CHEMICAL BIOLOGY

Small molecules as geneticists

Stuart Schreiber and colleagues show how small molecule sensitivities can be used to probe the natural genetic variation present in populations of organisms.

Although most laboratories have relied on genomics and proteomics approaches to provide biological insights into the function of organisms, the Schreiber lab at Harvard University's Broad Institute uses biological chemistry to this end. Their previous work has concentrated on using small molecules to manipulate cells as well as map the effects of artificial genetic mutations. With their recent publication in *Chemistry & Biology*, however, their lab has entered a new area: determining phenotypes resulting from natural genetic variation (Perlstein *et al*., 2006).

Ethan Perlstein, the graduate student who helped pioneer this project, says, "[This work] all started when another author, Stephen Haggarty, and I read a paper in *Nature* that was published a couple of years ago" (Steinmetz *et al*., 2002). The authors were dissecting a complex trait in yeast that had pathogenic relevance. Perlstein and colleagues obtained the strains and started to screen them using small molecules with the goal of finding good candidate compounds for antifungal use. They soon noticed patterns of sensitivity that were too complex to be to the result of variations in a single gene. This made them wonder whether the antiproliferative effects of different compounds could be used to segregate yeast on the basis of multiple natural genetic variations.

By mating two haploid yeast strains and testing the sensitivity of the progeny resulting from random genetic recombination to various compounds, they were able to determine whether sensitivity resulted from single or multiple linked or unlinked loci. Furthermore, groups of related compounds could be clustered based on the loci involved in sensitivity. Such grouped compounds tend to display similar mechanisms of action, showing how the method could be used to characterize unknown molecules.

Schreiber says, "Looking at loci in the genome that correlate with sensitivity of resistance can be a very powerful way of understanding the mechanism by which these cells are being perturbed by these small molecules." Work on mapping the loci responsible for resistance to these small molecules has continued. Schreiber says that in yet-to-be-published studies they have validated that these loci correlate with specific genes and have identified copy-number polymorphisms and single-nucleotide polymorphisms that correlate with sensitivity or resistance.

Perlstein considers this a practical approach for other organisms, too: "You could probably generalize this to most unicellular eukaryotes that you can grow in multiwell plates." Current genotyping efforts even make it possible to translate this method to mammals. Schreiber says, "With David Altschuler we're using the cell lines that were the basis of the human HapMap…, and with Mark Daley, also at the Broad Institute, we are looking at genotyped mice."

Such studies should provide valuable insights into the mechanisms of action of small molecules. If the mechanisms of toxicity of small molecules and off-target effects could be determined and linked to natural variation in the human genome, it should be possible to determine a drug's efficacy and toxicity within the variable patient population. Such information would help in the design of more effective clinical trials and could ultimately lead to designer medicines tailored to each individual's genotype.

Unsurprisingly, these screening experiments require new methods for handling and analyzing the unique data being generated to find useful correlations. To tackle these challenges, Schreiber's group has built a robust data import pipeline and analysis tools that they want to make publicly available through the ChemBank public database, which should make it much easier for other groups to apply this powerful methodology to their own organism or small molecules of interest.

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RESEARCH PAPERS

Perlstein, E.O. *et al.* Revealing complex traits with small molecules and naturally recombinant yeast strains. *Chem. Biol.* **13**, 319–327 (2006).

Steinmetz, L.M. *et al*. Dissecting the architecture of a quantitative trait locus in yeast. *Nature* **416**, 326–330 (2002).