Abstractions

LAST AUTHOR

The 'progress zone' model of limb development posits that the embryonic cells that become limbs are specified in a progressive manner: first, the upper part; then the middle; and last, hand or foot. Despite there being no direct evidence for this, the model remained unquestioned for more than 25 years. Then, in 2002, it was challenged by new observations, and an 'early specification' model was proposed, which suggested that progenitor cells forming each segment of a limb are specified all at once, early in development. On page 401, Gail Martin, a developmental biologist at the University of California, San Francisco, and her colleagues revise the early specification model.

What cast doubt on the progress zone model?

The model was based on observations that removing the apical ectodermal ridge — the cells rimming the tip of the limb bud — early in development stopped limb formation at the upper arm, and that later removal stopped it at the wrist. But, in 2002, Cliff Tabin's group at Harvard Medical School showed that ridge removal kills underlying progenitor cells that are required for limb formation, and went on to propose the early specification model. At the same time, my group showed that removal of signalling molecules called fibroblast growth factors (FGFs) from the ridge yielded limbs with hand elements even though a middle element was missing — findings not readily explained by the progress zone model.

Does your current work debunk the progress zone model?

No. The study shows that FGFs from the ridge instruct progenitor cells what part of the limb to form; the progress zone model assumed that the ridge only permitted development rather than instructing it. We carried out a genetic analysis, using a series of limb buds in which FGF signals were progressively reduced. Our results suggest that two signals — one, FGF, from the limb-bud tip and another presumably from the limb-bud base — are integrated in a dynamic process to specify the different limb segments.

What do you need to test the models?

We need to identify molecular markers that report specification of the progenitors for the different limb segments as soon as it occurs.

You discovered embryonic stem cells. Does medical usefulness drive your research?

No. I'm interested in basic biological processes. But I think that understanding how normal development is controlled is the most expeditious route to discovering therapies for many diseases. ■

MAKING THE PAPER

Paul Elliott

Thousands of urine samples point to the causes of high blood pressure.

Large-scale studies take patience, as epidemiologist Paul Elliott at Imperial College London knows all too well. More than a decade ago, he, Jeremiah Stamler of Northwestern University in Chicago, Illinois, and an international team began collecting data for the INTERMAP project — a study on the causes of high blood pressure. This condition is a leading cause of cardiovascular disease worldwide, and a large body of evidence suggests that it is determined primarily by environmental factors such as diet. "If we can determine the key environmental stressors, there is tremendous potential to prevent heart disease and stroke," says Elliott. To investigate just what impact different factors might have, the researchers combined information about environmental influences with metabolic profiling, an approach that Elliott describes as "a very exciting way forward".

They began collecting data in 1996, gathering details about diet, alcohol, drug and supplement use from more than 4,600 individuals aged between 40 and 59 living in the United States, United Kingdom, Japan and China. They also measured blood pressure and body mass index, and collected urine samples. "It was a massive undertaking," says Elliott.

Two urine samples were collected from every individual. Because urine contains the chemicals excreted by the body during metabolism, its composition is a rich source of information about the combined influences of environment, gut microbes and genetics.

Having analysed the amounts of certain urinary constituents and found links between them and a person's diet and blood pressure, Elliott and his collaborators decided to take a more systematic and detailed look at the samples. To do this, Elliott approached Jeremy Nicholson, an expert in nuclear magnetic resonance (NMR) spectrometry, also at Imperial College London. This technique analysed the entire spectrum of thousands of metabolites contained in each urine sample, a process referred to as metabolomics.

"We have shown it is possible to do metabolomics on a much larger scale than has been done before," says Elliott. It took members of Nicholson's lab almost two years to perform NMR analysis of all 10,000 samples — including controls — collected through the INTERMAP project. It took another three years for Elliott, Stamler and Nicholson's teams to make sense of the mountains of data, as they compared metabolite profiles between different populations. "That was a huge challenge," says Elliott. "We had to develop a very stringent statistical approach to identify discriminatory metabolites."

They found and quantified several metabolites that were associated with high blood pressure (see page 396). If further studies confirm these associations, following the pathways that lead to these compounds' production could reveal mechanisms underlying high blood pressure and heart disease.

Elliott hopes to be able to continue these collaborations to follow up on different lines of research. "This is big science and long-term science. It requires universities and funding agencies to take a long view of research," he says. "But the pay-off is potentially very high." ■

FROM THE BLOGOSPHERE

Scientific informatics programmes require massive financial investment, so it is difficult for governments to decide which ones to support. One programme that has been successful in securing funding is the iPlant Collaborative (http://iplantcollaborative.org/) — a 'cyberinfrastructure' collaborative for the plant sciences. Recently set up through an initial US$50 million grant from the US National Science Foundation to a five-institution consortium, the iPlant Community's mission is to enable conceptual advances through integrative, computational thinking.

Matt Day, NPG's database publisher, reports on the Nascent blog (http://tinyurl.com/44ms86) how the iPlant Collaborative, using workshops and other activities, will encourage plant scientists to decide on the range of projects that would be most useful to the field. The outcome should be a set of 'grand challenges' from which new informatics projects will grow. Because the collaborative is an open exercise, it should provide a fascinating window to anyone who wants to see how scientists discuss big, and no doubt contentious, issues. ■

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