance of the midbrain border.
FGF17	-	Cortex	
FGF18	-	Skin and cortical neurons	Similarity with FGF8, neocortex development, an autocrine growth factor in neoplastic prostate epithelial cells.
FGF9 subfamily			
FGF9	GAF; EKS	Neurons in the cortex hippocampus, thalamus, cerebellum, spinal cord, epithelium and mesothelium	Promoting chondrogenesis, cortical neurons and skin repair, neuroprotector.
FGF16	-	Embryonic brown adipose tissue and inner ear	Growth-stimulating effect on glial cells, fetal lung development, enhancing the survival of AChE-positive neurons.
FGF20	-	Brain	Proliferation of embryonic brown adipose tissue, fate decisions of the otic cells. Enhancing the survival of midbrain dopaminergic neurons, neuro-protective in Parkinson's disease.
FGF15/19 subfamily			
FGF15	-	Absorptive cells of mouse ileum	Feedback inhibition of hepatic bile acid synthesis, regulation of glucose and lipid metabolism.
FGF19	-	Absorptive cells of human ileum, can be found in the brain, skin, retina, gallbladder, small intestine, kidney and umbilical cord	As a hormone in response to bile acid absorption acting on infarcts, regulation of glucose and lipid metabolism, non-mitogenic effect.
FGF21	-	Muscle, liver, pancreas, thymus and adipose tissue	Playing important role in glucose, lipid and energy metabolism, a cardiovascular protector of the heart.
FGF23	-	Bone, lung, brain, heart, muscle and spleen	Regulating phosphate homeostasis in plasma by decreasing reabsorption and increasing excretion of phosphate in the kidney.
FGF homologous family			
FGF11	FHF3	Neuroblastoma, retinoblastoma and brain tumors	Induced in endothelial cells by HIF1 α and stimulating capillary-like endothelial tube formation in association with angiogenesis
FGF12	FHF1	Brain, eye, heart and testis	Contributing to skeletal growth and development failure of grade II and III KBD.
FGF13	FHF2	Brain and heart	Neural differentiation in xenopus early development and controlling proliferation and differentiation of skeletal muscle.
FGF14	FHF4; Sca27	Adult cerebellum	Regulating intrinsic excitability of cerebellum Purkinje neurons.

HBGF heparin binding growth factor, HST heparin-binding secretory transforming, GFAP glial fibrillary acidic protein, KGF keratinocyte growth factor, AIGF androgen-induced growth factor, GAF Glia-activating factor, EKS elbow-knee synostosis, FHF FGF homologous factor, KBD Kashin-Beck disease, HIF1 α hypoxia inducible factor-1 α , AChE acetylcholinesterase, bFGF basic fibroblast growth factor

for autocrine and paracrine FGFs to bind with high-affinity to and activate FGFRs in almost all tissues, while transmembrane co-receptors α -klotho (KL) and β -klotho (KLB) are required for endocrine FGFs to bind to and activate FGFRs in the endocrine and metabolic tissues. Though HS is not required for the potentiation of FGFR activation by endocrine FGFs, it is still important for dimer formation of FGFRs on the cell surface.

FGFRs form a family of four highly conserved prototypic transmembrane receptor tyrosine kinases (FGFR1–4). These FGFRs are single-pass transmembrane proteins that include an extracellular domain, a transmembrane domain and an intracellular tyrosine kinase domain. Three immunoglobulin-like domains, namely D1 to D3, an acidic amino acids rich region between D1 and D2, a heparin-binding domain on D2 and an alternatively spliced IIIb or IIIc region on D3 comprise the extracellular domain [17]. There are reportedly other atypical FGFRs, such as the so-called FGFR5 (also called FGFR1) that lacks the intracellular kinase domain [18]. Alternative splicing generates different isoforms for each prototype of FGFRs, notably the IIIb and IIIc isoforms that have distinct ligand-binding specificity [19].

Different FGFs, FGFR isoforms, co-factors and co-receptors are expressed in a more or less tissue-specific manner; however, together they are present in nearly all tissues and play a myriad of important roles in embryonic development, organogenesis, adult tissue remodeling, injury and regenerative responses, and metabolic homeostasis [20]. In the adult, both the metabolic and growth-promoting FGFs play critical roles in the response to tissue injury, damage repair and tissue-specific pathologies (Figure 1) [21–23]. FGF signaling was shown to elicit cardioprotective effects on the heart [24, 25] and to be important for epithelial repair in the lung [26, 27] and wound healing on skin [28]. FGFs are involved in regulating cerebral injury through promoting neuronal regeneration, neuroprotection and angiogenesis [29].

FGF–FGFR signal transduction

Like many other types of growth factors, the binding of FGF to the ectodomain of FGFR causes dimerization or a higher-order of oligomerization of FGFRs, followed by conformational changes. The binding of the autocrine/paracrine FGF1–10, FGF16–18, FGF20 or FGF22 to the FGFR ectodomain on the cell surface is dependent on the presence of cofactor HS chain that extends from the core of a transmembrane glycoprotein, such as glypican or syndecan, resulting in the formation of a stable 2:2:2 FGFR–HS–FGFR ternary complex [30, 31]. By contrast, the initial formation of a stable endocrine FGF–FGFR complex (e.g. 2:2:2 FGF23–KL–FGFR1) depends on the presence of single transmembrane co-receptor α KL or KLB, while the HS chain is only required for receptor dimerization but not ligand–receptor interaction [32], resulting in a stable 2:2:2 FGF23–KL–FGFR–HS quaternary complex. It was postulated that FGFR

exists as a ‘loose’ dimer on the cell surface that is ready to be fired by the docking of FGF in the presence of a HS motif and/or co-receptor KL or KLB. It is therefore possible that other unidentified protein partners impact the interaction of FGF–FGFR in a similar manner in specific tissues or cells, resulting in tissue-specific biological functions.

The conformation changes of the FGFR dimer or oligomers induced by binding of FGF and cofactor or co-receptor are then transmitted to two intracellular kinase domains, ensuring juxtaposition, relief of autoinhibition and thus activation of autophosphorylation of FGFR kinase domains at Tyr653 and Tyr654. Subsequent phosphorylation on potential tyrosine residues, including Tyr463, Tyr583, Tyr585, Tyr730 and Tyr766, leads to binding or recruitment of a number of intracellular adaptors, such as FGF receptor substrate (FRS)2/3, p38, CRK, phospholipase C γ (PLC γ) and signal transducers and activators of transcription (STATs), which then serve as diversifying signaling hubs that typically activate the SOS–Ras/Raf–MAPK–mTOR, GAB1–PI3K–AKT, DAG/IP3–Ca²⁺ and nuclear STAT signal pathways [10] with differential cellular growth, survival and metabolic effects, in a spatiotemporal manner and depending on the nature of the tissues and associated organs involved.

