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Omic omen for environmental health research

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The genocentric view that bad genes cause disease is no more. In its place, integrating 'omic' approaches, including proteomics and metabonomics, with toxicogenomics is the way to untie the Gordian knot of gene-environment interaction, says a US environmental health expert.

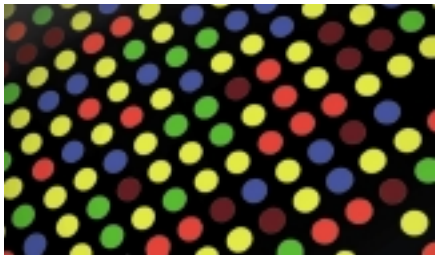
Disease development and the environment

The environment plays a bigger role in disease development than previously thought, says Kenneth Olden, director of the National Institute of Environmental Health Sciences (NIEHS; http://www.niehs.nih.gov) in Research Triangle Park, North Carolina, USA. 'Genetics loads the gun, but it's the environment that pulls the trigger,' said Olden.

Historically, toxicologists were limited to studying the effects of an environmental agent on just one enzyme or one metabolic pathway at a time. But now that the human genome has been sequenced, and DNA microarrays can fingerprint changes in the expression of thousands of genes at a time, the field of toxicogenomics – using genomic technology to decipher the interactions of several enzymes or pathways – is burgeoning.

Genetic polymorphisms

Manipulating human genes is tricky, therefore, an easier way to correct gene expression might be to understand how an environmental agent interacts with a gene and use that information to develop molecular interventions. To this end, the Environmental Genome Project was created at the NIEHS, which this



year announced that 217 of 544 environmental response genes have been completely resequenced for the purposes of identifying polymorphisms, variations in coding sequences that are believed to make each of us more or less susceptible to environmental exposures.

Paraoxonase (PON1), an enzyme known to metabolize organophosphorous insecticides, provides a good example of how genetic polymorphisms influence susceptibility to environmental toxins. Studying those polymorphisms demonstrates how toxicogenomics can unearth molecular mechanisms of disease that go beyond toxicity.

PON1 has two single nucleotide polymorphisms in the coding region, which lead to a change in amino acid sequence in the translated protein, increasing or decreasing the catalytic activity of the enzyme, depending on the substrate. Another polymorphism in the promoter region determines the level of PON1 expression. By using transgenic mice, knockouts that do not have PON1 and mice that express one or the other allele of the human PON1 on a knockout background, researchers recently discovered that both the level and type of PON1 expressed is important in determining susceptibility to certain insecticides. For example, an arginine substitution at one of the positions makes PON1 much better at metabolizing the pesticide paraoxon compared with a glutamine substitution at the same position.

The studies also uncover a surprise. PON1 polymorphisms might be important risk factors in the development of heart disease. PON1 investigator Lucio Costa, Professor of Environmental Health and Director of the Toxicology Program at the University of Washington in Seattle (http://www.washington.edu), explains that paraoxonase is tightly bound to high density lipoproteins (HDL) in the blood, appearing to play a role in the metabolism of oxidized lipoproteins. 'It's kind of the anti-oxidant component of HDL particles,' he said. PON1 polymorphisms might also be involved in the metabolism of cholesterol-lowering drugs, like Lipitor, demonstrating how omic approaches might help predict the efficacy of pharmaceuticals in individuals.

Revolutionizing drug discovery

Olden's data, presented at the *5th Congress of Toxicology in Developing Countries*, 10–13 November 2003 in Guilin, China (http://www.ciccst.org.cn/5ctdc/), will be published in the January issue of *Current Genomics* (http://www.bentham.org/cg/index2.html). They represent 'a whole new way of risk assessment,' said Olden, and reject the old 'one size fits all' assumption.

Costa agrees that the possibility of unraveling gene-environment interactions, clueing in on the pathophysiology of certain diseases and revolutionizing drug development is 'very exciting.' Nevertheless, he warned, 'The field is still in its infancy.'

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