Am J Clin Exp Urol 2023;11(6):452-466
www.ajceu.us /ISSN:2330-1910/AJCEU0152004

Review Article

Potential roles of FGF5 as a candidate therapeutic target in prostate cancer

Mary M Stangis[1,2*], Avan N Colah[1,4*], Dalton T McLean[1], Richard B Halberg[2,3], Lara S Collier[4], William A Ricke[1,3]

[1]Department of Urology, University of Wisconsin-Madison, Madison, WI, USA; [2]Department of Oncology, McArdle Laboratory for Cancer Research, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; [3]Carbone Cancer Center, University of Wisconsin-Madison, Madison, WI, USA; [4]Pharmaceutical Sciences Division, School of Pharmacy, University of Wisconsin-Madison, Madison, WI, USA. [*]Equal contributors.

Received June 30, 2023; Accepted September 13, 2023; Epub December 15, 2023; Published December 30, 2023

Abstract: Fibroblast growth factor (FGF) is a secreted ligand that is widely expressed in embryonic tissues but its expression decreases with age. In the developing prostate, FGF5 has been proposed to interact with the Hedgehog (Hh) signaling pathway to guide mitogenic processes. In the adult prostate, the FGF/FGFR signaling axis has been implicated in prostate carcinogenesis, but focused studies on FGF5 functions in the prostate are limited. Functional studies completed in other cancer models point towards FGF5 overexpression as an oncogenic driver associated with stemness, metastatic potential, proliferative capacity, and increased tumor grade. In this review, we explore the significance of FGF5 as a therapeutic target in prostate cancer (PCa) and other malignancies; and we introduce a potential route of investigation to link FGF5 to benign prostatic hyperplasia (BPH). PCa and BPH are two primary contributors to the disease burden of the aging male population and have severe implications on quality of life, psychological wellbeing, and survival. The development of new FGF5 inhibitors could potentially alleviate the health burden of PCa and BPH in the aging male population.

Keywords: Fibroblast growth factor 5, prostate cancer, FGF5 inhibitors, stromal-epithelial crosstalk

Introduction

In the aging male population, prostate cancer (PCa) is one of the principal contributors to overall health burden [1]. PCa is the second most frequently diagnosed malignancy in men worldwide with highest incidence rates observed in elderly men (>65 years of age) [2]. In the United States, PCa remains the leading new cancer diagnosis of men and is projected to cause 11% of cancer-related deaths among U.S. men in 2023 [3]. Mechanisms for the development of clinically relevant PCa often involve mutational events or dysregulation impacting the function of androgen receptor (AR), a ligand induced transcription factor which mediates cell proliferation, migration, invasion, and differentiation [4]. Targeting of AR through androgen deprivation therapy (ADT) is the current standard of care but relapse and disease progression are common [5]. Localized PCa has a 5-year survival rate of close to 98% in the USA, but survival statistics decrease in other global populations [2, 6]. Men who develop distant stage PCa or ADT insensitive castration-resistant prostate cancer (CRPC) have a 5-year survival rate of around 32% [6]. Additionally, studies have shown that the number of men diagnosed with late stage PCa is increasing over time [6] while treatment strategies for late stage PCa and CRPC remain ineffective [7]. Therefore, new therapeutic targets are necessary to improve overall survival of patients with PCa.

In the presence or absence of malignancy, benign enlargement of the prostate transition zone known as benign prostatic hyperplasia (BPH), is an increasingly common diagnosis among aging males [8]. Individuals with BPH often present with lower urinary tract symptoms (LUTS) which may include poor urinary flow, hes-

itancy, nocturia, and incontinence [9]. Together BPH/LUTS impairs quality of life, severely impacts psychological well-being, and heavily contributes to the health burden of the aging male population [9]. BPH is commonly treated with 5α-reductase inhibitors (5ARIs) to reduce the conversion of prostatic testosterone to dihydrotestosterone (DHT) [10-12]. DHT is a potent activator of AR, and limiting DHT production offers an alternative to ADT approaches to reduce prostate volume [11, 12]. However, existing therapeutic options are currently insufficient, and identification of new molecular targets to combat BPH will help to further alleviate the health burden in aging men.

The fibroblast growth factor (FGF) family includes 22 proteins that regulate signaling pathways crucial for tissue growth, morphogenesis, development, and repair. FGF5 is one of 18 secreted canonical FGFs within this family of ligands [13-15]. Secreted FGFs exert their downstream function through binding with FGF receptors (FGFRs). This receptor family includes four canonical receptor tyrosine kinases (RTKs) with substantial sequence homology (FGFR1-4) and one related FGFR (FGFRL1, also known as FGFR5) [14, 15]. Alternative splicing of the FGF ligands and receptors further contributes to the functional complexity of this signaling network [16].

Available literature on the functions of some FGF ligands is limited. Gaps in knowledge are particularly evident when considering FGF5, despite its overexpression being identified in many human cancers (**Table 1**). Functionally, FGF5 was identified as an inhibitor of hair growth when it was determined that angora mice are genetically deficient for *FGF5 (FGF5^{go}/FGF5^{go})*. Angora mice display abnormally long coats as a consequence of prolongation of the anagen phase of the hair cycle due to the absence of FGF5 [17, 18]. Since this discovery, increased expression of FGF5 has been studied as a contributing factor to hair cycle dysfunction and it was hypothesized that reduction in FGF5 activity could counteract male pattern baldness [19, 20]. These studies have prompted the development and discovery of candidate FGF5 inhibitors [19, 21]. However, knowledge of the functions of FGF5 and the therapeutic relevance of FGF5 inhibitors in cancer and other diseases is limited.

Since the identification of the FGF/FGFR signaling axis as a critical player in cancer, there has been an increased interest to develop therapeutics that inhibit FGFR signaling [22]. Candidate drugs targeting FGFRs have yielded varying degrees of success in cancer therapeutics due to heterogeneity of the FGF/FGFR family and frequency of resistance mutations to existing inhibitors [22]. A few small molecule tyrosine kinase inhibitors (TKIs) of FGFRs are now FDA approved to treat a limited number of cancer types with targetable genetic changes in FGFRs [22]. As these drugs inhibit multiple FGFRs they can cause side effects due to actions in normal tissues and cancer cells can develop resistance to specific FGFR inhibitors [22]. Therefore, a detailed investigation of the molecular functions of FGF ligands and their receptors in cancer development and progression is needed to establish new therapeutic targets within this signaling axis.

During prostate development, homeostasis, and disease, the roles of FGF5 are largely undefined. However, a small body of work describes potential associations between FGF5 expression and the following pathways: Hedgehog (Hh) signaling, androgen receptor (AR) signaling, and Sex Determining Region Y-box 2 (SOX2) signaling [23-26]. These studies have set the stage for further investigation of the roles of FGF5 in the context of prostate development and disease. In this review we will provide an overview of FGF5 and its signaling through FGFRs. Observational studies that have implicated FGF5 in prostate development, homeostasis, and cancer will be emphasized and we will discuss efforts that point towards FGF5 as an interesting candidate for functional investigation. Mechanistically, FGF5 has been vastly understudied in the context of PCa, BPH, and other cancers. We propose that development of FGF5 inhibitors could offer a viable mechanism for therapeutic advancement in multiple disease types.

Overview of FGF, FGFRs, and the FGF5/FGFR signaling axis

FGF5/FGFR signaling networks

FGF5 was first identified in 1987 through a screen for potential new oncogenes capable of transforming NIH3T3 murine fibroblasts [27].

