

The Role of Insulin-Like Growth Factors in Prostate Biology

Minireview

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Insulin-like growth factors (IGFs) are critical regulators of cell and tissue growth. Acting by endocrine as well as paracrine and autocrine mechanisms, the IGFs play unique roles in each organ or tissue. These unique roles of IGFs are in part mediated by the interrelated components of the greater IGF system, which includes IGF receptors, IGF-binding proteins (IGFBPs), receptors for IGFBPs, and IGFBP proteases (Cohick and Clemmons, 1993). The specific pattern of components present at any given time determines the overall impact of the IGFs at that specific site. Recently, we and others have become interested in characterizing the components of the IGF system in the prostate and in developing a model for the role of IGFs in normal prostate biology, in benign prostatic hyperplasia (BPH), and in prostate cancer. This minireview will summarize our present understanding of the IGF system in the prostate; current data suggest that IGFs are important elements in the development of BPH and cancer.

IGF System in the Epithelium

Initial studies have focused on the use of *in vitro* cell cultures in order to characterize the expression of IGF elements separately in each cellular compartment of the prostate. Such studies using primary cultures suggest that prostatic epithelial cells, whether from normal, BPH, or malignant tissues, do not synthesize or secrete significant

amounts of either IGF-I or-II (Cohen et al, 1991). However, Pietrzkowski et al (1993) reported that the established prostate cancer cell lines PC-3, DU 145, and LNCaP secrete IGF-I. Whether these different results reflect the metastatic origin of the established cell lines or are related to long-term culture of the lines is not known at this time. It is possible that IGF production is not a significant function of epithelial cells in the prostate, but may become a more prominent feature of cancer cells at metastatic sites.

Regardless of the extent of IGF secretion by prostatic epithelial cells, all, regardless of origin, express the type-I IGF receptor and respond to the mitogenic activity of IGFs (Cohen et al, 1991; Iwamura et al, 1993). In fact, IGF is a critical growth factor, and, even in the presence of other required mitogens, proliferation of prostatic epithelial cells does not occur in its absence (Cohen et al, 1991). This fact suggests that strategies to block the action of IGF may be therapeutic for prostate cancer and/or BPH.

The interaction of IGF with its receptor is the crux of its mitogenic action. However, the possibility of this interaction occurring depends not only on the presence of IGF and its receptor, but also on other components of the IGF system. Six related IGFBPs have been identified, and each may inhibit or enhance IGF mitogenic activity (Cohick and Clemmons, 1993). Inhibition versus enhancement is not necessarily intrinsic to a given IGFBP, but may depend on other factors. Prostatic epithelial cells express IGFBP-2 and-4 (Cohen et al, 1991) and possibly IGFBP-3 (Birnbaum et al, 1994) but not IGFBP-1. More recently identified IGFBPs,-5 and-6, have not been extensively investigated in the prostate.

IGFBPs have affinity for IGFs and inhibit or enhance IGF activity by modulating the availability of IGFs for the type-I IGF receptor. Recently, receptors for IGFBP-3 itself have been identified (Oh et al, 1993b). Furthermore, the effect of IGFBP-3 having bound to its receptor on breast cancer cells was to inhibit growth, independent of any interaction with IGFs (Oh et al, 1993a). The discovery of IGFBP-3 receptors adds a new element of complexity to the IGF system. It is not known if other IGFBPs also have their own receptors, or if IGFBP receptors are present on prostate cells.

Another component of the IGF system that may be particularly relevant to IGF action in the prostate is IGFBP

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proteases. Proteolytic cleavage of IGFbps reduces the affinity of the IGFbps for IGFs (Cohick and Clemmons, 1993). If the intact IGFbp prevented the interaction of IGF with its receptor, then proteolytic cleavage of the IGFbp would release IGF, permitting greater interaction of IGF and its receptor and increased mitogenic activity.

Prostate-specific antigen (PSA) cleaves IGFbp-3 (Cohen et al, 1992). The biological consequences of proteolytic cleavage of IGFbp-3 by PSA were clearly illustrated using cultured prostatic epithelial cells (Cohen et al, 1994b). In a serum-free growth assay, IGF was required for proliferation. The addition of IGFbp-3 blocked IGF-induced proliferation. The addition of PSA restored proliferation by cleaving IGFbp-3 and freeing IGF for interaction with its receptor.

IGF System in the Stroma

In contrast to the findings with primary cultures of prostatic epithelial cells, cultured prostatic stromal cells produce readily detectable levels of IGF-II, but not IGF-I (Cohen et al, 1994a). Like prostatic epithelial cells, stromal cells also have type-I IGF receptors and are therefore presumably responsive to the mitogenic activity of IGF-I or-II, although this has not been reported. IGF-II, then, could have autocrine stimulatory activity on the cells of origin in the stroma, or paracrine activity on the epithelium.

