Abstractions

LAST AUTHOR

Susceptibility to many common conditions and diseases, from obesity to cancer, involves the combined effects of many genes and of the many environmental factors that influence how these genes function. On pages 423 and 429, Eric Schadt of Rosetta Inpharmatics in Seattle, Washington, and his colleagues detail an approach to identifying such 'gene networks' — an advance that could potentially lead to diagnostic markers and therapeutic targets for common diseases.

When did you realize a gene-network approach was needed?

During my graduate training in mathematics and molecular biology, I realized that many changes — and not just at the DNA level — lead to disease. When I started this work in 2000, very few people thought this way. Luckily, our collaborators at the Icelandic pharmaceutical company deCODE Genetics and at the University of California, Los Angeles, immediately joined our push towards a more holistic, gene-network approach.

Is the traditional, reductionist appoach of searching for 'the disease gene' pointless?

Absolutely not. Genome-wide association studies comparing individuals' genomes identify the dominant genetic variations that lead to disease — if not 'the disease gene'. We've developed statistical methods to determine connections among genes on the basis of their activities in different tissues. We then combine these findings from humans with mouse models of disease to assess how perturbations to gene-expression networks could cause disease traits.

What computational power is involved in this approach?

We needed high-performance computing equivalent to 7,000 central processing units. Without that scale of computational horsepower, we couldn't have done this work.

Is Merck, Rosetta's parent company, adopting this approach?

Yes. Once you know how a whole network of genes is perturbed, you can better assess the best points for therapeutic intervention.

Are clinicians collecting the samples necessary for these types of studies?

Not as quickly as we'd like, but once clinicians see the point they will do it. To uncover the relevant gene networks, we need complementary sets of disease and normal tissues. For example, one clinician is collecting matched liver, stomach and fat tissues from his gastric bypass surgeries. These samples will help us to determine why the severity of diabetes is often greatly reduced following surgery. ■

MAKING THE PAPER

Benjamin List

Getting acetaldehyde to behave as a substrate for organic synthesis.

N. STARNICK

Organic chemists had all but given up on acetaldehyde when it came to certain types of reactions because this deceptively simple molecule has a tendency to go through many side reactions. Benjamin List's group at the Max Planck Institute for Coal Research in Mülheim an der Ruhr, Germany, have managed to tame the highly reactive molecule and use it in the Mannich reaction (a process for forming carbon–carbon bonds), opening the door to a broad range of applications in drug design.

Many small biological molecules come in two mirror-image forms, or enantiomers, that can have dramatically different biological effects. Chemical reactions that produce one enantiomer only were thought to be catalysed by either enzymes or heavy metals. But simple organic molecules such as amino acids recently burst on the scene as a third class of inexpensive catalysts for reactions with enantiomer selectivity, which are required for drug synthesis.

In 2000, List used the amino acid proline to catalyse a Mannich reaction — which combines a carbonyl, an aldehyde, and an amine compound to produce β-amino carbonyl compounds, and is used widely in the synthesis of biologically active molecules, including medicinal drugs. The new proline-catalysed Mannich reaction yielded high amounts of only one enantiomer.

But the simplest of all substrates, acetaldehyde, still wouldn't work. Acetaldehyde has many desirable qualities for chemistry: it's a small, plentiful and inexpensive molecule. But it also likes to react with itself. "The general feeling was that it would not work because it was considered a really troublesome reagent," says List.

His view changed in 2006, when his group discovered that the substrate *N*-tert-butoxycarbonyl (*N*-Boc)-imine gave very high amounts of essentially a single enantiomer in proline-catalyzed Mannich reactions. "Because these reactions were so extremely efficient, we decided to give acetaldehyde another try," says List.

The first time List's group tried combining acetaldehyde with *N*-Boc-imines in a proline-catalysed Mannich reaction they obtained only about 1% of product. "The yields were tiny, but the product was formed as essentially a single enantiomer, so in a sense this was encouraging," he explains.

Over the next few months, colleagues tried to improve the yield without much success. Then, during a Monday morning jog, inspiration struck and List realized how to tackle the problem. Back in the lab he put together a four-person team that sketched out the different conditions to test and what kind of products they should synthesize to demonstrate the reaction's applications. Four weeks later they had accomplished their goal (see page 453). They had optimized the reaction and were able to synthesize a newly approved anti-AIDS drug and several other biologically active substances .

List says pharmaceutical companies have already expressed an interest in this work and a number of researchers, including himself, are trying to use acetaldehyde in other types of chemical reactions. "The biggest challenge was not really a technical or chemical one but rather having to give up the notion that it was impossible to use acetaldehyde in these types of reactions," he says. "It was not easy to convince ourselves that this would work, given the initial ridiculous yields." ■

FROM THE BLOGOSPHERE

There is never a dull moment on 'In the Field', *Nature* reporters' blog for scientific conferences and events. Rachel Courtland recently blogged from the American Physical Society conference in New Orleans (http://tinyurl.com/37jjuy) on a Town Hall talk on ultra-high pressures: "The basic idea? Squeeze hard on any element, ratchet up the temperature, and you end up with some unexpected new phases. At high enough pressures and temperatures, ordinary, transparent water becomes opaque. Push even further, and it becomes transparent. Dive down into Jupiter's atmosphere, and the pressures quickly become so high that even hydrogen becomes metallic."

Simultaneously, Eric Hand was rocking at the lunar and planetary science conference in Houston (http://tinyurl.com/3axrrc). Read about the graduate student who was shot at Northern Illinois University, but still turned in his conference poster on time, and enjoy a valedictory account of NASA administrator Mike Griffin's lecture and the characteristically blunt question and answer session that followed it. ■

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