RNA

Really New Advances

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Molecular biology is undergoing its biggest shake-up in 50 years, as a hitherto little-regarded chemical called RNA acquires an unsuspected significance

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IT IS beginning to dawn on biologists that they may have got it wrong. Not completely wrong, but wrong enough to be embarrassing. For half a century their subject had been built around the relation between two sorts of chemical. Proteins, in the form of enzymes, hormones and so on, made things happen. DNA, in the form of genes, contained the instructions for making proteins. Other molecules were involved, of course. Sugars and fats were abundant (too abundant, in some people). And various vitamins and minerals made an appearance, as well. Oh, and there was also a curious chemical called RNA, which looked a bit like DNA but wasn't. It obediently carried genetic information from DNA in the nucleus to the places in the cell where proteins are made, rounded up the amino-acid units out of which those proteins are constructed, and was found in the protein factories themselves.

All that was worked out decades ago. Since then, RNA has been more or less neglected as a humble carrier of messages and fetcher of building materials. This account of the cell was so satisfying to biologists that few bothered to look beyond it. But they are looking now. For, suddenly, cells seem to be full of RNA doing who-knows-what.

And the diversity is staggering. There are scnRNAs, snRNAs and snoRNAs. There are rasiRNAs, tasiRNAs and natsiRNAs. The piRNAs, which were discovered last summer, are abundant in developing sex cells. No male mammal, nor male fish, nor fly of either sex, would be fertile without them. Another RNA, called XIST, has the power to turn off an entire chromosome. It does so in females because they, unlike males, have two X chromosomes and would otherwise get an unhealthy double dose of many proteins. There is even a “pregnancy-induced non-coding RNA”, cutely termed PINC. New RNAs are rushing forth from laboratories so rapidly that a group called the RNA Ontology Consortium has been promised half a million dollars to prune and tend the growing thicket of RNA-tailed acronyms.

In the light of this abundance, perceptions about what a gene is need to change. Genes were once thought of almost exclusively as repositories of information about how to build proteins. Now, they need to be seen for what they really are: RNA factories. Genes for proteins may even be in the minority. In a human, the number of different microRNAs, one of the commonest of the newly discovered sorts of RNA, may be as high as 37,000 according to Isidore Rigoutsos, IBM's genome-miner in chief. That compares with the 21,000 or so protein-encoding genes that people have.

Philosophers of science love this sort of thing. They refer to it as a paradigm shift. Living through such a shift is confusing for the scientists involved, and this one is no exception. But when it is over, it is likely to have changed people's views about how cells regulate themselves, how life becomes more complex, how certain mysterious diseases develop and even how the process of evolution operates. As a bonus, it also opens up avenues to develop new drugs.

Increase and multiply

Not everyone agrees with Dr Rigoutsos about how many microRNAs there are. But the results of a project called the Encyclopaedia of DNA Elements (ENCODE), published in this week's *Nature*, suggest he is on the right track. The project looked in detail at 1% of the human genome. When ENCODE started, four years ago, the conventional wisdom was that only a few percent of this 1%, corresponding mainly to the protein-coding genes, would actually be transcribed into RNA. In fact, most of it is. What this means is unclear—just how unclear being shown by the fact that although the consortium was willing to identify only eight places where this transcription definitely results in an RNA molecule with a job other than passively carrying the code for a protein, they found another 268 where there was likely to be one, and several thousand more where the data hinted there might be one. That compares with 487 protein-coding genes in the same sequence.

Other evidence suggests that microRNAs regulate the activity of at least a third of human protein-encoding genes. This means there are very few cellular processes that do not happen under their watch. Around 20 microRNAs, for instance, are made only in human embryonic stem cells. These molecules could turn out to be the key to understanding how such cells remain in a state from which they can become any other type of cell—the very reason embryonic stem cells hold such great medical promise.

The existence of microRNAs may also help to explain why some creatures are more complex than others. Until their discovery, this was something of a paradox.

Knowing that DNA stores data that then get translated into living organisms, and that the complexities of development must require lots of information, biologists naturally expected that the more intricately formed an organism is, the more genes it would have in its cells. They therefore struggled when they found that *C. elegans*, a tiny worm that lacks a proper brain but is nevertheless widely studied by geneticists, has about 20,000 genes—only a little bit short of the number in a human. Indeed, this seems to be a general number for animals. Another geneticists' favourite, the fruit fly *Drosophila*, has a similar number. But, of course, the genes in question are protein-coding genes. Add in the genes whose RNA does other things and the balance changes.

It changes even more if exactly what those RNA molecules do is examined. Single microRNAs, for example, often regulate the levels of hundreds of different proteins. They are like powerful strings controlling copious protein puppets. Super-imposed on this, some types of regulatory RNA edit other kinds of RNA. The effect of extra genes for both of these sorts of RNA molecules is therefore multiplicative rather than additive.

The picture that is emerging is thus one of “hard-wired” simple organisms, which mostly stick to using RNA for fetching and carrying, and “soft-wired” complex ones that employ it in a management capacity. In the complexity stakes, it is not how many protein-coding genes you have, but how you regulate them, that counts.

What's up, Doc?

Another consequence of RNA's rise to prominence is that researchers have a new source of explanations for illness. Small RNAs have been linked to many types of cancer, to genetic diseases of the central nervous system, and even to infections. Some scientists, for instance, think that RNA molecules help the protein that causes Creutzfeldt-Jakob disease to recruit non-infectious proteins to join its ranks.

The new RNA world is also a source of ideas about how diseases might one day be treated. In this line of work it is best to start simple, which is why the main hunt for new drugs centres on a technology called RNA interference, or RNAi (see article). This, in theory at least, promises to turn down the production of any single protein to very low levels. That distinguishes it from microRNAs, which control many proteins simultaneously.

A hypothetical RNAi drug might, for instance, become the ultimate analgesic by affecting the activity of SCN9A, a gene recently pinpointed as the reason why a Pakistani street performer—who put knives through his arms and walked on burning coals—could not feel pain. The technology has also helped over-eating mice stay slim and live a fifth longer. That was done by choking an insulin-receptor gene in the animals' fat cells. This made the cells less inclined to store every calorie. The technique has even created edible cottonseed (for anyone who might want to try it) by eliminating cotton's gossypol toxin. Not least, it can claim to have produced allergy-friendly soya beans, by turning off the gene that encodes the protein that provokes the reaction.

It is also a technology that can be used at one remove. Recently, Michael White of the University of Texas and his colleagues used RNAi not to treat lung cancer directly, but to convert tumorous cells that do not respond to Taxol, a widely used anti-cancer drug, into cells that are sensitive to it. They did this by silencing Taxol-suppressing genes that were usually active in those cancer cells.

RNAi drugs work by mugging another sort of RNA—one of the classes of the molecule discovered decades ago. These are the messenger-RNA molecules that shuttle information from DNA to the cell's protein factories. The drugs themselves are short pieces of RNA made of strands about 21 genetic letters long. What is unusual about these molecules is that they have two parallel strands, instead of a single one.

One of DNA's differences from RNA is that it comes as a double-stranded helix. Molecules of RNA usually have only a single strand. When a double-stranded RNAi drug enters a cell, an “argonaute” protein picks the molecule up and unzips it down the middle. It chops one strand in two and discards those remnants. The other strand acts as a guide for the argonaute. It can pair with a messenger-RNA molecule—at least, it can do so as long as this messenger contains a sequence of 21 letters that complement those of the drug.

When such RNA molecules do pair, the argonaute slices the messenger to oblivion like a sword-swinging samurai, just as it did with the other half of the original RNAi drug. Thus the gene whose message it was carrying is silenced. This is how RNAi drugs stop the production of disease-related proteins at source—they hold the tap turned off whereas most medicines try to mop up a continuous leak. Messenger destruction is specific because 21 letters of code are nearly always enough to identify the instructions for one type of protein over another.

The most probable explanation for RNAi is that it evolved as a defence against viruses. Double-stranded RNA is rare in nature, but viruses often make it when they reproduce. This means that organisms which have evolved the ability to recognise and destroy double-stranded RNA molecules have a competitive advantage over those that do not.

