

New Doctorial Cancer Research

Novel Animal Models to Study the Role of the Growth Hormone Insulin-like Growth Factor I Axis in Prostate Cancer



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Prostate cancer is the most common of any nonskin cancer in the human body. Some recent clinical and epidemiologic studies suggest that the growth hormone/insulin-like growth factor-I (GH/IGF-I) axis may influence prostate carcinogenesis. The purpose of this dissertation study was to establish the first animal models to directly test the hypothesis that a normal, functional GH/IGF-I axis is required for prostate cancer progression.

The Tag/*Ghr*^{-/-} mouse model was established by crossing the GH receptor (GHR) knockout mouse with the C3(1)/Tag mouse, which harbors the large T antigen (Tag) driven to expression in the prostate by the 5-flanking region of the rat C3(1) gene. All progeny carried one allele of Tag and was homozygous for the wild type GHR or null for GHR. Results from this new model showed that progression of prostate cancer from Tag-initiated epithelial cells to prostate intraepithelial neoplasia (PIN) was significantly inhibited in the absence of GHR (incidence of PIN, 70% and 62.5% decrease in dorsal lateral and ventral prostate, $P < 0.01$; multiplicity of PIN, 28% and 26% decrease in dorsal lateral and ventral prostate, $P < 0.05$). Disruption of the GHR gene did not alter the expression of Tag oncogene, prostate androgen receptor, or serum testosterone titers. Cancer inhibition appears to be associated with decreased proliferation and increased apoptosis of the prostate epithelium of Tag/*Ghr*^{-/-} mice. The findings suggest that PIN may require GH signaling for progression.

Tag/*Gh*^{dr/dr} rat model, which was established by crossing the spontaneous dwarf rat with the Probasin/Tag rat, demonstrated that prostate cancer progression induced by Tag was significantly inhibited in the absence of GH signaling. The prostate tumor incidence was significantly reduced and tumor latency was delayed in Tag/*Gh*^{dr/dr} relative to Tag/*Gh*^{+/+} controls. Also, the tumor burden was significantly reduced in Tag/*Gh*^{dr/dr}. At 25 weeks of age, loss of GH resulted in a 20% and 80% decrease ($P < 0.05$ and $P < 0.0001$) in the area of microinvasive carcinoma in the dorsal and lateral lobes, respectively. By 52 weeks of age, the invasive prostate adenocarcinomas were observed in 100% of Tag/*Gh*^{+/+} rats with metastasis found in pelvic lymph nodes and mammary glands, while the majority of Tag/*Gh*^{dr/dr} (60%) did not develop invasive tumors. This inhibition is not due

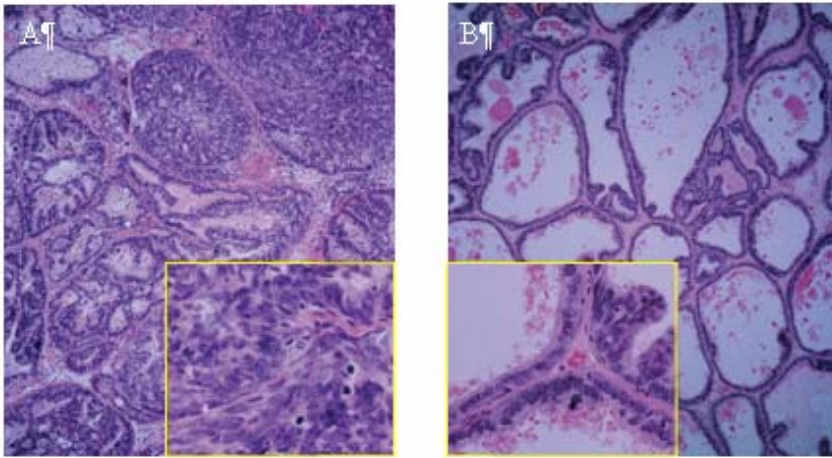


FIGURE 1. Representative H&E-stained sections of LP from 25-week-old Tag/*Gh*^{+/+} and Tag/*Gh*^{dr/dr} rats. **(A)** an example of high-grade PIN and microinvasive carcinomas in Tag/*Gh*^{+/+} rats. **(B)** Normal epithelium and PIN in Tag/*Gh*^{dr/dr}, which was the predominant phenotype in this rat. Original magnification for panels A and B was 10 × and the inserts, which highlight areas within the larger panels, was 40 ×.

to insufficient Tag expression or altered androgen signaling in Tag/*Gh*^{dr/dr} relative to Tag/*Gh*^{+/+} rat. Rather, cancer inhibition in Tag/*Gh*^{dr/dr} appears to be associated with the loss of prostate GHR, which is inhibiting the proliferation pathway, and the increase of prostate IGF-1R, which is inducing a differentiation pathway that suppresses the malignant phenotype. The findings suggest that an intact GH signaling may be required for progression from latent to malignant prostate cancer. The GH/IGF axis may represent important targets for the development of agents against prostate cancer.

Comment by Gail S. Prins
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Zhuohua Wang was able to combine two genetically engineered mouse and rat models to yield rodents that carried one allele of the large T antigen (Tag) targeted for expression in the prostate with growth hormone signaling either normal or inhibited by lack of the hormone itself (rat model) or the receptor (mouse model). This work is significant on several levels. First, the results suggest that both indolent and aggressive prostate cancers respond to downregulation of growth hormone signaling in a manner that is independent of either serum testosterone levels or androgen receptor, two proteins that are already targeted by therapies used in the clinic. Therefore, anti-GH therapies might be effective

against androgen-independent prostate cancers, for which few treatment modalities are available. Second, the observation that the prostate GH receptor is upregulated while the IGF-I receptor is downregulated indicates that GH may directly effect prostate carcinogenesis in this model. Finally, an FDA-approved anti-GH medication (pegvisomant) is currently on the market, suggesting that the findings of this dissertation could be rapidly translated into the clinic.