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Review article

Subrenal capsule grafting technology in human cancer modeling and translational cancer research

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ABSTRACT

Patient-derived xenograft (PDX) cancer models with high fidelity are in great demand. While the majority of PDXs are grafted under the skin of immunodeficient mice, the Living Tumor Laboratory (LTL), using unique subrenal capsule grafting techniques, has successfully established more than 200 transplantable PDX models of various low to high grade human cancers. The LTL PDX models retain key biological properties of the original malignancies, including histopathological and molecular characteristics, tumor heterogeneity, metastatic ability, and response to treatment. The PDXs are stored frozen at early transplant generations in a resurrectable form, which eliminates continuous passaging in mice, thus ensuring maintenance of the high biologic and molecular fidelity and reproducibility of the models. The PDX models have been demonstrated to be powerful tools for (i) studies of cancer progression, metastasis and drug resistance, (ii) evidenced-based precision cancer therapy, (iii) preclinical drug efficacy testing and discovery of new anti-cancer drug candidates. To better provide resources for the research community, an LTL website (www.livingtumorlab.com) has been designed as a publicly accessible database which allows researchers to identify PDX models suitable for translational/preclinical cancer research. In summary, subrenal capsule grafting technology maximizes both tumor engraftment rate and retention of human cancer heterogeneity. Moreover, the method makes possible the recovery of PDXs from frozen stocks for further applications, thus providing a powerful platform for translational cancer research.

Contents

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1. Improvement of survival and growth of human cancer biopsies grafted under the renal capsule

The majority of PDXs has been established via subcutaneous grafting, a simple technique allowing non-invasive monitoring of tumor growth. However, the drawback of subcutaneous grafting is its low success rate. For example, van Weerden et al. (1996) reported successful grafting of only 2 out of every 150 subcutaneous prostate cancer xenografts. We attribute the low take rate in the subcutaneous graft site to paucity of the vasculature and poor blood supply. Accordingly, to improve take rate, we have used the subrenal capsule (SRC) graft site, one of the most vascular environments in the body, which also has a positive interstitial fluid pressure and a high rate of lymphatic flow (Ott and Knox, 1976). Taken together, the SRC graft site ensures an abundant supply of nutrients, hormones, growth factors and oxygen to transplanted cells and tissues even before vascularization of the graft is established (Cunha, 1976a, 1976b; Cunha et al., 1977, 1983; Bogden et al., 1979; Griffin et al., 1983; Bogden, 1985; Maenpaa et al., 1985). Fortunately, the SRC site can also accommodate tissues of a substantial size range and source (Robertson et al., 2007).

We have compared take rates of both benign and malignant human prostate tissues in the SRC, subcutaneous, and orthotopic sites of immuno-deficient mice, and have shown that successful take rate is highest for the renal site (Wang et al., 2005). This advantage of the SRC site for developing human prostate cancer models has been confirmed by others (Priolo et al., 2010; Zhao et al., 2010). It is evident from such comparisons that, of the three graft sites, the SRC site is the most efficient for growing human prostate cancer as well as normal prostatic cells. Furthermore, the greater vascularity of the renal graft site is associated with reduced selective pressure on the various cancer subpopulations present in the original heterogeneous primary tumor sample. Given the cellular heterogeneity within a primary prostate cancer, we have postulated that the various cell types within the cancer vary significantly in their ability to tolerate the anoxia associated with the initial phases of the grafting process. For this reason, we are convinced that preservation of the cellular complexity (heterogeneity) of the original primary tumor is superior in the more vascular SRC graft site. This interpretation is supported by the high similarity observed between SRC xenografts and the parent tumors in terms of histopathology, marker expression, genetic profiles and properties such as androgen sensitivity and metastatic ability (Lee et al., 2005; Wang et al., 2005; Cutz et al., 2006; Watahiki et al., 2006; Press et al., 2008; Dong et al., 2010; Lin et al., 2014a, 2014b). These advantages of SRC xenografting indicate that this technique maximizes both tumor engraftment rate as well as the retention of the original cellular complexity of the primary tumor. Accordingly, PDXs developed in the SRC site better reflect the wide spectrum of cancer cell types in the primary tumor rather than PDXs developed in the relatively anoxic subcutaneous site, which tend to lack cellular heterogeneity. Furthermore, once SRC PDXs are well established, they can be regrafted to, for example, the subcutaneous site, which facilitates monitoring of tumor growth as affected by e.g., therapeutics, or the orthotopic site (the mouse prostate) for assessment of metastatic ability (Wang et al., 2005; Lin et al., 2010). In the Living Tumor Laboratory (www.livingtumorlab.com), we graft a variety of low to high-grade human cancers (including prostate cancer), which have been developed via SRC grafting of patients' cancer *tissue*. Non-obese Diabetic Severe Combined Immuno-Deficient (NOD/SCID) or NOD/SCID IL2 receptor gamma chain null (NSG) mice are used as hosts according to methods described in this special issue (Cunha and Baskin, this issue). A high engraftment rate (~95%) has consistently been achieved, and presently more than 200 transplantable PDXs have been established and stored frozen at various generations in a resurrectable form (Lee et al., 2005; Wang et al., 2005; Cutz et al., 2006; Watahiki et al., 2006, 2011; Press et al., 2008; Cheng et al., 2010; Dong et al., 2010; Lin et al., 2010, 2014a, 2014b; Tung et al., 2011; Choi et al., 2014; Eirew et al., 2015; Jager et al., 2015).