Table 1. Summary of basic findings from functional studies investigating the oncogenic roles of FGF5 overexpression in cancer

Cancer type	FGF5 expression	Mechanism of action	Proposed role in tumorigenesis	Model to study disease	Citation
Breast Cancer	60-fold upregulation of FGF5 mRNA in stroma	Hh signaling pathway	Cell plasticity, proliferation, and stemness	Triple negative breast cancer (TNBC) patient derived xenograft	[102]
Pancreatic cancer	Overexpression of FGF5 mRNA	MAPK signaling pathway	Proliferation	12 patient samples; COLO-357 cell line	[101]
Esophageal squamous cell carcinoma (ESCC)	Reduced FGF5 expression	Undefined	Confers resistance to definitive chemoradiotherapy	117 ESCC samples; 11 ESCC cell lines	[103]
Hepatocellular carcinoma (HCC)	Overexpression of FGF5	MAPK signaling pathway	Proliferation, metastasis	192 HCC patient samples; 5 HCC cell lines; HCC mouse model	[104]
Glioblastoma multiforme (GBM)	Overexpression of FGF5 mRNA and protein	Undefined	Cell proliferation, viability, migratory capacity, angiogenesis, and malignancy	Astrocytic glioma patient samples (grades I-III) and GBM; GBM cell lines T98G, U373, MGC	[100]
Osteosarcoma (OS)	Overexpression of FGF5 mRNA and protein	MAPK signaling pathway	Dedifferentiation, metastasis, increased tumor size and stage	15 OS patient samples; U2OS, SAOS, MG63 cell lines; nude mouse orthotopic model	[98]
Melanoma	>50-fold upregulation of mRNA	MAPK NFAT signaling axis	Clonogenicity and invasion in vitro; tumor growth, angiogenesis, and proliferation in vivo	28 human melanoma cell lines; murine xenograft model	[99]
Papillary Thyroid Carcinoma (PTC)	Overexpression of FGF5 mRNA and protein	Undefined	Cell growth, proliferation, colony formation	30 human patient samples; Human PTC cell lines TPC-1 and K1	[113]

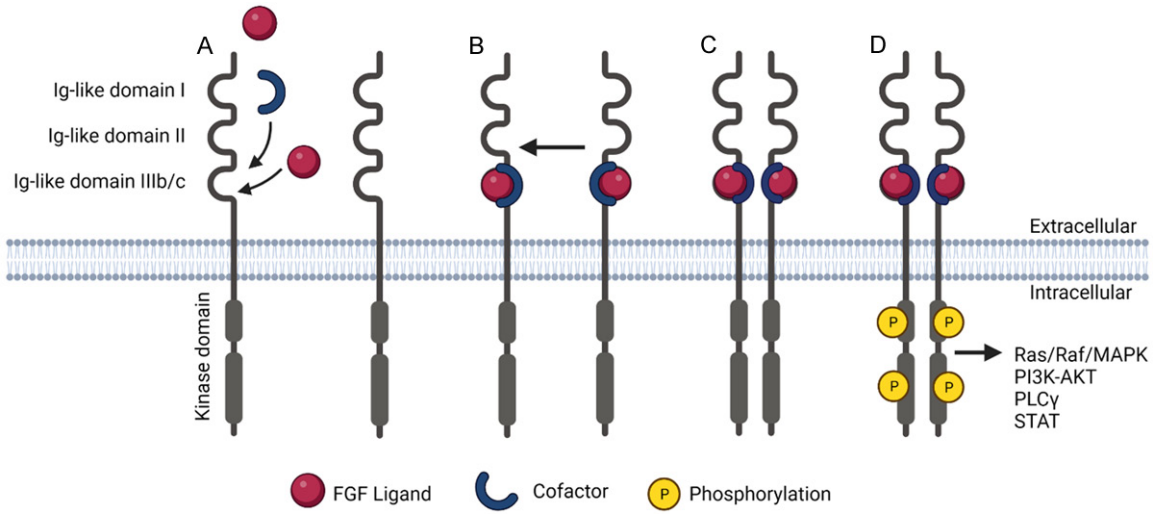

Figure 1. The FGF/FGFR signaling pathway. A. An FGF ligand (red) binds with a HSPG or Klotho cofactor (blue) to extracellular immunoglobulin-like domains on a compatible FGFR. B. Ligand binding stimulates a conformational change and promotes receptor dimerization. C. FGF-FGFR monomers dimerize to activate the FGFR. D. Autophosphorylation of the tyrosine kinase domains on the activated FGFRs stimulates downstream signaling pathways from the FGFR [16].

FGF5 can undergo alternative splicing yielding two different transcripts that encode two FGF5 isoforms - a 268 amino acid (AA) protein referred to as FGF5 or a 123 AA protein referred to as FGF5S [28]. Although the FGF5S variant was not initially characterized as a functional isoform of FGF5, both isoforms have been shown to bind to FGFR1, with FGF5S functioning as an FGF5 competitive antagonist for FGFR1 at increased concentrations [29]. Studies have shown that both isoforms can be heavily glycosylated prior to secretion; this generates proteins with molecular masses ranging from ~18.5-40 kDa [30, 31]. For the FGFS variant, it has been demonstrated that glycosylation allows for functional retention while increasing resistance to degradation when compared to non-glycosylated forms [31].

FGFRs are composed of an extracellular ligand binding region consisting of three immunoglobulin-like domains, a transmembrane helix, and a cytoplasmic tyrosine kinase domain (**Figure 1**) [16]. Classically, an FGF ligand binds to a compatible inactive FGFR monomer and induces a conformational change leading to receptor dimerization mediated by a heparin sulfate proteoglycan (HSPG) or Klotho co-factor [32]. However, FGFR homodimerization prior to ligand binding is also observed and has been proposed to prime receptors for activation by FGF ligands [33]. Ligand binding leads to trans-autophosphorylation of the tyrosine kinase domain to complete receptor activation [32, 34]. Homodimerization of FGFR monomers has been thoroughly characterized, and Förster resonance energy transfer (FRET)-based methodologies for studying heterodimers has led to evidence suggesting that heterodimerization diversifies downstream responses [35]. The four major signaling pathways associated with cancer and found downstream of FGFs/FGFRs are: Ras/Raf-MEK-MAPK (mitogen activated protein kinases), PI3K-AKT (phosphatidylinositol-3 kinase/protein kinase B), PLCγ (Phospholipase Cγ), and STAT (signal transducer and activator of transcription) (**Figure 1**) [36-48]. FGFR signaling can also be modulated by cell and ligand context, adaptor protein functionality, post translational modifications, receptor isoform expression due to alternative splicing, receptor internalization, and epigenetic mechanisms [48-52].

Alternative splicing of mRNA encoding the Ig-like domains of FGFR generates tissue specific expression of FGFR isoforms with different ligand binding capabilities [16, 53, 54]. For example, for FGFR1, 2, and 3, alternative splicing involving sequences encoding the extracellular Ig-like domain III leads to the production of one of two isoforms - IIIb or IIIc. These receptor

isoforms are typically differentially expressed by epithelial and mesenchymal lineages respectively, and can bind different ligands with high specificity [53-57]. FGF5 was found to preferentially activate the IIIc splice variant of FGFRs with relative activity at each receptor isoform as follows: FGFR1IIIc > FGFR2IIIc > FGFR3IIIc and little activity at FGFR4 [58]. In normal tissue, FGFR2IIIb variants are generally expressed in epithelial cells where IIIc variants are expressed in mesenchymal cells [59]. Interestingly, in pancreatic and prostate cancer, receptor isoforms have been shown to switch expression patterns where FGFR2IIIc is expressed in epithelium and FGFR2IIIb is expressed in the stroma [59-64]. Later in this review, we will further discuss how tissue specific FGFR splicing may contribute to prostate tumorigenesis.

Proposed roles of FGF5 in the healthy and diseased prostate

In adult prostate tissue, a study comparing prostate stromal cells from the prostatic peripheral zone (PZ) of young donors (averaging 27 years of age; n=5) to PZ samples from older donors (averaging 65 years of age; n=5) found significantly increased FGF5 expression in stromal cells from older donors [65]. Analysis of a cDNA microarray and verification by qPCR both showed a significant increase in *FGF5* expression in the old donor samples compared to young ones [65]. These findings demonstrate that increased *FGF5* expression coincides with the normal aging process and could subsequently enhance associated prostatic disease including PCa and BPH.

In support of a role for FGF5 in prostate cancer, studies of human donor-derived Cancer Associated Fibroblasts (CAFs) and matched Normal Prostate Fibroblasts (NPFs), found that FGF5 expression was higher in CAFs than NPFs [65]. Additionally, the human prostatic PZ is the predominant site of origin for PCa [66]. Studies demonstrating age-related increase in FGF5 transcript in the PZ of older donors during normal aging indicate the spatiotemporal relevance of *FGF5* and a potential connection between aging and carcinogenesis [65]. Additionally, *FGF5* and other age-related mitogenic factors may prime the prostate microenvironment for PCa tumor initiation and progression [65].

