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Secreted frizzled related protein 1 is a paracrine modulator of epithelial branching morphogenesis, proliferation, and secretory gene expression in the prostate

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Abstract

Previous in vitro studies identified *secreted frizzled related protein 1 (SFRP1)* as a candidate pro-proliferative signal during prostatic development and cancer progression. This study determined the in vivo roles of *SFRP1* in the prostate using expression studies in mice and by creating loss- and gain-of-function mouse genetic models. Expression studies using an *Sfrp1*^{lacZ} knock-in allele showed that *Sfrp1* is expressed in the developing mesenchyme/stroma of the prostate. Nevertheless, *Sfrp1* null prostates exhibited multiple prostatic developmental defects in the epithelium including reduced branching morphogenesis, delayed proliferation, and increased expression of genes encoding prostate-specific secretory proteins. Interestingly, over-expression of *SFRP1* in the adult prostates of transgenic mice yielded opposite effects including prolonged epithelial proliferation and decreased expression of genes encoding secretory proteins. These data demonstrated a previously unrecognized role for *Sfrp1* as a stromal-to-epithelial paracrine modulator of epithelial growth, branching morphogenesis, and epithelial gene expression. To clarify the mechanism of *SFRP1* action in the prostate, the response of WNT signaling pathways to *SFRP1* was examined. Forced expression of *SFRP1* in prostatic epithelial cells did not alter canonical WNT/β-catenin signaling or the activation of CamKII. However, forced expression of *SFRP1* led to sustained activation of JNK, and inhibition of JNK activity blocked the *SFRP1*-induced proliferation of prostatic epithelial cells, suggesting that *SFRP1* acts through the non-canonical WNT/JNK pathway in the prostate.
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Keywords: Prostate development; SFRP1; Non-canonical Wnt signaling; Branching morphogenesis; JNK; Knockout mice; Transgenic mice

Introduction

Organogenesis of the prostate is initiated by fetal androgens during embryonic development and includes extensive branching morphogenesis that results in the formation of a complex ductal–acinar gland residing at the base of the bladder (Marker et al., 2003). The prostate is also the site of two common male diseases, benign prostatic hyperplasia (BPH) and prostate cancer that arise in distinct anatomic regions of the prostate (McNeal, 1983). The organization of both the developing and adult prostate includes two tissue layers, the prostatic epithelium and a supporting mesenchyme/stroma. During development, reciprocal cell–cell signaling between the epithelium and the surrounding developmental mesenchyme coordinates several developmental processes, while in the adult reciprocal cell–cell signaling between the prostatic epithelium and surrounding stroma maintain gland architecture and function. In recent years,

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it has also become clear that abnormal stromal-to-epithelial signaling is an important part of cancer progression in the prostatic epithelium (Cunha et al., 2004).

Following an earlier study demonstrating that fibroblasts isolated from prostatic adenocarcinomas could promote prostate cancer progression in adjacent epithelia (Olumi et al., 1999), we identified *secreted frizzled related protein 1* (*SFRP1*) as a candidate stromal-to-epithelial paracrine signaling molecule over-expressed by cultured fibroblasts isolated from adenocarcinomas relative to cultured fibroblasts isolated from benign prostates (Joesting et al., 2005). Further evaluation of *SFRP1* expression using real-time RT-PCR in developing mouse prostates and in cultured human cell lines demonstrated that expression levels paralleled prostatic growth rates with high expression during developmental growth, low expression in normal adult mouse prostate, and high expression in tumorigenic prostatic cell lines and cultured fibroblasts from prostatic adenocarcinomas. Forced expression of *SFRP1* also increased proliferation in non-tumorigenic human prostatic epithelial cell lines. Collectively, these in vitro data identified *SFRP1* as a candidate pro-proliferative stromal-to-epithelial paracrine signal during prostatic development and cancer progression. However, the status and functional roles of *SFRP1* in the prostate in vivo remained untested.

