With the current interest in nuclear energy as a carbon-dioxide-free means of power generation, there is much interest in developing new methods for the chemical processing and reprocessing of uranium and other radioactive actinide elements. So the big question is whether Arnold and colleagues' discovery can be exploited in nuclear-fuel cycles of the future. It is much too early to say, but the fundamental chemistry that will be uncovered as we try to find out will be fascinating. ■

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CANCER

Hay in a haystack

Kevin M. Shannon and Michelle M. Le Beau

Although some diseases occur when both copies of a gene are mutated, mutation of just one copy of certain tumour-suppressor genes promotes tumorigenesis. Identifying such mutations is arduous, but worth the effort.

The myelodysplastic syndromes are thought to result from mutations in haematopoietic stem cells that result in the inefficient production of blood cells. Anaemia is a frequent manifestation, and patients often become dependent on red-blood-cell transfusions. These syndromes were previously called preleukaemia, because many affected patients ultimately progress to acute myeloid leukaemia. A subtype of the myelodysplastic syndromes, known as the 5q– syndrome, is characterized by loss of the q31–33 segment of the long arm of chromosome 5 (ref. 1), although the specific gene (or genes) within this region that are responsible for the disease are unknown. On page 335 of this issue, Ebert *et al.*[2] now pinpoint a culprit gene in the 5q– syndrome.

A cornerstone of modern cancer biology is Knudson's two-hit hypothesis[3], which postulates that the inactivation of both copies (alleles) of a tumour-suppressor gene has an essential role in cancer development. Indeed, this 'biallelic' inactivation of tumour-suppressor genes such as *RB1, TP53, APC, BRCA1, PTEN* and *NF1* is fundamental to tumorigenesis.

Uncovering further tumour-suppressor genes is a major priority for understanding cancer biology and developing new therapies. This process typically begins with identifying a discrete DNA segment that is likely to harbour a tumour-suppressor gene. Techniques used include performing linkage studies in familial syndromes that predispose patients to cancer, identifying the boundaries of recurring cancer-associated deletions, and using markers to define domains in which tumour cells show absence of one germline allele (also known as loss of constitutional heterozygosity). By integrating data from many tumours, investigators can define a genomic region that is lost in all cases. The 'endgame' involves identifying the genes in this deleted DNA segment and screening human tumours for mutations in, or silencing of, the remaining copy of the candidate tumour-suppressor genes.

The discovery of these genes has been greatly facilitated by the availability of the human genome sequence, together with efficient DNA-sequencing technologies, and techniques such as high-density single-nucleotide-polymorphism arrays, which detect single-nucleotide variations within the population. Unfortunately, this general procedure becomes problematic when tumorigenesis results from inactivation of a single allele (haploinsufficiency). Indeed, it now seems that haploinsufficiency is a frequent genetic mechanism underlying human cancers[4].

If discovering a 'classic' tumour-suppressor gene is like finding a needle in a haystack, the challenge involved in uncovering haploinsufficient tumour-suppressor genes is akin to finding a specific piece of hay in a haystack. This is because the traditional criterion for validating a tumour suppressor — mutations in both alleles — does not apply to haploinsufficient tumour-suppressor genes, as they retain one normal allele.

Several strategies have been used to address this formidable problem. One way is to look for cancer in animals that have inherited one mutant allele of a relevant gene. For example, studies of mice lacking the *p53* gene demonstrated[5] that inactivation of one or both alleles of this tumour-suppressor gene can promote tumorigenesis. Another way is to expose haploinsufficient mice and their normal littermates to chemical mutagens or radiation and to compare the incidence and acceleration of tumour formation in the two sets of animals[6]. Yet another strategy is chromosome engineering, which involves producing a chromosome that lacks a large region of DNA[7]. An elegant example of this approach is a study[8] that identified *CHD5* as the elusive tumour-suppressor gene in chromosomal band 1p36.3, a region of DNA that is commonly deleted in human cancers.

