Of mice and men, and cancer research

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A new research paper points towards distinct differences in the process by which mouse and human cells are transformed into cancer cells [1]. The paper, by scientists at Duke University Medical Center (http://www.mc.duke.edu/) and the University of North Carolina (UNC) at Chapel Hill (http://www.unc.edu/), emphasizes the need for caution when applying to humans what has been learned about disease pathways in mice.

Ras-induced cell transformation

The *ras* gene was one of the first oncogenes isolated from human tumours; it was found to be mutated and activated constitutively in one-third of all cancers. This discovery sparked much research into Ras-induced signaling pathways. Scientists were hoping that a better understanding of the pathway in which Ras signals could lead to the design of drugs to block that pathway, thus inhibiting human cancers.

Several Ras-mediated signaling routes have been identified so far:

- the Raf–MEK–ERK pathway (MEK or ERK kinase; extracellular signal-regulated kinase)
- the PI3-kinase–Akt pathway (PI3; phosphatidylinositol 3)
- the RalGEFs pathway (GEFs; guanine nucleotide exchange factors).

Previous evidence suggested that the Raf and PI3-kinase pathways were the key players in *Ras*-induced cell transformation [2]. Ronald Cannon, a Ras expert at the US National Institute of Environmental Health Sciences (www.niehs.gov), comments: 'We have tried every way we can to block the pathways, and it turns out that there are other pathways that Ras signals through, and that there are other genes that can take the place of the ones we know about.'

New research

The new paper now suggests that scientists have underestimated the importance of a pathway that could be the most crucial for transformation of human cells. Most of our information about Ras-induced cell transformation stems from experiments in mouse fibroblasts. Only recently did scientists find a way to convert normal human cells into tumourigenic cells [3,4] (Fig. 1). With this new method, the scientists from Duke and UNC went back to look at the key players involved in Ras-induced cell transformation in a variety of human cells.

The investigators introduced specific missense mutations into an oncogenic form of H-Ras that result in selective binding and activation of only one

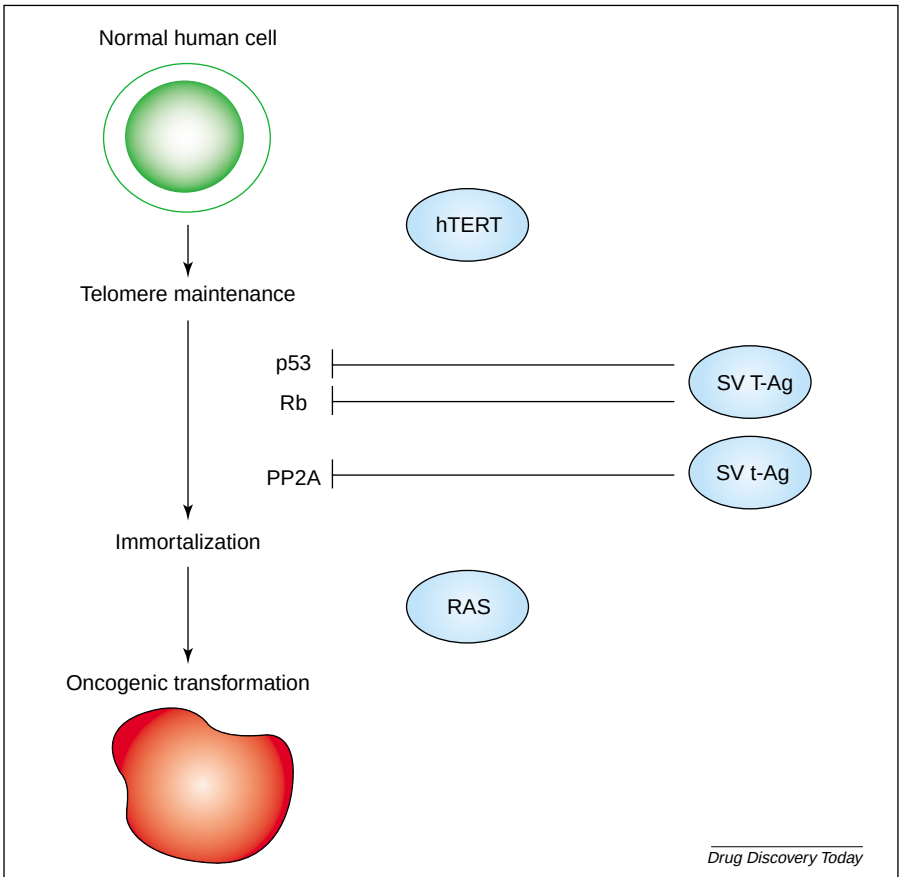

Figure 1. A variety of primary normal human cell types can be transformed by oncogenic Ras when expressed in association with other defined genetic alterations [3,4]. First, activation of telomere maintenance is achieved by ectopic expression of the human telomerase catalytic subunit hTERT. Second, disruption of the p53 and RB tumour suppressor pathways is accomplished by ectopic expression of the SV40 T-antigen viral oncogene protein; perturbation of protein phosphatase 2A is achieved by addition of the SV20 t-antigen. Finally, expression of an oncogenic form of H-ras results in aberrant growth transformation. Figure kindly provided by Channing Der, University of North Carolina at Chapel Hill (http://www.unc.edu/).

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effector; Raf, PI3-kinase or RalGEFs. They then tested the ability of the cells to form colonies in soft agar (a phenotype characteristic of cancer cells). Although there had been hints that Ras-induced tumourigenesis in humans and mice might not be identical [5], the results came as a surprise: activation of the Raf and PI3-kinase effector pathways, either alone or together, was not sufficient to cause transformation of human cells. Instead, activation of the RalGEF effector pathway did the trick.

'Here is a pathway that has been pretty well ignored, because it did not play a big role in making murine cells tumourigenic,' says Christopher Counter, senior author of the study. 'We find that it is far more important in human cells than it appears to be in mouse cells, at least in the approach we used to study Ras-induced transformation.'

Open questions

Anton Berns, Scientific Director of The Netherlands Cancer Institute (http://www.nki.nl/) in Amsterdam, believes that the paper is interesting, but warns not to overinterpret the results. 'I do not think it is justified to conclude that mouse models, at least in respect to the Ras pathway, are very different,' he said. Berns points towards recent reports that B-Raf is mutated in several human tumours [6] and suggests that both the Raf and the RalGEF effector pathways might be important. 'RalGEF might certainly be a little bit more significant in humans than in mice. But then, this conclusion is based on *in vitro* assays.'

Cannon strikes a similar note: 'I would have liked to have seen whether RalGEF is really malfunctioning in primary human tumours – whether it is overexpressed or mutated.'

'This finding does not diminish the importance of mouse models,' agrees Channing Der, co-author of the study. 'What it tells us is that we need to use both systems [mouse models and cultured human cells], because each system has its strengths and its limitations. We need to be cautious of extrapolating from one to the other.'

This applies to their own studies, Der says. His team is studying human cells, which is an advantage, but in cell culture, which is a disadvantage. In mouse studies, the species difference is a concern, but the fact that they are *in vivo* gives them 'a great advantage'. The message, he says, is to use both these systems rigorously and concurrently, to learn the most likely scenario for humans.

Implications for treatment

Counter and colleagues are now aiming to antagonize the RalGEF pathway as a means of treating *ras* mutation-positive cancers, such as lung, colon and pancreatic cancer. Counter concludes, 'There is no question that the best candidates have come from experiments in mice, and although they are clearly important in human cancers, it looks like there might be at least one other pathway that is open for targeting, and that is the RalGEF pathway.'

References

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Muscular dystrophy: toxic RNA to blame

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Researchers probing the genetic cause of adult-onset muscular dystrophy have found a totally new way for mutations to cause hereditary disease. Their research shows that the loss of muscle control in the most common form of this disease, myotonic dystrophy type 1 (DM1), is a result of a mutation that creates a toxic form of RNA [1–3]. The researchers call this 'a new way that a genetic mistake can harm the body.'

Myotonic dystrophy

Characteristics of myotonic dystrophy are hyperexcitability (myotonia; the ability to contract but not relax the muscles), progressive muscle wasting, insulin resistance, cardiac defects, cataracts and neuropsychiatric disorders. Most muscular dystrophies only affect the muscles.

The gene for DM1, found on chromosome 19, encodes a protein kinase (DMPK) that is found in skeletal muscle, where its pathophysiological role remains to be defined. Symptoms of the disorder become progressively worse as it is passed down through generations: the disorder has an incidence of about one in 8000

DM1 differs from many other hereditary diseases by having a variable genetic factor. (In most genetic disorders, you either have the gene or you do not.) In DM1, the severity of the disease varies

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