FRS2 is a known critical proximal adaptor recruited to phospho-Tyr463 upon FGFR activation, which leads to the activation of MAPK and AKT pathways that are critical for cell growth, survival and tissue repair [33]. It is also required as the downstream products of FGF19-induced FGFR4–KLB activation to regulate bile acid synthesis [34]. Whether FRS2 and homologs serve the downstream of the activated FGFR1–KLB and FGFR1–KL by FGF21 and FGF23 that regulate the homeostasis of energy and mineral metabolism, respectively, is an interesting subject for future investigation. It is also possible that the specific cellular milieu in metabolic tissues, such as white and brown adipose tissues, that contains intracellular adaptors different from FRS2 in non-metabolic tissues, is important for mediating the effects of FGFR1–KLB and FGFR1–KL signal pathways. Despite such a distinction, both the growth-promoting and metabolic pathways initiated by FGFRs are important for cell survival and homeostasis and are a prerequisite for injury repair.

The role of FGF signaling in skeleton and muscle repair

Skeleton Certain members of FGFs and FGFRs are expressed in characteristic spatiotemporal patterns throughout all stages of skeletal and muscle development. The FGF signal pathways regulate the development of limb bud and mesenchymal condensation, thus playing key roles in chondrogenesis, osteogenesis, bone formation and mineral homeostasis [35]. Both loss-of-function and gain-of-function mutations in FGFs and FGFRs are associated with dozens of congenital bone diseases that are broadly classified into chondrodysplasia syndromes and craniosynostosis syndromes. Consistently, growing

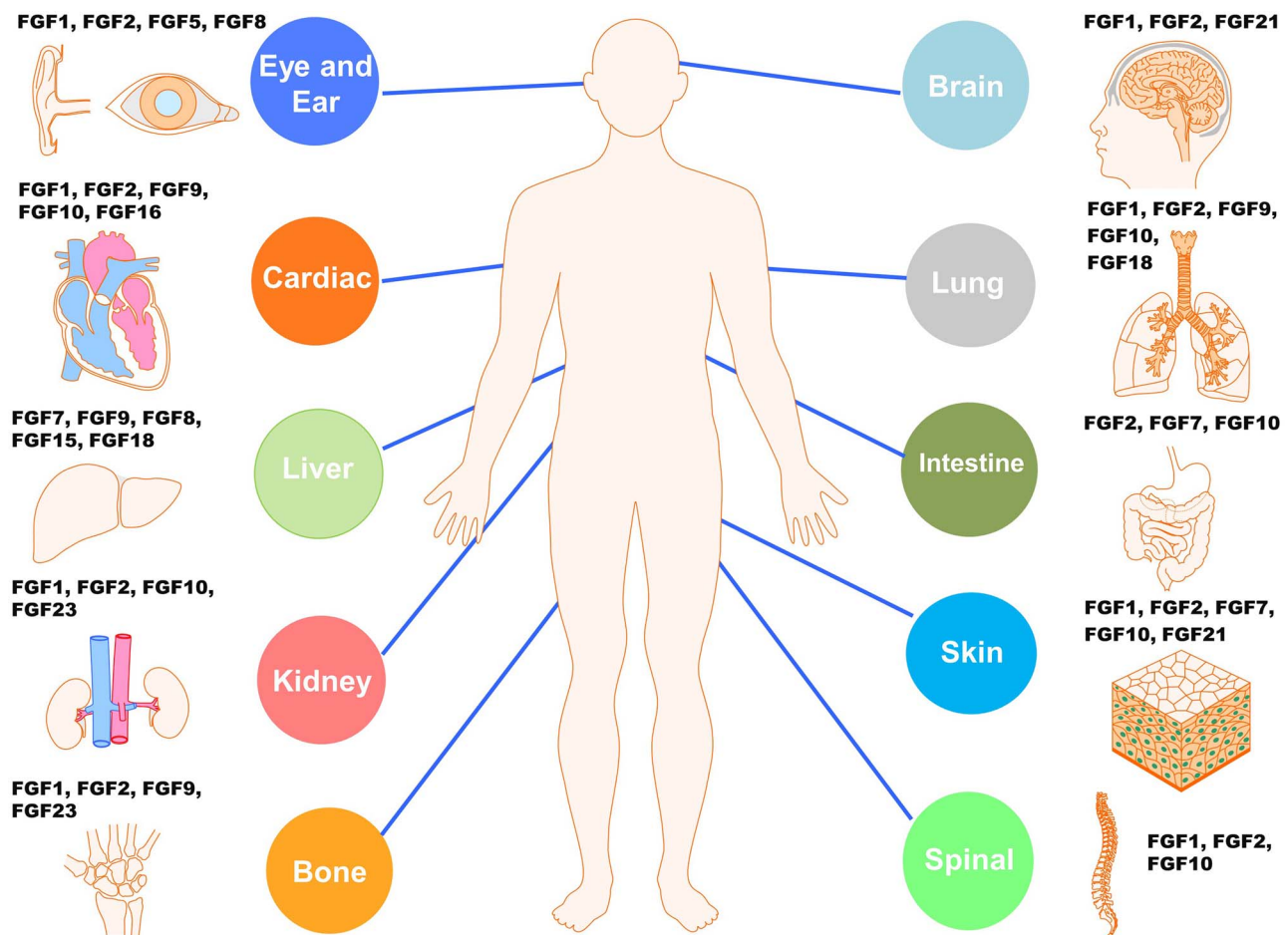


Figure 1. Summary of the known main FGF–FGFR signaling systems in the injury repair of diverse tissues or organs. FGFs and FGFRs participate in the cellular and metabolic homeostasis of all tissues and associated organs such as the nervous system, lung, heart and cardiovascular, skeleton, muscle, skin, ear and eye, to name but a few, and are critical for their remodeling, regeneration and repair of injuries resulting from diverse types of traumatic and pathological insults. FGF fibroblast growth factor, FGFR fibroblast growth factor receptor

evidence supports important roles of FGFs and FGFRs in the repair of injured or malfunctioning skeleton. As a part of the skeleton, cartilage and growth plate are types of connective tissue and are prone to injury [36]. One study found that growth-arrest-specific5 (Gas5) regulates the proliferation and apoptosis of growth plate by controlling FGF1 expression [37]. Osteochondral defects can potentially progress to osteoarthritis, and a recent study showed that FGF2 delivered by recombinant adenoviral vector enhances osteochondral repair [38]. Saw *et al.* [39] showed that metalloprotease regulation of FGF2 is essential in the chondrocyte maturation program by promoting growth plate development and bone elongation. FGF2 combined with low-intensity pulsed ultrasound could promote the synthesis and secretion of collagen and thus the differentiation and maturation of chondrocytes [40]. FGF9 promotes chondrocyte hypertrophy in the early stage and regulates blood vessels and osteogenesis of growth plate in the late stage of bone development [41].