Furthermore, increased *FGF5* in the PZ during carcinogenesis could be involved in a growth process analogous to the “embryonic reawakening” proposed as a potential driver of BPH in the prostatic transition-periurethral zone (TPZ). During the embryonic reawakening, prostate epithelial cells are thought to proliferate in response to a transient induction of stromal signaling factors, resulting in benign enlargement of the prostate gland due to hyperplastic growth of epithelial cells within glandular nodules [67, 68]. Candidate factors for inducing episodic reawakening of the TPZ stroma are likely to be growth factors, with studies citing FGF2 and FGF7 as key drivers of pathogenesis in BPH [69-71]. Given recent work describing increased expression of *FGF5* in the healthy PZ of aging donors [65], we hypothesize that identification of a transient increase in *FGF5* in the TPZ during normal aging or during episodic stromal reawakening could describe a new candidate driver and therapeutic target for BPH. However, gene expression studies profiling *FGF5* expression in the TPZ throughout aging, and functional studies defining a link between FGF5 and BPH are necessary to investigate this hypothesis.

Dysregulation of tissue specific FGFR splice variants in prostate cancer

Crosstalk between cell compartments in the prostate is an important modulator of development, homeostasis, and disease (**Figure 2**). Directional paracrine signaling from stromal to epithelial cells is androgen sensitive and is necessary for the growth and differentiation of prostate epithelial cells [72]. A 1993 study in the Dunning Tumor (DT) rat model investigated epithelial and stromal cells from an androgen-responsive, differentiated, slowly growing transplantable rat prostate tumor. This work was the first to demonstrate how switching of receptor isoform expression between stromal and epithelial cells creates an entirely new dynamic within the prostate tumor microenvironment (TME) [62]. Here, data suggested that autocrine signaling of FGFs through aberrant FGFR2IIIc in epithelial cells promotes independence of epithelial cell growth from stromal cell support to drive malignancy [62]. Concurrent activation of FGF2, FGF3, and FGF5 in the prostate TME was also observed, and it was predicted that differential isoform expression by prostate epithelial cells is necessary but not

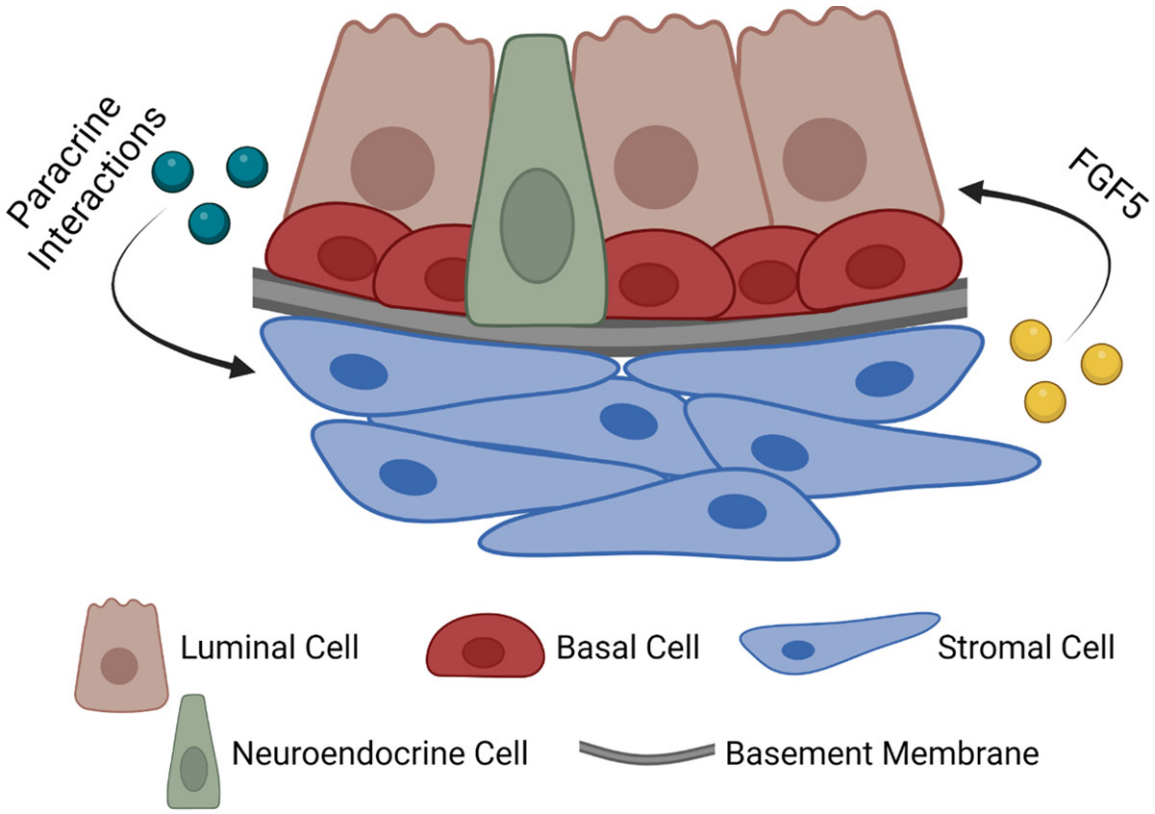

Figure 2. Representation of cell compartments in the human prostate and proposed mechanism for crosstalk between prostate epithelial and stromal cells. Data suggests that epithelial cells stimulate increased FGF5 production in stromal cells through paracrine interactions. Secreted FGF5 produced by stromal cells may result in increased proliferation and differentiation in the prostate epithelium.

sufficient to drive disease progression [62]. This study highlights how dysregulation of tissue specific FGFR splice variants in combination with FGF5 activation may contribute to malignant transformation of prostate epithelial cells and could have much broader implications across a variety of disease states [62].

FGF5 as a potential target gene of paracrine Hh pathway signaling in the prostate

During the development of many organs, including the prostate, the Hh pathway has been proposed to play a modulatory role [73]. Sonic hedgehog (Shh), a Hh pathway ligand, can act through its receptor Patched (Ptc) and downstream G-protein receptor smoothened (Smo) to stimulate developmental processes [74-76]. A series of studies investigating Hh signaling in the developing prostate proposed that the Hh pathway guides tissue polarity and morphology through paracrine interactions and identified Shh target genes in the stroma that may be involved in this process [77-81]. Specifically, *Fgf5* was identified as a Shh target gene in the embryonic immortalized stromal cell line Urogenital Sinus Mesenchymal-2 (UGSM-2) [80]. However, studies using primary mesenchymal cells or cultures did not see a change in *Fgf5* levels when Hh signaling was manipulated [80]. In adult prostate tissue, Hh signaling is active at low levels compared to developmental time points and Smo localizes to the primary cilia in prostatic fibroblasts. In prostate cancer, however, the Hh pathway can become dysregulated through increased growth factor driven Hh signaling in the tumor stroma or through autocrine pathways impacting the epithelium [23, 82, 83]. A line of evidence connecting *FGF5* to PCa reported that increased *FGF5* levels were observed when NPFs were transduced with a constitutively active Smo:RFP construct to mimic aberrant Hh signaling (SmoM2-NPF). When SmoM2-NPFs were recombined with non-tumorigenic human prostate epithelial cells (BPH-1), and grafted *in vivo*

(SmoM2-NPF + BPH-1 graft) they generated enlarged grafts approximately twice the size of controls (NPF + BPH-1 grafts and BPH-1 grafts alone). Further analysis demonstrated aggressive and dedifferentiated phenotypes of epithelial cells in the SmoM2-NPF + BPH-1 graft [23]. In a more recent study of Hh signaling in the stroma of control and Shh stimulated biclonal xenograft tumors, *FGF5* was shown to be one of 9 genes whose expression is regulated by Shh [24]. These data suggest that Shh secretion from epithelial cells into the tumor microenvironment leads to upregulation of Hh signaling in UGSM-2 stromal cells and subsequent overexpression of FGF5 [24]. Additionally, studies involving blocking of Hh signaling in CAFs or activation of Hh signaling in NPFs did not find consistent impacts of Hh signaling on *FGF5* levels [65]. Therefore, additional studies are necessary to understand FGF5 as a target gene of the Hh pathway in PCa.