Analysis of human cancers can also provide evidence for haploinsufficiency. For instance, monoallelic mutations in genes that encode various components of a B-lymphocyte differentiation pathway were identified through studies of acute lymphoblastic leukaemia in children[9].

Ebert *et al.*[2] describe a creative new approach to the search for haploinsufficient tumour-suppressor genes that harnesses the technique of RNA interference. Using this technique, they systematically reduced the expression of each candidate tumour-suppressor gene associated with the 5q– syndrome. In this disorder, the commonly deleted segment of 5q31–5q33 spans about 1.5 megabases of DNA and includes 40 genes. Molecular investigation did not reveal mutations in the second allele of any candidate tumour-suppressor gene in this DNA segment, suggesting that the disease is caused by haploinsufficiency.

To determine which gene (or genes) might be involved in the 5q– syndrome, Ebert *et al.* synthesized several short, 'hairpin' RNA sequences that were complementary to each candidate gene. They then expressed these molecules in immature haematopoietic ($CD34^+$) cells from normal bone marrow, and induced the cells to differentiate into precursors of red blood cells (erythroid cells) in culture.

The authors identify the haploinsufficient tumour-suppressor gene associated with the 5q– syndrome as *RPS14*. They validate this connection by showing that expressing *RPS14* in $CD34^+$ cells from patients with the 5q– syndrome enhances erythroid-cell differentiation and normalizes the activation level of genes specifically expressed in these red-blood-cell precursors. They also show that reducing *RPS14* expression in normal $CD34^+$ cells induces a gene-expression profile that correlates with responsiveness to the drug lenalidomide. Treatment with this drug results in loss of the abnormal population of 5q– cells and improvement of the anaemia in most 5q– syndrome patients. Together, the results provide strong evidence that *RPS14* functions as a haploinsufficient tumour-suppressor gene in the 5q– syndrome.

The protein encoded by *RPS14* is an essential component of the 40S subunit of a cellular organelle known as the ribosome, the site of protein synthesis. The RPS14 protein is essential for efficient formation of the RNA–protein complexes involved. Ebert *et al.* find that ribosome synthesis in $CD34^+$ cells of 5q– syndrome patients is impaired. They also note that two

other ribosomal genes — *RPS19* and *RPS24* — are mutated in people with Diamond–Blackfan anaemia, a congenital form of anaemia that shares certain disease features with the 5q– syndrome[10].

Several questions arise from these results. For example, how do reduced levels of RPS14, RPS19 and RPS24 proteins impair the formation of red blood cells? Are further mutations required for the 5q– syndrome to transform into acute myeloid leukaemia, and if so, what are they? Does *RPS14* haploinsufficiency contribute to the pathogenesis of other subtypes of myelodysplastic syndrome or acute myeloid leukaemia that are also associated with abnormalities in chromosome 5, perhaps by interacting with the effects of loss of genes on other regions of 5q? What are the molecular mechanisms underlying the dramatic genetic and clinical responses to lenalidomide in the 5q– syndrome, and why do some patients either fail to respond to this drug or relapse after an initial remission? And will treatment with lenalidomide or a related drug be beneficial in severe cases of Diamond–Blackfan anaemia?

It is also worth considering how the RNA-interference strategy developed by Ebert *et al.* might be extended to identify other haploinsufficient tumour-suppressor genes. In many respects, the 5q– syndrome is an optimal setting for using this approach — patients show consistent characteristics at a cellular level; the short hairpin RNA sequences used by the authors can readily be introduced into cultured immature bone-marrow cells; and there are established systems for monitoring cell survival and cell differentiation in liquid cultures. By contrast, deletions of chromosome bands 5q31, 7q22 and 20q12, which are found in many blood-related cancers, are frequently associated with other cytogenetic and molecular abnormalities that might influence the behaviour of cultured cells. Extending this approach to non-blood-related cancers poses yet other challenges, although these might be met by carefully investigating matched cell lines with or without deletions of a specific chromosomal segment. Despite the potential difficulties, however, the work of Ebert *et al.*[2] is a *tour de force* that holds great potential for addressing the problem of discovering and validating haploinsufficient tumour-suppressor genes. ■

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ASTRONOMY

Elliptical view of galaxies past

Andrea Cimatti

How and when galaxies assembled their mass to become the structures seen today are among astronomy's big outstanding questions. A comprehensive study of nearby galaxies provides a new angle on the issue.