FGFs play important roles in bone regeneration during the fracture healing process. FGF1 was shown to promote

bone repair by inhibiting adipogenic differentiation and increasing the number of osteoblasts [42]. A low molecular weight isoform of FGF2 promoted bone fracture healing [43]. Local delivery of FGF7 induced bone formation by enhancing osteogenesis and chemoattraction in a rat model of mandible defects [44]. A novel therapeutic fiber scaffold containing FGF2 and FGF18 promoted the repair and regeneration of calvarium defects [45]. FGF8 functions as a negative regulator of osteogenic fate and was shown to be sufficient to convert a subset of cranial neural crest cell-derived mesenchymal cells into cartilage in the anterior hard palate [46]. FGF9 from mature osteoblasts was shown to regulate skeletal homeostasis in male mice [47]. Administration of exogenous FGF9 halted cartilage degradation while aggravating osteophyte formation in post-traumatic osteoarthritis [48]. FGF21 acts as a negative regulator of bone density by enhancing peroxisome proliferator-activated receptor γ (PPAR γ) activity [49]. FGF23 contributed to wntless-integration (Wnt)/ β -catenin signaling-mediated osteoarthritis in mice [50] and promoted the differentiation of osteoarthritic

chondrocytes [51]. Patients with X-linked hypophosphatemic rickets exhibit skeletal or bone deformities including short stature, leg deformities, bone pain, dental abscesses and radiographic evidence for rickets and osteomalacia, as a result of elevated FGF23 signaling. Burosumab, a humanized monoclonal antibody against FGF23, significantly increased the maximum renal tubular threshold for phosphate reabsorption, serum phosphate and 1,25(OH)₂D with a favorable safety profile [52].

FGFR1, 2 and 3 were shown to be involved in the FGF-initiated regulation of cartilage and bone formation. Although there are some discrepancies, it is generally believed that FGFR3 inhibited the proliferation and differentiation of chondrocytes while promoting the apoptosis of cartilage cells. Both FGFR1 and FGFR2 were shown to promote the proliferation and differentiation of osteoblasts. FGFR1 gene polymorphism is associated with fracture non-unions [53], while FGFR2 polymorphisms are associated with osteogenic differentiation [54]. Upon bone marrow ablation, an inducible expression of the gain-of-function mutant FGFR2-P253R at the adult stage resulted in anabolic effects on trabecular bone via promoting bone formation and inhibiting bone resorption in a Wnt/ β -catenin-dependent manner [55]. FGFR3 inhibited the formation of callus and delayed the repair of bone injury by negatively regulating endochondral osteogenesis [56, 57]. Deletion of FGFR3 in osteoclast cell lineage led to bone mass increase by inhibiting osteoclast bone resorption in mice [58]. In an osteoarthritis model, a competitive FGFR1 inhibitor protected articular cartilage [59]. By contrast, FGFR3 delayed osteoarthritis progression in mouse knee joints at least in part by down-regulating Indian hedgehog signaling in articular chondrocytes [60, 61]. FGFR3 deficiency accelerated CXCL12-dependent macrophage chemotaxis, leading to exacerbation of joint destruction while CXCR7 inhibition reversed the damage effect [62]. Taken together, the above studies suggest that FGFR1–2 can exert a deleterious effect on osteoarthritis development under certain conditions whereas FGFR3 plays a protective role.

Muscle Adult skeletal muscle retains a remarkable ability to rapidly repair the damage caused by exercise, trauma, toxins and diseases [63], in which the satellite cells (SCs) that are considered the stem cells contribute the most [64]. FGFs are important mitogens for the self-renewal of SCs and thus the repair and regeneration of muscle after injury or upon aging. Satellite cells express FGFR1 and FGFR4 at high levels and FGFR3 at low levels, but not FGFR2. Studies have demonstrated that FGF1, FGF2, FGF4 and FGF6 regulate the growth, survival and renewal of SCs by activating ERK1/2 and p38 α / β MAPKs, PI3 kinase, PLC γ and STATs [65]. FGF21 was found to control muscle mass [66] and alleviate glucocorticoid-induced injury through inhibition of myostatin expression [67]. Excessive FGF2 removed age-associated proliferative inhibition of SCs [68]. FGF19 was also reported to control skeletal muscle mass by stimulating

the enlargement of muscle fiber size and protecting muscle from atrophy through activation of ERK1/2 and the ribosomal protein S6 kinase [69].

Although significant progress has been made in the past in our understanding of the roles of FGFs and FGFRs in the repair and healing of skeletal and muscle system injury and diseases, the precise roles of individual FGFs and FGFRs at different stages and sites of injury, diseases and aging-associated wasting remain to be dissected in detail. Targeting the FGF system represents a promising avenue for treating bone and muscle injury and aging-associated muscle wasting; however, the application dose, timing and duration of FGFs, the delivery system and the possible combination with other modulating signaling molecules need to be optimized.

Roles of FGF in nerve injury and repair

FGFs play important roles in the development of the nervous system by promoting the growth, proliferation, differentiation, migration and survival of both neurons and non-neural cells, such as astrocytes, microglia and oligodendrocytes, as well as in repair, regeneration, demyelination, remyelination and angiogenesis after damage or injury in the nervous system.

Roles of FGFs in the repair of nerve injury after stroke

Stroke is an acute cerebrovascular disease attributable to blockade or sudden rupture of blood vessels in the brain that prevents blood from effectively flowing into the brain or the nervous tissues [70], leading to reduced availability or loss of supply of nutrients and oxygen and thus death of brain cells via necrosis and apoptosis [71]. Studies showed that FGF1 could protect the blood–brain barrier (BBB) from dysfunction by upregulating tight junction proteins and inhibiting RhoA through the PI3K–AKT–RAC1 pathway [72]. Intranasal FGF1 administration enhanced angiogenesis via the sphingosine-1-phosphate receptor 1 signaling pathway [73]. FGF2 was found to upregulate platelet-derived growth factor receptor β in cultured pericytes and in peri-infarct areas in a mouse stroke model [74] and to contribute to the effects of salidroside on dendritic and synaptic plasticity after cerebral ischemia/reperfusion (I/R) injury [75]. Intranasal administration of FGF2 in nanoliposomes designed to bypass the BBB was used for treatment of ischemic stroke injury [76]. Endocrine FGF21 is known to have no retention in the extracellular matrix and potentially a better ability to cross the BBB. Administration of FGF21 alleviated middle cerebral artery occlusion-induced brain injury via activation of the PI3K/AKT pathway [77], protected against Ang II-induced cerebrovascular aging and I/R-mediated hippocampal injury [78, 79], and reduced cerebral injury via decreasing endoplasmic reticulum stress [80]. Under hypoxia conditions, FGF21 protected against injury to cerebral microvascular endothelial cells

and [81] alleviated motor nerve dysfunction by modulating microglia/macrophage-mediated neuroinflammation [82].

