Role of androgens and fibroblast growth factors in prostatic development

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This review focuses on the role of androgens and fibroblast growth factors (FGFs) in regulating the growth and development of the prostate. It is known that androgens and mesenchymal–epithelial interactions are required for the formation and growth of the prostate, but little is known of the molecular mediators regulating prostatic organogenesis. Paracrine signalling from the mesenchyme to the epithelium is a key element of prostatic development and the action of androgens in mesenchymal cells is essential for prostatic development. This finding has led to the hypothesis that androgens regulate the expression of paracrine-acting growth factors. Although several families of growth factors play a role in regulating prostatic growth, the FGF family contains members that have been studied most comprehensively in regard to prostatic growth and branching morphogenesis. The role of FGFs in prostatic development is described in detail, since two members of the FGF family function as mesenchymal paracrine-acting factors in the prostate. It has been shown that FGF7 and FGF10 play important roles during prostatic development but they do not appear to be regulated directly by androgens. Current models propose that growth factor expression (including FGF7 and 10) is regulated directly by androgens. However, it is possible that androgen regulation is indirect and a model outlining indirect androgen regulation of growth factors is proposed.

The prostate surrounds the urethra close to the base of the bladder and consists of a ductal acinar gland that is highly secretory. The earliest signs of formation of the prostate are observed at day 17 of embryonic development in mice, at day 18 in rats, and at approximately weeks 9–10 in humans (approximately 50 mm crown–rump length). In rodents, the prostate is subdivided into morphologically and biochemically distinct lobes that are named according to their anatomical position: anterior (also called coagulating gland), dorsal, dorso-lateral and ventral (Fig. 1). The human prostate does not show such discrete lobes, although it has been subdivided into three zones: central, peripheral and transitional (McNeal, 1980, 1983). The prostate is formed by the outgrowth of urogenital sinus epithelium into the surrounding urogenital sinus mesenchyme. The prostate epithelium is derived from the endoderm layer of the embryo, in contrast to Wolffian structures such as the seminal vesicle, vas deferens and epididymis that are derived from the mesoderm. The different origin of the tissues may have important implications for differences in mechanisms of growth between prostate and Wolffian derived organs, although both show androgen-dependent growth.

The prostate contains highly branched epithelial ducts that grow at their tips during development (Sugimura et al., 1986). The pattern of branching is subtly different within different prostatic lobes, but the mechanisms involved in these different branching patterns are unclear. It has been demonstrated that 80% of the ductal branching morphogenesis is complete by day 10 of neonatal life in mice (Donjacour and Cunha, 1988). There are biochemical differences in the secretions of the different prostatic lobes and these are specified by differences in the mesenchyme that induce the individual lobes (Hayashi et al., 1991). These mesenchymal differences may also be involved in the subtle differences in branching patterns between lobes. The distribution of prostatic mesenchyme in the day 0 reproductive tracts of male and female rats is shown (Fig. 1). Comparison of male and female reproductive tracts shows a similarity in the condensed mesenchyme in ventral areas (compare VP with VMP in Fig. 1), although females do not usually form a prostate (discussed in detail below). There may be similarities in the mechanism of branching morphogenesis in the prostate and that observed in other branched organs such as the mammary gland, lung, kidney and salivary gland. Branching morphogenesis has been studied extensively in the kidney and lung, but there appears to be only partial conservation of branching mechanisms or molecules. In the kidney, GDNF/c-Ret, HGF/c-met and Wnt family members have been studied in detail, but these do not appear to have been characterized...
in lung branching. Fibroblast growth factor (FGF) signalling in lung branching has been thoroughly characterized (Peters et al., 1994; Bellusci et al., 1997) and FGF7 appears to be involved in both lung (Post et al., 1996) and kidney development (Qiao et al., 1999). The lung and prostate may share some aspects of branching morphogenesis, but these do not extend to the kidney. For example, FGF10 regulates lung and prostate development, but does not play an extensive role in the kidney. Consequently, it is unclear whether there are conserved mechanisms regulating branching morphogenesis in all organs. It is possible that there are multiple conserved mechanisms, but only a subset of these is used in any particular type of organ.