Potential links between FGF5 and hormone signaling that may translate to prostate disease

A promising route of exploration in prostate cancer was first established in skin-based models where a potential link between FGF5 and androgen receptor signaling was identified. In a variety of mammalian models, FGF5 has been most thoroughly studied in the context of cyclical hair growth [17, 84-86]. Reports indicate that FGF5 is important for determining both the duration of the anagen (active hair growth phase) and the induction of catagen (hair follicle regression) [85]. In mice, as well as other animals, *FGF5* genetic ablation results in the development of abnormally long hair [18, 84-86]. This phenotype is also observed in humans with FGF5 mutations, resulting in longer body hair, eyebrows, and eyelashes [28]. Androgens are known to have effects on hair growth which vary across body location. For example, androgenetic alopecia (AGA) is a common form of hair loss which is mediated by excessive androgen activity in the scalp [87, 88]. Androgen signaling in the skin is modulated by the 5α-reductase (SRD5A1) enzyme isotype which is responsible for converting testosterone to DHT, and subsequently effects hair growth. However, in dermal papilla cells (DPCs), where hair follicle induction and hair growth occur, crosstalk between androgens and the Wnt/β-catenin pathway contribute to hair follicle miniaturization [89-91]. A study in the skin of CRISPR/Cas9 *FGF5*-Knock Out (KO) Dorper sheep has begun to elucidate cross-talk between FGF5 and androgen signaling in regulating hair growth [25]. While most use of *FGF5*-KO models involves potential application in the agricultural industry [25, 92, 93], data linking *FGF5* to androgen provide insight for future directions of research on *FGF5* in prostate cancer and castration resistance.

Results from investigation into *FGF5*-KO in Dorper sheep identified affected downstream signaling cascades in the skin including: FGFR1, androgen/AR, Shh/Gli2, and Wnt/β-catenin among others. Downstream of Wnt/β-catenin, the Shh signaling pathway has been implicated in hair-follicle induction and it was hypothesized that each of these signaling components would be disrupted in response to *FGF5*-KO [25, 94]. Consistent with the hypothesis, similar levels of testosterone were detected in the *FGF5*-KO Dorper sheep compared to controls. However, the level of DHT was significantly diminished in the *FGF5*-KO group, indicating disruption to the enzymatic function of 5α-reductase. At the mRNA and protein level, both SRD5A1 and AR were significantly reduced in the *FGF5*-KO group compared to control group whereas the protein level of β-catenin was significantly increased [25]. Functional work in DPCs treated with DHT, finasteride, and DMSO verified observations of crosstalk between androgen and the Wnt/β-catenin pathway. However, further work needs to be completed to define the mechanism by which *FGF5*-KO reduces AR [25]. Further investigation of *FGF5*-KO in other androgen target tissues including the prostate is merited as dysregulation of AR is a driver of prostatic disease and a contributor to castration resistance.

FGF5 as a potential player in castration resistance

In prostate cancer cells, work examining the relationship between FGF5 and SOX2 has indirectly linked *FGF5* to castration resistance. Specifically, SOX2 has been implicated as a regulator of *FGF5* expression. In castration sensitive LAPC-4 prostate cancer cells, ectopic expression of SOX2 caused an 18.81-fold increase in *FGF5* levels. Moreover, expression

of *FGF5* was also increased significantly in xenografts of both LAPC-4 and castration resistant CWR-R1 cells grown in castrated vs. intact hosts [26]. This same study also found that SOX2 promoted castration resistance in prostate cancer cell lines, and SOX2 was found to be expressed in the majority of human castration resistant PCa metastasis [26, 95]. However, it has not yet been determined if the ability of SOX2 to promote castration resistance involves FGF5, or if FGF5 expression is correlated with SOX2 expression in human tumors. Nonetheless, these data support further research into a potential role of FGF5 in castration resistance.

FGF5 as an alternative to current PCa therapeutics

Currently, the majority of clinical PCa therapeutics focus on modulation of androgen production through ADT or AR signaling inhibition via first- and/or second-generation androgen receptor antagonists [96]. However, a variety of AR dependent and AR independent mechanisms can develop to bypass existing therapeutic options and allow for PCa progression to CRPC [96]. One mechanism by which AR-dependent CRPC develops that may be related to FGF5 signaling is through co-factor based transcriptional regulation of AR. In this circumstance, transcriptional co-factors facilitate nuclear localization of AR to stimulate the AR signaling pathway in the absence of androgen [96, 97]. Although the mechanism of action of FGF5 in PCa is unknown, the FGF/FGFR signaling axis becomes increasingly diverse in the context of disease, and aberrant modulation of one or multiple AR transcriptional cofactors by the FGF5/FGFR signaling axis could contribute to disease progression. Here, it can be predicted that supplementation of existing therapeutic methods with AR co-factor targeting drugs may reduce the progression of PCa into CRPC in some subtypes of PCa.

FGF5 in other cancers

FGF5 has been gaining traction as a possible target for cancer therapeutics as evidence is accumulating that it has oncogenic roles in a broad range of human cancer types (**Table 1**). In malignancies where FGF5 transcript and protein are reported to be overexpressed, functional studies are beginning to define the mechanism of action by which FGF5 may contribute to tumorigenesis and disease progression. Given the established roles of FGF5 in guiding development and wound healing; some studies hypothesize dysregulation of related processes as drivers of pathologies [16, 98-101]. Consistent with expectations, studies completed primarily in cell lines demonstrate that FGF5 overexpression influences stemness, metastatic potential, and proliferative capacity [98, 99, 101-105]. In human tumor samples, FGF5 levels correlate with tumor size, and tumor grade [99-101, 105]. FGF5 is often implicated in activating the MAPK signaling pathway to drive tumorigenesis [98, 99, 101, 104]. Findings from these studies may offer a basis for future directions where FGF5 can be investigated in relevant prostate cancer models. Given the relative newness in the identification of FGF5 overexpression in cancers, it is likely that targeted investigation of FGF5 will reveal diverse complexity in crosstalk and downstream signaling. Although our summary of functional studies in cancer models may not fully encompass what is known about FGF5, our goal is to draw attention to the broader therapeutic potential of targeting this ligand in cancer treatments.

Current FGF5/FGFR targeting strategies

Some studies have worked to disrupt the FGF5/FGFR signaling axis through targeting of the FGF5 ligand rather than its receptor(s). Though FGF5 is implicated as a potential drug target in multiple pathologies, there are currently no FDA approved therapeutics available that target this ligand. To date, the only treatments designed to reduce FGF5 activity remain in preclinical development and consist of RNA aptamers, modified siRNAs, miRNA delivery, and a synthetic decapeptide [22]. None of the therapeutic options for FGF5 targeting have progressed into clinical trials as of this review, and most existing work in preclinical animal models has been done in the context of male pattern baldness [106]. Additionally, the drugs previously developed for hair loss treatment were designed to be delivered topically or subcutaneously [22, 107]. This presents a fundamental restriction on the translatability of existing FGF5 inhibitors to cancer therapeutics in their current formulation. Here, we will briefly introduce some recent work identifying new therapeutic candidates for targeting FGF5.

RNA aptamers targeting FGF5

RNA aptamers are small structured single-stranded RNAs that function to bind specific targets with high affinity and specificity. Aptamers are emerging as promising therapeutics due to their selectivity, stability, low toxicity, low immunogenicity, and improved safety profiles [108]. A 2021 study described the development of a panel of RNA aptamers targeting FGF5 using Systematic Evolution of Ligands by Exponential enrichment (SELEX) and demonstrated functionality of the RNA aptamers with high affinity and specificity for FGF5 [109]. A pool of seven unique aptamers were assessed for specificity of binding to exogenous FGF5 and their ability to inhibit FGF5 induced cellular proliferation in NIH3T3 cells expressing FGFR1. Western blotting of pFGFR1 demonstrated dose-dependent inhibition of receptor phosphorylation that was not observed in random RNA controls. Binding affinity was evaluated by surface plasmon resonance (SPR) and the F5f1 aptamer variant was confirmed not to bind to FGF1, FGF2, FGF4, FGF6, or the extracellular domain of FGFR1; and was able to outcompete FGF5 for FGFR1. It was predicted that specificity of anti-FGF5 aptamers will reduce side effects compared to FGFR targeting drugs when used as therapeutic agents and will have broad applications in FGF5-associated cancers and hair loss [109].