Taken together, the potent neurotropic and angiogenic activities suggested that FGFs are promising therapeutic agents for ischemia stroke. One of the important directions of future research is to explore the roles of FGFs and FGFRs in different stages of stroke pathogenesis. The safety, efficacy and dose-dependent response of administered FGFs in stroke animals and patients also require careful examination.

FGFs in spinal cord injury and repair Spinal cord injury (SCI) is the physical and psychological damage to any part of the spinal cord or nerves that change the bodily functions primarily below the site of injury, with many neurological complications including paraplegia or quadriplegia [83]. The pathological process of SCI is a combination of primary trauma and sequential secondary injuries [83]. Target therapies for improving the clinical outcome of SCI include limiting inflammation, preventing secondary cell death and enhancing the recovery, regeneration and plasticity of neuronal circuits [84]. A number of studies revealed that FGFs target the neuropathological cascades associated with secondary injurious events following SCI [85, 86]. Wang *et al.* [87] revealed that FGF1 improved the functional recovery of SCI by inducing PRDX1 to modulate autophagy and reduce reactive oxygen species in a rat model. Application of novel FGF1-loaded thermosensitive heparin-poloxamer hydrogel protected spinal cord neuronal and peripheral cells from deterioration and promoted regeneration upon SCI. A novel scar-homing delivery system for FGF1 improved neuronal survival and plasticity and promoted axon regeneration following SCI [88]. FGF2 improved the recovery of the blood–spinal cord barrier after SCI by increasing junction proteins and Cav-1, inhibiting the expression and activation of MMP-9 involved in the interaction with FGFR1 [89] and inhibiting ER stress-induced cell death [90]. The intracrine FGF13 was shown to stabilize microtubules and enhance mitochondrial functions, promoting neuronal polarization, axon formation, growth cone initiation and function recovery following SCI [89, 91]. The expression levels of FGF10 in neuron and microglia/macrophages increased post SCI, and treatment with FGF10 inhibited microglia/macrophages activation and proliferation and reduced inflammatory damage via the FGFR2/PI3K/AKT and TLR4/NF κ B pathways, promoting the recovery process in SCI in animals [92].

Overall, the recovery of SCI is a complex process as it interferes with a range of normal motor, sensory and autonomic functions. The mechanisms underlying pathological processes of secondary injury upon SCI remain largely unclear. Although certain members of the FGF family are present in spinal cord neurons, peripheral cells and canal structure, how they promote the repair of damaged neurons and the ligation and regeneration of new axons has yet to be determined. Furthermore, clinical evidence for the efficacy of FGF-based agents among patients with SCI is still lacking.

The roles of FGFs in the repair of other types of neural injury Traumatic brain injury (TBI) is a form of acquired brain injury occurring as a result of sudden physical or traumatic damage, resulting in abnormal brain function such as short-term or long-term sensory and motor deficits [93]. Wang *et al.* showed that FGF2 enhanced cell proliferation and neuronal survival and protected the BBB from breakdown by activating the PI3K/AKT/RAC1 signaling pathway, promoting the expression of tight junction proteins such as claudin-5, occludin and zonula occludens-1 following TBI [94]. It protected against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride-induced onset of Parkinson's Disease (PD), preventing dopaminergic neuron loss by activating the AMPK–PGC1 α axis to promote mitochondrial function and reduce inflammation in mouse brains [95]. Furthermore, Yoshimura *et al.* [96] suggested that FGF-2 could upregulate neurogenesis and protected neurons against degeneration in the adult hippocampus after TBI. GF21 is an endocrine hormone with effects of anti-inflammation, anti-oxidative stress and anti-ER stress, promoting metabolic homeostasis. Activation of the FGFR1–KLB signal pathway by FGF21 was shown to preserve BBB integrity by upregulating PPAR γ and increasing proteins in tight junctions and adhesion junctions, accompanied by marked reductions in neurofunctional behavior deficits, degree of cerebral edema, brain tissue loss and neuron apoptosis in a mouse model of TBI [97]. In an Alzheimer's disease model, administration of FGF21 alleviated memory dysfunction, amyloid plaque pathogenesis and tau hyperphosphorylation in part by modulating the astrocyte–neuron lactate shuttle via monocarboxylate transporters and correcting brain metabolic defects [98, 99]. FGF20 is highly expressed in the substantia nigra pars compacta of the central nervous system. In a 6-hydroxydopamine-lesioned rat model of PD, administration of an FGF20 variant with enhanced permeability across the BBB prevented the loss of dopaminergic neurons in the substantia nigra pars compacta [100]. Increases in oxidative stress contribute to Huntington's disease, another neurodegenerative disorder in the brain. FGF9 was shown to upregulate and activate the ERK–NRF2 pathway and the downstream glutathione synthesis and antioxidant system, attenuating oxidative stress damage and neuron cell death [101, 102].

Peripheral nerves relay signals from the brain and spinal cord to the rest of the body. Peripheral nerve injury or malfunction as a result of a traffic accident, trauma or tumor resection can give rise to the loss of sensory and motor functions, chronic pain and other activity deficits. Although surgical techniques are a traditional restoration approach [103], exogenous supplement of neurotrophic factors has increasingly become an important strategy for the treatment and recovery of peripheral nerve injury. Heparin-based coacervate or hydrogel delivery of FGF2 facilitated nerve regeneration by inhibiting ER stress, accelerating remyelination and axon fiber regeneration, and promoting Schwann cells proliferation and the recovery of motor function in models

of sciatic nerve crush injury with diabetic neuropathy, mental nerve crush injury or digital nerve severing injury [104–107]. FGF5 was shown to be an autocrine regulator of Schwann cells and FGF5 administration rapidly promoted Schwann cell migration and adhesion via upregulation of N-cadherin following distal sciatic nerve injury [108].

Neonatal hypoxia–ischemia encephalopathy, the most important cause of morbidity, mortality and neurological deficits in term-born infants, is a type of brain damage that occurs often with insufficient reception of oxygen and blood. A study showed that FGF2 gene expression was upregulated in the hippocampus of neonatal rats, and intraperitoneal injection of exogenous FGF2 enhanced cell proliferation in the hippocampal dentate gyrus region following neonatal hypoxia–ischemia brain damage [109]. A combination of neural stem cells and overexpression of FGF2 reduced brain damage and restored sensorimotor function following such brain damage [110]. Similarly, a combination of FGF2 with pluripotent astrocytic stem cells improved cognitive function in neonatal rats with hypoxic–ischemic brain injury [111].

