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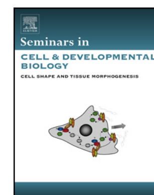

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Review

Role of fibroblast growth factors in organ regeneration and repair

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ABSTRACT

In its broad sense, regeneration refers to the renewal of lost cells, tissues or organs as part of the normal life cycle (skin, hair, endometrium *etc.*) or as part of an adaptive mechanism that organisms have developed throughout evolution. For example, worms, starfish and amphibians have developed remarkable regenerative capabilities allowing them to voluntarily shed body parts, in a process called autotomy, only to replace the lost parts afterwards. The bizarre myth of the fireproof homicidal salamander that can survive fire and poison apple trees has persisted until the 20th century. Salamanders possess one of the most robust regenerative machineries in vertebrates and attempting to draw lessons from limb regeneration in these animals and extrapolate the knowledge to mammals is a never-ending endeavor.

Fibroblast growth factors are potent morphogens and mitogens that are highly conserved among the animal kingdom. These growth factors play key roles in organogenesis during embryonic development as well as homeostatic balance during postnatal life. In this review, we provide a summary about the current knowledge regarding the involvement of fibroblast growth factor signaling in organ regeneration and repair. We also shed light on the use of these growth factors in previous and current clinical trials in a wide array of human diseases.

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1. Introduction

1.1. Historical background

Fibroblast growth factors (FGFs) constitute a family of evolutionary conserved polypeptides that are involved in diverse morphogenic and organogenic programs during embryonic development as well as homeostatic balance during postnatal life.

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The FGF story dates back to the mid-70s when Hugo A. Armelin observed that pituitary extracts had a proliferative effect on NIH3T3 fibroblasts growing *in vitro* [1]. Reasonably, the putative mitogen was dubbed FGF, although it was later discovered that some FGF subfamilies act as "epithelial growth factors" that target the epithelial lining of many organs. Soon after Armelin's discovery, basic FGF (bFGF or FGF2) was purified from bovine pituitary gland and acidic FGF (aFGF or FGF1) was purified from bovine brain [2–4]. To date, the mammalian *FGF* gene family, which maps to multiple chromosomes, has been shown to consist of 22 members (*FGF1–23*). *FGF15* has not been identified in humans whereas *Fgf19* has not been identified in mice or rats.

Rapid scientific and technological breakthroughs in mouse mutagenesis and the emergence of transgenic mouse technology in the 80s (reviewed in [5,6]) paved the way for the generation of knockout (KO) mice for most known *Fgfs* (at that time) during the late 90s, allowing to study the functions of various FGF subfamilies (reviewed in [7]). The only FGF that still lacks a reported KO phenotype is FGF11.

1.2. Modes of action

According to their mode of action, FGFs can be broadly classified into paracrine, endocrine and intracrine FGFs. Paracrine FGFs (FGF1, 4, 7, 9 and 8 subfamilies) bind with high affinities to heparin/heparan sulphate (H/HS), which serve as cofactors for their interaction with FGF receptors (FGFRs). FGFR1–4 are receptor tyrosine kinases that activate downstream signaling cascades including RAS/RAF/MAPK, PI3K/AKT, PLCγ and STAT. Paracrine FGFs are involved in the development of multiple organs such as the heart, lung, brain, muscle, kidney, hair, ear and limb (reviewed in [8]).

Endocrine FGFs (FGF15/19, 21 and 23) are vertebrate-specific hormone-like FGFs that are involved in multiple metabolic pathways such as glucose, lipid and phosphate metabolism. They have low affinities to FGFRs and H/HS, which enables them to function in a hormone-like fashion. Endocrine FGFs require α/β-Klotho as a coreceptor to mediate metabolic effects [9–14].

Unlike other FGFs, intracrine FGFs (FGF11–14) do not signal through FGFRs. Rather, they are retained inside the cells where they interact with the cytoplasmic domain of voltage-gated sodium channels and subsequently control neuronal excitability [15,16].