MicroRNAs targeting FGF5

MicroRNAs (miRNAs) are also emerging targeted therapeutic in cancer as they are suspected to impact the initiation and progression of many cancer subtypes [110]. MiRNAs are non-coding single-stranded RNA molecules that are approximately 22 nucleotides long and regulate genes through sequence matching with target mRNA to inhibit protein expression [111, 112]. Identification of miRNAs and their targets offers new therapeutic candidates that can be modulated by exogenous delivery of miRNAs or anti-miRNA oligonucleotides (AMOs) [110]. Studies identifying direct modulation of *FGF5* through miRNAs in multiple cancer subtypes provide potential for effective delivery of miRNAs to decrease FGF5 activity.

Dysregulation of *miR-188-5p/FGF5* regulatory networks in Papillary Thyroid Carcinoma (PTC) was investigated to determine underlying mechanisms driving tumor progression. Low expression of *miR-188-5p* correlates with high expression of *FGF5* mRNA and protein in PTC cell lines and tumor compared to the normal thyroid samples. These cell lines were subsequently transfected to overexpress *miR-188-5p* and significant growth suppression was observed in response. 3'-UTR luciferase assays were used to confirm direct binding of *miR-188-5p* to *FGF5* mRNA in PTC cell lines, and silencing of *FGF5* by shRNA also yielded tumor-suppressive function in cell lines [113]. This indicates that delivery of exogenous *miR-188-5p* could be used to therapeutically target FGF5.

A separate study determined that *miR-567* regulates *FGF5* expression in osteosarcoma (OS). *FGF5* was predicted and validated as a direct target gene of *miR-567* by luciferase reporter assay. *miR-567* was found to be downregulated in OS tissues and in OS cell lines MG63, U2OS, and Saos-2 compared to controls. *In vitro*, transfection of OS cell lines with *miR-567* reduced cell viability and restricted migratory capacity and invasion of OS cells in a transwell assay. The inhibitory effects of miR-567 in OS cell lines were partially rescued by overexpression of *FGF5*. Together, this data implicates *miR-567* as a negative regulator of FGF5 and a potential therapeutic aimed at impacting FGF5 in treatment of OS [114].

Conclusion

There is extensive literature suggesting that FGFs and FGFRs play important roles in prostatic development and disease [14, 16, 104, 115, 116]. Specifically, the FGF5/FGFR signaling axis offers a new route for therapeutic investigation but remains understudied. In a range of other cancers, FGF5 overexpression has been reported, and studies indicate an oncogenic role for FGF5. Current literature introduces gene expression data suggesting a possible role for FGF5 in prostate development and PCa progression. Studies have found that *FGF5* may be a downstream Hh target in the stroma and a SOX2 target in tumor cells. However, functional studies are absent from this body of work and more research is required to determine if FGF5 is a candidate for PCa therapeutics. The field would benefit greatly from focused studies on FGF5 including meta-analysis of existing human datasets and mechanistic studies in relevant models of PCa to supplement published work on FGF5.

Given the pivotal roles that AR signaling plays in prostate development and disease, and the link between FGF5 and AR signaling first identified in skin based FGF5-KO models, it will be important to determine if a similar interaction occurs in the prostate. Moving forward, consideration of reputable and relevant model systems of PCa will be critical to properly evaluate the relationship between FGF5 and AR in PCa disease progression. Importantly, studies should not be limited to models of AR dependent PCa progression and should attempt to profile AR low/negative PCa models as well. More broadly, advancement of research into the discovery and development of FGF5 inhibitors is critical to move drug development past preclinical stages and provide strategies to alleviate the health burden of FGF5 related disease on affected populations.

Acknowledgements

We acknowledge support from U54DK104310.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. William A Ricke, Department of Urology, Wisconsin Institutes for Medical Research, No. 1111 Highland Avenue, Madison, WI 53705, USA. Tel: 608-265-3202; E-mail: rickew@urology.wisc.edu

References

[1] Gandaglia G, Leni R, Bray F, Fleshner N, Freedland SJ, Kibel A, Stattin P, Van Poppel H and La Vecchia C. Epidemiology and prevention of prostate cancer. Eur Urol Oncol 2021; 4: 877-892.

[2] Rawla P. Epidemiology of prostate cancer. World J Oncol 2019; 10: 63-89.

[3] Siegel RL, Miller KD, Wagle NS and Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023; 73: 17-48.

[4] Culig Z and Santer FR. Androgen receptor signaling in prostate cancer. Cancer Metastasis Rev 2014; 33: 413-427.

[5] Singh P, Uzgare A, Litvinov I, Denmeade SR and Isaacs JT. Combinatorial androgen receptor targeted therapy for prostate cancer. Endocr Relat Cancer 2006; 13: 653-666.

[6] Siegel DA, O'Neil ME, Richards TB, Dowling NF and Weir HK. Prostate cancer incidence and survival, by stage and race/ethnicity - United States, 2001-2017. MMWR Morb Mortal Wkly Rep 2020; 69: 1473-1480.

[7] Makino T, Izumi K and Mizokami A. Undesirable status of prostate cancer cells after intensive inhibition of ar signaling: post-AR era of CRPC treatment. Biomedicines 2021; 9: 414.

[8] Berry SJ, Coffey DS, Walsh PC and Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol 1984; 132: 474-479.

[9] Pinto JD, He HG, Chan SW and Wang W. Health-related quality of life and psychological well-being in men with benign prostatic hyperplasia: an integrative review. Jpn J Nurs Sci 2016; 13: 309-323.

[10] Strand DW, Costa DN, Francis F, Ricke WA and Roehrborn CG. Targeting phenotypic heterogeneity in benign prostatic hyperplasia. Differentiation 2017; 96: 49-61.

[11] Grino PB, Griffin JE and Wilson JD. Testosterone at high concentrations interacts with the human androgen receptor similarly to dihydrotestosterone. Endocrinology 1990; 126: 1165-1172.

[12] Loughlin KR. The clinical applications of five-alpha reductase inhibitors. Can J Urol 2021; 28: 10584-10588.

[13] Itoh N and Ornitz DM. Functional evolutionary history of the mouse Fgf gene family. Dev Dyn 2008; 237: 18-27.

[14] Giacomini A, Grillo E, Rezzola S, Ribatti D, Rusnati M, Ronca R and Presta M. The FGF/FGFR system in the physiopathology of the prostate gland. Physiol Rev 2021; 101: 569-610.

[15] Szybowska P, Kostas M, Wesche J, Haugsten EM and Wiedlocha A. Negative regulation of FGFR (fibroblast growth factor receptor) signaling. Cells 2021; 10: 1342.

[16] Xie Y, Su N, Yang J, Tan Q, Huang S, Jin M, Ni Z, Zhang B, Zhang D, Luo F, Chen H, Sun X, Feng JQ, Qi H and Chen L. FGF/FGFR signaling in health and disease. Signal Transduct Target Ther 2020; 5: 181.

[17] Hébert JM, Rosenquist T, Götz J and Martin GR. FGF5 as a regulator of the hair growth cycle: evidence from targeted and spontaneous mutations. Cell 1994; 78: 1017-1025.

[18] Sundberg JP, Rourk MH, Boggess D, Hogan ME, Sundberg BA and Bertolino AP. Angora mouse mutation: altered hair cycle, follicular dystrophy, phenotypic maintenance of skin grafts, and changes in keratin expression. Vet Pathol 1997; 34: 171-179.

[19] Zhao J, Lin H, Wang L, Guo K, Jing R, Li X, Chen Y, Hu Z, Gao S and Xu N. Suppression of FGF5 and FGF18 expression by cholesterol-modified siRNAs promotes hair growth in mice. Front Pharmacol 2021; 12: 666860.