Prostatic rudiments survive well in an in vitro organ culture system and this represents a highly tractable system in which to study basic mechanisms of prostatic growth and branching ductal morphogenesis.

Endocrinology

Androgens masculinize the reproductive tract during the ambisexual stage of development and lead to the formation of the prostate. Androgens are required to initiate prostatic development, to continue embryonic and neonatal prostatic growth, and subsequently to begin secretory activity at puberty. During adult life, androgens maintain the production of secretory proteins as well as maintaining the tissue architecture of the prostate. If androgens are removed, secretory activity ceases and the prostate regresses by apoptotic cell death (Isaacs et al., 1994). The concentrations of androgens are relatively high at the end of gestation, decrease 1 day after birth, remain low until puberty and increase to adult concentrations when the testes begin to synthesize large amounts of testosterone (Corpechot et al., 1981). During the course of development, the role of androgens may change. Androgens are required for prostatic development, growth and differentiation that occur during periods of relatively low serum androgen concentrations. Subsequently, androgens are required to initiate and regulate secretory activity as well as to maintain the gland during adult life. Indeed, throughout adult life androgen concentrations are high, yet cells in the prostate divide at a very low rate. Thus, there may be a change in the response to androgens between the low concentrations of androgens required for the growth and development of the prostate during embryonic and neonatal life and the high concentrations required for maintenance of function in adults. This potential change in response to androgens is very poorly defined or understood.

An important step in the function of testosterone is its conversion to 5α-dihydrotestosterone (DHT) by 5α-reductase. DHT is bound more efficiently by the androgen receptor and is thus a more potent androgen; impairment of 5α-reductase activity reduces but does not completely inhibit prostatic development (Imperato-McGinley et al., 1985). Androgens that cannot be converted to DHT will elicit the growth of prostatic rudiments in vitro (Foster and Cunha, 1999). This finding supports the idea that there is no absolute requirement for DHT in prostatic development (Imperato-McGinley et al., 1992), but it is likely that DHT is more effective in stimulating prostatic development.

Oestrogens administered during neonatal life exert many effects upon the growth and differentiation of the prostate. These effects might be due to the alteration of androgen concentrations via the hypothalamic–pituitary–gonadal axis or through direct effects upon the prostate. Oestrogen receptor α and β have been identified in cells of the prostate and the effects of oestrogen treatment on the neonatal prostate are well characterized (Prins, 1992; Prins et al., 1993). Although most studies have reported
Interactions between mesenchyme and epithelium

Mesenchymal–epithelial interactions play a key role in directing the growth and development of the prostate, and paracrine signalling from the mesenchyme to the epithelium is essential for prostatic development. In particular, the action of androgen in mesenchymal cells results in the proliferation of epithelial cells and this is presumed to be mediated by paracrine factors made by the mesenchyme. The identity of these factors is unknown although members of the FGF family are excellent candidates. Although paracrine signalling from the mesenchyme regulates epithelial proliferation and development, signalling also occurs in the other direction: from epithelium to mesenchyme. It is likely that epithelial signalling regulates differentiation of mesenchyme into ‘stroma’ composed of smooth muscle and fibroblasts (Hayward et al., 1996a). This has been demonstrated by the ability of different prostatic epithelia to elicit different patterns of stromal development (Hayward et al., 1998).

