MOLECULAR ONCOLOGY 6 (2012) 473–483

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Review

Maintenance of genomic integrity after DNA double strand breaks in the human prostate and seminal vesicle epithelium: The best and the worst

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ARTICLE INFO

Article history:
Received 14 May 2012
Received in revised form
7 June 2012
Accepted 8 June 2012
Available online 18 June 2012

Keywords:
DNA double strand break
Androgen signaling
DNA damage
Cell cycle checkpoint
Repair
Cancer

ABSTRACT

Prostate cancer is one of the most frequent cancer types in men, and its incidence is steadily increasing. On the other hand, primary seminal vesicle carcinomas are extremely rare with less than 60 cases reported worldwide. Therefore the difference in cancer incidence has been estimated to be more than a 100,000-fold. This is astonishing, as both tissues share similar epithelial structure and hormonal cues. Clearly, the two epithelia differ substantially in the maintenance of genomic integrity, possibly due to inherent differences in their DNA damage burden and DNA damage signaling. The DNA damage response evoked by DNA double strand breaks may be relevant, as their faulty repair has been implicated in the formation of common genomic rearrangements such as *TMPRSS2-ERG* fusions during prostate carcinogenesis. Here, we review DNA damaging processes of both tissues with an emphasis on inflammation and androgen signaling. We discuss how benign prostate and seminal vesicle epithelia respond to acute DNA damage, focusing on the canonical DNA double strand break-induced ATM-pathway, p53 and DNA damage induced checkpoints. We propose that the prostate might be more prone to the accumulation of genetic aberrations during epithelial regeneration than seminal vesicles due to a weaker ability to enforce DNA damage checkpoints.

1. Introduction

DNA double strand breaks (DSBs) are considered the most serious type of DNA lesions, as they can lead to cell death and chromosomal translocations (Polo and Jackson, 2011). They arise from endogenous and exogenous sources, and a single cell has been estimated to encounter at least 10–30 DSBs every day. Defective repair of these DNA breaks is associated with many human disorders including cancer (Jackson and Bartek, 2009). Cells respond to DSBs by activating complex signaling pathways commonly denoted as the DNA damage response (DDR) (Ciccia and Elledge, 2010). DDR regulates many

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http://dx.doi.org/10.1016/j.molonc.2012.06.001

processes that are important for genomic integrity, including DNA repair, DNA damage induced checkpoint control, modulation of transcriptional programs and activation of apoptosis or senescence (Medema and Macurek, 2011; Warmerdam and Kanaar, 2010). The main damage sensor kinases initiating the DSB signaling cascade are ATM, ATR and DNA-PK. They activate various mediator and transducer proteins via rapid phosphorylation events followed by other posttranscriptional modifications. The mediators and transducers amplify the signal and mediate the presence of DNA damage to effectors, such as p53, CDC25A and Wee1 that regulate the appropriate cellular responses (Harper and Elledge, 2007).

DSBs have been shown to be relevant in prostate tumorigenesis, as their faulty repair can result in genomic rearrangements (Haffner et al., 2011; Nambiar and Raghavan, 2011). In 2005, recurrent gene fusions between androgen regulated *TMPRSS2* gene and a family of ETS-transcription factors (*ERG*, *ETV1*, *ETV4*) were identified (Tomlins et al., 2005). *TMPRSS2-ERG* fusion, found in approximately 50% of prostate cancer, is one of the most common gene fusions detected in solid tumors (Kumar-Sinha et al., 2008). More recently, androgen signaling has been connected to their formation (Haffner et al., 2010; Lin et al., 2009; Mani et al., 2009). While the *TMPRSS2-ERG* translocations are probably the most scrutinized, they are not the only ones detected in prostate cancer (PCa). In order to identify the full spectrum of somatic alterations in PCa, Berger et al. sequenced the complete genome of seven prostate tumors, and discovered a novel pattern of complex chain of balanced translocations (Berger et al., 2011). They suggested that the translocations might arise from erroneous repair of DSBs of genes migrated into same transcription factories or located in same chromatin compartment. Formation of these inter- and intrachromosomal fusions of multiple genes could deregulate several pathways at once, and thus efficiently drive prostate tumorigenesis (Berger et al., 2011).