As this review aims to highlight the role of FGF signaling in organ regeneration and repair, we will try to provide a comprehensive overview about the history and current knowledge regarding this specific aspect. For a more in-depth description and phylogenetic analysis of FGFs and their receptors, and their involvement in normal development, homeostatic maintenance and disease, we refer the readers to excellent reviews previously published [7,8,17–23].

2. FGFs in tissue regeneration and repair

Following the discovery of FGF1/2 in bovine brain and pituitary gland, extracts from these organs and later recombinant proteins were used to stimulate wound healing in skin [24,25], cornea [26,27], cartilage [28], peritoneum [29], peripheral nerve [30], vasculature [31], brain [32,33], eardrum [34], striated muscle [35], duodenal ulcers [36], salivary glands [37], tibia [38] and sternum [39], just to name a few. Most of these studies were conducted on mammalian species such as rats, mice, rabbits and dogs.

FGF7 (or keratinocyte growth factor; KGF) was first purified in 1989 [40] and its skin-wound healing capability was later demonstrated [41,42]. Interestingly, expression of a dominant negative form of *Fgfr2*, the cognate receptor of FGF7, resulted in blockage of branching morphogenesis in the embryonic mouse lung [43], a phenotype that would later be shown to be characteristic of FGF10/FGFR2b blockage. Moreover, *Fgf7* KO mice displayed impaired hair development but a normal wound-healing capacity, suggesting the presence of redundancy between FGF7 and another unknown factor [44]. Around the same time, FGF10 (KGF2) was discovered by homology PCR [45,46] and its roles in chick limb bud outgrowth [47] and murine lung endoderm branching [48] were reported. Whereas *Fgf7* KO mutation in mice showed to be viable, *Fgf10* KO mice died shortly after birth due to multi-organ agenesis [49,50].

As mentioned previously, KO mice for almost all FGF members have already been generated and characterized. Some of these KOs have congenital/built-in defects related to regeneration and repair after injury such as *Fgf2* (impaired heart regeneration) and *Fgf6* (impaired muscle regeneration). On the other hand, many *Fgf* KOs are lethal (embryonic or postnatal) due to the critical roles of FGF ligands in blastocyst formation (*Fgf4*), gastrulation (*Fgf8*), organogenesis (*Fgf9, 10, 18*) or metabolism (*Fgf15/19, 21, 23*) (reviewed in [8]). Thus, their therapeutic and regenerative potential has been studied in the context of injury models accompanied by recombinant FGF treatment or genetic intervention such as inducible overexpression of ligands, inducible conditional KO of ligands or receptors and inducible overexpression of dominant negative decoy receptors. Using the soluble FGFR2b decoy receptor to inhibit FGFR2b ligand activity, our group has already shown that FGFR2b signaling is critical for the maintenance of the apical ectodermal ridge (AER) during limb organogenesis [51], controls the regenerative capacity of the adult mouse incisors [52] and is important for postnatal mammary gland development [53]. We also showed, using *Fgf10-lacZ* reporter mice, that *Fgf10* expression is induced in the ileal crypt epithelium after massive small bowel resection, suggesting a role for FGF10 in gut adaptation [54]. Our group was one of the few groups to perform lineage-tracing studies on *Fgf*-expressing cells, in particular FGF10 [55]. We showed that *Fgf10*-expressing cells give rise to multiple mesenchymal lineages during murine lung development [56]. We also showed that *Fgf10*-expressing tanycytes add new neurons to the appetite and energy balance-regulating centers in the adult mouse hypothalamus [57,58].

In the following sections, we will summarize the main findings from studies that investigated the role of FGFs in organ regeneration and repair, with emphasis on the heart, lung, liver, skeletal muscle and adipose tissue. An FGF homunculus that shows the sites where FGFs have shown to contribute to organ repair and regeneration is depicted in Fig. 1.