2. Subrenal capsule grafting technology makes the recovery of PDX models from DMSO frozen stocks feasible

Typically, once PDXs are established in mice, they are maintained by continuous serial transplantation in mice. Serially transplanted PDXs have two major problems: (1) long-term serial transplantation in mice may promote genetic and epigenetic drifts, which may affect biologic fidelity of the PDXs; (2) continuous serial transplantation has significant financial costs and labor. Accordingly, attempts were made to cryo-preserve the xenografts, and re-grow them as needed. Overall recovery rate of the frozen stocks was exceptionally low for conventional subcutaneous grafts. In contrast, in the Living Tumor Laboratory, we use the SRC grafting methodology to recover/regrow PDXs from frozen stocks with ~85% success rate (unpublished data). Thus, the PDXs are stored frozen at early generations in a resurrectable form in the lab. The SRC grafting methodology ensures a high biologic fidelity and reproducibility of the models.

3. SRC PDX models are highly similar to donors' original tumors

The SRC grafting methodology enhances the retention of important properties of the patients' malignancies as indicated, for example, by (i) retention of tumor heterogeneity, androgen and drug sensitivity (Wang et al., 2005; Lin et al., 2014a); (ii) retention of tumor progression-related properties and suitability for predicting clinical drug responses for personalized chemotherapy (Dong et al., 2010; Collins et al., 2012; Beltran et al., 2015) and (iii) retention of genetic profiles and targeted drug sensitivity (Andersen et al., 2010; Cheng et al., 2010; Dong et al., 2010; Kortmann et al., 2011; Lin et al., 2014a).

The transplantable prostate cancer PDXs, which were established by the Living Tumor Laboratory using the SRC xenograft method and NOD/SCID mice, not only retain key biological properties of the original malignancies, e.g., histopathology, growth rate, metastatic ability and response to androgen-ablation therapy (sensitivity or resistance) (Fig. 1C), but also preserve genetic/epigenetic characteristics, e.g., expression of androgen receptor (AR), prostate-specific antigen (PSA), and other molecular markers. For example, the LTL352 line, developed from a neuroendocrine prostate tumor, retained its pathological signiture and expressed the neuroendocrine markers of the original tumor, namely CD56, chromogranin, synaptophysin and neuron-specific enolase. Array Comparative Genomic Hybridization analysis of this tumor line identified a 5′-deoxy-5′-methylthioadenosine phosphorylase deletion, which was also found in the original tumor (Collins et al., 2012). Similarly, the