The role of FGFs in lung injury repair

FGFs and FGFRs play important roles in lung development, and aberrant FGF signaling has been implicated in the pathogenesis of pulmonary fibrosis and lung diseases [112]. FGFR3 and FGFR4 function cooperatively to direct alveogenesis of mouse lung [113]. FGF10 is considered the main morphogen driving multi-stage lung branching morphogenesis in rodents. It regulates the mobilization and differentiation of mesenchymal stem cells and the homeostasis of intrinsic cells of lung structure [114, 115] and plays important roles in lung injury repair, while its signaling defects lead to neonatal lung diseases [116–118]. FGF10 mutations increase the risk of chronic airway disease in adulthood [119]. Following injury, FGF10 functions to maintain progenitor cell populations in the airway and promotes alveolar type 2 cell expansion and differentiation. Overexpression of FGF10 in bronchial epithelial stem cells enhanced fibrosis resolution after lung damage [120–122] and promoted the proliferation and trans-differentiation of lung stem cells, accelerating lung repair [123].

Idiopathic pulmonary fibrosis (IPF) is characterized by an accumulation of extracellular matrix proteins and fibroblasts in the distal airways. In IPF pathogenesis, FGF1 is upregulated 7.5-fold more than in the normal lung [124]. FGF1 counteracted IPF pathogenesis by inhibiting fibroblast collagen production and differentiation into myofibroblasts and reverting epithelial–mesenchymal transition via suppressing TGF- β 1 signaling pathways to induce alveolar epithelial cell proliferation [125]. Similarly, FGF2 was shown to be antifibrotic in the lung by decreasing collagen deposition and fibroblast to myofibroblast differentiation [126], thus exerting a protective or reparative effect following lung injury. Endogenous FGF2 was not required for bleomycin-induced pulmonary fibrosis, but was essential for epithelial repair and

integrity after bleomycin-induced lung injury in mice [127]. FGF2 reduced oxidative stress, inflammation and apoptosis of alveolar epithelial cells and prevented pulmonary capillary leakage, alleviating acute lung injury [128, 129]. FGF9 is an antiapoptotic and promigratory factor, maintaining lung fibroblasts in an undifferentiated state via activating the FGFR3 signaling pathway. Both FGF9 and FGF18 are mediators of epithelial–mesenchymal interactions critical for lung development, and promote the survival and migration of lung epithelial cells while inhibiting myofibroblast differentiation in IPF [130].

FGFs in cardio-vasculature injury repair

FGF members and associated FGFRs play important roles in cardiovascular and lymphatic development, homeostasis and diseases. In heart development, the roles of FGFs range from the formation of outflow tracts to the proliferation of cardiomyocytes and the formation of heart chambers. FGF8, FGF9, FGF10 and FGF16 were shown to act as paracrine signals during embryonic heart development, while FGFs 1, 2, 9, 16, 19 and 21 mediate adaptive responses to cardiac regeneration, including restoration of cardiac contraction rate after myocardial infarction and reduction of the extent of myocardial infarcts. Even though FGF15/19, FGF21 and FGF23 are typical endocrine FGFs, they can function as paracrine signals in cardiovascular development or pathophysiology. Note that, although the expression and activation of FGFs and associated signaling pathways are important for cardiovascular repair, they may also contribute to fibrosis, remodeling and dysfunction [131]. In heart diseases, serum levels of FGF15/19, FGF21 or FGF23 were shown to decrease or increase, indicating variable roles of these factors in heart pathophysiology.

Injection of FGF1 coacervate was sufficient to reduce the injury and pathologies caused by myocardial infarction [132]. FGF1 loaded in poly-(lactic-co-glycolic acid) and polyethylene glycol microparticles promoted heart regeneration in a rat model [133]. A combination of FGF1 and Wnt1 agonist/GSK3 β antagonist CHIR resulted in substantial reduction in infarct size and improved left ventricular chamber function [134–136]. Similarly, FGF2 was shown to be a cardiovascular protector in myocardial infarction and I/R injury, by reducing oxidative stress via activating NRF2-mediated antioxidant defense in conjunction with AKT–GSK3 β –FYN pathway activation [137] or by inhibiting apoptosis and promoting angiogenesis via a HIF1 α -mediated mechanism [24, 138]. Administration of FGF2 promoted angiogenesis and attenuated cardiac remodeling in ischemic heart disease [139–141] or in a rat ischemic cardiomyopathy model with surgical ventricular restoration [142]. FGF9 was shown to inhibit vascular cell apoptosis, activate c-Kit⁺ progenitor cells and enhance angiogenesis and neovascularization, improving cardiac function [143]. FGF9 treatment of diabetic mice with infarcted myocardium increased anti-inflammatory cytokines and M2 macrophage differ-

entiation, resulting in reduced adverse cardiac remodeling [144]. Similarly, administration of FGF16 or FGF10 coacervate reduced infarct size, interstitial fibrosis, myocardial monocyte infiltration and damage to cell populations [145, 146], preventing myocardial infarction-induced injury.

A recent study showed that FGFR signaling is a critical regulator of vascular development, which is achieved by FGF-dependent control of c-MYC expression that, in turn, regulates expression of the glycolytic enzyme hexokinase 2. FGFR1 and FGFR3 double-mutant mice exhibited blood and/or lymphatic vascular defects, while hexokinase2 overexpression partly rescued such defects [147]. Mice with endothelial cell-specific double knockout of FGFR1 and FGFR2 showed significantly decreased vessel density, increased endothelial cell apoptosis and worsened tissue hypoxia in the peri-infarct areas following reperfusion, demonstrating an essential role of endothelial FGFR1 and FGFR2 in cardiac functional recovery and vascular remodeling during cardiac injury [25].

FGFs in kidney injury repair

FGFs and FGFRs play important roles in kidney development and defects of the FGF signal pathways contribute to renal pathologies. Evidence has shown that many FGF members, particularly those signaling through FGFR1 and FGFR2, such as FGF1, FGF2, FGF7 and FGF10, are mitogenic and antiapoptotic for various kidney cell types, such as collective, tubular and glomerular cells, promoting the survival and outgrowth of the associated renal tissues [148, 149]. FGF-stimulated FGFR2 signaling played important roles in protecting against tubular cell death and acute kidney injury through ERK1/2 activation [150]. FGF1 was reported to suppress oxidative stress, inflammation and diabetic nephropathy via activating the PI3K/AKT-mediated pathway [151]. FGF2 is abundant in tissues such as brain, kidney and cartilage. It was shown to protect against renal I/R injury by inhibiting the High-mobility group box 1-mediated inflammatory response and attenuating mitochondrial damage [152]. FGF7 was shown to modulate ureteric bud growth and nephron number in the developing kidney and contribute to tubular cell growth and repair upon kidney damage [23, 153]. FGF10 treatment improved renal function and histological integrity and suppressed excessive autophagy and ER stress in models of renal I/R injury [154, 155]. FGF23 levels were reported to be higher upon acute kidney injury than in normal situations [156], due in part to the increased production of FGF23 in osteoblasts. Elevated serum FGF23 levels are both an indicator and a mediator of poor outcome in chronic kidney disease [157].