2.1. Heart

Contrary to organs and tissues like liver, pancreas, intestine, skin, lung, brain and blood, the mammalian heart lacks any robust regenerative capacity. Whereas cardiomyocyte proliferation in the second heart field is a robust event during early organogenesis, this event is absent during adulthood in mammals, thus hindering heart regeneration and repair after myocardial infarction. Stem cell research during the past 15 years has enabled the isolation of embryonic and postnatal cardiomyocyte progenitor cells, established protocols to differentiate them into mature (beating) cardiomyocytes *in vitro* and subsequently inject these cells into the injured mouse heart where they repair the scars caused by myocardial infarction (reviewed in [59]). These achievements have tempted the scientific and clinical communities to believe that the heart might yet possess a regenerative potential that can be stimulated and manipulated.

Many FGFs have been shown to control cardiomyocyte proliferation during embryogenesis including FGF9, 16 and 20. KO pups for these FGFs suffer from congenital heart defects due to impaired

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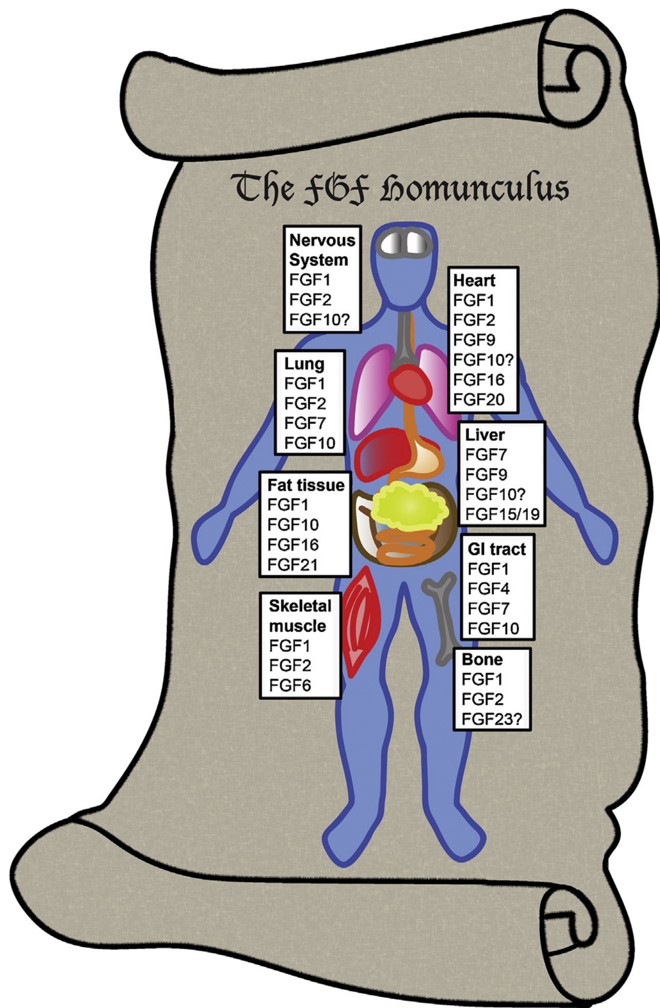

Fig. 1. The FGF homunculus. The main FGFs that are involved in organ regeneration and repair are shown.

cardiomyocyte proliferation [60,61]. Another key player in this context is FGF10, which is expressed in the second heart field during early heart development. *Fgf10*-expressing cells serve as progenitors for the outflow tract and right ventricle [62]. It was shown that FGF10, secreted by the myocardium, acts on the epicardium expressing FGFR1/2b to induce an epicardial-to-myocardial transition. Epicardial-derived cells would then give rise to cardiomyocytes [63]. Additionally, *Fgf10* KOs suffer from misplacement of the heart inside the thoracic cavity and right ventricular hypoplasia due to decreased cardiomyocyte proliferation [64]. FGF10 has also been shown to induce cardiomyocyte cell cycle re-entry in the fetal heart, a phenomenon mediated by FOXO3/p27^{kip1} [65]. Whereas *Fgf10* overexpression in adult mice promotes cell-cycle re-entry of cardiomyocytes but not cardiac fibroblasts [65], it does not seem to offer any benefit in a mouse model of neonatal heart injury, although it leads to epicardial expansion [66].