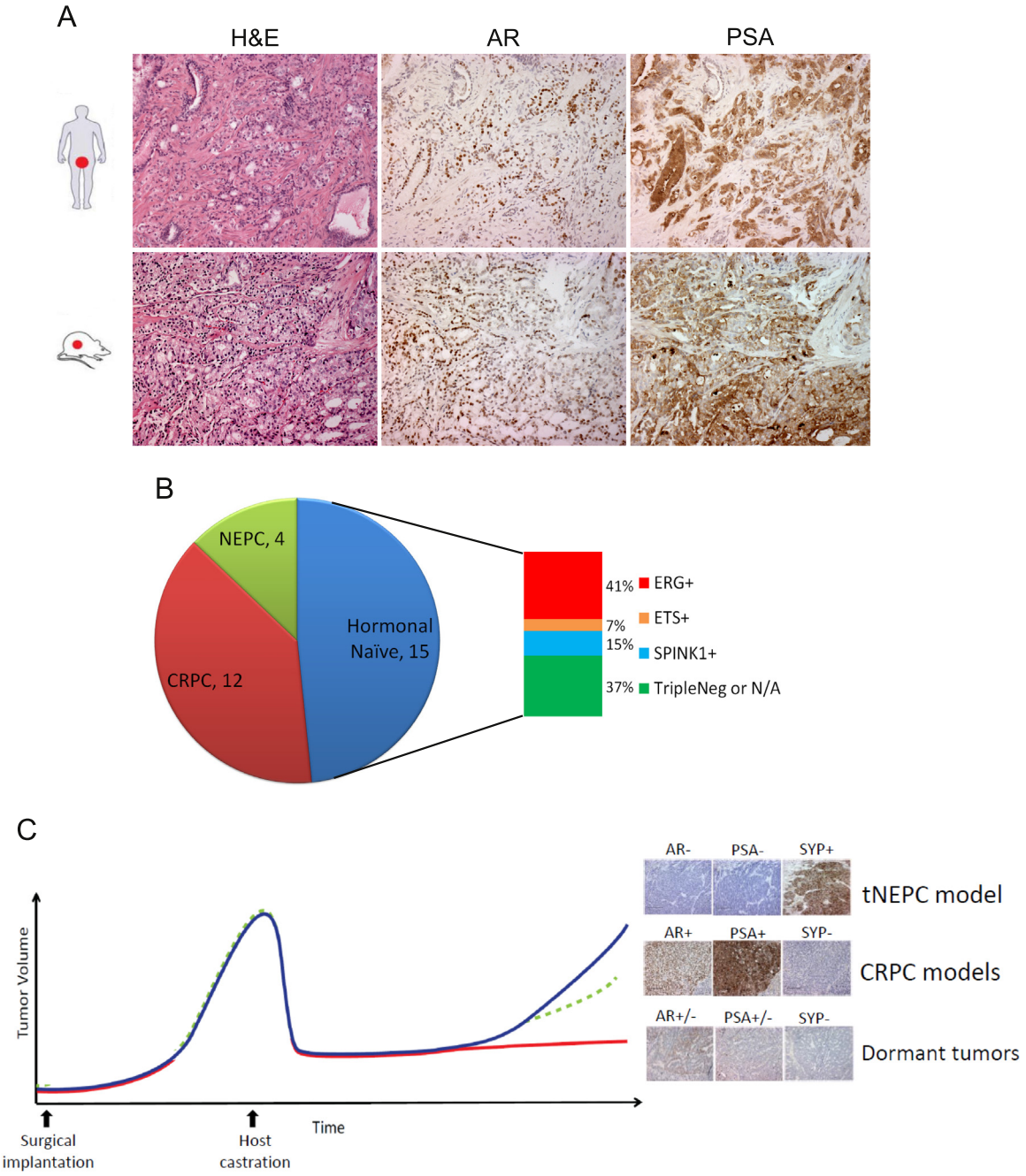

Fig. 1. High fidelity PDX models recapitulate biological and molecular heterogeneity of clinical prostate cancer (PCa) and present various responses to androgen ablation. A) A PCa PDX model retains the histolopathological characteristics of its original patient tumors; B) a panel of PCa PDX models represents various pathological and molecular subtypes of prostate cancer; E) androgen-dependent PCa PDX models show various responses to androgen ablation and led to the development of AR-positive castration resistant prostate cancer (CRPC) or AR-negative NEPC.

