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Chemical Genomic Approaches to Study Model Microbes

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Abstract

Ascent genome-scale analyses of genetic interactions in model microbes have revealed the inherent functional organization of the cell as a dense network of highly interconnected pathways. While classical one gene at a time paradigms offer limited insight into cellular systems, genome-scale approaches are making considerable headway. Indeed, where small organic compounds are ideal probes of biological complexity, systematic chemical genomic methods are emerging as requisite and powerful approaches to describing both the small molecule probe and network with which it interacts. Here, we highlight various chemical genomic approaches that are being pioneered in model microbes.

Introduction

In light of the explosion in sequencing efforts and the expansion in genome-scale approaches to chart genetic interactions, our view of the cell is changing. With this new wealth of information comes a new appreciation and understanding of complex biological systems. While classical genetics has played a pivotal role in elucidating biology by investigating relationships between genes and phenotypes, we are now increasingly turning to small molecules as modulators [1]. The thesis is that small molecules are ideal probes of biological systems with advantages over genetic manipulation. It has been pointed out that genetic inactivation is effectively permanent and technically tedious, even in the most tractable systems, and that these limitations can be circumvented through the use of small molecules.

Probing biological functions with small molecules has helped elucidate functional roles for enigmatic areas of biology in which conventional genetic and biochemical approaches have provided limited understanding. Insights gained over the last 80 years into microbial physiology have frequently come from efforts to understand the mechanisms of action of antibiotics discovered during this same period. Indeed, our understanding of basic processes of nucleic acid, protein, and cell wall synthesis has often been due to remarkable discoveries in model microbes, enabled by antibiotic compounds. Despite the advantages of small molecules as probes, efforts to discover and characterize their interactions within biological systems have been narrowly focused and limited for the most part to traditional nongenomic approaches [2]. The new understanding of cellular complexity that has come from large-scale studies of protein and genetic interactions, has sparked a demand for genome-scale techniques to characterize both new and old chemical probes. Such chemical genomic methodologies, it is reasoned, more fittingly describe complex biology by informing on how network components interact to produce physiological responses or maintain phenotypic stability under states of stress.

Along with providing a global view of the biological system under study, chemical genomics also provides remarkable new tools to understand the mechanism of action of small molecules of unknown function. This is a daunting hurdle in both new probe development and in drug discovery. Classically, protein targets have been identified through biochemical screens using labeled or immobilized molecules. A growing repertoire of new approaches to study the mode of action of small molecules now includes transcriptional profiling, network inference models, small-molecule, as well as protein microarrays. Further, breakthrough genome-scale approaches in *Saccaromyces cerevisiae*, which take advantage of its diploid nature, have emerged and been successful in identifying cellular targets of small molecules. Chemical genomic strategies have also advanced the field of natural product research by facilitating the characterization of the ever-increasing repertoire of novel natural products. These studies in yeast were among the first to yield biological insights in response to chemical perturbants on a network level and have inspired the establishment of postgenomic tools in a variety of bacterial organisms. The present review emphasizes the successful use of these approaches in model microbes, principally bacteria and yeast. Chemical genomics in *S. cerevisiae* has been recently reviewed and accordingly, we have emphasized principles and included work in bacterial systems here. The value of genome-wide approaches in tackling cellular complexity and exploiting the activity of small molecules is enabling biological investigations previously not deemed possible [3]. Herein, we describe the emerging tools for chemical genomic studies including genome-scale clone sets, microarray-based transcriptional profiling, chemical proteomics, and computational methodologies, highlighting success stories of intriguing biological and mechanistic findings.

Genome-Scale Clone Sets—Altering Gene Dosage to Infer Function

With the availability of comprehensive genome sequence information, it was inevitable that efforts would follow to construct elaborate genome-scale clone sets well suited to studying genetic and chemical-genetic interactions. Chemical genomics has been best established with extraordinary genomic tools available for the baker's yeast *Saccharomyces cerevisiae* Among the most exciting developments in genome-wide approaches has been the creation of barcoded homozygous and heterozygous deletion clone sets where high-throughput competitive growth assays have allowed the parallel study of multiple *S. cerevisiae* strains. Thus, by exploiting the diploid nature of *S. cerevisiae*, the effect a small molecule has on the fitness of a particular strain can be examined when gene dosage is tuned from 0% [4].

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Promoter-Reporter Construct Libraries

Bacterial promoter-reporter construct librarie have also found utility in chemical genomic studies in assessing transcription patterns on a global level in response to small molecules. In contrast to microarray technology, these libraries provide high resolution, data-rich time courses of promoter response to bioactive small molecules. These advantages facilitated the investigation of the action of antibiotics in *Salmonella typhimurium* at subinhibitory concentrations. Here, significant transcriptional activation of various promoters revealed that antibiotics can have multiple effects on the cell by acting as chemical signals to control bacterial metabolic processes, suggesting a new role beyond therapeutic utility.

In 2006, Zaslaver et al. reported on the creation of a transcriptional fusion promoter library in *E. coli* , where ~2000 promoters were fused to *gfp*. Using this library, Bollenbach et al. looked to shed light on the mechanism of suppressive drug interactions between [5] DNA and protein synthesis inhibitors, whereby the combination of the two allows the cells to grow faster. Examination of the expression profiles of ~200 *E. coli* promoters in response to different antibiotics revealed that ribosomal levels are not optimally regulated under conditions of DNA stress, causing an imbalance between DNA and protein levels. Reducing protein levels with protein synthesis inhibitors restores this imbalance allowing cells to grow faster; this same trend is observed when mutations in the ribosomal RNA operons impinge on ribosome synthesis. Overall, promoter-reporter construct libraries provide a unique look at expression dynamics in cells and can reveal fascinating roles for even the most well-established antibiotics.

Conclusions

Microbial systems, characterized by redundant and complex functional pathways typify the modern view of the cell and, as such, modern technologies, used to perturb, explore, and even reconstruct these systems, are increasingly touted for studying biological systems.

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Conflict of Interest:

None

References

1. Frauchiger MT, Wenk C, Colombani PC (2004) Effects of acute chromium supplementation on postprandial metabolism in healthy young men. J Am Coll Nutr 351-357.
2. Joseph LJ, Farrell PA, Davey SL, Evans WJ, Campbell WW (1999) Effect of resistance training with or without chromium picolinate supplementation on glucose metabolism in older men and women. Metabolism 546-53.
3. Volpe SL, Huang HW, Larpadisorn K, Lesser II (2001) Effect of chromium supplementation and exercise on body composition, resting metabolic rate and selected biochemical parameters in moderately obese women following an exercise program. J Am Coll Nutr 293-306.
4. Bailey CH (2014) Improved meta-analytic methods show no effect of chromium supplements on fasting glucose. Biol Trace Elem Res 1-8.
5. Althuis MD, Jordan NE, Ludington EA, Wittes JT (2002) Glucose and insulin responses to dietary chromium supplements: a meta-analysis. Am J Clin Nutr 148-55.