That is one example of the role of RNA in evolution. But there are many more. The evolution of microRNAs, for instance, underlines their importance in the origin of complexity. Their number appears to have ballooned when land plants and vertebrates evolved. But it is early days in this research. Dave Bartel, of the Massachusetts Institute of Technology, is surveying grand lists of small RNAs in mosses, flowers, worms, flies and mice in the hope that he will learn when different families of microRNAs emerged and which genes these microRNAs are regulating.

Dr Bartel has already discovered microRNA genes interspersed among sets of protein-encoding genes called *Hox* clusters. *Hox* clusters contain basic instructions about body plans, and the genes within them are arranged in the order in which they influence their owner's shape during development. In short, a *Hox* gene at one end of a cluster contains the information: “Give this embryo a head”. The gene at the other end says: “And a tail, too”. The role of the interspersed microRNAs is to regulate these high-level commands.

Ronald Plasterk, of the University of Utrecht, in the Netherlands, suggests that microRNAs are important in the evolution of the human brain. In December's *Nature*

Genetics, he compared the microRNAs encoded by chimpanzee and human genomes. About 8% of the microRNAs that are expressed in the human brain were unique to it, much more than chance and the evolutionary distance between chimps and people would predict.

Such observations suggest evolution is as much about changes in the genes for small RNAs as in the genes for proteins—and in complex creatures possibly more so. Indeed, some researchers go further. They suggest that RNA could itself provide an alternative evolutionary substrate. That is because RNA sometimes carries genetic information down the generations independently of DNA, by hitching a lift in the sex cells. Link this with the fact that the expression of RNA is, in certain circumstances, governed by environmental factors, and some very murky waters are stirred up.

It's evolutionary, my dear Watson

What is being proposed is the inheritance of characteristics acquired during an individual's lifetime, rather than as the result of chance mutations. This was first suggested by Jean Baptiste Lamarck, before Charles Darwin's idea of natural selection swept the board. However, even Darwin did not reject the idea that Lamarckian inheritance had some part to play, and it did not disappear as a serious idea until 20th-century genetic experiments failed to find evidence for it.

The wiggle room for the re-admission of Lamarck's ideas comes from the discovery that small RNAs are active in cells' nuclei as well as in their outer reaches. Greg Hannon, of the Cold Spring Harbor Laboratory in New York State, thinks that some of these RNA molecules are helping to direct subtle chemical modifications to DNA. Such modifications make it harder for a cell's code-reading machinery to get at the affected region of the genome. They thus change the effective composition of the genome in a way similar to mutation of the DNA itself (it is such mutations that are the raw material of natural selection). Indeed, they sometimes stimulate actual chemical changes in the DNA—in other words, real mutations.

Even this observation, interesting though it is, does not restore Lamarckism because such changes are not necessarily advantageous. But what Dr Hannon believes is that the changes in question sometimes happen in response to stimuli in the environment. The chances are that even this is still a random process, and that offspring born with such environmentally induced changes are no more likely to benefit than if those changes had been induced by a chemical or a dose of radiation. And yet, it is just possible Dr Hannon is on to something. The idea that the RNA operating system which is emerging into view can, as it were, re-write the DNA hard-drive in a predesigned way, is not completely ridiculous.

This could not result in genuine novelty. That must still come from natural selection. But it might optimise the next generation using the experience of the present one, even though the optimising software is the result of Darwinism. And if that turned out to be commonplace, it would be the paradigm shift to end them all.

Biotechnology

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Biotechnology is the use of biological processes, and the manipulation of those processes, for practical advantage. Although still in its infancy, biotechnology holds promise for medicine, agriculture and industry.

Medical biotechnology has the potential to produce lots of breakthrough drugs, but will have to converge with big pharma if it is to gain needed funding. Agricultural biotechnology has been hindered by controversies over genetic modification, but its use is spreading gradually. Meanwhile, non-food genetic modification is set for more mundane triumphs that could help industry. But truly cost-effective industrial biotechnology is probably still some way off.

Synthetic biology goes a step further and assembles genes from different organisms to create new biological functions or even new organisms. Meanwhile, molecular biology is undergoing its biggest shake-up in 50 years, as a hitherto little-regarded chemical called RNA acquires significance.