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Patient-derived cell model for the study of prostate cancer biology and therapeutic development

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Prostate cancer is the most common male cancer in the United States and the second leading cause of male cancer death in the United States. African American men have a 60% higher incidence and mortality rate from prostate cancer compared to Caucasian men in North America, indicating that prostate cancer is a major public health problem in this population [1]. The etiology of these racial differences in the clinical manifestation of prostate cancer is not unclear: hormonal, genetic, behavioral and environmental factors have all been implicated [2]. To understand the many factors suspected of contributing to the development of this malignancy, there is a critical need for in vitro models representing primary tumors. However, no suitable in vitro models which accurately reflect the *in situ* characteristics of malignant epithelium for the study of African American prostate cancer are available. Studies of prostate cancer have been hampered by various factors including (1) restricted access to tissue (2) difficulties in propagating premalignant lesions and primary prostate tumors in vitro and (3) limited availability of prostate cell lines for in vitro studies. To date there is no commercially available pair of nonmalignant and tumor cells derived from the same prostate cancer patient.

\Only two reports have documented the establishment of African American prostate cancer-derived human prostate cancer cell lines: MDA PCa 2a and MDA PCa 2b cell lines were derived from a single bone metastasis in 1997 [3]. These cell lines exhibit androgen-independent growth in vitro and in vivo, however, retain androgen responsiveness. In 2004, a second cell line was derived from primary localized adenocarcinoma of the prostate. The E006AA cell line was established as spontaneously immortalized from a patient with a clinically localized prostate cancer. This cell line shows androgen-dependent growth but is not tumorigenic potential. In addition, the establishment and characterization of a highly tumorigenic African American cell line E006AA-hT has been reported in 2014 [4]. However, correction of the establishment and characterization of a primary androgen-responsive African American prostate cancer cell line E006AA cell line has been described in 2019 [5]. Unfortunately, this E006AA cell line is not derived from prostate cancer and is a subclone of the 786-0 renal adenocarcinoma line from a white male [5]. The STR profile of the E006AA cell line subclone E006AA-hT available at the American Type Culture Collection (ATTC) site has STRs match the profile of 786-0 cells (also available at ATCC site). These authors believe it may have been contaminated in their early passages of the E006AA cells with the 786-0 cells [5] in their laboratory. Thus, there was no report derived from primary located adenocarcinoma of the African American prostate until 2010. We reported for the first time the establishment of African American prostate cancer-derived cell line [6].

Primary prostate epithelial cells grow for a finite life span and then senesce. Immortalization is defined by continuous growth of otherwise senescing cells and is believed to represent an early stage in tumor progression. To examine this early stage, we have developed in vitro models of prostate epithelial cell immortalization. Methods were described for the processing of primary human prostate biopsy sample and generation of human primary epithelial (HPE) cells have been achieved using the serum-free human keratinocyte growth medium [7]. Retrovirus containing human telomerase reverse transcriptase (hTERT) was also used for generation of primary non-malignant and malignant tumor cells [8,9]. In addition, we have established the first immortalized cell lines of a pair of non-malignant and malignant tumor derived from an African American prostate cancer patient with HPV-16 E6 and E7 [6].

Interestingly, we have found that Rock inhibitor and feeder cells induced the conditional reprogramming (CR) of human epithelial cells – normal and tumor epithelial cells from many tissues to proliferate indefinitely in vitro without transduction of viral or cellular genes [10]. More recently (2016), using CR, we have established normal and tumor cultures respectively from a patient prostatectomy [11]. These CR cells grow indefinitely in vitro and retain stable karyology. The tumor-derived CR cells produced tumors in SCID mice. The use of novel pair of non-malignant and malignant tumor cells derived from the same patient provides a unique in vitro model for the studies of cancer biology, discovery of biomarker, anti-cancer drug and cancer precision medicine.

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