Roles of FGFs in intestinal injury and repair

All four FGF receptors and several FGF ligands are implicated in controlling cell proliferation, differentiation, epithelial cell

reconstitution and stem cell maintenance in the gastrointestinal tract. FGFR1 and FGFR2 are expressed in the human ileum and throughout adult mouse intestine [158]. FGFR3 is expressed in the lower half of the intestinal crypts while FGFR4 is restricted to the epithelium of the embryonic gut [159]. FGF1, FGF7, FGF8, FGF9, FGF10, FGF15/19 and FGF18 are reportedly expressed in the intestine in a spatiotemporal manner [158, 160].

In experimental models of intestinal I/R injury, both FGF1 and FGF2 were shown to be protective [161, 162]. FGF2 improved healing of colonic anastomoses through activating fibroblasts, collagen deposition and angiogenesis in rats [163] or cooperated with IL-17 to repair damaged epithelium in intestine [164]. FGF7 also promoted healing of colonic anastomoses by increasing cell proliferation and mucus production and reducing inflammation [165]. Similarly, FGF7 attenuated I/R and radiation-induced injuries by reducing intestinal epithelial cell apoptosis and the disruption of tight junctions via an AhR-E2F1-FGFR2IIIb signaling pathway [166, 167]. FGF7 and FGF10 promoted the repair of the resected small bowel via activating intestinal epithelial FGFR2IIIb [168, 169]. FGF2 and IL-17 in synergy promoted the repair of the damaged intestinal epithelium through GRB2-inhibiting Act1-mediated signal cross-talk [164]. In tissue reconstitution, patterning of the endoderm could be accomplished by the combined activities of Wnt, Bone morphogenetic protein and FGF. Palifermin, a truncated form of recombinant FGF7, has been clinically used to treat oral mucositis resulting from radio- or chemo-therapy [170]. Taken together, current studies revealed important roles of FGFs in intestinal development and adult tissue injury repair.

Advances in the roles of FGFs in liver repair

The liver is a vital organ and the hub of multiple biological processes including the various forms of nutrition handling and metabolism, endocrine and immune regulation and detoxification. It has a unique capacity for regeneration and injury repair. The liver tissue is a mass of cells tunneled through with bile ducts and blood vessels, with the parenchymal hepatocytes making up ~60% of the liver and performing more metabolic functions than any other group of cells in any other organ. By contrast, the non-parenchymal cells, including sinusoidal endothelial cells, Kupffer cells and stellate cells, comprise the rest of the liver tissue to assist the metabolic functions. Several FGFs and FGFRs have been shown to play important roles in liver development, health and disease. FGF8 and FGF10 as morphogens contribute significantly to embryonic liver development [171, 172]. FGF7 produced in Thy1(+) mesenchymal cells in close proximity to liver progenitor cells is a critical regulator of PLCs in response to liver injury [173]. Similarly, FGF9 is also a liver repair factor, providing a paracrine mitogenic signal from stellate cells to hepatocytes during acute liver injury [174]. FGF5 knockout mice fed a high-fat diet had higher levels of serum alanine transaminase and aspartate amino transferase

with nonalcoholic steatohepatitis (NASH)-like pathologies, including marked inflammation, focal necrosis, fat deposition and fibrosis [175].

FGFR3 and FGFR4 are the main FGFRs expressed in the liver and are involved in the development of hepatocellular carcinoma (HCC) [176, 177]. Ectopically gained FGFR1 and FGFR2 in hepatocytes have also been shown to play roles in HCC development [178]. FGF5, FGF8, FGF9, FGF17 and FGF18 act as paracrine signals while FGF19 acts as an endocrine signal in HCC development [179–182]. The endocrine FGF19 is produced in the ileum but acts as a negative regulator of hepatic bile acid metabolism and a stimulator of gallbladder filling [183]. It also functions as a postprandial, insulin-independent activator of hepatic protein and glycogen synthesis [184]. Mouse FGF15 was shown to protect against fibrosis through increased bile acid activation of farnesoid X receptor in hepatic stellate cells [185]. FGF21 is a hepatocyte secreted stress-responsive hormone and regulates glucose and lipid metabolism by targeting white adipose tissue [186–188]. Serum FGF21 levels were elevated in non-alcoholic fatty liver, and pharmacological FGF21 protected against non-alcoholic fatty liver diseases including hepatosteatosis and NASH [189]. Taken together, current findings reveal important roles of different composite members of the FGF signal transduction system in liver tissue homeostasis, functional performance, regeneration and injury repair, aiding in the potential design of novel therapeutic strategies for liver function recovery upon injury and in disease.

FGF signaling in skin repair

The skin as the largest superficial organ of our body consists of two main sections: the epidermis made of keratinocytes and epithelial cells and the dermis made of dense, irregular connective tissue housing blood vessels, fibroblasts, hair follicles, sweat glands and other structures. The hypodermis beneath the dermis is mainly composed of loose connective and fat tissues. Upon traumatic injury, the skin as the first and foremost outside defense system to any injury sets into motion an autonomous cascade of complex healing events that can be roughly divided into four overlapping phases, including hemostasis, inflammatory reactions, cellular proliferation and tissue remodeling, resembling that of many other tissues [190]. Among many important factors, members of the FGF family play diverse roles in these highly orchestrated biological processes [191–193]. FGF7 and its homologue FGF10 are known to be expressed in the mesenchymal fibroblasts in the dermis or hypodermis but act specifically on various types of epithelial cells including keratinocytes of the skin by activating the resident FGFR2IIIb [194–196]. Both FGF7 and FGF10 are effective for promoting wound healing, wound closure and better scar formation on skin wounded from physical trauma, burns and pathologies such as diabetic ulcers. FGF7 increased cell migration ability, improved antibacterial effect and promoted skin repair [197] or fibroblast contraction, and accelerated wound contraction

in a double-paracrine manner [198]. A lack of FGF7 could further delay cutaneous wound healing in diabetic mice. In diabetic rats, FGF10 enhanced wound repair of scalded skin together with FGF21 [199]. With novel delivery strategies that improve skin penetration, FGF10 was shown to inhibit ER stress and promote keratinocyte proliferation, accelerating wound healing and hair growth [200, 201]. The approval of parifermin for accelerating the healing of severe oral mucositis resulting from cancer chemoradiotherapy attests to the role and efficacy of FGF7 in the repair and regeneration of wounded skin or mucus [170, 202].

