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Fibroblast growth factors in epithelial repair and cytoprotection

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Growth factors are polypeptides that stimulate the division of certain cell types at low concentrations. Fibroblast growth factor (FGF) 7 (FGF-7) and its homologue FGF-10 act specifically on various types of epithelial cells including keratinocytes of the skin, intestinal epithelial cells and hepatocytes. In addition, FGF-7 and FGF-10 have been shown to be more than growth factors: they can protect epithelial cells from damaging effects induced, for example, by radiation and oxidative stress. Therefore, they are currently in clinical trials for the treatment of oral mucositis, a severe side-effect of cancer therapy characterized by painful inflammation and ulceration of the oral epithelium. To gain insight into the mechanisms of FGF-7/FGF-10 action in epithelial cells, we searched for genes that are regulated by these growth factors. Indeed, we identified genes that help us to explain the mechanisms that underlie the effects of FGF-7. Most interestingly, several genes were identified that are likely to mediate the cytoprotective effect of FGF-7 for epithelial cells *in vitro* and possibly also in injured and diseased tissues *in vivo*.

Keywords: fibroblast growth factor; hepatectomy; keratinocyte growth factor; mucositis; reactive oxygen species; wound healing

1. INTRODUCTION

FGFs comprise a family of related mitogens, which, in vertebrates, includes 22 members (Ornitz & Itoh 2001). Their biological functions are mediated through four high-affinity transmembrane receptor tyrosine kinases, known as FGFRs (FGFR1–FGFR4). The various FGFs can bind to these receptors with different affinities. Alternative splicing in the extracellular domain of FGFR1, FGFR2 and FGFR3 further enhances the complexity of the FGFR system since this splicing event generates receptor variants, which differ in their ligand-binding specificities (Johnson & Williams 1993).

FGFs have been shown to enhance the proliferation, migration and survival of many different cell types (Basilico & Moscatelli 1992; Werner 1998) and they are key regulators of the various stages of embryonic development, as revealed by their expression pattern and the phenotypes observed in FGF and FGFR knockout animals (Ornitz & Itoh 2001). In addition, their roles in the pathogenesis of human disease are emerging. Thus, inappropriate expression of FGFs or their receptors can contribute to the development of certain cancers, and FGF and FGFR gene mutations are the cause of several heritable human diseases—in particular, of skeletal disorders (Powers *et al.* 2000; Ornitz & Itoh 2001). Finally, crucial roles of FGFs in tissue-repair processes have recently been demonstrated, and FGF-7 (also called keratinocyte growth factor, KGF) and FGF-10 are being therapeutically explored for the treatment of chronic human venous ulcers or of chemotherapy-induced mucositis, a condition characterized by severe ulceration in the oral cavity, the oesophagus and the intestine (Robson *et al.* 2001; AMGEN press release 2003 (see http://www.amgen.com/news/news03/pressRelease030123.pdf); Human Genome Science press release 2003 (see http://www.hgsi.com/news/press/03-04-02_repifermin_ph2.html), see below).

2. FGFs ARE CRUCIAL REGULATORS OF WOUND REPAIR

Several years ago, we provided the first evidence for a role of FGF-7 in wound repair by demonstrating a strongly increased expression of this growth factor within a day after skin injury in mice (Werner *et al.* 1992). This lesion-induced upregulation was subsequently also observed in human wounds (Marchese *et al.* 1995). Fibroblasts of the dermis and the granulation tissue, as well as intraepithelial γδT cells, were identified as the sources for KGF-7 in the wound tissue (Werner *et al.* 1992; Jameson *et al.* 2002). These cells were also shown to express the related mitogen FGF-10 (Beer *et al.* 1997; Jameson *et al.* 2002). In addition, expression of the most recently identified FGF family member, FGF-22 (Nakatake *et al.* 2001), is enhanced after skin injury in mice. In contrast to FGF-7 and FGF-10, FGF-22 is produced by suprabasal keratinocytes of the hyperproliferative wound epidermis (Beyer *et al.* 2003).

