PC3's History

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Montrose T. Burrows was the first to report successful cultivation of prostate tissue outside the body. His culture medium was not defined and consisted of plasma, agar, saline and ascites. Eventually, he moved his laboratory to Pasadena, California. Dr. Burrows is a pioneer in prostate cell culture history.

The modern era of cell culture began with Richard G. Ham's successful identification of the nutritional needs of cells and the development of chemically defined media in the early 1970's. M. Edward Kaighn, a colleague of Dr. Ham, joined our laboratory in 1974 and directed his attention to the establishment of prostate cells in culture. Kaighn modified Ham's F-12 K, and developed a clonal growth assay to obtain an improved culture medium for growth of prostate cells. Ultimately, he was able to develop a defined medium, PFMR-4.

The thesis of this history is that cultured human cells in vitro, as exemplified here by PC3 prostate cancer cells, can reflect their inheritance and behavior at origin.

A 63-year-old case was presented in December 1975 with urinary retention, weight loss, and weakness. There was no family history of prostate cancer. The transurethral resection pathology showed poorly differentiated prostate cancer, with a Gleason grade 5+5. He underwent bilateral orchiectomy but failed to improve. He died 7 months later of anemia, diffuse bone pain, and ataxia. An autopsy showed that all bones were replaced with prostate cancer. The only other site of disease was a small focus of disease in the left adrenal gland. A sample of tissue from the 2nd lumbar vertebra provided the source for establishment in vitro. Thus began PC-3's history.

Initially, PC-3's rate of division was slower than that of the accompanying non-cancerous connective tissue cells. Kaighn isolated clones and propagated only those clones that maintained PC-3's characteristics. His collaborators purified PC-3 further by growing it in immunodeficient (nude) mice.

The cultured cells showed anchorage independent growth in both monolayers and in soft agar and produced subcutaneous tumors in nude mice. In vitro cultures of the xenografts yielded a cell line with characteristics similar to those used initially to produce the tumor. PC-3 had a greatly reduced dependence upon serum for growth when compared to normal prostate epithelial cells. PC-3 cells did not respond to androgens, glucocorticoids, or epidermal or fibroblast growth factors.

Karyotypic analyses revealed the PC-3 cells to be completely aneuploid with a modal chromosome number in the hypo triploid range. At least 10 distinctive marker chromosomes were identified. The overall karyotype as well as the marker chromosomes were distinct from those of HeLa cells. Electron microscopic studies revealed many features common to neoplastic cells of epithelial origin including numerous microvilli, abnormal nuclei and nucleoli, abnormal mitochondria, annulate lamellae, and lipid bodies. Overall, the functional and morphologic characteristics of PC-3 were those of a poorly differentiated adenocarcinoma.

PC-3 (prostate adenocarcinoma, human) cells have been deposited at early passages with the American Type Culture Collection. The cells exhibit low acid phosphatase, and testosterone-5α-reductase activity and can be readily adapted to growth in suspension culture systems. The HLA profile is A1, A9. It is near triploid with a modal number of 62 chromosomes.

Simultaneously with the reports of PC-3 came reports of the successful in vitro cultures of prostate cancer originating in the central nervous system (DU 145) and lymph node (LNCaP). There has been a sustained interest in the differences in phenotypic behavior between these lines. Establishment of a few other lines has more recently been reported. Nevertheless, PC-3 remains the prototype for prostate cancer's metastatic phenotype.

Modern techniques have begun to clarify allelic losses and gains in prostate cancer. LNCaP and PC-3 genes are
differentially expressed. PC-3’s strong androgen independence and proclivity for bone may soon be explained as the model for malignant progression of prostate cancer. For example, with regard to adhesion molecules, PC-3 expresses E-cadherin but lacks α-catenin. PC-3 also has a gene encoding human calbindin. PC-3 evidently lacks a genetic locus at 10pter-q11, which hinders programmed cell death. PC-3 also lacks the PTEN (10q23 locus) tumor suppressor gene.

PC-3 cells response to multiple growth factors including insulin-like growth factor, epithelial growth factor, fibroblast growth factor and others has been studied. PC-3 has high-affinity binding sites for some neuroendocrine molecules. Biologic response modifiers modify PC-3’s androgen receptor-mediated gene expression. A soybean isolate, Genistein, slows PC-3 growth and is accompanied by down regulation of numerous genes coding for tumor promoters. Inhibition or activation of these factors has important therapeutic implications especially as they apply to phenotypes such as PC-3.

Clinical history shows that PC-3’s progenitor was androgen independent. It is unlikely that PC-3’s androgen receptor mutations were induced by androgen deprivation since orchietomy not only failed to change the course of disease but also occurred moderately close to the demise of the host. The PC-3 cell line has an androgen receptor gene but no demonstrable normal receptor activity. PC-3 bears a surface antigen commonly found in prostate cancer specimens. However, PC-3 lacks the prostate specific antigen and the prostate specific membrane antigen.

PC-3’s metastatic activity in nude mice increases even more after in vivo passage. Studies of PC-3’s behavior in vivo have been aided by the incorporation of the light enabling luciferase gene.

Analysis of in vivo responsiveness to standard and investigational chemotherapeutic agents is challenging. However, PC-3’s responsiveness is of interest. PC-3 is susceptible to standard agents such as Taxol and vinblastine and investigational agents such as Nano-pesosulfan and cryptophycin-8. PC-3. Xenografts have also shown susceptibility to Mitoxantrone/dexamethasone ploys calcitriol, and to angiogenesis inhibitors. PC-3 has been shown to develop a multiple drug resistance phenotype in response to exposure from chemotherapeutic agents and radiation. Alpha-adrenergic antagonists and cardiac glycosides can potentiate PC-3’s radio sensitivity.

In summary, PC-3 has been a highly useful model in vitro systems for elucidating prostate cancer’s malignant phenotype since its establishment more than 25 years ago.