The role of mesenchymal–epithelial interactions in urogenital development has been studied extensively by Cunha and co-workers (Cunha and Chung, 1981) using tissue recombination methods. Tissue recombination studies involve the separation of organ rudiments into mesenchymal and epithelial constituents followed by re-association and grafting to a host to allow growth in vivo. This method can use tissue components from donors of different genetic backgrounds such as particular mouse strains or gene knockout lines. The Tfm mouse strain carries a mutation in the androgen receptor which inhibits its function (He et al., 1991) and results in a loss of prostatic development in individuals carrying the mutation (Quigley et al., 1995). Tfm males develop testes but not secondary sex accessory organs and show feminized external genitalia. Mesenchyme and epithelium from Tfm mice were used to examine the role of the androgen receptor in prostatic development using tissue recombination studies (Cunha and Chung, 1981). When tissue recombinants were made with epithelium lacking androgen receptor function (Tfm) and mesenchyme containing wild-type androgen receptor, prostatic tissue formed in the presence of androgens (Table 1). This finding demonstrates that androgen receptor is required in mesenchymal cells for prostatic development and that epithelial androgen receptor is not required. Furthermore, tissue recombinants containing epithelium from wild-type mice and mesenchyme from Tfm mice did not form prostatic tissue. This result demonstrates that androgen receptors are required in mesenchymal cells for development of the prostate and that epithelial androgen receptors are not sufficient for formation of the prostate.

Table 1. Development of prostate in recombination studies using wild-type and Tfm (lacking androgen receptor activity) tissues from mice

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<tr>
<th>Mesenchyme</th>
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<tr>
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<td>Wild-type</td>
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Taken together, these findings show that androgen receptor signalling in mesenchymal cells is both necessary and sufficient for prostatic development. The finding that prostatic development involves epithelial proliferation and differentiation has led to the hypothesis that there are mesenchymal paracrine-acting factors that are regulated by androgens. These androgen-regulated factors are not made in epithelial cells, despite the presence of the androgen receptor. In epithelial cells, the function of the androgen receptor is most likely the regulation of secretory proteins (Donjacour and Cunha, 1993) and perhaps epithelial differentiation.

The expression of the androgen receptor has been studied carefully to determine when and where it is expressed in the urogenital sinus and developing prostate. These studies have shown that the androgen receptor is first observed in mesenchymal cells, preceding the appearance of prostatic epithelial buds (Takeda et al., 1985). Once prostatic epithelial buds have formed and begun to develop, androgen receptor is observed in these growing epithelia (Hayward et al., 1996b). This finding supports the idea that prostatic induction is mediated by mesenchymal signals, since expression of the androgen receptor is restricted to the mesenchyme during prostatic induction and early growth. It is important to remember that the tissue recombination studies discussed above demonstrate that epithelial androgen receptor is not required for the induction and growth of the prostate. In contrast, epithelial androgen receptor is required for the expression of androgen dependent secretory molecules at later stages and possibly other elements of epithelial differentiation.

The andromedin hypothesis and androgen action

Since prostatic growth and development are regulated by the action of androgens in the mesenchyme, considerable effort has been directed at identifying paracrine-acting growth factors that could mediate the effects of androgens. At present, efforts are focused on known paracrine-acting factors to determine whether they are regulated by androgens. It has been assumed that paracrine factors are induced directly by the androgen receptor at the level of gene transcription, since the androgen receptor functions as a ligand-regulated transcription factor. However, the evidence demonstrating that androgens regulate epithelial...
development via mesenchymal androgen action does not prove that androgen-induced paracrine factors exist. The existence of androgen-regulated paracrine factors has been proposed as a hypothesis to explain how mesenchymal cells regulate epithelial cell development. It is possible that mesenchymal paracrine factors are produced constitutively and that androgens act via an indirect mechanism to control the activity or availability of these paracrine factors. Experimental evidence for androgenic regulation of known growth factors has produced conflicting data, particularly in regard to FGFs. At present, no growth factors expressed in mesenchyme have been shown, unequivocally, to be regulated directly by androgens.

