The FAT of the land

A budding new area of science means we can now get a snapshot of the health of an animal or plant long before it shows signs of serious problems. **Mark Viant** explains.

The author Mark Viant.

Doctors know high cholesterol levels mean a bigger risk of heart disease. Similarly, increased levels of glucose in a person's urine potentially mean diabetes of some sort.

Analysing fats and sugars and other chemicals provides an excellent way of getting a snapshot of people's health. The tests are often simple and don't require surgery. More importantly, they give early warnings of potential problems – before a patient even feels sick, or worse, dies. When doctors do these kinds of tests, they are looking at a person's metabolism; the fats and sugars are the metabolites.

In the last decade, a whole new area of research has sprung up to investigate the links between metabolic changes and an individuals genetics and lifestyle. But it goes much further than human health. We can use it to get a snapshot of the health of any living organism.

This new area of research is known as metabolomics. It is the next step in a line of 'omic' technologies that began with genomics – the study of genes and their functions.

One of the great challenges for environmental scientists is to develop tools to quantify how wildlife responds to a changing environment. Traditional methods, such as counting individuals to determine if a population is declining in response to stress, are inadequate. They are insensitive and have little predictive value. Worse still, they often rely on animals dying to indicate the health of a habitat. This is where metabolomics enters the picture.

Simple tests for fats, sugars and other biochemicals can be good for identifying particular problems. But metabolomics is much more powerful. It uses advanced measurement techniques that are more traditionally associated with an analytical chemistry laboratory to look at the 'downstream' effects of gene expression: genes code for proteins that eventually control the amounts of sugars and fats.

The advantage of metabolomics is it can measure tens, hundreds or even thousands of metabolites simultaneously, giving a snapshot of the biochemical processes going on within a cell at a given time in response to external pressures.

Fat and sugar levels give an early warning of potential problems – before a patient even feels sick, or worse, dies.

We can use it to create a specific biochemical signature – a metabolic fingerprint – for each individual plant or animal. And the key point is that different parts of the fingerprint will change in response to different stresses. This means the fingerprint has enormous diagnostic potential. It is also really helpful that these molecular changes occur early in the stress response, long before the organism becomes sick or dies.

The idea is like how miners used canaries to predict if the air in a mine was contaminated. But this new technology provides a much more sensitive molecular signal.

In November 2003, I started my NERC Advanced Fellowship in metabolomics at the University of Birmingham. I wanted to use new metabolomic methods to see how fish and aquatic invertebrates responded to pollution.

At that time hardly anybody had heard of metabolomics. The few environmental studies that did exist were toxicity experiments in terrestrial animals by scientists at Imperial College London and the Centre for Ecology & Hydrology at Monks Wood.

Around the same time several exciting metabolomics studies revealed a new insight into drug toxicity and gene function. But therein lay my first challenge. These pioneering studies were done on organisms in controlled laboratory environments, with a consistent food supply, temperature, light cycle etc. And the animals were typically of similar age, of the same sex and known genetic strain.

This biological similarity of the animals and the consistency in their environment meant that their metabolic fingerprints were also quite similar. The researchers could introduce a particular stress – a change in food supply or exposure to a drug – and detect this as a specific change to these fingerprints.

Mussel men

In my 'wisdom', I had embarked on a very different venture. In choosing to study marine mussels along the UK coastline, I was working in a constantly changing environment. I had no control over diet, water and air temperatures, tidal and light cycles. On top of this, the mussels were of unconfirmed species and unknown sex and age.

The problem with my approach was that, collectively, the wide variability threatened

Sampling mussels from the rocks at Port Quin, Cornwall.

Marine mussels used in the metabolomics studies.

to produce such highly diverse metabolic fingerprints across a population of mussels that they would obscure or perhaps completely swamp the molecular changes induced by a man-made stress. That would have resulted in a rather depressing start to my fellowship!

Working with my first now-graduated PhD student, Adam Hines, to our great surprise we found that our coastal mussels had much more consistent metabolic signatures than mussels that had spent a couple of days in a temperature- and light-controlled marine laboratory. And we found these metabolic signatures were a gold mine of information, with unique fingerprints for different species and for each sex.

This quickly highlighted our naïve understanding of mussel biochemistry. Just picking one example, we discovered that the amino acid glycine exists at much higher concentrations in the reproductive tissues of male mussels compared to females. This is the first time this observation has been reported for any species. In general, glycine is known to help with the process of osmoregulation – it helps maintain the correct balance between water and salts within cells. At this point we can only speculate on the role of glycine in male mussels, but we believe it's the male's sperm that have high amounts of glycine to protect against the high salinity of the seawater.

The most beautiful results came from research with scientists at the Centre for Environment, Fisheries and Aquaculture Science (Cefas)*. We showed a clear cyclical pattern in the biochemical fingerprints of mussels as they progressed, month by month, through their annual reproductive cycle.

This is the first time anyone has measured the complete seasonal changes in metabolism in this way. The information is invaluable for deciding at what time of year to carry out environmental monitoring, that is, when the natural biological variability between the mussels is small, so that metabolic fingerprints resulting from environmental stress can be most readily detected.

Ultimately, unravelling the baseline metabolism of organisms living in a pristine environment gives us essential reference data for working out if animals from other sites are healthy or not. We are now comparing mussels and European flounder across many pristine and industrialised sites**.

Monitoring pollution

We have discovered that animals from different sites have distinct metabolic fingerprints that are likely caused, in part, by exposure to pollutants. Our next task is to understand exactly which parts of this fingerprint are driven by pollution. This will help measure environmental quality.

The Birmingham team is now unravelling the metabolic disruption caused by liver cancer in dab flatfish, again in collaboration with Cefas. But our research subjects range from the very small – single water fleas – to the large – grey seals, with the Sea Mammal Research Unit in St Andrews.

So what next? It is now clear from research emerging in several countries that metabolomics has an important role to play in the environmental sciences. NERC has just funded an expansion of its former Molecular Genetics Facility (see News p2) to include both a metabolomics centre at Birmingham and a bioinformatics centre at the Centre for Ecology & Hydrology, Oxford.

The new facility at Birmingham will give UK environmental scientists access to world-class analytical and computational facilities for metabolomics research.

We are also working on several NERC Knowledge Exchange activities to promote the omics technologies within regulatory science, particularly with the Environment Agency.

What we hope to show is that integration of omics measurements with traditional site chemistry assessments will provide a more predictive and cost-effective approach to monitoring and protecting our environment through the 21st century. ❖

** CASE partners on Adam Hines's PhD studentship.*

*** This latter project was funded by NERC's Post-Genomics and Proteomics programme.*

MORE INFORMATION

Direct sampling of organisms from the field and knowledge of their phenotype: Key recommendations for environmental metabolomics. *Env. Sci. Technol.* 41: 3375-3381 (2007).

International NMR-based environmental metabolomics intercomparison exercise. *Env. Sci. Technol.* 43: 219-225 (2009).

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