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Lessons from patient-derived xenografts for better in vitro modeling of human cancer☆,☆☆

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ABSTRACT

The development of novel cancer therapeutics is often plagued by discrepancies between drug efficacies obtained in preclinical studies and outcomes of clinical trials. The inconsistencies can be attributed to a lack of clinical relevance of the cancer models used for drug testing. While commonly used in vitro culture systems are advantageous for addressing specific experimental questions, they are often gross, fidelity-lacking simplifications that largely ignore the heterogeneity of cancers as well as the complexity of the tumor microenvironment. Factors such as tumor architecture, interactions among cancer cells and between cancer and stromal cells, and an acidic tumor microenvironment are critical characteristics observed in patient-derived cancer xenograft models and in the clinic. By mimicking these crucial in vivo characteristics through use of 3D cultures, co-culture systems and acidic culture conditions, an in vitro cancer model/microenvironment that is more physiologically relevant may be engineered to produce results more readily applicable to the clinic.

Contents

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1. Introduction

Despite improvements in our understanding of the mechanisms of cancer pathogenesis and the continuous development of novel therapeutics, advanced cancers are in general still not curable. There is therefore a critical need for more effective treatments to improve disease management and patient survival. Use of in vitro cancer models has provided valuable information onthe understanding of cancer development and mechanisms of therapeutic action as they allow detailed analysis of these subjects under controlled conditions. As well, cancer cells grown in suspension culture, or as monolayers on plastic surfaces, are commonly used as cancer models in preclinical drug efficacy screenings. Major deficiencies of such models, however, include the lack of heterogeneity reflective of the original malignancy as well as an improper microenvironment, both of which are identified as major factors influencing cancer development and treatment resistance [1–3]. The poor resemblance of these in vitro models to human cancers and their microenvironments is considered a major reason why many preclinical findings fail to translate directly into clinical applications and the basis of the lack of predictive power of cultured cell-based models for drug efficacy and toxicity in humans [4]. As such, clinical tumor physiology, in addition to molecular and cellular biology, should be considered in the development of improved experimental cancer models.

To improve the clinical relevance of in vitro cancer models, it appears imperative to (i) use clinically relevant cancer tissue/cells that better represent the heterogeneity and complexity of cancers and (ii) mimic the tumor microenvironment more accurately. Although significant progress has been made over the past decade in the design of such models, current approaches still need further refinements that will allow reliable high-throughput analyses. In this review, we will discuss considerations regarding the use of in vitro systems of cancer cells/tissue, and then focus on critical microenvironmental factors observed in patient-derived xenografts and in the clinic that are worth contemplating. While it is expected that it will not be feasible to design in vitro systems that perfectly mimic the malignancy and its microenvironment, since that would likely lead to their loss of simplicity and ease of use, improvements in certain crucial aspects of cancer biology may be considered for the construction of clinically more relevant in vitro cancer models.

2. Tumor heterogeneity and model fidelity

The cellular and molecular heterogeneity of human cancers is well accepted. Tumor heterogeneity presents one of the greatest obstacles in model-based development of cancer therapeutics. Established human cancer cell lines can provide simplified cancer models and are commonly used in the preclinical studies of the disease. Such cell lines are valuable for basic studies but, unfortunately, have limited ability for predicting anti-cancer drug efficacy in the clinic [5]. One reason for this shortcoming is the relatively high homogeneity of established cell lines, a consequence of clonal selection during culturing, which is in contrast with the cellular heterogeneity of the parental tumors (Fig. 1). Furthermore, in vitro culture conditions can introduce additional evolutionary pressures such as oxidative stress [6], leading

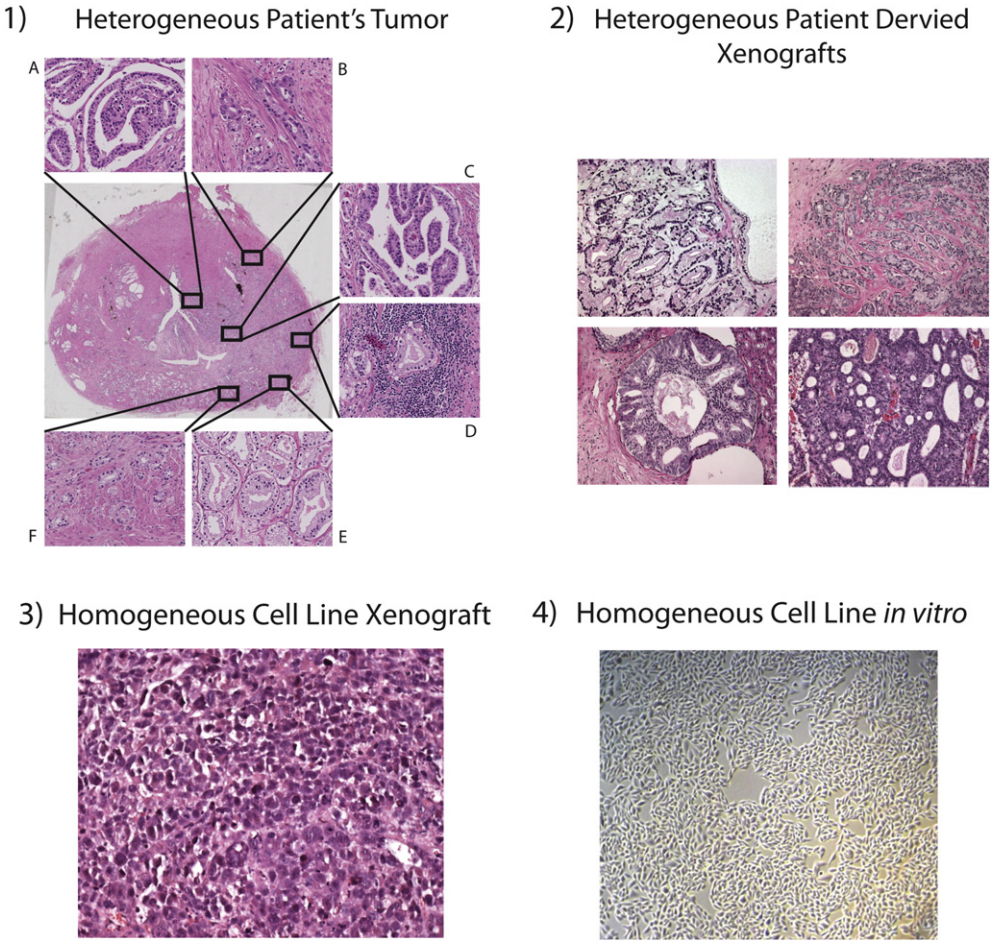

Fig. 1. Heterogeneity of a patient's tumor compared to homogeneity of cell line models. A sectioned whole-mount patient's prostate imaged at different cancerous regions (panel 1) show highly heterogeneous morphology. A–C: pattern of high Gleason grade (Grade 4); D–F: pattern of low Gleason grade (Grades 2–3). While this heterogeneity can be mostly recapitulated in patient-dervied xenograft models (panel 2), it is lost when using a cell line model in vivo (panel 3: image of PC3 prostate cancer cell line tumor grown in vivo) or in vitro (panel 4: image of PC3 prostate cancer cell culture).