FGF-7, FGF-10 and probably also FGF-22, exert their functions by binding to FGFR2-IIIb, a splice variant of FGFR2, which is predominantly or even exclusively expressed by cells of epithelial origin (Miki *et al.* 1992; Igarashi *et al.* 1998; S. Werner, unpublished data). Thus, it is expressed by keratinocytes of the epidermis and the hair follicles in normal and wounded skin, but not by cells

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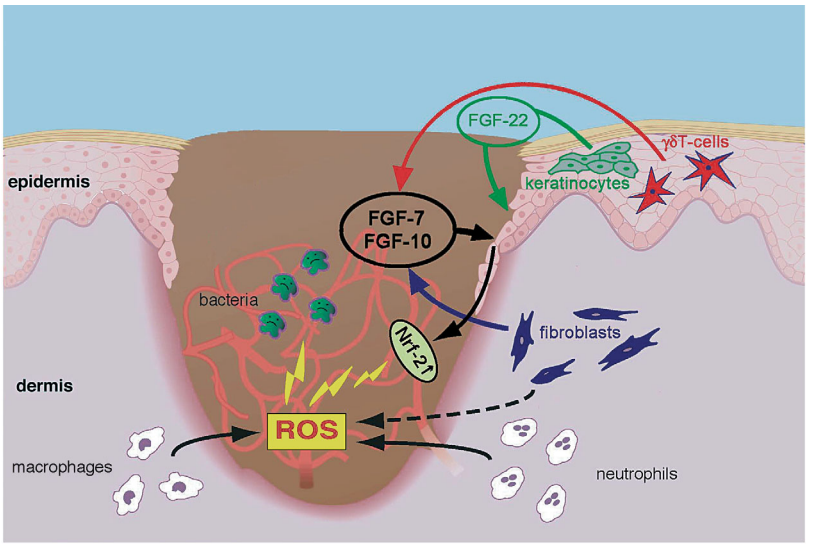

Figure 1. Cartoon to illustrate the functions of FGFs in a healing skin wound. Upon injury, dermal fibroblasts (blue) and γδT cells (red) secrete FGF-7 and FGF-10; suprabasal keratinocytes (green) express FGF-22. In a paracrine (blue and red arrows) or autocrine manner (green arrow), respectively, they activate keratinocytes at the wound edge and stimulate re-epithelialization. In addition, they induce the expression of cytoprotective genes in keratinocytes, including the gene that encodes the Nrf2 transcription factor. Nrf2 then regulates the expression of proteins involved in the detoxification of ROS. The latter are produced in large amounts by neutrophils and macrophages as a defence against invading bacteria.

in the dermis or the granulation tissue (Werner *et al.* 1992). This expression pattern of FGF-7, FGF-10 and FGF-22 and their receptor suggests a paracrine mechanism of action of FGF-7 and FGF-10, whereas FGF-22 seems to act in an autocrine manner.

To determine the importance of FGFR signalling in wound repair, we generated transgenic mice expressing a dominant-negative FGFR2-IIIb mutant in the epidermis. Interestingly, these mice suffered from an atrophic epidermis, dermal fibrosis and hair follicle abnormalities and, after wounding, showed a severe delay in re-epithelialization (Werner *et al.* 1994). Unexpectedly, incisional wounds healed normally in mice lacking FGF-7 (Guo *et al.* 1996), suggesting that the lack of FGF-7 can be compensated by other FGFR2-IIIb ligands. The most likely candidate is FGF-10, which is also present in normal and wounded skin (Beer *et al.* 1997). Although the healing process cannot be studied in FGF-10 knockout mice, since they die shortly after birth (Min *et al.* 1998; Sekine *et al.* 1999), a recent study supports this hypothesis (Jameson *et al.* 2002). These investigators demonstrated reduced keratinocyte proliferation and wound closure after injury of mice deficient for FGF-7- and FGF-10-producing γδT-cell receptor-bearing dendritic epidermal T cells. Thus, the reduced levels of these FGFs in T-cell-receptor δ-knockout mice are likely to be responsible for the impaired wound repair in these animals. Finally, keratinocyte-derived FGF-22 might also contribute to efficient epidermal repair (Beyer *et al.* 2003). The proposed action of FGF-7, FGF-10 and FGF-22 in wounded skin is summarized in figure 1.