[20] Lee KH, Choi D, Jeong SI, Kim SJ, Lee CH, Seo HS and Jeong HS. Eclipta prostrata promotes the induction of anagen, sustains the anagen phase through regulation of FGF-7 and FGF-5. Pharm Biol 2019; 57: 105-111.
[21] Burg D, Yamamoto M, Namekata M, Haklani J, Koike K and Halasz M. Promotion of anagen, increased hair density and reduction of hair fall in a clinical setting following identification of FGF5-inhibiting compounds via a novel 2-stage process. Clin Cosmet Investig Dermatol 2017; 10: 71-85.
[22] Facchinetti F, Hollebecque A, Bahleda R, Loriot Y, Olaussen KA, Massard C and Friboulet L. Facts and new hopes on selective FGFR inhibitors in solid tumors. Clin Cancer Res 2020; 26: 764-774.
[23] Wilkinson SE, Furic L, Buchanan G, Larsson O, Pedersen J, Frydenberg M, Risbridger GP and Taylor RA. Hedgehog signaling is active in human prostate cancer stroma and regulates proliferation and differentiation of adjacent epithelium. Prostate 2013; 73: 1810-1823.
[24] Shaw A, Gipp J and Bushman W. The Sonic Hedgehog pathway stimulates prostate tumor growth by paracrine signaling and recapitulates embryonic gene expression in tumor myofibroblasts. Oncogene 2009; 28: 4480-4490.
[25] Zhang R, Li Y, Jia K, Xu X, Li Y, Zhao Y, Zhang X, Zhang J, Liu G, Deng S and Lian Z. Crosstalk between androgen and Wnt/β-catenin leads to changes of wool density in FGF5-knockout sheep. Cell Death Dis 2020; 11: 407.
[26] Kregel S, Kiriluk KJ, Rosen AM, Cai Y, Reyes EE, Otto KB, Tom W, Paner GP, Szmulewitz RZ and Vander Griend DJ. Sox2 is an androgen receptor-repressed gene that promotes castration-resistant prostate cancer. PLoS One 2013; 8: e53701.
[27] Zhan X, Bates B, Hu XG and Goldfarb M. The human FGF-5 oncogene encodes a novel protein related to fibroblast growth factors. Mol Cell Biol 1988; 8: 3487-3495.
[28] Higgins CA, Petukhova L, Harel S, Ho YY, Drill E, Shapiro L, Wajid M and Christiano AM. FGF5 is a crucial regulator of hair length in humans. Proc Natl Acad Sci U S A 2014; 111: 10648-10653.
[29] Suzuki S, Ota Y, Ozawa K and Imamura T. Dual-mode regulation of hair growth cycle by two Fgf-5 gene products. J Invest Dermatol 2000; 114: 456-463.
[30] Goldfarb M, Bates B, Drucker B, Hardin J and Haub O. Expression and possible functions of the FGF-5 gene. Ann N Y Acad Sci 1991; 638: 38-52.
[31] Ajisaka K, Miyasato M, Ito C, Fujita Y, Yamazaki Y and Oka S. Linkage of sugar chains to a fragment peptide of FGF-5S by a chemoenzymatic strategy and changes in the rate of proteolytic hydrolysis. Glycoconj J 2001; 18: 301-308.
[32] Farrell B and Breeze AL. Structure, activation and dysregulation of fibroblast growth factor receptor kinases: perspectives for clinical targeting. Biochem Soc Trans 2018; 46: 1753-1770.
[33] Sarabipour S and Hristova K. Mechanism of FGF receptor dimerization and activation. Nat Commun 2016; 7: 10262.
[34] Furdui CM, Lew ED, Schlessinger J and Anderson KS. Autophosphorylation of FGFR1 kinase is mediated by a sequential and precisely ordered reaction. Mol Cell 2006; 21: 711-717.
[35] Del Piccolo N, Sarabipour S and Hristova K. A new method to study heterodimerization of membrane proteins and its application to fibroblast growth factor receptors. J Biol Chem 2017; 292: 1288-1301.
[36] Goetz R and Mohammadi M. Exploring mechanisms of FGF signalling through the lens of structural biology. Nat Rev Mol Cell Biol 2013; 14: 166-180.
[37] Eswarakumar VP, Lax I and Schlessinger J. Cellular signaling by fibroblast growth factor receptors. Cytokine Growth Factor Rev 2005; 16: 139-149.
[38] Kouhara H, Hadari YR, Spivak-Kroizman T, Schilling J, Bar-Sagi D, Lax I and Schlessinger J. A lipid-anchored Grb2-binding protein that links FGF-receptor activation to the Ras/MAPK signaling pathway. Cell 1997; 89: 693-702.
[39] Kanazawa S, Fujiwara T, Matsuzaki S, Shingaki K, Taniguchi M, Miyata S, Tohyama M, Sakai Y, Yano K, Hosokawa K and Kubo T. bFGF regulates PI3-kinase-Rac1-JNK pathway and promotes fibroblast migration in wound healing. PLoS One 2010; 5: e12228.
[40] Tan Y, Rouse J, Zhang A, Cariati S, Cohen P and Comb MJ. FGF and stress regulate CREB and ATF-1 via a pathway involving p38 MAP kinase and MAPKAP kinase-2. EMBO J 1996; 15: 4629-4642.
[41] Lamothe B, Yamada M, Schaeper U, Birchmeier W, Lax I and Schlessinger J. The docking protein Gab1 is an essential component of an indirect mechanism for fibroblast growth factor stimulation of the phosphatidylinositol 3-kinase/Akt antiapoptotic pathway. Mol Cell Biol 2004; 24: 5657-5666.
[42] Reilly JF, Mickey G and Maher PA. Association of fibroblast growth factor receptor 1 with the adaptor protein Grb14. Characterization of a new receptor binding partner. J Biol Chem 2000; 275: 7771-7778.
[43] Cross MJ, Lu L, Magnusson P, Nyqvist D, Holmqvist K, Welsh M and Claesson-Welsh L. The Shb adaptor protein binds to tyrosine 766 in