Prostatic induction

Studies conducted 30–60 years ago examined the formation of a prostate in female rats (Mahoney, 1940) using either specifically inbred strains or species found in the wild (Shehata, 1972, 1975). The appearance of a prostate gland in females was probably due to the selection of strains that had abnormally high concentrations of androgens, although concentrations were not measured in most studies. The appearance of a prostate in females has also been documented in another rodent, Praomys (Mastomys) natalensis (Ghanadian et al., 1975, 1977). In these studies, the androgen concentrations were measured and it was demonstrated that females had lower serum concentrations of testosterone, but there were equal concentrations of testosterone in male and female prostate tissue. Furthermore, administration of androgens to female urogenital tracts in vitro led to prostatic budding (Takeeda et al., 1986). Taken together, these results indicate that the growth of a prostate in females is largely dependent upon androgens. However, surprisingly, females produce a condensate of mesenchyme (ventral mesenchymal pad, VMP) that is similar in function and anatomy to that found in males (shown in Fig. 1 and discussed below). The formation of this mesenchymal condensate is independent of androgens. It is clear that females have the capacity to form a prostate but that they do not do so because of a lack of androgens. This observation is of importance when considering how the prostate is induced since it is possible that females make prostatic inducing molecules constitutively, but that these are not ‘activated’ unless androgens are present. This is an alternative hypothesis to that discussed above, namely, that prostatic inducing molecules are regulated directly in response to androgens.

Spatially discrete regions of mesenchyme induce development of the separate prostatic lobes, since the lobes can be identified by their anatomy, morphology and different secretions (Sugimura et al., 1985). Thus, ventral prostate is induced by ventral mesenchyme and dorsal prostate is induced by dorsal mesenchyme (Hayashi et al., 1991). The mesenchyme involved in induction of the ventral prostate is condensed mesenchyme, which forms a distinct structure that is visible to the naked eye. The most defined inducing mesenchyme is that found in the VMP (Fig. 1), which induces the ventral prostate and lies ventral to the urethra (Timms et al., 1995). The VMP is formed in both males and females, yet only males develop a ventral prostate due to the action of androgens. The VMP forms in the absence of androgens and is present in both sexes. If androgens are administered to females, or the female VMP is grafted into a male host (with a heterologous epithelium), the female VMP will induce the development of a ventral prostate (Timms et al., 1995). The VMP appears to express FGF10 transcripts constitutively and FGF10 is a growth factor that acts as key regulator of prostatic growth (Thomson and Cunha, 1999). This finding raises the question of why females do not form a ventral prostate. A possible explanation is that although the FGF10 gene is expressed in both sexes there is an androgen-dependent mechanism involved in regulation of FGF10 signalling. This regulation could be via the control of FGF10 protein synthesis, distribution, activation or other steps in FGF10 signal transduction. The VMP forms in the absence of androgens (in females), thus it is important to understand how androgens regulate the prostatic inductive activity of the VMP. Currently, the functional evidence for mesenchymal induction does not distinguish between androgen-dependent factor expression or constitutive expression of growth factors and androgen regulation of their signalling activity.

Fibroblast growth factors in prostatic development

The fibroblast growth factor (FGF) family contains at least 23 proteins of conserved structure and sequence homology which regulate organogenesis in many tissues during embryogenesis (Hogan, 1999). Members of the FGF family play key roles in the development of several organs and tissues including limbs, lung, brain, hair follicles and keratinocytes. There are probably very few (if any) organs in which FGFs do not perform some developmental role. In limbs, FGFs 4, 8 and 10 are involved in initiating and maintaining limb outgrowth in a complex regulatory pathway with other growth factor families (Martin, 1998). In the lung, FGF signalling is essential for bronchial development and branching morphogenesis (Peters et al., 1994; Bellusci et al., 1997). Since FGFs are key regulators of organogenesis in general, it is not surprising that they function in prostatic organogenesis. FGF7, also known as keratinocyte growth factor (KGF), and FGF10 play important roles in the growth of the prostate, and it remains to be seen whether other members of the FGF family are also involved in prostatic regulation. There are four known FGF receptors (FGFR 1–4) that mediate FGF signalling. Each FGFR may mediate the signalling of two or more FGFs and this is accomplished by alternate splicing of FGF receptor genes. However, the receptor specificity for all FGFs is not yet known. In addition, heparan sulfate and other proteoglycans are a very important and underestimated component of FGF and other growth factor signalling pathways.
Androgens and FGFs in prostatic development

(Perrimon and Bernfield, 2000) and may be an essential part of FGF–FGFR interaction and specificity (Kan et al., 1999).