LTL313H line was developed from a prostatic adenocarcinoma carrying the *TMPRSS2-ERG* fusion gene, a gene commonly observed in clinical prostate cancer. As expected, deep DNA sequencing showed that the xenograft line also harbored this fusion gene. In other cases, multiple tumor tissue lines were successfully established from different foci of a single patient's primary prostate cancer specimen, yielding the following transplant lines: PCa1-met, PCa2 (Wang et al., 2005; Lin et al., 2008); LTL220M, LTL220N and LTL221 (Lin et al., 2010); LTL313A, LTL313B, LTL313C, LTL313D and LTL313H (Lin et al., 2014a). These tumor transplant lines retained histopathological markers found in the original heterogenous primary tumor, e.g., AR and PSA (Fig. 1A), but individually showed different growth rates and responses to androgen-ablation therapy (Lin et al., 2014). By regrafting xenografts into the orthotopic site (the mouse prostate), a number of paired metastatic and non-metastatic prostate cancer tissue sublines were successfully developed. Examples of paired metastatic versus non-metastatic lines derived from a single primary tumor include the metastatic PCa1-met and non-metastatic PCa2 sublines (Wang et al., 2005; Lin et al., 2008), the metastatic LTL220M and non-metastatic LTL220N sublines (Lin et al., 2010), and the metastatic LTL313B and non-metastatic LTL313H sublines (Andersen et al., 2010). Differences in growth rate, response to androgen-ablation therapy, and the metastatic properties of sublines derived from a single patient's tumor appear to reflect the heterogeneity within the original cancer. Thus, models based on SRC xenografts more accurately mimic the malignancies in patients when

compared to conventional, cultured cell line-based models subjected to serial subcutaneous transplantation. As such, SRC PDXs are more clinically relevant and have greater predictability of drug efficacies in the clinic.

In total, the spectrum of prostate cancer transplant models developed via SRC grafting and limited serial transplantation represents in substantial fashion the biological variants of this disease. To more fully represent the biological and molecular characteristics of prostate cancer, a *panel* of established PDXs, covering a range of prostate cancer subtypes, is required for use in preclinical and translational research of the disease (Fig. 1B). For specific in vivo investigations (e.g., targeted therapy, metastatic ability investigations), the components of a panel can be applied and selected based on certain characteristics that are best suited to answer a particular question. Once established via SRC grafting, PDXs can furthermore be used in the subcutaneous and orthotopic graft sites to answer relevant questions such as the genetic/epigenetic signatures of the metastatic versus non-metastatic state. Furthermore, to reliably determine optimal chemosensitivities of individual cancers for personalized chemotherapy, it is essential to use PDX models that closely mimic the biology of the patient's cancer (Voskoglou-Nomikos et al., 2003; Sharpless and Depinho, 2006). Such models allow testing of drugs within a short time frame (6–8 weeks), which is compatible with timely initiation of the patient's therapy. In a study of Non-Small Cell Lung Cancers, first or early generation xenografts derived from patients' primary tumors generated information predictive of drug sensitivity of the patients' tumor (Dong et al., 2010; Gout and Wang, 2012).

4. Applications of SRC PDX models

Prostate cancer PDX models established via SRC grafting are useful for (i) basic prostate cancer research (e.g., identification of metastasis-related genes, new therapeutic targets), (ii) translational research (e.g., efficacy testing of potential and established anticancer drugs, novel targeted therapeutic approaches) and (iii) personalized cancer therapy.

4.1. Cancer discovery

Prostate cancer PDX sublines displaying marked differences in specific biological and molecular characteristics are not only useful for the identification of novel biomarkers, but also the identification of therapeutic targets. For example, using a comprehensive gene and miRNA expression profiling, molecular signatures of prostate cancer progression and metastasis can be identified by comparing metastatic and non-metastatic sublines. Hence, a comparative Serial Analysis of Gene Expression (SAGE) of the paired metastatic PCa1-met and non-metastatic PCa2 sublines led to the identification of a novel gene, *ASAP1,* which is associated with prostate cancer metastasis. In clinical specimens, ASAP1 protein expression was found to be elevated in metastatic prostate cancer when compared to primary cancers and also benign prostate. Functional studies indicated that the *ASAP1* gene plays an important role in migration of prostate cancer cells and tissue invasion (Lin et al., 2008). Similarly, we have utilized Next Generation Sequencing to identify differentially expressed known and novel miRNAs in a pair of metastatic and non-metastatic prostate cancer sublines, LTL313B and LTL313H, that likely include potential biomarkers for prostate cancer metastasis (Watahiki et al., 2011).

