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Commentary

Pharmaco-omics data sheds light on therapy-oriented prospects of precision medicine

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HDAC inhibitors have been approved for treatment for hematological cancers and are still under clinical trials for patients with solid tumours [1]. Due to tumour heterogeneity, identification of molecular subtypes benefiting from HDAC inhibitors in solid tumours remains a major challenge. In this issue of EBioMedicine, Yang et al. performed integrative analysis of pharmacological and transcriptomics data in pan-solid tumour cell lines and identified sensitive and resistant gene signatures of HDAC inhibitors, which were able to be generalized to the external assays [2]. Using these signatures, they identified the subtype of low-grade glioma harboring IDH1/2 mutation and non-YAP1-driven subtype of small-cell lung cancer (SCLC) that can potentially benefit from the treatment of HDAC inhibitors. Based on the resistant signature, the combination therapies of BCR/ABL-SRC inhibitor Dasatinib with HDAC inhibitors were further developed for SCLC.

Tumour heterogeneity poses great challenges for anticancer therapies, causing treatment resistance and failure. Thereby accurate patient stratification and rational drug combinations are crucial for patients to gain benefit from clinical practice. Studies over decades have focused on finding molecular subtypes within histopathologically defined tumour types by analysing large-scale genomic, transcriptomic, proteomic and epigenomic alterations. A variety of molecular signatures have been identified to distinguish intrinsic molecular subtypes associated with patient survival, prognosis and response to different therapeutic modalities [3,4]. Nevertheless, to further substantially achieve therapy-oriented prospect underlying complex tumour heterogeneity, a large-scale exploration of compound treatment data is increasingly playing vital role. The NCI-60 Human Tumour Cell Line Screen [5] was the initial project for human tumour cell line anticancer drug screen developed in the late 1980s. The project used 60 different human tumour cell lines to identify and characterize novel compounds with growth-inhibiting or tumour-killing properties. More recently, a series of pharmaco-omics projects were conducted to comprehensively produce compound treatment and high-throughput omics data including mutation, expression and copy number variations. In 2006, Connectivity Map (CMAP) [6] generated a library containing gene expression profiles from compound treatment tested in multiple cells. Subsequently in 2012, Cancer Cell Line Encyclopedia (CCLE) [7] and Genomics of Drug Sensitivity in Cancer (GDSC) [8] performed sequencing of over 1000 tumour cell lines and sensitivity analysis of hundreds of drugs. Following this, the Cancer Therapeutics Response Portal (CTRP) [9] has tested the drug response of nearly 500 drugs against almost 900 cancer cell lines in 2016. In addition, The Cancer Genome Atlas (TCGA) project generated a wealth of genomic, epigenomics, transcriptional, proteomic data and clinical information in patients with 33 cancers.

With the availability of these data, connecting compound treatment and genetic information can yield new insights into novel targets discovery and personalized therapeutics. For example, CMAP created a library of gene signatures connecting to a number of genetic perturbations including compound treatment. A gene signature includes a list of genes whose expressions are changed following compound treatment, whose high similarity with the researcher's own gene signature in a disease context provides the potential novel therapeutics. However, due to the complexity of the CMAP signatures, the interpretation of the results remains an issue. Additionally, GDSC, CCLE, CTRP and NCI-60 datasets measure basal gene expression before compound treatment. Correlating basal gene expression and drug sensitivity is an alternative approach to accurate patient stratification and precision medicine. The study by Yang et al. demonstrated how pharmacological data and transcriptomics data can be integrated and used to stratify the lineage-derived tumours, for improving the therapeutic efficiency and represented a prototype of such analytical strategy applied to HDAC inhibitors in SCLC. Their findings were validated in cell lines and xenografts, and further studies are needed for translating the findings to clinical practice. This could be a proof of principle study applicable to any anticancer drugs for unraveling the subtypes, guided by sensitivity and resistant gene signatures. Similarly, we recently published an integrative pharmacogenomics analysis for the identification of potential drug target casein kinase 2A1 (CSNK2A1) as a mediator of MEK/ERK inhibitor resistance, to overcome MEK/ERK inhibitor resistance in lung cancer cell lines with KRAS(G12C) mutation [10].

There are still great challenges to understand tumour heterogeneity, develop efficient therapeutic options, and translate basic research into clinical practice. Data-driven integrative analysis of public pharmacological and high-throughput omics data can provide new

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insights into our understanding of tumour heterogeneity and speed up discovery of novel therapeutics. The valuable findings on data analysis will move to the next stages in vitro and *in vivo* experiments, and clinical trials. Furthermore, single-cell sequencing technology can also help us understand intra-tumour heterogeneity and provide high-resolution tumour characteristics for developing more accurate and individualized treatment options, for overcoming the primary and secondary drug resistance determined by the intrinsic molecular heterogeneity.

Declaration of Competing Interest

The authors declare no conflicts of interests.

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