FGF7 regulates the growth of the ventral prostate (Sugimura et al., 1996) and seminal vesicle (Alarid et al., 1994). FGF7 functions as a paracrine regulator of growth since it is made by mesenchymal cells and acts upon epithelial cells. Mesenchymal cells make FGF7 but not its receptor (FGFR2iiib), whereas epithelial cells make the receptor FGFR2iiib but not FGF7. FGF7 protein is mitogenic for epithelia and stimulates development of the ventral prostate and seminal vesicle when added to serum-free organ cultures in vitro. Transcripts for FGF7 are abundant during the development of the ventral prostate and seminal vesicle in vivo and concentrations are greatest during periods of active growth (Thomson et al., 1997). Addition of an antibody to FGF7 partially inhibits the growth of the ventral prostate and seminal vesicle (in response to testosterone), indicating that FGF7 might be required for the growth of the prostate (Sugimura et al., 1996). However, deletion of FGF7 by gene knockout has not been reported to affect the formation of the male reproductive tract (Guo et al., 1996).

Fig. 2. In situ hybridization of FGF10 mRNA (shown in red) in rat embryonic urogenital tracts. Male (a) and female (b) reproductive tract in longitudinal section on embryonic day 20.5. In both cases FGF10 transcripts are restricted to mesenchyme in the ventral mesenchymal pad. (c,d) Male reproductive tracts in horizontal and transverse planes of section. Mesenchyme expressing FGF10 is observed distal to or surrounding elongating epithelial buds (identified by green arrowheads). MDE: Mullerian duct epithelium; SV: seminal vesicle; SvB: sino-vaginal bulb; UGE: urogenital epithelium; UGM: urogenital mesenchyme; UR: urethra; VMP: ventral mesenchymal pad; WD: Wolffian ducts. Scale bars represent 100 μm.

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It has been suggested that FGF7 functions as a mediator of androgen action or ‘andromedin’ (Peehl and Rubin, 1995). Studies on prostatic stromal cells grown in vitro indicated that FGF7 was upregulated directly by androgens (Yan et al., 1992). Conversely, studies in vivo showed that FGF7 mRNA was downregulated rather than upregulated in response to androgens (Nishi et al., 1996; Thomson et al., 1997). FGF7 mRNA content was inversely proportional to androgen concentrations in vivo and decreased in response to testosterone in organs grown in vitro (Thomson et al., 1997). Taken together these results indicate that FGF7 plays an important role in signalling between mesenchyme and epithelium in the prostate but that the FGF7 gene is not upregulated by androgens in vivo. This hypothesis is supported by studies of FGF7 protein distribution in the prostate, which showed a broad distribution of FGF7 and no significant changes in protein content after hormonal manipulation (Nemeth et al., 1998).

FGF10 plays an important role as a paracrine regulator of development of the ventral prostate and seminal vesicle (Thomson and Cunha, 1999). FGF10 transcripts were most abundant in neonatal ventral prostate and seminal vesicle, but were also detected in the lung, epididymis and skin. FGF10 mRNA content was highest during prenatal and neonatal periods of prostatic organogenesis and was low or absent in growth quiescent adult organs. Thus, FGF10 expression was considerably more restricted than that of FGF7 but was not prostate specific. In addition, high FGF10 mRNA content correlated well with periods of prostatic growth.

In both ventral prostate and seminal vesicle, FGF10 mRNA was observed in a small subset of mesenchymal cells by in situ hybridization. In the neonatal ventral prostate, FGF10 mRNA was restricted to mesenchymal cells peripheral to the peri-urethral mesenchyme and distal to the tips of elongating prostatic buds (Thomson and Cunha, 1999). At later stages, FGF10 mRNA was found in mesenchyme surrounding epithelial buds undergoing branching morphogenesis. The FGF10 gene was expressed in embryonic female urogenital sinus in the VMP. Expression of FGF10 mRNA during prostatic induction is shown (Fig. 2).

