MOLECULAR ONCOLOGY 7 (2013) 190–205

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Review

Genetically engineered mouse models of prostate cancer

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ARTICLE INFO

Article history:
Received 21 January 2013
Accepted 6 February 2013
Available online 14 February 2013

Keywords:
Transgenic
Knock-out
Conditional somatic mutagenesis
Cre
Androgen
Stem cells

ABSTRACT

Despite major improvement in treatment of early stage localised prostate cancer, the distinction between indolent tumors and those that will become aggressive, as well as the lack of efficient therapies of advanced prostate cancer, remain major health problems. Genetically engineered mice (GEM) have been extensively used to investigate the molecular and cellular mechanisms underlying prostate tumor initiation and progression, and to evaluate new therapies. Moreover, the recent development of conditional somatic mutagenesis in the mouse prostate offers the possibility to generate new models that more faithfully reproduce the human disease, and thus should contribute to improve diagnosis and treatments. The strengths and weaknesses of various models will be discussed, as well as future opportunities.

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1. Introduction

Prostate cancer is the most common malignant visceral neoplasm in males in Western societies and the second leading cause of cancer-related deaths in these populations (Bray et al., 2010; Ferlay et al., 2010; Jemal et al., 2010; Siegel et al., 2012). It is a multistage disease that develops during decades; even though men in their 20s can display preneoplastic lesions called prostatic intraepithelial neoplasia (PIN), clinically detectable prostate cancer usually appears after the fifth decade. Its etiology remains largely unknown and its clinical course unpredictable. In western world 1 man in 6 will be diagnosed with this disease during his lifetime. If detected at early stages when locally confined, prostate cancer is eradicated in 70–80% of the patients by radical prostatectomy, radiation therapy or cryotherapy (Siegel et al., 2012). Unfortunately, around 5 years after primary treatment, the remaining 20–30% develop metastasis, mainly in bone, as well as in liver, lung and adrenal glands. Relapses can be managed efficiently only for a limited time period by targeting the androgen–androgen receptor (AR) axis through androgen ablation therapy and/or androgen receptor (AR) antagonists (castration) (Bubendorf et al., 2000; Denmeade and Isaacs, 2002). These treatments are not curative, and ultimately lead to the recurrence of highly aggressive tumors. Following the emergence of castrate-resistant prostate cancer, docetaxel chemotherapy has been shown to be therapeutically efficacious, but the median increase in survival was only 4 months (Petrylak et al., 2004; Singh et al., 2010). Serum prostate specific antigen (PSA) is widely used as a biomarker for prostate cancer detection, but does not predict whether tumors will remain indolent or become clinically aggressive. Large scale clinical

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http://dx.doi.org/10.1016/j.molonc.2013.02.005

Table 1 – Common transcriptional regulatory elements used to drive transgene expression in the mouse prostate.

Promoter	Expression	Ectopic expression	Reference
Rat C3(1)	VP > DP	Seminal vesicles, testis, thyroid and salivary gland, cartilage.	(Allison et al., 1989; Maroulakou et al., 1994; Zhang et al., 1997, 2000b)
−426 bp to +28 bp rat probasin	VP > DLP, AP (starts before puberty)	Seminal vesicles	(Greenberg et al., 1995, 1994)
−11.5 kb to +28 bp rat probasin	VP > LP > DP > AP (starts before puberty)	Seminal vesicles	(Yan et al., 1997)
ARR_2PB	VP, DLP > AP (starts in newborn mice)	Prostate stroma, seminal vesicles, testis	(Wu et al., 2001; Zhang et al., 2000a)
6 kb PSA	LP > DP > VP, AP (starts at puberty)	None reported	(Cleutjens et al., 1997)

studies indicate that systematic use of this marker leads to many unnecessary transrectal prostatic needle biopsies, over diagnosis and over treatment with severe side effects on patients and increased costs for healthcare systems (Schroder et al., 2012; Whitson and Carroll, 2010). Thus, there is an urgent need for improvements in both diagnosis and therapy for prostate cancer.