Primary seminal vesicle carcinomas (SVCas) are exceedingly rare. The factors that protect seminal vesicle (SV) epithelium from acquiring genetic aberrations are currently not known. The studies have been limited by the fact that only a few models of the SV have been established, and the existing ones have mostly been applied to studies on the male reproductive function. Some *in vivo* studies have been carried out in mouse and rat models (Jara et al., 2004; Kumano et al., 2008; Tanji et al., 2003; Yeh et al., 2009). Primary epithelial SV cells have been isolated from rats and guinea pigs and used to study the secretory functions of the SVs (Kierszenbaum et al., 1983; Lieber et al., 1980). Most studies on human SV have been conducted using immunohistochemical analysis of paraffin-embedded tissue sections that are readily available from radical prostatectomies and cystectomies (Billis et al., 2007; Laczko et al., 2005; Leroy et al., 2003; Ormsby et al., 2000; Thompson et al., 2008). We have recently described two novel models of the human SV; propagation of primary SV cells, and the establishment of an organotypic *ex vivo* tissue culture of SV tissue. We have analyzed their DDR after ionizing radiation (IR) and compared to primary prostate epithelial cells and similar *ex vivo*–prostate tissue cultures (Jäämaa et al., 2012). The *ex vivo* tissue culture models, which are based on culturing of thin (300–500 μm) tissue sections derived from tumor-free regions of surgical patient specimens, retain the normal histology of the prostate and SV. Primary epithelial cells can be isolated from same patient material. Both models have their advantages and limitations. *Ex vivo* –tissue culture allows studies on terminally differentiated cell types that are difficult to culture otherwise, and cell–cell and cell–stroma interactions are maintained. DNA damage can be induced using irradiation or drugs. On the other hand, genetic manipulation or direct regulation of gene expression of the tissue slices is technically challenging. Primary epithelial cells are heterogeneous populations of normal, non-transformed human cells. They are genetically stable, but have a limited lifespan and are more difficult to culture and transfect. Most cells in *ex vivo* tissue cultures are quiescent, while the use of primary epithelial cells allows studies on actively dividing cells.

In this review, we will overview prostate and SV structure and physiology, discuss processes that induce DSBs in both tissues especially in relation to tumorigenesis, and summarize DSB signaling in benign prostate and SV epithelia in order to shed light on the early events of PCa initiation.

2. DNA damage in prostate and seminal vesicle epithelium

2.1. *Prostate and seminal vesicle tissue structure and function*

Prostate and SVs are accessory sex glands of the male reproductive system. Prostate is located below the urinary bladder, and SVs lie between the urinary bladder and the rectum at the base of the prostate gland. SVs share their blood supply and innervation with the prostate. Anatomically the prostate can be divided into four distinct zones, i.e. central, transition, peripheral and anterior fibromuscular zone, which differ in their disease profiles. Most prostate tumors arise in the peripheral and transition zones. Interestingly, the embryological origin of the central zone of the prostate and SVs is the Wolffian duct, while the peripheral and transition zones are derived from the urogenital sinus (Aumuller and Riva, 1992).

The prostate epithelium is pseudostratified, and consists of an outer layer of basal cells that supports the layer of secretory luminal cells (Figure 1). Occasional neuroendocrine cells can be found interspersed with the two epithelial cell types (Peehl, 2005). The SV epithelium is structurally similar with two exceptions; the basal cell layer is discontinuous, and the neuroendocrine cells are absent (Laczko et al., 2005). Both prostate and SV epithelia are surrounded by strands of smooth muscle cells. Small blood vessels pierce through the smooth muscle cell layers and form a sub-epithelial capillary network (Figure 1). SVs produce 50–70% of the seminal fluid, while mainly the prostate secretes the remaining. SV epithelium secretes various substances important for male fertility, such as amino acids, prostaglandins, fructose, small peptides and proteins (Aumuller and Riva, 1992; Gonzales, 2001). Equally, luminal cells of the prostate gland produce proteolytic enzymes such as prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP).