This behaviour — which is described as 'digital' because the magnitude of the input is translated into a number of discrete outputs — is important in some biological systems, such as spiking neurons, but defies theoretical expectations of how a negative-feedback relationship should operate. It's a trickly problem to address, but the authors speculate that the gradual increase in p53 protein that is afforded by repeated pulses is a fail-safe mechanism that prevents the downstream repair enzymes from swamping the cell and triggering its death.

Tanita Casci

References and links

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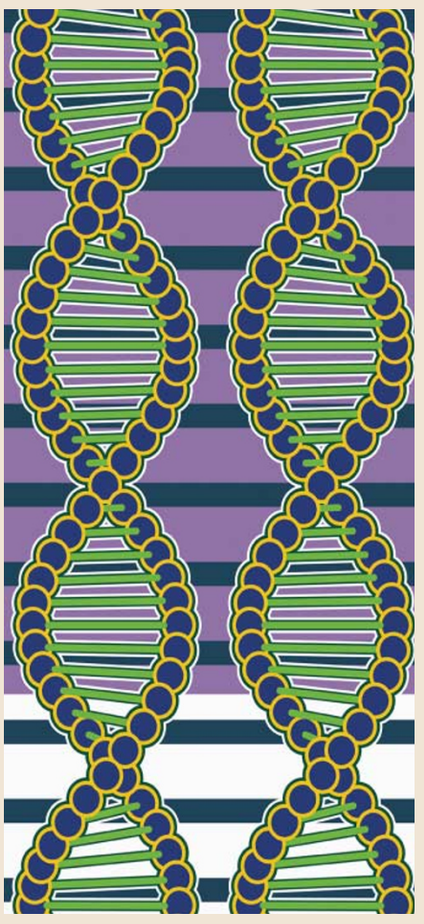
WEB SITE

Uri Alon's laboratory: http://www.weizmann.ac.il/mcb/UriAlon



DEVELOPMENTAL BIOLOGY

Those tricky first steps

Every parent anxiously awaits their little one's first word or wobbly steps, but the most significant developmental milestone happened much earlier, when the oocyte became an embryo and established itself in the lining of the womb. This early stage in a mammal's life is tucked away and so cannot be studied genetically using phenotypic assays. Two groups have now investigated the development of the mouse pre-implantation embryo using microarray-based transcriptional profiling. They show that it is possible to build a temporal profile of gene expression on which to base hypotheses about how genes interact during this early stage of life.

Q. Tian Wang and colleagues examined the expression profile of ~12,000 genes across 12 morphological time points from unfertilized egg to late blastocyst. The expression of a surprising number — more than one-third — of the genes varied by more than fivefold during this period. As well as being sensitive in identifying genes for which transcripts go up or down, the method also faithfully picked up the complexity of a particular stage, such as the increased transcript complexity that occurs following fertilization owing to the transition from maternal gene expression to zygotic genome activation (ZGA). Perhaps the most revealing discovery was that several members of familiar signalling pathways, such as those downstream of Notch, Wnt and BMP, were active at several crucial times — just before implantation, for example — thereby providing candidate genes for further study. The temporal resolution afforded by the array also allows promising candidates to be selected by virtue of their co-expression with known genes.

A similar analysis — this time by monitoring the expression of ~22,000 genes over 7 defined morphological pre-implantation stages — was carried out by Toshio Hamatami and colleagues. A general look at global-transcription trends defines two main developmental transitions — one at the 0–2-cell stage, when ZGA begins, and another, unanticipated one, at the 4–8-cell transition. A thorough study of the behaviour of individual genes that were expressed at each stage revealed some new and useful information: most gene transcription is activated in four transient waves that quickly tail off. This peculiar pattern indicates that many genes are stage-specific (a conclusion also drawn by Wang *et al.*); short bursts of expression presumably ensure that one stage-specific gene product does not spill over into the next stage. But how might these transitions be timed? Experiments *in vitro* that use gene-expression inhibitors support the view that the first wave, which coincides with ZGA, might be activated by maternal factors, with the following waves depending on genes that were expressed in the immediately preceding one, in a stepwise fashion.

The two reports do not always agree: for example, Wang *et al.* found that the main developmental transition occurs at the 2–4-cell stage. Nevertheless, this is the first time that microarrays have been applied to the study of pre-implantation development in the mouse and they have produced a thorough, accurate and quantitative picture of early embryonic development. What's more, they have provided us with a list of genes — thousands of them — to follow up on.

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