FGF2 treatment promoted epithelium–mesenchyme transition in skin wounds, accelerating wound closure [203], possibly through a feedback regulatory loop involving the Wnt/ β -catenin signal pathway [204] or NF κ B/JNKs pathway, independent of the PI3K/JNKs pathway, in fibroblasts and blood vessel endothelial cells [205]. In addition to metabolic correction, FGF21 encapsulated in a thermosensitive heparin–poloxamer hydrogel accelerated wound healing in diabetic animals [206]. FGFs were also tested for the repair and remodeling of dermis as a potential anti-aging cosmetic utility. Recombinant FGF1 strongly stimulated fibroblast and keratinocyte proliferation, suggesting a high potential for repairing skin conditions [207]. It increased type 1 procollagen synthesis and reduced the generation of reactive oxygen species, protecting ultraviolet B ray (UVB)-induced skin damage and photoageing [208]. Similarly, FGF2 contained in dalteparin and protamine nanoparticles inhibited ultraviolet B ray irradiation-induced apoptosis of dermal fibroblasts and epidermal keratinocytes and alleviated the decline of elasticity and acanthosis [209]. A combination of platelet-rich plasma and FGF2 was effective in treating wrinkles and the depressed areas of the skin [210].

In summary, current studies show the potential of FGFs in promoting the repair of skin from damage or injury of varied etiologies. Future studies should focus on improving wound-healing efficacy while reducing the risk of scar formation and side effects, improving formulation and application convenience, and lowering treatment cost when used for cosmetic purposes.

FGFs in eye and ear damage repair

FGF signaling is critically required during several steps of vertebrate lens and optic nerve development, including induction of the lens vesicle, proliferation of lens epithelial cells, differentiation of lens fiber cells and elongation of ganglion nerve axon [211]. Genetic deficiencies of FGF receptors disrupted the expression of lens-specific genes *Cdh1*, *Crystallins*, *Maf*, *Pax6* and *Prox1*, affecting the survival and proliferation of lens epithelial cells and elongation of fiber cells [212, 213]. Transgenic overexpression of FGF1 or FGF3 resulted in premature differentiation of lens epithelial cells [212, 214], whereas over-activation of FGF signaling as a result of NF1 and SPR1/2 deletion abrogated lens induction and fiber cell differentiation, respectively [215, 216]. Regeneration of the

adult mammalian optic nerve upon injury is often very limited and a recent study showed that the speed of regeneration of retinal ganglion cell axonal could be accelerated by a single application of FGF2 [217], which increased the number of M2-like macrophages that is beneficial for axonal regrowth in adult *Rana pipiens* [218]. In a diabetic retinopathy model, FGF5 promoted retinal ganglion cell survival, delaying diabetic retinopathy [219].

Corneal neovascularization is a pathological change as a result of invasion of new blood vessels into the cornea from the limbus, which can lead to inflammation, edema, scarring and poor corneal transparency and visual acuity. It was shown that FGFs, in particular FGF2, played a role in corneal neovascularization, and anti-FGF agents could be used to treat this disease [220]. FGF2 also contributed to the development of posterior capsule opacification after lens extraction surgery, partly by promoting epithelium to mesenchyme transition [221]. A human FGF1 derivative TTHX1114 ameliorated short-term nitrogen mustard damage to cultured rabbit corneas and improved corneal endothelial dystrophies by stimulating the proliferation, survival and regeneration of corneal endothelial cells [222, 223]. The teleost retina can grow throughout the lifetime with a robust regenerative response following injury, in which the Muller glial cells play important roles in producing progenitors that feed into retinal growth and repair. It was found that FGF8a might serve as a niche factor for Muller glial cells, acting through Notch signaling to regulate spontaneous and injury-dependent Muller glia (MG) proliferation or quiescence [224].

Tympanic membrane or eardrum is a layer of cartilaginous connective tissue with skin on the outer surface and mucosa covering the inner surface between the external auditory canal and the middle ear and ossicles, which functions to sense sound waves and convert them into nerve impulses for hearing. Studies showed that FGF2 was induced upon tympanic membrane perforation as a result of traumatic injury or infection damage, and facilitated perforation closure by promoting the mitotic phases of fibroblast and endothelial cells, inducing neovascularization and arrangement of collagenous fibers and preventing eardrum atrophy [225]. Hydrogel or collagen membrane impregnated with FGF2 promoted the repair or regeneration of the pierced or ruptured tympanic membrane [226, 227].

Progress in clinical application of FGF analogs

As mentioned previously, FGF signal transduction systems play many key roles in the genesis of various tissues and associated organs during embryonic development by serving as mitogens and morphogens. In adults, these systems are important for maintaining both metabolic and cellular homeostasis and are viable targets for repair or regeneration of injured tissues or organs. The FGF-based agents can be roughly categorized into three classes, FGF signal-enhancing therapeutics, FGF signal-blocking therapeutics and FGF gene-related therapy. As of today, recombinant FGFs or FGF analogs, such as FGF1, FGF2 (trafermin), FGF7 (palifermin), FGF10

(repifermin), FGF18 (sprifermin), FGF19 (e.g. NGM282) and FGF21 (e.g. LY2405319 and PF-05231023), have been developed as pro-FGF signaling therapeutics, which activate FGFRs to enhance the effects of both proliferation-promoting and metabolic FGFs (Table 2). Trafermin as a recombinant form of FGF2 was approved in 2001 in Japan for the treatment of patients with skin ulcers [228, 229]. Palifermin, a recombinant, truncated form of human FGF7, was approved in 2004 in the USA for the treatment of cancer patients with oral mucositis [230]. Burosumab, neutralizing antibodies for FGF23, was approved as a first-in-class treatment for X-linked hypophosphotemia, relieving pathologically low serum phosphate-caused damage to the bone and kidney.

Several clinical trials have been undertaken for some FGF-based agents for human diseases related to tissue injury repair. The phase II/III safety and efficacy trials of trafermin showed that FGF2 could be given safely to acute ischemic stroke patients, and the ideal effective time window might exceed 5 h [231, 232]; however, it could cause adverse neurological outcomes, such as fever, leucocytes, vomiting and hypokalemia. FGF2 was also assessed for efficacies of repairing large traumatic and sub-acute tympanic membrane perforation [233–237], and of regenerating aged atrophic vocal fold [238] in human clinical trials. In patients with critical limb ischemia having high rates of amputation and mortality, FGF1, delivered via expression from a non-viral naked DNA plasmid, improved pain and skin ulcers in Phase I and II clinical trials, but failed in a Phase III clinical trial for reduction of amputation or death [239]. The use of FGF1 for spinal cord injury was shown to be safe and feasible in a small sample trial [240]. In patients with symptomatic knee osteoarthritis, intra-articular application of sprifermin, a recombinant form of human FGF18, showed benefits of increasing cartilage thickness and reducing cartilage loss without any local or systemic safety concerns in a phase I trial [241, 242]. In a phase II randomized, controlled trial in patients with more symptomatic knee osteoarthritis, administration of sprifermin improved total femorotibial joint cartilage thickness after 2 years with statistical significance but uncertain clinical importance [243]. FGF-21 or FGF-19 analogs were used as a new approach to alleviate hepatic fat accumulation and the resultant metabolic stress in non-alcoholic fatty liver disease [244]. Furthermore, non-FGF based FGFR agonists were also proposed as useful alternatives to FGFs in the treatment of ischemic vascular disease [245].