FGF1 has also been shown to induce cardiomyocyte cell-cycle re-entry [67]. In the latter study, the authors showed that FGF1/p38 MAPK inhibitor treatment induces cardiomyocyte proliferation, reduces heart scarring and rescues heart function. This work was followed up by a study demonstrating that the interaction between FGF-inducible 14-kDa protein (Fn14) [68] and FGFR1 mediates the proliferative effect conferred by FGF1 on cardiomyocytes [69].

Another member of the FGF family that has been studied in this context is FGF2. When cardiac progenitors were isolated from wild type and *Fgf2* KO mice and infused into WT or *Fgf2* KO adult mice, both cell populations were capable of homing to the cardiac infarct. However, it was only in the presence of FGF2 that progenitors were able to differentiate into mature cardiomyocytes *in situ* [70].

2.2. Lung

Although the adult mouse lung generally has a low cell turnover rate, this organ has proven to possess a decent regenerative capacity after injury. In the adult C57BL6 mouse lung, the most significantly expressed FGFs are FGF1, 2, 7, 9, 10, 18 and 23 [71]. Some of these ligands have already been investigated during lung injury and repair. FGF1, which binds with high affinity to all known FGFRs, has shown to be upregulated in fibrotic lungs and could be detected on alveolar epithelial cells (AECs) and macrophages [72]. FGF1 has also been shown to inhibit α-smooth muscle actin (*αSma*) expression and induce apoptosis in normal human lung fibroblasts [73]. The same group also showed that FGF1 treatment inhibits TGFβ1-induced epithelial-to-mesenchymal transition (EMT) through effects on MAPK/ERK pathway, leading to ERK1 phosphorylation and SMAD2 dephosphorylation *in vitro* [74]; thus, FGF1 is generally regarded as an anti-fibrotic agent in idiopathic pulmonary fibrosis (IPF).

FGF2, the other member of the FGF1 subfamily, is expressed by epithelial, inflammatory and endothelial cells, and binds with high affinity to the mesenchymal "c" splice isoform of FGFRs (and with lower affinity to epithelial FGFRs). FGF2 has been shown to mediate TGFβ1-induced myofibroblast differentiation and proliferation [75]; thus it is mostly regarded as a pro-fibrotic agent. In fact, inhibition of FGFR2c signaling has been shown to inhibit *αSma* expression and thus attenuate lung fibrosis in mice [76]. Interestingly, *Fgf2* KO mice do not seem to be protected against bleomycin-induced pulmonary fibrosis; rather, FGF2 seems to be critical for epithelial recovery after Naphthalene injury [77]. Both, FGF1 and 2, were shown to induce proliferation of rat alveolar type 2 cells *in vitro* [78] and are therefore believed to be beneficial for epithelial stem cell protection and maintenance in the lung.

FGF1 and 2 have also been studied in the context of pulmonary hypertension (PH) and they seem to mediate hypoxia-induced endothelin receptor A upregulation in pulmonary artery smooth muscle cells [79]. FGF2 levels are elevated in urine and plasma of patients with pulmonary arterial hypertension (PAH) [80]. In the lung, endothelial-derived FGF2 signals in an autocrine fashion and alters endothelial cell phenotype, thus contributing to the progression of PH in humans and rodents [81,82]. It was also demonstrated that FGF2, along with interleukin (IL)-6, mediates increased pericyte coverage and that the latter cells serve as a source of smooth muscle-like cells in PH [83]. Furthermore, deficiency in *Apelin*, a gene encoding a peptide that is highly expressed by endothelial cells and important for homeostatic maintenance in these cells, controls the expression of *miR424* and *miR503*, an event that in turn targets the expression of *FGF2* and *FGFR1* in pulmonary artery endothelial cells (PAECs). Impaired Apelin signaling in multiple PAEC cell lines, derived from idiopathic PAH (IPAH) and familial PAH (FPAH), leads to downregulation of *miR424* and *miR503* that in turn lead to augmented FGF2/FGFR1 signaling [84].