Also similar to epithelial cells, prostatic stromal cells secrete IGFbp-2 and-4, and they definitely make IGFbp-3 as well (Cohen et al, 1994a). This pattern of expression is typical only of cultured stromal cells derived from normal or malignant tissues, however. Stromal cells derived from BPH have dramatically decreased expression of IGFbp-2 and detectable levels of IGFbp-5 (which is not significantly expressed by normal or cancer-derived stromal cells) (Cohen et al, 1994a).

IGF System in BPH

During our studies of the IGF system in cultured prostatic stromal cells, we noted several differences between cells derived from BPH versus those derived from normal tissues or adenocarcinomas (Cohen et al, 1994a). The different pattern of expression of IGFbps was described in the preceding section of this minireview. We also observed that BPH stromal cells had higher levels of IGF-II transcripts compared to normal or cancer-derived cells, and that type-I IGF receptor levels were also elevated.

Based on these findings, we have generated a model that suggests that these abnormalities in the IGF system have an important role in the etiology of BPH (Peehl et al, 1995). The numerous aberrations in several elements of the IGF system indicate the possibility of a defect in a key transcription factor that may regulate these separate but interrelated elements. The presence of this defect and

the resulting abnormalities in the stroma, but not the epithelium, support the hypothesis for the stromal origin of BPH (McNeal, 1990). The model suggests that a transcription defect leads to overproduction of the growth factor IGF-II and its receptor in stromal cells. This is accompanied by a loss of expression of IGFbp-2, which generally is reported to inhibit IGF activity, and increased expression of IGFbp-5, which may enhance IGF activity. These changes could lead to increased growth of both the stroma, in an autocrine manner, and the epithelium, in a paracrine manner.

Cancer and the IGF System

No qualitative or quantitative differences in any elements of the IGF system have been detected among epithelial or stromal cells cultured from normal versus malignant prostatic tissues. Expression of IGF-I or IGFbp-3 by established prostate cancer cell lines may distinguish the lines from primary cultures, but the significance of this is not known.

One aspect of the IGF system that has been associated with prostate cancer is changes in the IGFbp pattern in sera. Elevated levels of IGFbp-2 and decreased levels of IGFbp-3 were measured in the sera of patients with prostate cancer (Cohen et al, 1993; Kanety et al, 1993). Increased levels of IGFbp-2 were correlated with increased PSA in the sera, and it is likely that IGFbp-2, like PSA, is abnormally leaked into the circulation from malignant prostate tissue. Decreased levels of IGFbp-3, however, are presumably due to proteolysis, because cleavage fragments of IGFbp-3 were found in the sera. The cleavage fragments did not concur with the pattern of fragments generated by PSA, and in any case PSA is bound by inhibitors in serum and is not enzymatically active. Some other unknown proteolytic activity associated with prostate cancer is apparently responsible for the cleavage of IGFbp-3.

Although PSA is inactive in serum, PSA may be active at the site of secretion from prostate cells. In a previous section of this review, evidence was presented for the proteolysis of IGFbp-3 by PSA, and studies demonstrating that cleavage of IGFbp-3 by PSA led to increased mitogenic activity of IGF were described. In normal prostatic tissues, PSA is confined to the lumina of epithelial acini. Cleavage of IGFbp-3 by PSA and release of IGF at this site may be biologically insignificant, because normal luminal cells in the immediate area are seemingly terminally differentiated and incapable of proliferation. In malignant tissue, in contrast, the acinar arrangement of normal glands is lost, and PSA may leak into the surrounding stroma. If PSA cleaved IGFbp-3 and released free IGF at this location, IGF could have direct mitogenic activity on the prostate cancer cells in the area. A similar scenario could occur at metastatic sites. In this way, the

inappropriate release of a protease (PSA) may indirectly result in enhanced growth factor activity in prostate cancer.

PSA may also link IGF and androgen growth-regulatory systems. Although there is little evidence yet for androgenic stimulation of IGFs, IGFs, or IGF receptors, PSA expression is stimulated by androgen. Increased levels of PSA induced by androgen would indirectly result in increased free IGF and increased mitogenic activity. Indirectly, IGF may be a mediator of androgen-stimulated growth.

Summary

Characterization of the IGF system in cultured prostatic epithelial and stromal cells has established a model for the biological role of IGFs in the prostate. The specific components of the IGF system differ between the stroma and the epithelium, and they may differ among normal, BPH, and malignant tissues. Abnormalities in the IGF system that have been observed in stromal cells derived from BPH may provide a basis for the etiology of BPH and for new therapeutic strategies. Several abnormalities in the IGF system, including increased IGFBP-2 and decreased IGFBP-3 in sera, may be associated with prostate cancer. Furthermore, PSA may cause increased mitogenic activity of IGF by cleavage of IGFBP-3 in local areas surrounding prostate cancer at either primary or metastatic sites. Future studies will aim to validate these models *in vivo* by *in situ* hybridization, immunohistochemistry, and other techniques.

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