A major consideration in the clinical application of FGF analogs for injury repair is the likelihood of development of hypertrophy, benign tissue mass, hyperplasia or even cancer, due to their potent activity in promoting cell proliferation that is difficult to predict and control. Amplification and overexpression of FGFs are associated with different types of cancers [20]. Muscle-specific overexpression of FGF19 in mice promoted the development of hepatocellular carcinoma [182]. In 2000, recombinant human basic fibroblast growth factor was approved by the Chinese Food and Drug Administration for treating chronic wounds,

Table 2. Selected list of FGF-based therapies for various diseases

Drug	Alternative name	Targets	Disease	Application stage
FGF1		FGFR	T2DM	Preclinical
FGF2	Trafermin	FGFR	Skin ulcers stroke	Approved (Japan) Phase 2/3
FGF7	Palifermin (Kepivance)	FGFR2IIIb	Oral mucositis	Approved (USA)
FGF10	Repifermin	FGFR2IIIb	Mucositis	Phase 2
rhFGF18	Sprifermin	FGFR	Osteoarthritis	Phase 2
FGF19	NGM282	FGFR4-KLB	T2DM; PSC	Phase 2
	FGF19-4/5/6	FGFR4	Tumorigenicity	Preclinical
	FGF19 variants		Mitogenic	Preclinical
FGF21	LY2405319	FGFR1-KLB	T2DM	Phase 1
	FGF21 variant		T2DM	Preclinical
	PF-05231023		T2DM	Phase 1

T2DM type 2 diabetes mellitus, PSC primary sclerosing cholangitis, KLB β -Klotho, FGF fibroblast growth factor

Table 3. The disease indication, dose and side effects of clinically approved fibroblast growth factor (FGF) analogs

Drug	Clinical dose	Disease	Side effects	Status
FGF1	0.7 $\mu\text{g}/\text{cm}^2$	Second-degree burns, chronic ulcers	Not noted	Approved (China)
FGF2	1 $\mu\text{g}/\text{cm}^2$	Wounds, burns and ulcers	Not noted	Approved (Japan, China)
FGF7	60 $\mu\text{g}/\text{kg}/\text{day}$	Oral mucositis	Skin and oral toxicities	Approved (USA)
FGF10	50 $\mu\text{g}/\text{kg}/\text{day}$	Mucositis		Abandoned

including chronic granulating wounds, ulcers, bedsores, traumatic and surgical wounds and burn wounds, without apparent adverse effects [246]. In 2005, recombinant human acidic fibroblast growth factor was approved for the treatment of deep second-degree burns and chronic ulcers, including residual traumatic wounds, diabetic ulcers, vascular ulcers and bedsores [247]. Based on clinical research and good safety data, the *Clinical Practice Guidelines for Burn Injuries* published by the Japanese Society for Burn Injuries in 2009 recommended bFGF as treatment for second-degree burns. bFGF has become widely used as a treatment modality for burn and burn ulcers in the clinical setting in Japan [248]. A randomized, controlled trial revealed that bFGF can improve healing of ulcers or second-degree burns [249]. For children, pediatric burn wounds present unique challenges due to instability. A previous study proved that bFGF can improve healing of partial thickness skin burns in children [250]. In addition, the topical bFGF regeneration technique offers a promising, minimally invasive alternative to conventional myringoplasty in pediatric patients with comparable success and reduced morbidity and cost [251]. However, children with an active infection or inflammation are not suitable for the bFGF technique. Palifermin, a truncated form of FGF7, is clinically used to reduce the incidence and duration of severe oral mucositis resulting from chemotherapy or radiotherapy in patients with certain types of cancers [252]. The most common adverse reactions were skin and oral toxicities, such as rash, erythema, edema and pruritus in skin, oral dysesthesia, tongue discoloration and tongue thickening (Table 3). Due to the short-term and topic use of these FGF

analogs, a risk for local hypertrophy, hyperplasia or cancer development was not noted.

Altogether, an increasing number of FGF analogs, antagonists or FGFR agonists have been put forward into clinical practice or trails for a pyramid of human diseases including, but not limited to, wound healing and repair of injuries of diverse etiologies, with varied treatment efficacy and severity of side effects. The short half-life and poor stability of FGFs are concerns that limit their clinical application. A thorough comparison of the similarity of the merit for each tissue such as ‘transparent’ cornea regeneration and ‘scar-less’ or less scarring tissue repair would be beneficial in understanding the universal merit of the FGF signal transduction systems. Above all, a clear understanding of the spatial and temporal roles and effects of individual FGFs and FGFRs is paramount to the development of novel, effective FGF system-based therapies for multiple tissue injury-related diseases and beyond.

Conclusions

The FGF signal transduction systems with unique, diverse combinations of FGF ligands, FGFR tyrosine kinases, cofactors and co-receptors play pleotropic roles in cellular and metabolic homeostasis at different molecular, cellular, tissue and organismal levels. Aberrant signaling of these systems contributes to a large array of human diseases. As complex as these systems can be, the therapeutic opportunities based on the systems for the associated diseases are equally large in number, at least conceptually. However, only when we start to understand more clearly the molecular mechanisms and

cellular events underlying the cellular and pathophysiological roles of these systems can we better utilize them effectively for the intended therapeutic purposes. The advent of increasingly powerful genetic, molecular and structural technologies should enable the accurate, targeted modulation of FGFs, FGFRs and associated signaling pathways, as well as the development of novel modalities for the clinical management of numerous associated diseases such as the repair or regeneration of the injured tissues as mentioned previously.

Abbreviations

BBB: Blood–brain barrier; FGF: Fibroblast growth factor; FGFR: Fibroblast growth factor receptor; FRS: FGF receptor substrate; HCC: Hepatocellular carcinoma; HS: Heparan sulfate; IPF: Idiopathic pulmonary fibrosis; I/R: Ischemia/reperfusion; KLB: β -Klotho; PD: Parkinson's disease; PLC γ : phospholipase C γ ; PPAR γ : Peroxisome proliferator-activated receptor γ ; SC: Satellite cells; SCI: Spinal cord injury; STAT: Signal transducers and activators of transcription; TBI: Traumatic brain injury; Wnt: Wingless-integration.

Conflicts of interest

The authors declare that they have no competing interests.

Authors' contributions

KY.C was the major contributor in writing the manuscript. ZH.R, SY.D, YJ.C and XL.W performed the literature review and were contributors in writing the manuscript. YD.L, FH.G and XK.L made major contributions to defining the scope of the review, literature review, and editing the manuscript. All authors read and approved the final manuscript.

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