The human prostate is a glandular organ composed of central, peripheral and transitional zones that are not clearly demarcated. The three zones contain acini located within a fibromuscular stroma. Acini are formed by columnar epithelial cells which secrete prostatic proteins and fluids from their apical surfaces into a lumen, and are surrounded by basal cells attached to the basement membrane and scattered neuroendocrine cells. PIN lesions are formed by cells that proliferate within the prostatic epithelium and disrupt its well-defined architecture (Bostwick and Qian, 2004; McNeal and Bostwick, 1986; McNeal et al., 1986; Timms, 2008). They are graded according by their degree of atypia. Low grade PINs (LGPINs) define areas of proliferative glandular epithelial cells that present enlarged nuclei, variable in size, non-prominent nucleoli and an intact basal cells layer (Bostwick, 1989). High grade PINs (HGPINs) mainly differ from LGPINs by the presence of prominent nucleoli, a nuclear hyperchromasia and a fragmented or lack of basal cells layer (Montironi et al., 2011), and are broadly accepted to be precursors of prostate carcinoma (Chrisofos et al., 2007; Montironi et al., 2011). Most of the human prostate cancers correspond to acinar adenocarcinoma, while neuroendocrine prostate cancers represent less than 2% of the cases (Grignon, 2004). However, focal regions of neuroendocrine differentiation are more commonly observed following recurrence after prostatectomy and androgen deprivation therapy (Komiya et al., 2009; Yuan et al., 2007).

A large number of studies have been performed with immortalized human prostate cancer cell lines, such as LNCaP, VCap, PC-3 or MDA-PCa, to gain insight into the biology of tumor progression, androgen-independent diseases and metastatic prostate cancer, and test putative chemopreventive compounds (Peehl, 2005; Wang et al., 2005). These lines are derived from advanced/metastatic tumors, and thus do not allow to recapitulate the various stages of the human disease. Moreover, studies of clonal cell lines in culture do not reproduce their interaction with the various cellular compartments of the prostate, such as the basal and neuroendocrine epithelial cells, stromal cells, or of the metastatic site (e.g. osteoblasts, osteoclasts), with vascular and lymphatic circulation and immune cells. In addition, xenograft transplantation models based on transformed human cell lines do not mimic the heterogeneity of human tumors and their microenvironment, and require immunodeficient host animals, that lack crucial modulators of tumorigenesis.

These major limitations prompted the development of animal models of prostate cancer to investigate tumor genetics and gene–environment interactions. Even though the gross anatomy of the mouse prostate differs from that of the human prostate, as it is composed of four distinct lobes [i.e. anterior (AP), ventral (VP), dorsal (DP) and lateral (LP)], the prostate of both species are composed of glands and ducts of similar organization (Cunha et al., 1987). Mouse prostatic glands contain however fewer basal and neuroendocrine cells, and looser and less fibromuscular stroma, with only few smooth muscle cells (Marker et al., 2003). Mice are not prone to develop spontaneous benign or malignant prostate pathologies, and rodent models of prostatic hyperplasia and malignancy using chemical carcinogenic agents are not sufficiently reliable (Bosland and Prinsen, 1990; Pollard et al., 1989). Importantly, the possibility to genetically manipulate the mouse genome with various technologies developed over the last 3 decades allowed the generation of a number of models of prostate cancer. This review presents an historical synopsis of various genetically engineered mouse (GEMs) lines of prostate cancer, highlighting their strengths and weaknesses, and future directions for research in the field, with an emphasis on the opportunities offered by temporally-controlled targeted somatic mutagenesis in the prostate to generate mouse models faithfully mimicking prostate carcinogenesis in humans.

2. Prostate cancer mouse models generated by targeted protein overexpression

The mouse genetic tools developed during the late 70s led to the establishment of a number of transgenic mice that express oncoproteins. Transgene expression in the mouse prostate became possible with the characterization of

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