FGF7 and 10 have been shown to be critical for lung regeneration and repair in many models of lung injury. Application of recombinant FGF7 confers beneficial effects in the hyperoxia model of bronchopulmonary dysplasia (BPD) in newborn rats [85] as well as the elastase model of lung emphysema in adult mice [86,87]. *FGF10* is downregulated in lungs from BPD patients [88] and the therapeutic potential of FGF10 in the hyperoxia model of BPD in mice is currently being investigated in our group. Additionally, our group has previously demonstrated that *Fgf10* overexpression is protective and curative against bleomycin-induced pulmonary

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fibrosis in mice [89]. Interestingly, *FGF10* haploinsufficiency has been shown to be associated with chronic obstructive pulmonary disease (COPD) [90] and it will be tempting to speculate that FGF10 might have a therapeutic effect in the cigarette-smoke exposure model of lung emphysema in mice.

Apart from its therapeutic effects in diseases related to pulmonary parenchymal remodeling, FGF10 has also been shown to contribute to epithelial regeneration. Following Naphthalene injury that depletes the lung epithelium from secretory (Clara) cells, *Fgf10* expression is induced in the underlying airway smooth muscle layer, and FGF10 acts on surviving Clara cells at the bronchoalveolar duct junction and near neuroepithelial bodies to activate Notch signaling and induce transient EMT. These cells then regenerate the nude epithelium [91]. Lastly, *Fgf10* is expressed by resident mesenchymal stem cells that represent a main component of the niche that supports the growth of lung epithelial stem cells, a feature that is inhibited by TGFβ1 [56,92–94].

2.3. Liver

The liver is known for its robust regenerative capacity. Hepatic stellate cells (HSC; previously called hepatic lipocytes) are lipid-containing pericyte-like cells that are involved in the repair process following liver injury [95]. These cells are believed to be the main source of collagen in liver cirrhosis [96,97]. *Fgf7* is upregulated in activated HSC in the fibrotic liver [98]. In mice, liver regeneration appears to be highly dependent on FGFR2b signaling since attenuating FGFR2b signaling, *via* the overexpression of a soluble dominant negative form of *Fgfr2b*, greatly compromises the repair process after hepatectomy [99]. HSC-derived FGF7 improves liver regeneration and promotes hepatocyte proliferation *via* signaling through FGFR2b [100]. FGF7 has also been shown to be expressed by liver progenitor cells (LPC) and its signaling is critical for LPC-mediated repair in severely injured livers where hepatocyte proliferation is significantly impaired [101]. Although FGF10 is critical for liver growth during embryogenesis [102], it remains to be established whether it is also involved, like FGF7, in liver regeneration during adulthood.

FGF9 is upregulated in HSC, and acts on hepatocytes to induce proliferation during toxic liver injury [103]. More recently, it was shown that the FGF15/FGFR4/STAT3 signaling pathway also plays an important role in promoting hepatocyte proliferation in compensatory liver growth [104–106].

2.4. Skeletal muscle

Satellite cells are considered to be the stem cells in skeletal muscle. Similarly to stem cells in other organs and tissues, satellite cells represent a minority in the muscle tissue. Their proliferation, differentiation and fusion into myofibers during muscle growth have been thoroughly studied [107]. In this context, FGF2 has been shown to induce proliferation of skeletal muscle satellite cells *in vitro* [108,109]. The expression patterns of FGF1 and 2 have been described in the degenerating and regenerating areas of dystrophic striated muscle in mice, suggesting a role in muscle regeneration [35,110]. Indeed, it was shown that injection of recombinant FGF2 or *FGF2*-overexpressing myoblasts improves muscle regeneration in rodents [111,112]. An interesting phenomenon was reported when investigating the status of satellite cells in aged mice. It was shown that muscle fibers, constituting the stem cell niche, express *Fgf2* under homeostatic conditions. FGF2 signals to satellite cells to break their quiescence, but by virtue of expressing the FGF signaling inhibitor *Sprouty1* (or *Spry1*), satellite cells are able to maintain their quiescent status ($p27^{+}$ $Spry1^{+}$). On the other hand, aged muscle fibers significantly upregulate *Fgf2*, forcing satellite cells to break their quiescence, leading to their depletion. Thus, FGF2/FGFR1 signaling blockade might offer a therapeutic opportunity to prevent muscle stem-cell depletion during aging [113].

