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Commentary

Orthotopic tumours, a hot topic for xenograft models?

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It has been reported that nine out of ten attempts to bring a new oncology therapy to the clinic will fail, about half as successful as therapeutic efforts in other fields [1]. Insufficiencies in preclinical animal models are a key factor in the high failure rates of oncology drug discovery and development [2]. The classical models for cancer drug screening include cultured human tumour cell lines and rodent xenografts comprising human cells grown subcutaneously in immunodeficient animals. The ease of maintenance in cell culture and the uniformity in injecting consistent cell counts are advantageous in setting up experimental protocols. One problem with these models is the artificial nature of tumour cell lines, typically passaged for many generations in enriched culture media. These models may not be generally representative of the genetic and epigenetic heterogeneity of the original primary tumour [2,3]. Recently, a novel preclinical cancer model, patient-derived xenograft (PDX), has become increasingly refined and widely used in oncology drug discovery. This model involves the direct implantation, serial transplantation, and propagation of freshly excised primary human tumours into immunodeficient mice to create a primary human tumourgraft. The PDX technique preserves and stabilizes both the genotypic and phenotypic features of the original human tumour [3,4]. PDX tumours retain the architecture and stromal components of the original tumour better than xenograft derived from cell lines and more accurately represent the complex biochemical and physical interactions between cancer cells and their microenvironment, affording a powerful, experimentally rigorous, and more clinically-predictive approach for therapeutic cancer drugs testing.

Although PDXs possess notable advantages compared to classical xenografts, they do have notable limitations. Subcutaneous implantation does not accurately represent all components of the site of origin. This limits studies evaluating the role of the tumour microenvironment as cells of the tumour vasculature, fibroblasts and inflammatory cells, are critical components of tumour biology and in-turn, are key in evaluating cancer-drug sensitivity [5,6]. Orthotopic implantation of tumours, in which placement is based on the corresponding site from which the original carcinoma grew in the patient, is based on Paget's principle that tumour growth is favourable when based in “congenial soil” [6]. Implantation of patient-derived xenografts into their orthotopic location (PDOX) is an approach that best recapitulates the tumour microenvironment [6]. Since 1991, PDOX models have been developed using samples obtained at surgery for patients with colon cancer, pancreatic cancer, gastric cancer, breast cancer, lung cancer and many other cancers [6,7]. The research on adenoid cystic carcinoma (ACC), a rare relentless neoplasm arising in secretory glands, was limited by contaminated cell lines and traditional PDX, and a more accurate model system exhibiting important molecular features of this tumour was needed. To this end, Cornett and coworkers carried out the study published in this issue of *EBioMedicine* [8]. The group performed PDOX in salivary submandibular glands of immunodeficient mice and evaluated the fidelity of ACC during subsequent passages. They found that ACC tumour growth rate was retained within the local epithelial, stromal and neuronal environment. PDOX tumours displayed similar pathological patterns amongst sibling and serial passages, with ACC's hallmark presentations of cribriform, tubular, solid areas and innervation. This highlights the stability within and across multiple passages. Furthermore, genomic and molecular alterations unique to the original ACC were retained. Their data also demonstrates PDOX tumours as a sound model for drug testing [8].

Another major limitation of PDXs is that tumours fail to progress or metastasize and therefore do not precisely model all patterns of the disease course observed in patients [5]. To this point, several reports have shown the advantages of PDOX models. DeRose et al. [9] reported that the establishment of breast tumours into the mammary glands of mice maintain clinical features of original tumours as the majority of mice developed metastases corresponding to patient metastatic sites, including lymph nodes, lungs, bone and peritoneum. Additionally, in a PDOX model of HER2-positive cervical cancer, the study showed differential sensitivity to chemotherapy between primary tumour and metastasis [10], indicating PDOX models are preferable in anti-metastatic drug screening. Unfortunately, in the ACC PDOX study reported in this issue, there was no metastases to the lung or other organs. Further studies will be needed to fully characterize this model using more samples from the patients with metastatic ACC.

The orthotopic implanting of tumour fragments directly into the organ of origin (PDOX) to better-mimic the complexity of human malignancy is becoming a hot topic as a preclinical model for oncology drug discovery. This exciting new model demands further studies and should be extensively adopted.

Conflict of interest

The author declares no conflicts of interest.

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