HHS Public Access

Author manuscript

Expert Rev Anticancer Ther. Author manuscript; available in PMC 2016 March 01.

Published in final edited form as:

Expert Rev Anticancer Ther. 2015 March ; 15(3): 261–263. doi:10.1586/14737140.2015.1003046.

Prostate cancer organoids: a potential new tool for testing drug sensitivity

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Summary

Recent technical advances have enabled for the first time, reliable in vitro culture of prostate cancer samples as prostate cancer organoids. This breakthrough provides the significant possibility of high throughput drug screening covering the spectrum of prostate cancer phenotypes seen clinically. These advances will enable precision medicine to become a reality, allowing patient samples to be screened for effective therapeutics ex vivo, with tailoring of treatments specific to that individual. This will hopefully lead to enhanced clinical outcomes, avoid morbidity due to ineffective therapies and improve the quality of life in men with advanced prostate cancer.

Keywords

organoids; prostate cancer; in vitro; therapeutics; precision medicine; 3D culture

The past five years have witnessed the simultaneous characterization of the mutational landscape of prostate cancer and the unprecedented development of multiple FDA approved drugs. Many genetic aberrations in prostate cancer are poorly studied and their effects on therapeutic response are not known. Prostate cancer research has been hampered by several well documented technical limitations. These primarily relate to the lack of in vitro model systems due to the limited number of prostate cancer cell lines available, which do not represent the diverse phenotypes of clinical disease. Secondarily, from a therapeutics

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Financial and competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

discovery and testing aspect, the traditional two dimensional culture systems used for drug screening, identification and development may have significant shortcomings in the areas of drug dosing, complexity of interactions seen in the in vivo environment and applicability of results to the clinic. In response to both of these issues, the recent development of prostate cancer “organoid”, three dimensional in vitro culture technology, allows for the first time consistent and reproducible primary culture of a large number metastatic prostate cancer cell lines in a more biologically complex and relevant culture system [1, 2].

The under-representation of cell line models for prostate cancer research stems from the difficulty in propagating prostate cancer cells in vitro for extended periods. Despite a large number of attempts by multiple investigators, only seven cell lines have been previously available through public cell line repositories [3–7]. These do not represent the spectrum of clinical disease and whilst have helped progress the field, new cell lines are clearly needed which demonstrate the commonly observed clinical phenotypes.

Historically, normal cells in culture can be grown for only a limited number of passages before undergoing cellular senescence. This “Hayflick limit” can be bypassed using artificial immortalization that reactivates telomerase and inactivates the p53 and RB tumor suppressor pathways. Recently, Clevers and colleagues developed a novel system through which normal human and murine prostate epithelial cells can be cultured indefinitely without immortalization, in an in vitro 3D system that recapitulates normal prostate glandular structure [2]. This system has been optimized for human metastatic prostate specimens and has successfully generated seven new lines which represent more completely the phenotypic spectrum of clinical disease, and express previously identified common genetic alterations seen in advanced prostate cancer [1].

It has been well known for some time that cellular behavior is strongly influenced by the surrounding microenvironment, specifically the supporting tissues and stroma. The complex interactions between the different supporting cell types affects proliferation, differentiation and metabolism of both benign and malignant cells. These interactions as well as oxygen and nutrient gradients in human malignancy drive significant differences in drug sensitivity seen with in vitro 2D systems compared to “real world” in vivo responses [8]. These differences provide a major obstacle to high throughput therapeutics screening, which traditionally has used 2D culture systems due to their ease of use, reproducibility and cost effectiveness compared to in vivo models.

Various in vivo models of tumor propagation have been developed in order to assess therapeutic effectiveness, including patient-derived xenograft (PDX) models and genetically engineered mouse (GEM) models. These models have significant limitations of cost and the time required for tumors to develop and an inability to screen large numbers of compounds in an effective manner. Murine physiology and sensitivity to therapies also potentially provide confounders for interpretation of screening/efficacy/toxicity studies. Despite these limitations, regulatory bodies generally require in vivo animal studies prior to in human therapeutic trials.