Another player in muscle regeneration is FGF6. *Fgf6* KO mice display impaired skeletal muscle regeneration due to decreased numbers of *MyoD*- and *Myogenin*-expressing activated satellite cells after injury [114]. Gene delivery of *Fgf6* or *Fgf2* has been shown to enhance skeletal muscle regeneration in animal models of muscle injury [115,116].

2.5. Adipose tissue

White and brown adipose tissues (WAT and BAT) play critical roles in energy preservation and heat generation respectively. WAT is the major fat depot in humans and other mammals, whereas BAT plays a critical role in heat production in the newborn infant and in arousal of hibernating mammals. Four FGF ligands are regarded as adipokines: FGF1, FGF10, FGF16 and FGF21. FGF10 is expressed by both preadipocytes and mature adipocytes and its role in the differentiation of preadipocytes in WAT is well established [117]. *Fgf10* KO newborns display impaired WAT formation [118]. FGF10 confers mitogenic and adipogenic effects on WAT preadipocytes expressing *FGFR2b*. The proliferative effect is mediated by the activation of the MAPK pathway, leading to the induction of *Cyclin D2* expression [119]. At the same time, FGF10-FGFR2b-mediated MAPK activation induces the expression of retinoblastoma protein (*pRb*) that binds CCAAT/enhancer binding protein alpha (C/EBPα) leading to the induction of peroxisome proliferator-activated receptor γ (*Pparg*) expression [120], the master regulator of adipogenesis.

FGF21, first cloned by homology-based PCR from embryonic mouse cDNA [121], has been discovered as a regulator of glucose and lipid metabolism in a screen for novel proteins with antidiabetic potential [122]. FGF21 is a circulating hepatokine that activates the MAPK pathway in adipocytes expressing *Fgfr1c* and *β-Klotho* [123] and regulates PPARγ activity by preventing sumoylation [124]. FGF21 has also been shown to activate BAT in mice [125].

The involvement of FGF1 in the dynamic WAT remodeling has recently been demonstrated in mice [126]. In response to a high-fat diet, *Fgf1* expression is induced in WAT of wild type mice. *Fgf1* KO mice develop a severe form of diabetes with vascular defects and abnormal adipocyte size within the WAT when fed a high-fat diet, a phenotype that does not properly resolve when the mice return to a normal diet. PPARγ regulates the expression of *Fgf1* at the transcriptional level by binding to a conserved PPAR response element within the promoter of the *Fgf1* gene [126].

FGF16 is expressed in the rat fetus from embryonic day (E) 17.5 to E19.5, and at lower levels during neonatal life in rat BAT. Recombinant FGF16 has been shown to induce proliferation of primary brown adipocytes isolated from rat embryonic BAT by binding and activating FGFR4. When adult rats are exposed to cold, *Fgf16* shows decreased rather than increased expression in BAT [127].

