Mouse xenograft models for elucidating drug resistance mechanisms

Wenfa Ng

Yong Loo Lin School of Medicine, National University of Singapore

Email: ngwenfa@alumni.nus.edu.sg

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Abstract

Chemotherapy is the mainstay in cancer treatment. Nevertheless, divergence of treatment responses exists across patients, often with the underlying mechanisms unknown. More disturbingly, some patients exhibits worsened outcome upon treatment. Genomic approaches hold promise for fundamentally altering the cancer treatment landscape. Nevertheless, the goal of formulating effective personalized treatment by profiling the mutational landscape of primary tumour remains elusive, due to current deficiencies in predicting drug sensitivity from genotype. Xenografts, both indirect (cell line as intermediary) and direct (from primary tumours), are better physiologic mimics of human cancers relative to cell lines and transgenic animal models. Their utility in informing cancer treatment, however, is constrained by high cost of generating and maintaining animals, and the paucity of tissue sample available from biopsies, the latter affecting the site of tissue implantation and, by extension, model relevance. Recent advent of various high throughput profiling techniques finally affords the tools for decoding the expansive molecular fingerprints that encode observed phenotypes in xenografts; thus, providing a holistic set of biological information that justifies their use. This abstract-only preprint describes a short essay that introduces the scientific and clinical possibilities offered by xenografts for understanding drug resistance mechanisms, and validating functional roles of putative mutations as either oncogenes or tumour suppressors. More important, possibility and workflow of generating a predictive platform for informing drug treatment options based on non-invasive blood biomarkers would be discussed. Known as an integrated genomic classifier, combination of physiological response of direct xenografts to drug treatment and bioinformatics-enabled correlation of blood biomarkers with observed phenotype, at cell and animal levels, provides the biological basis for predicting patients' prognosis without invasive biopsy of solid tumours. Elucidation of drug resistance mechanisms via xenograft models entails: (i) recapitulating *in vivo* tumour behavior using primary tissue derived cell lines; (ii) identifying mutations and longitudinal profiling of phenotypic response; and (iii) validating mutations and phenotype via both knockout mice and direct allogenic xenografts. Biological models seek to recapitulate human physiology at specific levels of abstraction for answering targeted questions, but some incongruence is inevitable. Nevertheless, xenografts remain powerful tools for addressing basic, clinical and treatment-related questions using a close functional replica of patient physiology in an animal model. Residual incompatibility between model and observed patient response would require the expertise and clinical experience of oncologists for fine-tuning model suggested drug regimen to particular patient.

Keywords: drug resistance; direct xenograft; indirect xenograft; next-generation sequencing; transgenic mice; tumour suppressor; loss-of-function; non-invasive biomarkers; solid tumour;