In an attempt to address the limitations of 2D in vitro cultures and the cost and inability for high throughput screening in in vivo animal model systems, various 3D in vitro model systems have been developed. 3D cultures have been developed with culture on inserts, supportive matrices of different composition and multicellular aggregates as typical examples which have been reviewed in detail elsewhere [8–10]. These techniques attempt to recapitulate the important structural relationships of cancer cells and stroma to mimic in vivo form and function to more accurately predict responses to treatment and therapeutic compound efficacy. Cell to cell interactions, alterations to gene expression and oxygen, nutrient and growth factor gradients all impact heavily on cellular responses in the in vivo situation. 2D culture systems are incapable of mimicking such complex interplay [11]. Successful generation of 3D primary culture systems in other cancers (e.g. colorectal cancer) and their potential utility in drug screening and individual patient risk stratification has prompted investigation of such technologies in multiple other cancer types[12].

The recently described prostate organoid system by our group uses Matrigel® as the biologic scaffold which allows 3D organization of both benign and malignant prostate cancer cells. The key breakthrough however is the culture media in this system which allows the indefinite propagation of both benign and malignant prostate cells without the need for artificial transformation, maintains the genome without evidence of genetic drift and allows development of new cell lines with a high success rate [2]. From the first seven new prostate cancer cell lines generated, cell lines expressing disease specific mutations such as ETS-translocations, *SPOP* mutations, *FOXA1* mutations and *CHD1* loss are now available for which previously there were no model systems [1]. As the collection of lines continues to accumulate, no doubt further novel mutations will be identified.

This technology will enable for the first time, a large scale prostate cancer “encyclopedia” or repository of cancer and benign organoid cell lines which will allow high throughput in vitro screening of compounds across the spectrum of clinical disease. In order to maximize utility including identification of biomarkers of therapeutic response, it is critical that every organoid line of this encyclopedia is extensively clinically and molecularly annotated, with the patient’s disease characteristics, treatment response, mutational status and gene expression profile. Given the technical advantages of 3D culture systems, we suggest that this will provide a cost and time effective approach to drug discovery and development and predict that this approach will identify a slue of novel therapeutic targets and compounds. The relationship of in vitro organoid response to therapy and in vivo response in the whole patient setting is currently unknown. Retrospective analysis of the newly generated lines to treatment and response is currently on going. Careful study and prospective validation of such an approach in a clinical trial setting however is required before this approach could be widely adopted.

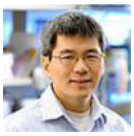
The aim of precision medicine is to identify on an individual basis, the genetic changes specific to that individual’s cancer in order to identify therapeutic targets of maximum benefit. Most anticancer agents selectively benefit a subset of patients, but the traditional approach of disease specific therapeutics (instead of target specific therapeutics) and serial therapeutic trials fails to identify this subset. An agent becomes approved if the trial is sufficiently powered such that the benefitting subset can lead to a statistically significant

improvement of the entire cohort and “fails” otherwise. For the individual patient, this leads to overtreatment with available drugs that do not benefit and a lack of availability of some drugs that would benefit. Through the development of technologies such as the prostate organoids discussed here, the first steps toward achieving this goal are being taken. The ability to generate sufficient material from a biopsy specimen for next generation sequencing or in vitro therapeutic trials in a clinically meaningful time frame is a major technological advance.

The report also of the first prostate cancer circulating tumor cell (CTC) line opens an extremely exciting avenue of research with potential “liquid biopsy” allowing patients to avoid painful and technically challenging investigations such as core biopsy of metastatic sites and instead have a simple blood draw [1]. The role of CTCs in metastasis and the relevance of the features of these cells to the dominant cancer is subject to controversy and ongoing investigation. Recent reports of ex vivo culture of CTCs for the purpose of therapeutic screening in breast cancer indicates that this approach may be feasible and relevant in advanced solid organ malignancies [13].

We are currently at an exciting crossroad in prostate cancer research. The potential for novel discoveries and new therapeutics has never been greater with the developments of next generation sequencing, organoid culture technologies and the possibilities of precision medicine. The ultimate goal of developing and delivering the right therapeutics, for the right cancer in the right patient means that outcomes, morbidity and ultimately survival should be improved for the benefit of all men with advanced prostate cancer.

Biographies



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