4.2. Preclinical drug screening

Models for reliable testing of anticancer drug efficacies are particularly important for aggressive malignancies, such as prostatic Small Cell Carcinoma (SCC), for which a standard therapeutic regimen has yet to be adopted. The use of the neuroendocrine prostate cancer tissue line LTL352 indicates that irinotecan, a topoisomerase I inhibitor, is potentially useful for therapy of refractory prostatic SCC, particularly in combination with cisplatin (Tung et al., 2011). There are currently no curative treatment options for castration-resistant prostate cancer (CRPC). However, the use of LTL313, an androgen-dependent prostate cancer tissue line characterized by AR expression and serum PSA, has recently been instrumental in eliciting regression of castration-recurrent prostate cancer through use of a small-molecule inhibitor of the amino-terminus domain of the androgen receptor (Andersen et al., 2010). Our PDX models have also been used for a number of other drug evaluations (Andersen et al., 2010; Cheng et al., 2010; McPherson et al., 2010; Beltran et al., 2011; Kortmann et al., 2011; Qu et al., 2014).

4.3. Evidence-based personalized cancer therapy

Cancer generally consists of subpopulations of cells, which can differ markedly in population size and sensitivity to specific treatments. Differences in biologic properties are thought to underlie the varying responses of patients to certain therapeutics. Since each patient's cancer is unique, therapy should ideally be tailored to individual patient's cancers. Choosing the most effective, most affordable, and least toxic chemotherapeutic regimen for a patient is one of the major challenges faced by oncologists today (Gout and Wang, 2012). The high toxicity from ineffective treatments can prohibit a patient from undergoing alternative treatments. Use of PDXs that closely mimic the primary cancer is predictive of drug efficacy in personalized cancer therapy. Such testing of drug sensitivity is timely and can facilitate subsequent implementation of the optimal drug treatment regimen for the patient. For this purpose, first or early generation SRC xenografts of the patient's own malignancy are useful to define the optimal drug treatment. Such xenografts express most, if not all, of the molecular heterogeneity and histological complexity of the patient's original cancer because it contains stroma from the original tumor and mimics the cell-to-cell interactions of the tumor microenvironment. The suitability of first generation xenografts for application in personalized cancer chemotherapy is indicated by our study of predicting the patient's drug response (Dong et al., 2010).

An example of the potential utility of prostate cancer transplant lines for personalized chemotherapy has recently been obtained. Massively Parallel Sequencing of a patient's neuroendocrine prostate tumor showed a homozygous deletion on chromosome 9p21 spanning the 5′-deoxy-5′-methylthioadenosine phosphorylase (*MTAP*) and *CDKN2-ARF* genes, a common genetic deletion in various cancers. A SRC xenograft line (LTL352), generated from the tumor, also had the same genetic deletion as shown by Array Comparative Genomic Hybridization. Treatment of mice carrying the *MTAP*-deficient LTL352 xenografts with high doses of 6-thioguanine (6-TG) in combination with methylthioadenosine (to protect normal cells from 6-TG toxicity) caused the regression of the tumor transplants without significant host morbidity/mortality, indicating that this drug combination may be optimal for treatment of the patient. This study demonstrated that use of appropriate, PDX models in combination with techniques, such as Massively Parallel Sequencing, can lead to the identification of key therapeutic targets and therapies that are potentially useful for personalized chemotherapy (Collins et al., 2012). In another example, using genomic sequencing information, researchers (Beltran et al., 2015) discovered a hemizygous deletion of the *FANCA* gene in a prostate cancer patient, and hypothesized that the patient should be sensitive to platinum. FANCA is a member of the Fanconi anemia core complex, which is critical for DNA crosslink

repair. Impressively, the prediction was functionally tested in a FANCA-deleted PDX model.

5. Conclusions

Prostate cancer PDXs developed via SRC grafting of patients' cancer specimens into SCID mice faithfully resemble the patients' malignancies in terms of histopathology, tumor heterogeneity, molecular markers, genetic/epigenetic alterations and drug sensitivity. As such, SRC PDX models appear to better mimic the properties of the original cancers when compared to xenografts generated at the subcutaneous and orthotopic graft sites. SRC PDX models provide valuable tools with high clinical relevance for studying the molecular and cellular development and progression of prostate cancer, developing new therapies and potential use in evidence-based precision cancer therapy.

Competing interests

The authors declare that they have no competing interests.

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