3. FGFs IN THE REPAIR OF INTERNAL EPITHELIA

In addition to the skin, FGF-7 appears to play a crucial role in the repair of other tissues and organs. Thus, a strong upregulation of this growth factor was observed after injury to the kidney, the bladder, the stomach, the pancreas and the intestine (reviewed by Werner 1998). The increase in FGF-7 expression upon injury to the gut is likely to be of particular importance for the pathogenesis of human disease. Thus, we, and others, observed a strong expression of FGF-7 in affected areas of patients suffering from Crohn's disease and ulcerative colitis, the two major forms of inflammatory bowel disease (Brauchle *et al.* 1996; Finch *et al.* 1996). To gain insight into the possible role of FGF-7 in these disorders, Chen *et al.* (2002) employed a mouse model for colitis, where intestinal injury is induced by addition of DSS to the drinking water. The authors demonstrated that both FGF-7 knockout animals and T-cell-receptor δ-deficient mice, which express reduced levels of FGF-7, suffer from increased inflammation upon DSS treatment and delayed repair of the intestinal epithelium after DSS withdrawal. Thus, the enhanced levels of FGF-7 seen in the injured gut appear to be important for epithelial cytoprotection early after injury and also for the repair of the damaged intestinal epithelium. Therefore, it seems likely that FGF-7 fulfils similar functions in patients with Crohn's disease and ulcerative colitis.

Owing to the obvious importance of FGFR2-IIIb and its ligands in epithelial repair and the strong expression of this type of receptor in hepatocytes, in particular after injury (Hu *et al.* 1995), we speculated about a role for FGFR signalling in the liver. To address this question, we generated transgenic mice expressing a dominant-negative FGFR-2IIIb mutant under the control of the liver fatty-acid-binding protein promoter, which targets expression of transgenes to intestinal epithelial cells and to hepatocytes (Steiling *et al.* 2003). Whereas no obvious phenotype was detected in the non-injured gut and liver of these animals, old transgenic mice had a high incidence of fatty liver development. Following partial hepatectomy, proliferation of hepatocytes was strongly reduced in the transgenic animals. The observed inhibition of hepatocyte proliferation was shown to result from an arrest in the late

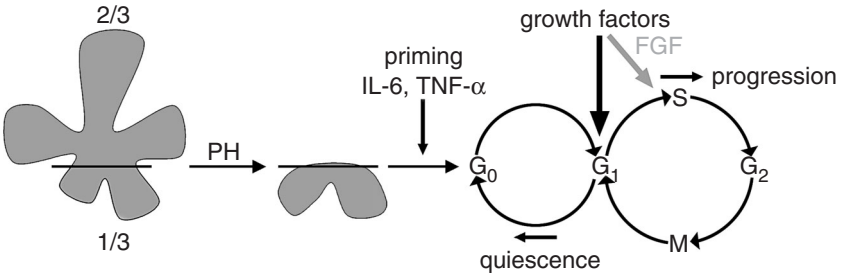

Figure 2. The role of FGFs in liver repair. The two-thirds hepatectomy procedure is shown schematically. After resection of two liver lobes, the regeneration process is initiated by a priming step, which has been shown to be regulated by the pro-inflammatory cytokines interleukin-6 (IL-6) and tumour necrosis factor α. As shown by Steiling *et al.* (2003), the subsequent cell cycle progression requires signalling via FGF receptors.