3. Clinical applications of recombinant FGFs in organ regeneration and repair

The use of recombinant human FGFs, produced in Escherichia coli or Saccharomyces cerevisiae, to treat human diseases has already been implemented. Recombinant FGF2, mostly used as an angiogenic therapy under the name Trafermin, has shown beneficial effects on patients with pressure sores [128], chronic diabetic neuropathic ulcer of the foot [129], nonsteroidal anti-inflammatory drug (NSAID)-induced gastric ulcer relapse [130], coronary heart disease [131,132], second-degree burns [133], intermittent claudication [134], sensorineural deafness

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[135], chronic sinusitis [136], surgical osteotomy [137], facial depression [138], traumatic ulcers [139], periodontitis [140], atrophied vocal folds [141], myocardial infarction [142], tibial shaft fracture [143], post-operative color uniformity [144], LASIK-induced neurotrophic epitheliopathy [145], peripheral artery disease [146], tympanic membrane perforation [147], photorefractive keratectomy [148] and minor recurrent aphthous stomatitis [149]. FGF2 gene therapy through DVC1-0101 is currently being tested for peripheral arterial disease treatment.

Treatment with recombinant FGF1 led to only modest nerve regeneration in patients with cervical spinal cord injury [150] but facilitated nerve regeneration and motor function recovery in patients with peripheral nerve lesions [151]. Riferminogene pecaplasmid (or NV1FGF), an expression plasmid encoding recombinant FGF1, significantly reduced the risk of major amputation in patients with severe limb ischemia when administered intramuscularly [152]; however, it did not seem to offer significant benefit in another study [153]. FGF1 and NV1FGF are also being tested in the treatment of intermittent claudication, coronary heart disease, diabetic or venous stasis ulcers and peripheral artery occlusive disease. FGF4 gene therapy, through Alferminogene tadenovec (or Ad5FGF4), is being tested for myocardial ischemia in patients with stable angina due to coronary artery disease [154].

Palifermin contains a truncated form of human FGF7 and is used to treat and prevent oral mucositis and dysphagia in hematologic cancer patients undergoing severe chemotherapy and radiation therapy prior to bone marrow transplantation [155]. Palifermin is introduced intravenously and helps to regenerate the mucosal barrier.

Repifermin contains a truncated form of FGF10 and was developed to treat wounds, oral and intestinal mucositis and inflammatory bowel diseases [156]. Repifermin has been shown to accelerate healing in patients with chronic venous ulcers [157] but did not show to be effective in treating active ulcerative colitis in clinical trials [158]. Thus, the development of this drug was ceased in 2004. Yet, attempts to enhance Repifermin's unfolding temperature [159] and ensure sustained release [160] have proven successful in increasing bioavailability and efficacy of Repifermin. This suggests that this drug could be revived and possibly tested in other settings.

4. Conclusions

FGF biology has witnessed an exponential growth since the last quarter of the 20th century. Developmental biologists interested in organogenesis and the associated growth and rearrangement of cells and tissues in space and time have selected 'hot' genes that proved to be indispensable for proper embryonic development, mostly in Drosophila melanogaster. FGFs are among the various growth factors that control survival, proliferation, differentiation and migration of stem/progenitor cells in a wide array of species ranging from flies to humans.

The scientific literature is rich with examples on the involvement of developmental signaling pathways in organ regeneration during postnatal life. The FGF signaling pathway is clearly one of the top candidates in this regard. FGF therapy, *via* recombinant proteins or gene delivery, has shown promising results in experimental animals and clinical trials, mostly with cardiovascular disease, skin wounds and burns, bone fractures, gastric ulcers and colitis.

A word of caution has to be stated about the association of aberrant FGF/FGFR signaling with cancer. As mentioned previously, FGFs are potent mitogens and their signaling *via* their cognate FGFRs induces cell survival, proliferation, EMT, invasion and angiogenesis. Thus, aberrant FGF/FGFR signaling can acquire an oncogenic nature and this has been shown in tumors of many human organs including, but not limited to, the breast and lung (mutations leading to amplification of *FGFR1* and *FGFR2* genes), stomach and endometrium (mutations enhancing kinase activity or altering ligand specificity of FGFR2), bladder and prostate (mutations leading to enhanced kinase activity of FGFR3), brain (mutations leading to enhanced kinase activity of FGFR1) and connective tissue (FGFR4 mutations) (reviewed in [161,162]). This oncogenic feature represents a challenge when the manipulation of FGF/FGFR signaling to promote tissue repair and regeneration is desired.

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