Compared with other scientists, astronomers are at a disadvantage: they cannot perform laboratory experiments on stars and galaxies. But they can exploit a unique advantage: thanks to the finite speed of light, they can observe objects as they were in the past. Current telescopes allow galaxies to be observed as they were back to about 13 billion years ago. What a palaeontologist wouldn't give for a similar time machine for taking pictures of dinosaurs when they were alive!

Unfortunately, however, the direct study of astronomical objects at very great distances using the current generation of telescopes is fraught with difficulty, and the available sample of such objects is still rather small. Writing in *The Astrophysical Journal*, Jimenez and colleagues[1] circumvent this problem by analysing the spectra of a very large sample of nearby (that is, present-day) 'early-type' galaxies to decode their history. Their results place tight constraints on the different evolutionary paths of galaxies as a function of their mass, providing a crucial reference for observational studies of distant galaxies and for theoretical models of galaxy formation.

In the currently favoured model of the Universe's evolution, galaxies formed gradually through hierarchical merging of 'haloes' of invisible dark matter[2]. The first galaxies are

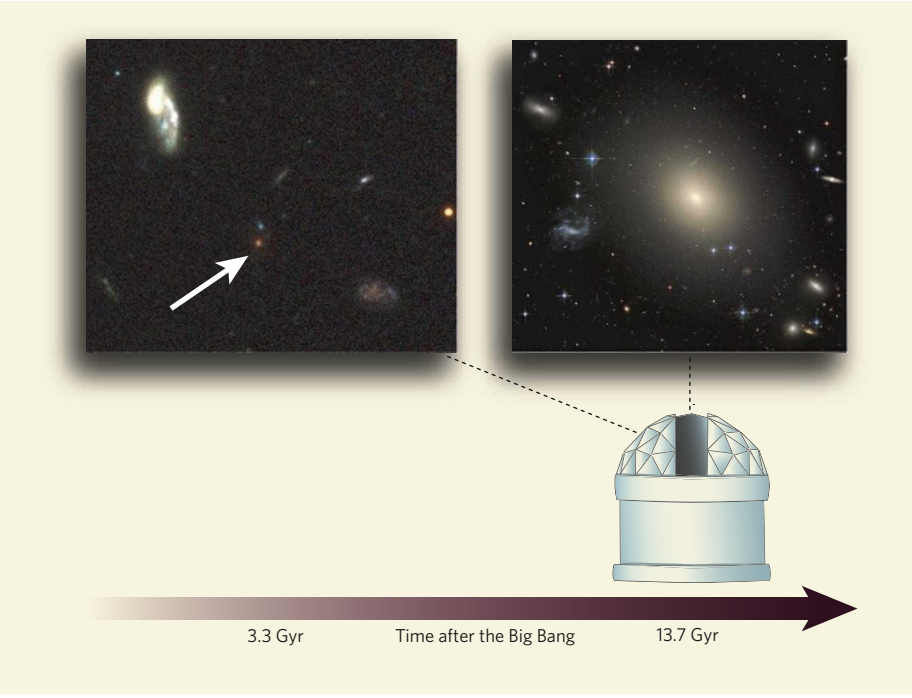

Figure 1 | Without looking back. With the current generation of large telescopes, we can — just about — study the physical and evolutionary properties of distant elliptical galaxies when the Universe was just 3 billion years (Gyr) old. But the sample of galaxies at this distance is small. Jimenez *et al.*[1] adopt a different approach, in which they study in detail the properties of the elliptical galaxies in the present-day Universe and reconstruct their past evolution from the clues present in their spectra. Here, the tiny, compact red galaxy of the left-hand image (arrow) has become the large, diffuse elliptical galaxy of the right-hand image.