In a study of prostatic fibroblasts grown in vitro, FGF10 mRNA was observed to increase in response to testosterone (Lu et al., 1999). Consequently, these authors proposed FGF10 as an ‘andromedin’. However, in vivo, FGF10 mRNA content is inversely correlated with androgens and FGF10 mRNA is also observed in female embryos. Furthermore, in ventral prostate grown in vitro, FGF10 mRNA did not appear to be regulated by androgens (Thomson and Cunha, 1999) and thus it is unlikely that FGF10 is regulated directly by androgens.

Recombinant FGF10 protein stimulated the growth of prostatic epithelial cell lines, but did not stimulate the growth of a prostatic stromal cell line or primary seminal vesicle mesenchyme (Thomson and Cunha, 1999). Recombinant FGF10 also stimulated the development of ventral prostate organ rudiments grown in serum-free organ cultures (Fig. 3) and resulted in growth similar to that induced by FGF7 or testosterone. When both FGF10 and androgens were added to organs grown in vitro no synergism was observed, although it is possible that the response was limited by the in vitro system. Development induced by the addition of FGF10 could not be inhibited completely by the addition of an anti-androgen, indicating that the effect of FGF10 was not mediated by the androgen receptor. In conclusion, FGF10 functions directly as a paracrine regulator of prostatic growth and is expressed during the earliest periods of prostatic development.

FGF7 and FGF10 show a high degree of sequence homology, stimulate development of prostatic organ rudiments and are mitogenic for prostatic epithelia. The similarities between FGF7 and FGF10 might lead to the erroneous conclusion that they are functionally interchangeable or redundant. The difference in expression pattern between FGF7 and FGF10 transcripts may be significant. FGF7 transcripts are expressed diffusely throughout mesenchyme in most organs of the body (Mason et al., 1994; Finch et al., 1995), whereas FGF10 transcripts are restricted to a few organs and a subset of mesenchymal cells closely associated with growing epithelia (Bellusci et al., 1997; Thomson and Cunha, 1999). This difference in mRNA distribution may account for the differences observed between the phenotypes of FGF7 (Guo et al., 1996) and FGF10 null mice (Min et al., 1998; Sekine et al., 1999). Deletion of FGF10 by gene knockout resulted in a loss of several organs including the prostate and seminal vesicle (A. Donjacour, personal communication). This finding demonstrated that FGF10 is required for the formation of the prostate and thus FGF10 is the first mesenchymal gene known to be required for prostatic organogenesis. In contrast, deletion of the FGF7 gene did not lead to male reproductive organ agenesis, indicating that there was no absolute requirement for FGF7. It is possible that in the FGF7 null mouse, FGF10 was compensating for the loss of FGF7; however, it is clear that the converse was not true in the FGF10 null mouse (since FGF7 was not able to compensate for the loss of FGF10).
Other signals from mesenchyme or stroma

Although signals from the mesenchyme stimulate the development of the prostate, there may also be negative regulatory signalling from the mesenchyme or stroma. A well characterized growth inhibitor made by prostatic stroma is PS20 (Rowley et al., 1995; Larsen et al., 1998). PS20 was originally identified in conditioned medium from a prostatic mesenchymal cell line, and appears to be made by smooth muscle in many organs. Mesenchyme differentiates into smooth muscle, probably in response to signals from epithelia (Hayward et al., 1998). It is not known whether expression of PS20 is a consequence or cause of the differentiation of mesenchyme into smooth muscle. Little is known of the differentiation mechanism of mesenchyme into smooth muscle in the prostate, although this may have important effects on the nature or type of growth regulatory signals that are produced. For example, less differentiated cells (such as mesenchyme) may express growth stimulatory factors like FGF10, whereas smooth muscle cells might express growth inhibitors such as PS20 or molecules involved in homeostatic tissue interactions. Androgens might regulate the state of differentiation of the mesenchyme and stroma and consequently the growth of the prostate (see below and Fig. 4). This idea is similar to the hypothesis proposed by Nemeth and Lee (1996), in which localized areas of stroma perform different functions in regulating epithelia. The prostate grows from the tips of the epithelial cords and during prostatic regression it appears to recede from the tips backwards, possibly reversing the normal growth pattern.

