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Consideration`s on Prostate Cancer Mouse Models. What's New?

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Abbreviations: PCa: Prostate Cancer; GEM: Genetically Engineered Mouse; PIN: Prostatic Intraepithelial Neoplasia; RP: Radical Prostatectomy

Introduction

The advances in prostate cancer (PCa) cure invariably pass through the knowledge of its biology; the development of translational models would allow researchers to find new treatment options. A large number of studies have been performed with human prostate cancer cell lines, such as LNCaP, Du145, or PC-3 to gain insight into the biology of tumor progression, androgen-independent disease, and metastatic prostate cancer and to test new therapies [1]. Besides the obvious limitations of the in vitro studies, these lines do not allow to replicate the different stages of the human disease being derived from advanced/metastatic tumors. In addition, their transplantation in xenograft models do not mimic the heterogeneity of human tumors and their microenvironment, and require immune deficient host animals, that lack crucial modulators of tumor genesis.

These major limitations prompted the development of animal models of prostate cancer. In this context, mice have been definitively the most widely used animals thanks to their 95% homology with human genome, their adaptability to laboratory conditions, and relatively low costs. Even though the gross anatomy of the mouse prostate differs from that of the human prostate, the prostate of both species are made of glands and ducts of similar organization [2].

Discussion

In the last decades, several mouse models of PCa have been developed, studied and characterized [3]. The first generation of genetically engineered mouse (GEM) models utilized the newly discovered and characterized probasin promoter driving viral oncogenes such as Simian virus 40 large T antigen. With the second generation of models, single and multiple molecular changes observed in human disease, such as loss of Pten and over expression of Myc have been incorporated. These models and their application have provided vital information for understanding the biology of PCa initiation, progression, and treatment modalities [4].

Another advantage of using GEM models of PCa is that the disease progresses in a shorter-lived, immune competent host within a genetically homogeneous animal population allowing for well controlled temporal observations on the effect of gene manipulations and drug treatments. Despite the first models displayed some neuro-endocrine characteristics [5-7], today a wide number of cancer promoters have been driven such as Pten, Myc etc. The increased knowledge of genetic changes in human PCa allows to precisely addressing GEMs toward a human-like adenocarcinoma of the prostate [8]. Hill and colleagues showed a prostate cancer mouse model based on the loss of the proteins of the Rb family (Rb/p107/p130) and Pten. The first leads to the progression to a prostatic intraepithelial neoplasia (PIN) lesions. The latter, yields` to proper prostate adenocarcinoma characteristics [9]. Other pathways such as the expression of Tag or nuclear β-Catenin are linked to m PIN development while the activation of both Tag and the Wnt/β-Catenin pathway resulted in invasive prostate adenocarcinoma as demonstrated by Yu et al. [10]. Also, Foxa2, a forkhead transcription factor, was induced by active Wnt/β-Catenin signaling; and the expression of Foxa2 was associated with the invasive phenotype in the primary PCa [10].

Proper preclinical models with an intact immune system and an orthotopic onset of the tumor are essential for translational oncological studies and establishing innovative anticancer therapies. However, the proper setting to set new post-surgical therapy has not yet been reproduced in vivo. In particular, the lack of preclinical models of radical prostatectomy (RP) deserves notice in translational research, since RP represents one of the most widely used primary treatment for PCa. The absence of models in this context can be partially justified by the more complex anatomy

of the mouse prostate compared to the human one [11] along with the difficulty of preserving the urinary function after the surgery. We recently presented the first model of RP in the mouse. Precisely, we were able to completely remove prostate and seminal vesicles in living mice with and without PCa. A definitive cystostomy was performed at the end of the operation to guarantee the bladder outflow. After a close evaluation of the health conditions, the majority of the mice reached the end of the observation, reporting the 75% survival rate after 3 months [12].

This work represents an absolute novelty in the field of PCa modeling. To date none reproduced in a preclinical setting the conditions of a RP. This model opens to the scientific community new opportunities of research to further study PCa disease.

Conclusion

Prostate cancer disease is one of the main fields of interest for urooncologists. Over the year several models have been presented increasing our knowledge on PCa genetics. The study of these models prompted to the need of the surgical model for PCa recently presented.

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