The Awesome Power of Synergy from Chemical-Chemical Profiling

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DOI 10.1016/j.chembiol.2010.08.002

Chemical-chemical profiling, as described in Farha and Brown (2010), delivers all the power of chemical-genomic profiling while untethering researchers from model systems and thereby enabling us to pursue cell-based drug target identification in almost any organism.

Chemical genomics approaches enable us to explore the targets of bioactive compounds and usually involve screening via functional genomic resources, such as genome-wide gene deletion or gene overexpression libraries, for chemical response. In general, chemical genomics requires a genetically tractable model organism because they facilitate the development of the relevant functional genomic resources. Consequently, the field of chemical genomics has largely been developed with the exclusion of undomesticated but important organisms, such as our own pathogens. However, here in this issue, Farha and Brown (2010) describe a very simple but new and systematic approach for target identification in cell-based systems and, significantly, one that does not depend on a specialized model organism.

A major advantage of a model system is that a genome-wide set of genetic interaction profiles serves as a key for interpreting chemical-genomic profiles, which enables us to link previously uncharacterized compounds to their cellular targets (Costanzo et al., 2010). Building upon drug synergies, chemical-chemical profiling uses the same concept of chemical-genomic profiling to probe for interactions between unknown compounds and their target pathways; however, genes are reversibly inhibited using chemicals of a known target and mode-of-action (MOA), rather than deletion to render a gene nonfunctional (Figure 1A). With a sufficient collection of diverse reference drugs of known action and target, one can screen for synergistic (or antagonistic) interactions and create a profile much

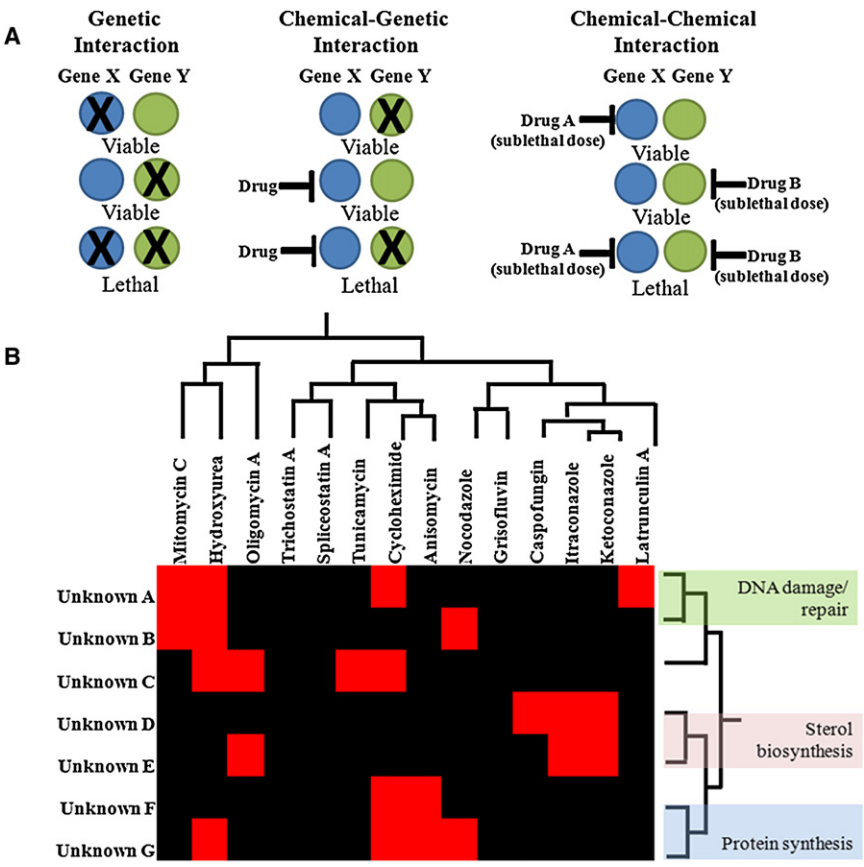

Figure 1. Comparison of Genetic, Chemical-Genetic, and Chemical-Chemical Interactions

(A) Two interacting gene products are presented as blue and green with the phenotype presented below. In genetic interactions, two genes are inactivated via targeted deletion and the resultant double mutant assessed for viability (Tong et al., 2004). In chemical-genetic interactions, one gene product is inactivated via gene deletion and the other is inactivated by chemical inhibition (Parsons et al., 2006). In a chemical-chemical interaction, the activities of two independent compounds are synergistic. A library of unknown compounds can be screened against a suite of known compounds of diverse targets and modes-of-action to create a chemical-chemical profile of interactions (B) (red indicates a synergistic interaction), and used to predict the target process of unknown agents. Here, known compounds on the x axis are clustered based on mode of action, and the y axis shows clustering of unknowns with similar profiles. This example is specific to antifungal agents.

like a chemical-genomic or genetic interaction profile that leads to a prediction of an unknown compound's MOA and target (Figure 1B).

Using chemical combinations to probe genetic networks is an area of active research, and has potential not only in identifying genetic interactions, but also in developing polytherapies for drug-resistant pathogens using approved drugs (Lehar et al., 2007, 2008; Jansen et al., 2009). The step taken by Farha and Brown (2010) was to use the phenomena to systematically screen a number of novel compounds to predict MOA. They describe a synergy screen of 186 unknown bioactive compounds against 14 well-known bioactive compounds, identifying 255 synergistic combinations. The authors then used the chemical-chemical interaction profile to predict the mode-of-action of two unknown bioactive compounds. This is the first report that uses simple synergy screening to derive predictive information on unknown compounds. While the predicted targets presented require detailed validation via more traditional biochemical and biophysical methods, this method may significantly shorten the steps from hit to putative target in alternative systems.

Because a deletion collection is not required, there is no prerequisite model system, enabling chemical-chemical profiling of unknown compounds with almost any microorganism. Moreover, while the authors have demonstrated their chemical-chemical profiling concept using *E. coli*, it can be extended to eukaryotes as well. Farha and Brown (2010) lay the groundwork for further developing chemical-chemical profiling, but this well-informed approach is limited by a small number of compounds with specifically-defined targets, which anchor the profiles in a mechanistic understanding.

Nevertheless, the power of chemical-chemical profiling lies in its simplicity and broad application. As long as you have a set of compounds with known and diverse targets in an organism, you can test for synergies and create a profile for target prediction in nearly any system. Moreover, as more screens over a broader taxonomic range and chemical space are conducted, the chemical-chemical profiles will increase in complexity and subsequent information. These data will greatly benefit from a centralized database of chemical-chemical as well as chemical-genomic and genetic interactions. The next decade of chemical genomics will see an exponential increase in data generation and target identification, which will undoubtedly lead to novel chemical probes and accentuate the power of this approach. With the system-independent tools as described in Farha and Brown (2010), we can now start to explore broader evolutionary questions of genetic networks, or screen novel compounds libraries against emerging or resistant infectious pathogens, expanding the field beyond the awesome power of our favorite model organisms.

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