G_1 phase of the cell cycle, as demonstrated by reduced and delayed expression of cyclin A in these animals after partial hepatectomy (figure 2). The FGF family member, which is crucial for liver regeneration, remains to be identified, since neither FGF-7 nor FGF-10 are expressed in the liver before or after hepatectomy (Steiling *et al.* 2003). A possible ligand is FGF-1, which also binds to FGFR2-IIIb and which is upregulated in the liver after hepatectomy (Marsden *et al.* 1992; Steiling *et al.* 2003). These results are the first demonstration of a functional role of FGFs in liver regeneration and suggest that exogenous FGFs could be therapeutically explored to enhance the regenerative capacity of the liver.

4. FGFs ARE CYTOPROTECTIVE FOR EPITHELIAL CELLS *IN VITRO* AND *IN VIVO*

Whereas the therapeutic potential of FGFs in liver disease has not yet, to our knowledge, been explored, FGF-7 and FGF-10 are currently in clinical trials for the treatment of other disorders. Based on the findings that FGF-7 and FGF-10 increase the speed of re-epithelialization in various animal models (Abraham & Klagsbrun 1996; Jimenez & Rampy 1999), FGF-10 is currently in clinical trials for the treatment of venous ulcers (Robson *et al.* 2001). The beneficial effect of these growth factors for the treatment of poorly healing wounds is most probably due to their mitogenic effect for keratinocytes. However, the cytoprotective function of FGF-7 and FGF-10 might also contribute to the efficacy, since these growth factors are likely to enhance survival of epithelial cells in inflamed tissues, where high levels of aggressive ROS are produced by inflammatory cells. Thus, a series of studies revealed that FGF-7 protects lung epithelial cells from hyperoxia-induced cell death (reviewed by Werner 1998). Furthermore, it was found to protect thymic epithelial cells after bone marrow transplantation and preserve normal thymopoiesis and thymic microenvironment during experimental graft-versus-host disease (Min *et al.* 2002; Rossi *et al.* 2002). Finally, FGF-7 was successfully used in preclinical models of mucositis induced by radiation and/or chemotherapy. In these studies pre-treatment with FGF-7 reduced atrophy of the oral epithelium, accelerated its regrowth after therapy and decreased the incidence of ulcer formation in the oral cavity. In the small intestine, crypt survival was improved and villus atrophy was prevented (Farrell *et al.* 2002).

The mechanisms underlying the protective effect in different tissues and organs are under intensive investigation. Most results have, as yet, been obtained in the lung. In this organ, FGF-7 stimulated the proliferation of type II alveolar cells and expression of the lung surfactant protein. Furthermore, it enhanced the levels of Na^+/K^+-ATPase, and improved the DNA repair capacity of these cells (reviewed by Werner 1998). In addition, FGF-7 was shown directly to inhibit hyperoxia-induced death of lung epithelial cells *in vivo* through activation of the anti-apoptotic Akt-signalling pathway (Ray *et al.* 2003).

