PRECISION ONCOLOGY

Drivers of intrinsic resistance

Precision oncology requires an understanding of the genes and pathways that dictate therapeutic response. Through specialized analysis of drug sensitivity patterns across hundreds of genomically annotated cancer cell lines, specific and actionable drivers of intrinsic resistance have been identified.

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There exists a large and rapidly growing armamentarium of drugs targeting diverse biological processes required for cancer cell survival. However, deploying these agents with precision — for example, in the proper tumor genomic contexts or drug combinations — requires a nuanced understanding of the genes and pathways that dictate response to each drug[1,2]. Various correlative and functional approaches have been developed to address this challenge. In this issue of *Nature Chemical Biology*, Rees et al. add a new approach, demonstrating that recurrent, specific and often actionable drivers of intrinsic drug resistance can be identified by carefully integrating transcriptional profiles of cancer cell lines with their drug response behaviors[3].

A growing number of potent and selective drugs against protein targets known to be important in at least some cancer contexts exist. However, in most cases, we lack a complete understanding of the genes and pathways that dictate response to these agents. As such, it is often difficult to define biomarkers identifying tumors that will respond most robustly to these agents or design broadly effective combination therapies. For example, even for highly studied drugs like the clinically approved EGFR, ALK and BRAF inhibitors, our incomplete understanding of the secondary determinants of response makes it difficult to predict which patients, among those harboring sensitizing *EGFR*, *ALK* and *BRAF* alterations, respectively, will exhibit intrinsic resistance or how to overcome that resistance[4]. This problem is even worse for molecularly targeted therapies related to processes such as chromatin regulation or cellular metabolism, for which even primary response determinants are often still undefined.

Several approaches have been developed in recent years to address this problem. By correlating the presence or absence of specific genomic alterations (most commonly, mutations or copy number alterations) with drug response across