Other factors that may play an important role in inhibiting prostatic growth are members of the transforming growth factor β (TGF-β) family. Members of the TGF-β family play a variety of roles in growth regulation and may either stimulate or inhibit growth, depending on the type of cell upon which they are acting (Peehl and Sellers, 1997). In the prostate, it appears that TGF-βs are made by both stromal and epithelial compartments, although it is likely that most TGF-βs are produced by epithelial cells.

Regulation of epithelial patterning

Although epithelial development is stimulated by mesenchymal signals, epithelial molecules may be important in the patterning and differentiation of the prostatic epithelia. These molecules include NKX3.1, HNF3 and members of the Hox10 and 13 families, which are all transcription factors and may regulate cell fate or the ability to respond to inducing signals from the mesenchyme. NKX3.1 is the earliest known marker of prostatic epithelia and may exert some control over epithelial mitogenesis, since deletion of the NKX3.1 gene resulted in prostatic hyperplasia in aging males (Bhatia-Gaur et al., 1999). Similarly, deletion of Hox D13 resulted in a reduction in prostatic size, whereas deletion of Hox A10 had an effect on only one prostatic lobe (Podlasek et al., 1997, 1999). Deletion of both Hox D13 and Hox A10 resulted in a severe phenotypic change consisting of a loss of male secondary sex organs including the prostate and Wolffian structures (Warot et al., 1997).

A model for prostatic induction and growth

It is clear that androgens regulate prostatic induction and that the action of androgens upon mesenchymal cells regulates epithelial growth. However, the molecular details of this pathway are unknown. It has been assumed that androgens induce paracrine-acting factors within the mesenchyme, but it is equally possible that these factors are expressed constitutively and that androgens regulate the activity of these factors indirectly. This proposal is supported by the observation that female embryos contain structures consisting of condensed mesenchyme in a position analogous to that in which the prostate forms in males. This condensed mesenchyme (for example the VMP) forms in the absence of androgens, yet is able to induce a prostate in the presence of androgens. Furthermore,
the VMP constitutively expresses transcripts for FGF10, a molecule shown to regulate prostatic growth. So how might androgens be involved in controlling the activity of FGF10 or other prostatic growth regulatory molecules? Androgens may regulate the distribution or activity of growth factors (rather than expression), or the rate at which ‘inductive’ mesenchyme differentiates into a ‘maintaining’ stroma (shown in Fig. 4). Androgens might stimulate prostatic organogenesis by delaying the differentiation of mesenchyme, resulting in continued expression of ‘inductive’ growth factors including FGF10. Signalling from the epithelium promotes the differentiation of mesenchyme into smooth muscle and fibroblasts, and it is possible that androgens regulate these signals or interact with this pathway to control differentiation.

It is well established that androgens are the key determinants of prostatic organogenesis and that it is the action of androgens upon mesenchymal cells that drives prostatic development. This led to the hypothesis that androgens might stimulate the production of mesenchymal paracrine-acting growth factors. FGF7 and FGF10 are currently the best characterized mesenchymal paracrine-acting growth factors in the prostate, yet neither appears to be regulated directly by androgens. It is possible that there are, as yet, unidentified growth factors that are regulated directly by androgens and which function as true ‘andromedin’. However, it is also possible that there are no such ‘andromedin’ or growth factors and that androgens regulate development via an indirect pathway to control cell differentiation and consequently growth factor expression (that is, androgens regulate growth factor expression indirectly by directing cellular differentiation). It is interesting to note that ‘prostatic inducing mesenchyme’ is present in both males and females, yet androgens facilitate prostatic development and thus only males develop a prostate. An important aim is to identify the full range of growth factors expressed in the prostate and determine which function as general growth regulators and which are specifically paracrine-acting mesenchymal factors. Once the latter group of factors has been identified, it will be possible to begin to unravel the mechanism of prostatic induction.

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