Recent studies from our laboratory demonstrated that FGF-7 can also protect keratinocytes from the toxic effects of ROS. In an attempt to determine the underlying mechanisms, we performed differential display reverse transcriptase polymerase chain reaction, subtractive cDNA hybridization and a microarray analysis to identify FGF-7-regulated genes in these cells. The genes that we found to be regulated by FGF-7 help to explain how this growth factor regulates migration, proliferation and differentiation of keratinocytes. Most interestingly, some of these genes are candidate mediators of the cytoprotective effect. One of them encodes peroxiredoxin VI, a cytoplasmic enzyme that detoxifies hydrogen peroxide and organic peroxides (Frank *et al.* 1997). Two follow-up studies suggested that peroxiredoxin VI is also a target of FGF-7 *in vivo*: in a first set of experiments, we demonstrated a temporal and spatial correlation between FGF-7 and peroxiredoxin VI expression in wounded skin. As shown by *in situ* hybridization, peroxiredoxin VI mRNA was predominantly produced by the FGFR2-IIIb-expressing keratinocytes of the hyperproliferative wound epidermis, suggesting that these cells express peroxiredoxin VI in response to FGF-7 and possibly to FGF-10 and FGF-22 (Munz *et al.* 1997). In a second study, the peroxiredoxin VI gene was identified as an FGF-7 target in the intestine *in vivo*, since intestinal epithelial cells expressed this enzyme in response to systemic FGF-7 treatment (Farrell *et al.* 2002). A second FGF-7 target gene encodes Nrf2, a transcription factor responsible for the activation of various cytoprotective genes, which encode ROS-detoxifying enzymes and other anti-oxidative proteins (Braun *et al.* 2002). Nrf2 is expressed at high levels in the FGF-7/FGF-10-responsive keratinocytes of the wounded epidermis of mice (Braun *et al.* 2002), suggesting that endogenous FGFs may also regulate Nrf2 expression *in vivo*. The identification of Nrf2 as a target of FGFs in keratinocytes

could be of particular importance during wound healing, where large amounts of ROS are produced by neutrophils and macrophages as a defence against invading micro-organisms (figure 1). Therefore, we analysed the healing process of full-thickness excisional wounds in Nrf2 knock-out mice. Although the inflammatory phase was extended in these animals and the expression of various key players involved in wound repair was altered, no obvious macroscopic or histological abnormalities of the wound healing process were observed. This normal healing rate might at least partly be due to an increased expression of the related transcription factor Nrf3. The latter was also identified as a target of FGF-7 *in vitro* and it was coexpressed with Nrf2 in the healing skin wound (Braun *et al.* 2002). The analysis of mice deficient in the response to both transcription factors will reveal the role of Nrfs in cutaneous wound repair. Furthermore, downregulation of these genes in keratinocytes will allow us to identify the role of Nrf2 and Nrf3 in the cytoprotective effect of FGF-7. In any case, the identification of Nrf2, Nrf3 and peroxiredoxin VI as targets of FGF-7 in keratinocytes suggests that this growth factor mediates its protective effect at least partly by enhanced detoxification of ROS.

5. FGFs FOR THE TREATMENT OF HUMAN DISEASE

The studies described above demonstrate a crucial role of FGFR2-IIIb ligands in epithelial repair processes. Furthermore, their cytoprotective potential makes them promising candidates for the treatment of conditions associated with epithelial damage. Indeed, FGF-10 is currently in clinical trials for the treatment of venous ulcers (Robson *et al.* 2001; http://www.hgsi.com/news/press/03-01-06_progress.html). Most recently, successful phase 2 (FGF-7 and FGF-10) and phase 3 (FGF-7) clinical trials with FGF-7 and FGF-10 were announced for the treatment of oral mucositis, a condition characterized by severe oral ulcerations that occur in cancer patients undergoing chemotherapy and/or radiotherapy (http://www.amgen.com/news/news03/pressRelease030123.pdf; http://www.hgsi.com/news/press/03-04-02_repifermin_ph2.html). Thus, FGF-7 decreased the duration and incidence of these debilitating conditions in patients with bone marrow transplantation treatment for haematological malignancies. These promising studies suggest that the cytoprotective effect of FGF-7 and related growth factors could indeed be therapeutically explored, and highlight the importance of studies aimed at elucidating the molecular mechanisms of FGF action in epithelial cells.

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GLOSSARY

DSS: dextran sulphate sodium
FGF: fibroblast growth factor
FGFR: fibroblast growth factor receptor
KGF: keratinocyte growth factor
Nrf2: nuclear factor, erythroid-derived 2-related factor 2
Nrf3: nuclear factor, erythroid-derived 2-related factor 3
ROS: reactive oxygen species