the FGFR-1 and regulates the Ras/MEK/MAPK pathway via FRS2 phosphorylation in endothelial cells. Mol Biol Cell 2002; 13: 2881-2893.
[44] Manning BD and Cantley LC. AKT/PKB signaling: navigating downstream. Cell 2007; 129: 1261-1274.
[45] Su WC, Kitagawa M, Xue N, Xie B, Garofalo S, Cho J, Deng C, Horton WA and Fu XY. Activation of Stat1 by mutant fibroblast growth-factor receptor in thanatophoric dysplasia type II dwarfism. Nature 1997; 386: 288-292.
[46] Heath C and Cross NC. Critical role of STAT5 activation in transformation mediated by ZNF198-FGFR1. J Biol Chem 2004; 279: 6666-6673.
[47] Dudka AA, Sweet SM and Heath JK. Signal transducers and activators of transcription-3 binding to the fibroblast growth factor receptor is activated by receptor amplification. Cancer Res 2010; 70: 3391-3401.
[48] Haugsten EM, Zakrzewska M, Brech A, Pust S, Olsnes S, Sandvig K and Wesche J. Clathrin- and dynamin-independent endocytosis of FGFR3--implications for signalling. PLoS One 2011; 6: e21708.
[49] Auciello G, Cunningham DL, Tatar T, Heath JK and Rappoport JZ. Regulation of fibroblast growth factor receptor signalling and trafficking by Src and Eps8. J Cell Sci 2013; 126: 613-624.
[50] Francavilla C, Rigbolt KT, Emdal KB, Carraro G, Vernet E, Bekker-Jensen DB, Streicher W, Wikström M, Sundström M, Bellusci S, Cavallaro U, Blagoev B and Olsen JV. Functional proteomics defines the molecular switch underlying FGF receptor trafficking and cellular outputs. Mol Cell 2013; 51: 707-722.
[51] Belov AA and Mohammadi M. Molecular mechanisms of fibroblast growth factor signaling in physiology and pathology. Cold Spring Harb Perspect Biol 2013; 5: a015958.
[52] Zhu X, Lee K, Asa SL and Ezzat S. Epigenetic silencing through DNA and histone methylation of fibroblast growth factor receptor 2 in neoplastic pituitary cells. Am J Pathol 2007; 170: 1618-1628.
[53] Goldstrohm AC, Greenleaf AL and Garcia-Blanco MA. Co-transcriptional splicing of pre-messenger RNAs: considerations for the mechanism of alternative splicing. Gene 2001; 277: 31-47.
[54] Yeh BK, Igarashi M, Eliseenkova AV, Plotnikov AN, Sher I, Ron D, Aaronson SA and Mohammadi M. Structural basis by which alternative splicing confers specificity in fibroblast growth factor receptors. Proc Natl Acad Sci U S A 2003; 100: 2266-2271.
[55] Wuechner C, Nordqvist AC, Winterpacht A, Zabel B and Schalling M. Developmental expression of splicing variants of fibroblast growth factor receptor 3 (FGFR3) in mouse. Int J Dev Biol 1996; 40: 1185-1188.
[56] Orr-Urtreger A, Bedford MT, Burakova T, Arman E, Zimmer Y, Yayon A, Givol D and Lonai P. Developmental localization of the splicing alternatives of fibroblast growth factor receptor-2 (FGFR2). Dev Biol 1993; 158: 475-486.
[57] Beer HD, Vindevoghel L, Gait MJ, Revest JM, Duan DR, Mason I, Dickson C and Werner S. Fibroblast growth factor (FGF) receptor 1-IIIb is a naturally occurring functional receptor for FGFs that is preferentially expressed in the skin and the brain. J Biol Chem 2000; 275: 16091-16097.
[58] Ornitz DM, Xu J, Colvin JS, Mcewen DG, Macarthur CA, Coulier F, Gao G and Goldfarb M. Receptor specificity of the fibroblast growth factor family. J Biol Chem 1996; 271: 15292-15297.
[59] Kornmann M, Lopez ME, Beger HG and Korc M. Expression of the IIIc variant of FGF receptor-1 confers mitogenic responsiveness to heparin and FGF-5 in TAKA-1 pancreatic ductal cells. Int J Pancreatol 2001; 29: 85-92.
[60] Kornmann M, Ishiwata T, Matsuda K, Lopez ME, Fukahi K, Asano G, Beger HG and Korc M. IIIc isoform of fibroblast growth factor receptor 1 is overexpressed in human pancreatic cancer and enhances tumorigenicity of hamster ductal cells. Gastroenterology 2002; 123: 301-313.
[61] Tian X, Chen G, Zhou S, Henne-Bruns D, Bachem M and Kornmann M. Interactions of pancreatic cancer and stellate cells are mediated by FGFR1-III isoform expression. Hepatogastroenterology 2012; 59: 1604-1608.
[62] Yan G, Fukabori Y, McBride G, Nikolaropolous S and McKeehan WL. Exon switching and activation of stromal and embryonic fibroblast growth factor (FGF)-FGF receptor genes in prostate epithelial cells accompany stromal independence and malignancy. Mol Cell Biol 1993; 13: 4513-4522.
[63] Kornmann M, Beger HG and Korc M. Role of fibroblast growth factors and their receptors in pancreatic cancer and chronic pancreatitis. Pancreas 1998; 17: 169-175.
[64] Seghezzi G, Patel S, Ren CJ, Gualandris A, Pintucci G, Robbins ES, Shapiro RL, Galloway AC, Rifkin DB and Mignatti P. Fibroblast growth factor-2 (FGF-2) induces vascular endothelial growth factor (VEGF) expression in the endothelial cells of forming capillaries: an autocrine mechanism contributing to angiogenesis. J Cell Biol 1998; 141: 1659-1673.
[65] Wang YC, Yu SQ, Wang XH, Han BM, Zhao FJ, Zhu GH, Hong Y and Xia SJ. Differences in phenotype and gene expression of prostate stromal cells from patients of varying ages and

their influence on tumour formation by prostate epithelial cells. Asian J Androl 2011; 13: 732-741.
[66] Knudsen BS and Vasioukhin V. Mechanisms of prostate cancer initiation and progression. Adv Cancer Res 2010; 109: 1-50.
[67] McNeal JE. Origin and evolution of benign prostatic enlargement. Invest Urol 1978; 15: 340-345.
[68] Bostwick DG and Egevad L. Prostatic stromal proliferations: a review. Pathology 2021; 53: 12-25.
[69] Devlin CM, Simms MS and Maitland NJ. Benign prostatic hyperplasia - what do we know? BJU Int 2021; 127: 389-399.
[70] Lee KL and Peehl DM. Molecular and cellular pathogenesis of benign prostatic hyperplasia. J Urol 2004; 172: 1784-1791.
[71] Soulitzis N, Karyotis I, Delakas D and Spandidos DA. Expression analysis of peptide growth factors VEGF, FGF2, TGFB1, EGF and IGF1 in prostate cancer and benign prostatic hyperplasia. Int J Oncol 2006; 29: 305-314.
[72] Yan G, Fukabori Y, Nikolaropoulos S, Wang F and McKeehan WL. Heparin-binding keratinocyte growth factor is a candidate stromal-to-epithelial-cell andromedin. Mol Endocrinol 1992; 6: 2123-2128.
[73] Jiang J and Hui CC. Hedgehog signaling in development and cancer. Dev Cell 2008; 15: 801-812.
[74] Ingham PW, Nakano Y and Seger C. Mechanisms and functions of Hedgehog signalling across the metazoa. Nat Rev Genet 2011; 12: 393-406.
[75] Bushman W. Hedgehog signaling in prostate development, regeneration and cancer. J Dev Biol 2016; 4: 30.
[76] Gonnissen A, Isebaert S and Haustermans K. Hedgehog signaling in prostate cancer and its therapeutic implication. Int J Mol Sci 2013; 14: 13979-14007.
[77] Berman DM, Desai N, Wang X, Karhadkar SS, Reynon M, Abate-Shen C, Beachy PA and Shen MM. Roles for Hedgehog signaling in androgen production and prostate ductal morphogenesis. Dev Biol 2004; 267: 387-398.
[78] Freestone SH, Marker P, Grace OC, Tomlinson DC, Cunha GR, Harnden P and Thomson AA. Sonic hedgehog regulates prostatic growth and epithelial differentiation. Dev Biol 2003; 264: 352-362.
[79] Lamm ML, Catbagan WS, Laciak RJ, Barnett DH, Hebner CM, Gaffield W, Walterhouse D, Iannaccone P and Bushman W. Sonic hedgehog activates mesenchymal Gli1 expression during prostate ductal bud formation. Dev Biol 2002; 249: 349-366.
[80] Yu M, Gipp J, Yoon JW, Iannaccone P, Walterhouse D and Bushman W. Sonic hedgehog-responsive genes in the fetal prostate. J Biol Chem 2009; 284: 5620-5629.
[81] Shaw A, Papadopoulos J, Johnson C and Bushman W. Isolation and characterization of an immortalized mouse urogenital sinus mesenchyme cell line. Prostate 2006; 66: 1347-1358.
[82] Sanchez P, Hernández AM, Stecca B, Kahler AJ, Degueme AM, Barrett A, Beyna M, Datta MW, Datta S and Ruiz i Altaba A. Inhibition of prostate cancer proliferation by interference with SONIC HEDGEHOG-GLI1 signaling. Proc Natl Acad Sci U S A 2004; 101: 12561-12566.
[83] Fan L, Pepicelli CV, Dibble CC, Catbagan W, Zarycki JL, Laciak R, Gipp J, Shaw A, Lamm ML, Munoz A, Lipinski R, Thrasher JB and Bushman W. Hedgehog signaling promotes prostate xenograft tumor growth. Endocrinology 2004; 145: 3961-3970.
[84] Housley DJ and Venta PJ. The long and the short of it: evidence that FGF5 is a major determinant of canine 'hair'-itability. Anim Genet 2006; 37: 309-315.
[85] Pethö-Schramm A, Müller HJ and Paus R. FGF5 and the murine hair cycle. Arch Dermatol Res 1996; 288: 264-266.
[86] Kehler JS, David VA, Schäffer AA, Bajema K, Eizirik E, Ryugo DK, Hannah SS, O'Brien SJ and Menotti-Raymond M. Four independent mutations in the feline fibroblast growth factor 5 gene determine the long-haired phenotype in domestic cats. J Hered 2007; 98: 555-566.
[87] Leirós GJ, Ceruti JM, Castellanos ML, Kusinsky AG and Balañá ME. Androgens modify Wnt agonists/antagonists expression balance in dermal papilla cells preventing hair follicle stem cell differentiation in androgenetic alopecia. Mol Cell Endocrinol 2017; 439: 26-34.
[88] Ceruti JM, Leirós GJ and Balañá ME. Androgens and androgen receptor action in skin and hair follicles. Mol Cell Endocrinol 2018; 465: 122-133.
[89] Leirós GJ, Attorresi AI and Balañá ME. Hair follicle stem cell differentiation is inhibited through cross-talk between Wnt/β-catenin and androgen signalling in dermal papilla cells from patients with androgenetic alopecia. Br J Dermatol 2012; 166: 1035-1042.
[90] Ito M, Yang Z, Andl T, Cui C, Kim N, Millar SE and Cotsarelis G. Wnt-dependent de novo hair follicle regeneration in adult mouse skin after wounding. Nature 2007; 447: 316-320.
[91] Kishimoto J, Burgeson RE and Morgan BA. Wnt signaling maintains the hair-inducing activity of the dermal papilla. Genes Dev 2000; 14: 1181-1185.