In the mouse, prostatic development begins during late fetal stages, but most developmental growth, branching morphogenesis, and cellular differentiation occur between birth and reproductive maturity at approximately 5 weeks after birth. The prostate develops from the urogenital sinus (UGS), which arises by embryonic day 13 (e13) and remains morphologically ambisexual until around e17.5. At that time, androgen initiated and androgen dependent prostatic morphogenesis begins with the outgrowth of epithelial buds from the urogenital sinus epithelium (UGE) into the surrounding urogenital sinus mesenchyme (UGM). The epithelium initially invades the surrounding mesenchyme as solid epithelial cords that elongate within the UGM, bifurcate, and produce ductal side-branches to create a complex branched network of prostatic ducts (Risbridger et al., 2005; Sugimura et al., 1986). Branching morphogenesis is largely complete by 2 weeks after birth and ultimately gives rise to 3–4 bilaterally symmetrical prostatic lobes, each harboring a unique pattern of ductal branching (Hayward et al., 1996; Marker et al., 2003; Sugimura et al., 1986). During the initial phase of prostatic development, both the UGM and UGE are composed of undifferentiated cells. The epithelial cells forming the initial buds and elongating cords that invade the UGM co-express genes that later become restricted to specific differentiated cell types including cytokeratins 5, 8, 14, and 18 as well as p63 (Wang et al., 2001). As the epithelial cords mature into ducts containing a lumen, most epithelial cells differentiate into either luminal epithelial cells that express cytokeratins 8 and 18 or basal epithelial cells that express cytokeratins 5 and 14 as well as p63. Several minor epithelial cell populations are also present in maturing prostatic ducts including neuroendocrine cells, postulated transit amplifying cells, and candidate stem cells. As the prostate approaches reproductive maturity from 3–5 weeks after birth, luminal epithelial cells initiate expression of androgen-induced secretory proteins in a region-restricted manner in the adult prostate gland (Thielen et al., 2007).

Many years of genetic and experimental embryologic studies have investigated the roles of androgen signaling and epithelial–mesenchymal interactions in prostatic development. Androgens are necessary and sufficient to specify the UGS as prostate. This is shown by the absence of a prostate in Tfm mice that lack functional androgen receptors, and by the induction of a prostate in female UGSs treated with androgens (Brown et al., 1988; Cunha, 1975; He et al., 1994; Takeda et al., 1986) Experiments utilizing recombinant grafts of UGE and UGM from wild type and Tfm mice demonstrated the requirement for androgen receptor expression in the UGM, and not the UGE for prostatic bud induction and branching morphogenesis (Cunha and Lung, 1978; Donjacour and Cunha, 1993). These data led to the theory that one or more factors act in a paracrine fashion to stimulate prostatic development in the UGE. Several candidate paracrine factors expressed in the UGM such as FGF10 (Donjacour et al., 2003) and BMP4 (Lamm et al., 2001) have been investigated for their roles in prostatic development. However, known paracrine signals do not yet explain all of the paracrine interactions that have been inferred from experimental embryological studies. The initial data for *Sfrp1* in the prostate (Joesting et al., 2005) raised the possibility that it may also act as a paracrine regulator of epithelial development in the prostate.

Sfrp1 is one of 5 structurally related genes that encode secreted proteins homologous to the Frizzled receptors for WNT ligands (Rattner et al., 1997). SFRP1 has been reported to bind WNT ligands and modulate their signaling activity (Dennis et al., 1999; Uren et al., 2000). Expression studies using in situ hybridization demonstrated strong *Sfrp1* expression at developmental time points in the mouse kidney, heart, salivary gland, bone, teeth, and brain (Bodine et al., 2004; Esteve et al., 2003; Garcia-Hoyos et al., 2004; Jaspard et al., 2000; Leimeister et al., 1998). Despite this broad expression, experiments utilizing *Sfrp1* knockout mice have thus far revealed more anatomically restricted phenotypes in the developing bone (Bodine et al., 2004). In addition, experiments using double knockout mice for both *Sfrp1* and *Sfrp2* demonstrated a crucial but redundant role for these genes during early embryogenesis (Satoh et al., 2006). These previous studies did not report a detailed analysis of prostatic development in *Sfrp1* knockout mice.

In the present study, the roles of *SFRP1* in the prostate were determined through expression studies and by creating loss- and gain-of-function mouse models. *Sfrp1* was expressed in the developing mesenchyme of the mouse prostate. *Sfrp1* loss-of-function mutants exhibited multiple prostatic developmental defects including reduced branching morphogenesis, delayed proliferation, and increased expression of genes encoding prostate-specific secretory proteins while gain-of-function transgenics gave opposite effects including prolonged epithelial proliferation and decreased expression of genes encoding secretory proteins. Forced expression of *SFRP1* in cultured prostatic epithelial cells also led to sustained activation of JNK that was essential for *SFRP1*-induced epithelial proliferation, suggesting that SFRP1 acts through the non-canonical WNT/JNK pathway in prostatic epithelial cells.

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