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50 & 100 YEARS AGO

50 YEARS AGO

A further Committee of the Commonwealth Education Conference considered the extent to which the countries of the Commonwealth could help each other to meet their needs for training teachers ... Already more than 2,500 teachers a year leave the United Kingdom for service in other Commonwealth countries and the Government is to make every effort to increase this number. Canada, Australia and New Zealand made definite offers of assistance at the Conference, and both India and Pakistan hope to encourage their teachers to serve in other Commonwealth countries ... Steps should also be taken to promote a climate of opinion which will recognise service abroad as a professional asset.

From *Nature* 20 February 1960.

100 YEARS AGO

The first part of a general description of the engineering and constructional features of the Panama Canal appears in *Engineering* for February 11 ... An average of 1,000,000 lb. of dynamite per month is consumed for the entire work, and the number of accidents has been relatively small, although, owing to the number of men in contracted areas, the casualties have been great. Premature explosions, attributable to concussion during loading, led to the substitution of pine-rammers for those of lignum vitæ ... No holes are now loaded which cannot be fired the same day, a precaution necessitated by the premature explosion of 22 tons of 45 per cent. dynamite at Bas Obispo, probably owing to some of the nitroglycerine having been liberated and exploded by concussion by a dobie shot in the vicinity. Accidents have occurred during electric storms, and the only possible precaution is now taken by stopping work.

From *Nature* 17 February 1910.

redundancy (for example, *end-1* and *end-3* perform essentially the same function: activating *elt-2*), which ensures that wild-type embryos show no variability in their phenotype[4].

To study random fluctuations in gene expression in this regulatory network, Raj *et al.*[2] used a fluorescence-based technique that detects single messenger RNA molecules in cells[5]. They were thus able to count the absolute numbers of mRNA molecules for *med-1*, *med-2*, *end-1*, *end-3* and *elt-2* in wild-type embryos and in embryos that had mutant versions of *skn-1*. It is known that *skn-1* mutants show an incompletely penetrant failure to induce intestine (they die late in the embryo's development, with most, but not all, embryos lacking intestinal cells). The authors observed that *skn-1* mutant embryos essentially fail to express *med-1/2* and *end-3*, whereas the expression of *end-1* was highly variable, ranging continuously from zero to almost wild-type levels.

Interestingly, Raj *et al.* found that *elt-2* — which in the absence of *end-3* was now controlled by *end-1* alone — did not follow this continuous pattern, but seemed to be activated in a bimodal manner. In other words, in any particular cell, *elt-2* mRNA either was absent or was present at almost wild-type levels. This suggests that when *end-1* mRNA molecules reach a threshold level, the *elt-2* auto-activating feedback loop is initiated, leading to near wild-type-level expression of *elt-2* and intestinal differentiation of the corresponding cell. If the *end-1* threshold is not reached, then *elt-2* expression collapses and intestinal differentiation fails.

To test this hypothesis, the authors counted *end-1* and *elt-2* mRNAs simultaneously in mutant embryos. Sure enough, none of the embryos that had low *end-1* mRNA levels expressed *elt-2*. But in *elt-2*-expressing cells, the authors found clear indications that *elt-2* is expressed once a threshold level of *end-1* expression has been reached, rather than observing a linear relationship between the numbers of *elt-2* and *end-1* mRNAs. It remains to be seen how the absence of *skn-1* function leads to the observed variability; additional techniques will need to be used to pinpoint the exact mechanism.

Raj and colleagues' findings[2] indicate how stochastic, continuous variation in gene expression can lead to a bimodal output and to the incomplete penetrance of a mutant phenotype. The simple regulatory network that controls the differentiation of intestinal cells in *C. elegans* also illustrates that such stochastic events can be buffered through connectivity and redundancy to ensure that essential developmental processes are protected. Redundancy, although long known to geneticists, has always been hard to study experimentally. The single-molecule technique used by Raj *et al.* opens up new opportunities for studying this phenomenon at the molecular level.

So, what might all this mean for identical twins? Non-essential regulatory processes might often be less robust than the system investigated in the present study[2]. Mechanisms that are closely similar to the one that leads to incomplete penetrance of *skn-1* mutations are therefore likely to contribute to the generation of random phenotypic differences among genetically identical individuals. Further investigations are needed to confirm this, and to address other questions of incomplete penetrance. ■

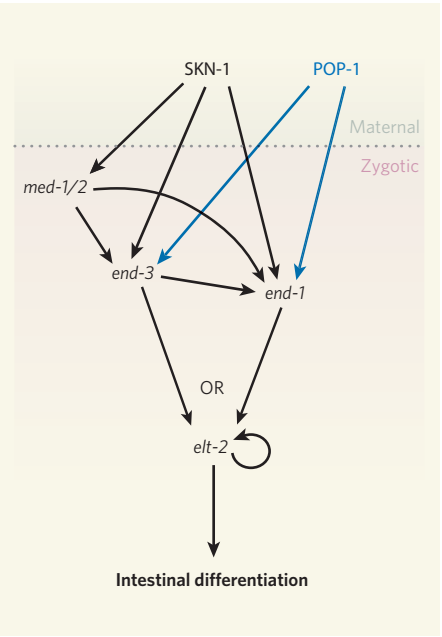

Figure 2 | Control of intestinal differentiation in the embryos of *Caenorhabditis elegans*. The intestinal cells of *C. elegans* are derived from the E cell (not shown), a great-grand-daughter cell of the fertilized egg (the zygote). A network of genes and transcription factors ensures that the E cell's descendants turn into intestinal tissue only. The factors POP-1 and SKN-1 in the worm embryo are provided by the mother. POP-1 activates the genes *end-1* and *end-3*; SKN-1 also activates *med-1* and *med-2*, which in turn activate *end-1* and *end-3*. The *end-1* and *end-3* genes encode transcription factors that activate *elt-2*, a gene that controls intestinal differentiation and also activates itself to ensure its continuous expression. Mutant embryos in which SKN-1 activity is abolished die, with most, but not all, of these embryos lacking intestinal cells. Raj *et al.*[2] report that this indeterminate differentiation is controlled by variability in the expression of *end-1*.

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