[92] Li WR, Liu CX, Zhang XM, Chen L, Peng XR, He SG, Lin JP, Han B, Wang LQ, Huang JC and Liu MJ. CRISPR/Cas9-mediated loss of FGF5 function increases wool staple length in sheep. FEBS J 2017; 284: 2764-2773.
[93] Zhang L, He S, Liu M, Liu G, Yuan Z, Liu C, Zhang X, Zhang N and Li W. Molecular cloning, characterization, and expression of sheep FGF5 gene. Gene 2015; 555: 95-100.
[94] Veltri A, Lang C and Lien WH. Concise review: Wnt signaling pathways in skin development and epidermal stem cells. Stem Cells 2018; 36: 22-35.
[95] Yu X, Cates JM, Morrissey C, You C, Grabowska MM, Zhang J, Degraff DJ, Strand DW, Franco OE, Lin-Tsai O, Hayward SW and Matusik RJ. SOX2 expression in the developing, adult, as well as, diseased prostate. Prostate Cancer Prostatic Dis 2014; 17: 301-309.
[96] Vellky JE and Ricke WA. Development and prevalence of castration-resistant prostate cancer subtypes. Neoplasia 2020; 22: 566-575.
[97] Heemers HV and Tindall DJ. Androgen receptor (AR) coregulators: a diversity of functions converging on and regulating the AR transcriptional complex. Endocr Rev 2007; 28: 778-808.
[98] Han D, Wang M, Yu Z, Yin L, Liu C, Wang J, Liu Y, Jiang S, Ren Z and Yin J. FGF5 promotes osteosarcoma cells proliferation via activating MAPK signaling pathway. Cancer Manag Res 2019; 11: 6457-6466.
[99] Ghassemi S, Vejdovszky K, Sahin E, Ratzinger L, Schelch K, Mohr T, Peter-Vörösmarty B, Brankovic J, Lackner A, Leopoldi A, Meindl D, Pirker C, Hegedus B, Marian B, Holzmann K, Grasl-Kraupp B, Heffeter P, Berger W and Grusch M. FGF5 is expressed in melanoma and enhances malignancy in vitro and in vivo. Oncotarget 2017; 8: 87750-87762.
[100] Allerstorfer S, Sonvilla G, Fischer H, Spiegl-Kreinecker S, Gauglhofer C, Setinek U, Czech T, Marosi C, Buchroithner J, Pichler J, Silye R, Mohr T, Holzmann K, Grasl-Kraupp B, Marian B, Grusch M, Fischer J, Micksche M and Berger W. FGF5 as an oncogenic factor in human glioblastoma multiforme: autocrine and paracrine activities. Oncogene 2008; 27: 4180-4190.
[101] Kornmann M, Ishiwata T, Beger HG and Korc M. Fibroblast growth factor-5 stimulates mitogenic signaling and is overexpressed in human pancreatic cancer: evidence for autocrine and paracrine actions. Oncogene 1997; 15: 1417-1424.
[102] Cazet AS, Hui MN, Elsworth BL, Wu SZ, Roden D, Chan CL, Skhinas JN, Collot R, Yang J, Harvey K, Johan MZ, Cooper C, Nair R, Herrmann D, McFarland A, Deng N, Ruiz-Borrego M, Rojo F, Trigo JM, Bezares S, Caballero R, Lim E, Timpson P, O'Toole S, Watkins DN, Cox TR, Samuel MS, Martín M and Swarbrick A. Targeting stromal remodeling and cancer stem cell plasticity overcomes chemoresistance in triple negative breast cancer. Nat Commun 2018; 9: 2897.
[103] Iwabu J, Yamashita S, Takeshima H, Kishino T, Takahashi T, Oda I, Koyanagi K, Igaki H, Tachimori Y, Daiko H, Nakazato H, Nishiyama K, Lee YC, Hanazaki K and Ushijima T. FGF5 methylation is a sensitivity marker of esophageal squamous cell carcinoma to definitive chemoradiotherapy. Sci Rep 2019; 9: 13347.
[104] Feng S, Shao L, Castro P, Coleman I, Nelson PS, Smith PD, Davies BR and Ittmann M. Combination treatment of prostate cancer with FGF receptor and AKT kinase inhibitors. Oncotarget 2017; 8: 6179-6192.
[105] Zhou Y, Yu Q, Chu Y, Zhu X, Deng J, Liu Q and Wang Q. Downregulation of fibroblast growth factor 5 inhibits cell growth and invasion of human nonsmall-cell lung cancer cells. J Cell Biochem 2019; 120: 8238-8246.
[106] Freshour SL, Kiwala S, Cotto KC, Coffman AC, McMichael JF, Song JJ, Griffith M, Griffith OL and Wagner AH. Integration of the drug-gene interaction database (DGIdb 4.0) with open crowdsource efforts. Nucleic Acids Res 2021; 49: D1144-D1151.
[107] Yue S, Li Y, Chen X, Wang J, Li M, Chen Y and Wu D. FGFR-TKI resistance in cancer: current status and perspectives. J Hematol Oncol 2021; 14: 23.
[108] Razlansari M, Jafarinejad S, Rahdar A, Shirvaliloo M, Arshad R, Fathi-Karkan S, Mirinejad S, Sargazi S, Sheervalilou R, Ajalli N and Pandey S. Development and classification of RNA aptamers for therapeutic purposes: an updated review with emphasis on cancer. Mol Cell Biochem 2023; 478: 1573-1598.
[109] Amano R, Namekata M, Horiuchi M, Saso M, Yanagisawa T, Tanaka Y, Ghani FI, Yamamoto M and Sakamoto T. Specific inhibition of FGF5-induced cell proliferation by RNA aptamers. Sci Rep 2021; 11: 2976.
[110] Tan W, Liu B, Qu S, Liang G, Luo W and Gong C. MicroRNAs and cancer: key paradigms in molecular therapy. Oncol Lett 2018; 15: 2735-2742.
[111] Macfarlane LA and Murphy PR. MicroRNA: biogenesis, function and role in cancer. Curr Genomics 2010; 11: 537-561.
[112] Kohlhapp FJ, Mitra AK, Lengyel E and Peter ME. MicroRNAs as mediators and communicators between cancer cells and the tumor microenvironment. Oncogene 2015; 34: 5857-5868.
[113] Zhou P, Irving A, Wu H, Luo J, Aguirre J, Costa M, Khamsuree M, Gerads N and Liu W. Va-

lidation of microRNA-188-5p inhibition power on tumor cell proliferation in papillary thyroid carcinoma. Cell Transplant 2020; 29: 963689720918300.
[114] Liu D, Zhang C, Li X, Zhang H, Pang Q and Wan A. MicroRNA-567 inhibits cell proliferation, migration and invasion by targeting FGF5 in osteosarcoma. EXCLI J 2018; 17: 102-112.
[115] Gowardhan B, Douglas DA, Mathers ME, Mckie AB, Mccracken SR, Robson CN and Leung HY. Evaluation of the fibroblast growth factor system as a potential target for therapy in human prostate cancer. Br J Cancer 2005; 92: 320-327.
[116] Lucia MS and Lambert JR. Growth factors in benign prostatic hyperplasia: basic science implications. Curr Urol Rep 2008; 9: 272-278.