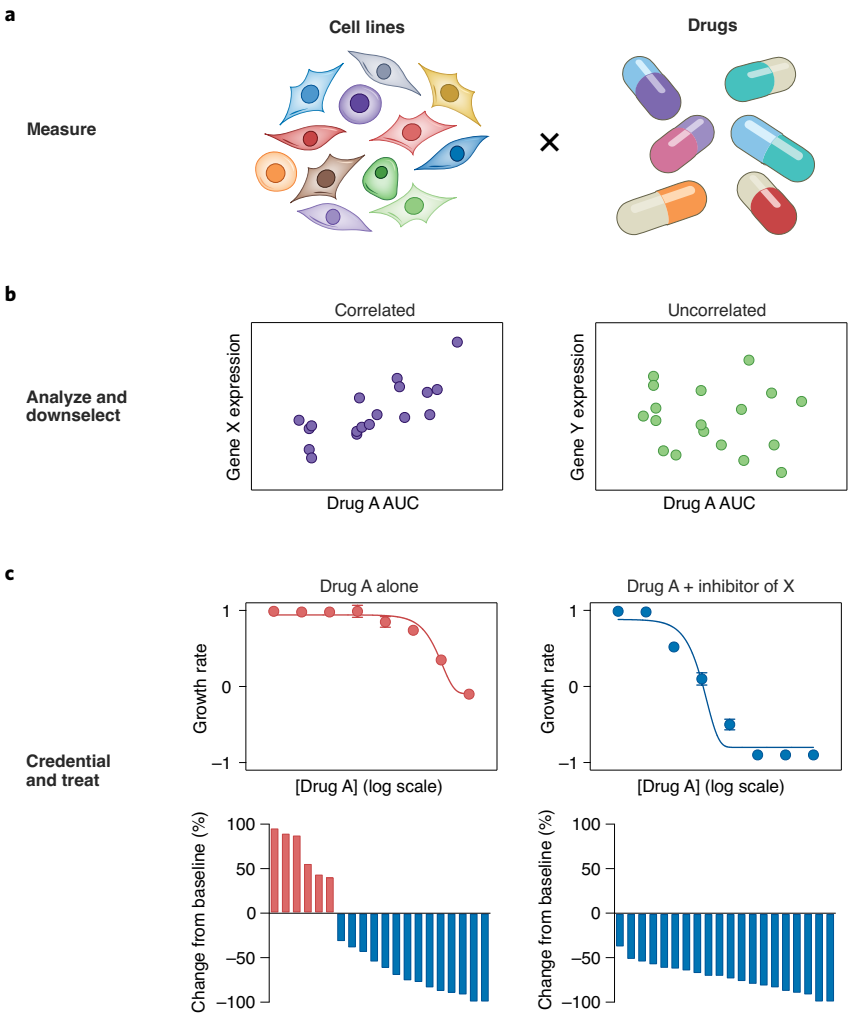

Fig. 1 | Discovery of actionable genes driving intrinsic resistance. a–c, Using data from large pharmacogenomic datasets describing the responses of hundreds of genomically credentialed human cancer cell lines to diverse drugs (**a**), investigators identified those genes whose expression levels across the dataset positively correlate with measures of drug potency such as area under the curve (AUC) (**b**, left), in contrast with most genes whose expression levels are uncorrelated (**b**, right). Down-selection steps enabled the removal of genes whose expression levels serve as proxies of other co-expressed genes and those that are correlated with sensitivity to large numbers of drugs. The remaining, high-priority candidate genes can then be credentialed to identify those that functionally drive intrinsic resistance, enabling the potential identification of combination therapies that overcome this resistance, thereby leading to more penetrant and durable therapeutic responses (**c**).

diverse cell lines or even human tumors, it is possible in principle to identify biomarkers of response and resistance, but only if those responses are being driven by the genomic features that are being measured[5–7]. Functional genomic screens—which use, for example, CRISPR–Cas9, RNA interference (RNAi) and open reading frame (ORF)-based libraries to systematically activate or repress the functions of genes across the genome—readily identify genes that can regulate drug sensitivity[8]. However, it is often difficult to define which of the many genes identified in these screens are the true drivers of response and resistance in human tumors. Finally, by screening libraries of drugs to identify those that sensitize cancer cells to a given primary drug, it is possible to identify mechanisms of intrinsic resistance and potential biomarkers of response[9]. However, performing such screens across cell lines and primary drugs, to gain a broad understanding of the sensitivity landscape of existing targeted therapies, requires an experimental scale that is currently infeasible. Further, this approach can only identify response determinants targeted by specific, potent drug compounds found in the screening library.

Taking advantage of two large pharmacogenomic datasets comprising hundreds of human cancer cell lines with deeply annotated genomic, transcriptomic and drug response features[5–7] (Fig. 1a), Rees et al. tested the hypothesis that the basal expression levels of genes driving intrinsic resistance may be inversely proportional to drug sensitivity[3]. After calculating the correlation between each drug's potency and the expression levels of all individual genes across cell lines (Fig. 1b), the authors took the important step of removing genes that serve as proxies of other co-expressed genes, in the process removing some 80% of significant gene–drug relationships. Next, they defined the selectivity of each gene's effect, which allowed them to exclude genes whose expression levels are correlated with sensitivity to large numbers of drugs, surmising that such genes are likely to mark tissue lineage or differentiation state instead of mechanistic resistance pathways or transporters. Of the drug–gene relationships that remained, most were reproduced using two distinct measures of association. The authors then functionally validated a panel of candidate intrinsic resistance driver genes by demonstrating that forced expression of each gene of interest conferred resistance to its associated drug, whereas pharmacological inhibition of the same genes enhanced sensitivity to the drug, often rendering even highly resistant cell lines quite sensitive (Fig. 1c). In one particularly interesting example, they demonstrated that the expression of *MGLL* or *CES1*, which encode serine hydrolase enzymes, drives strong intrinsic resistance to GSK-J4, an annotated inhibitor of the histone lysine demethylases KDM6A/B, but not to other compounds with shared structural features or targets. This paradox was explained by their subsequent discovery that MGLL and CES1 enzymatically convert GSK-J4 to a related compound known as GSK-J1, blocking the precursor compound from driving copper-dependent, likely KDM6A/B-independent cell death.

This study demonstrates that by accounting for gene co-expression and gene–drug specificity, it is possible to use relatively simple measures of gene expression–drug sensitivity correlation, applied to large existing pharmacogenomic datasets, to identify robust drivers of intrinsic resistance that are likely to serve as both biomarkers of response and targets for therapies designed to overcome this resistance. Further, the authors provide a tool for potentially selecting compounds that inhibit a desired target while avoiding undesired metabolic or efflux regulation that may affect other drugs in the same target class. By implementing the analytical filtering steps described in this study into publicly available pharmacogenomic data portals or even appropriately designed clinical studies, interested users will be empowered to more effectively distinguish specific and functional drivers of intrinsic resistance from mere gene expression correlates. Future studies that combine this approach with complementary measures of biochemical pathway activation (mutational data, expression data for multiple pathway members or phosphoproteomic data, for example), or results of functional genomic drug modifier screens, may conceivably increase users' power to define functionally important and actionable resistance mechanisms, even when multiple such mechanisms exist for a given drug. Together, the principles outlined by Rees et al.[3] provide an important new tool that, when used alone or integrated with other complementary strategies, will accelerate progress in the development of cancer therapeutics. ❐

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Competing interests

The author declares no competing financial interest.