ONCOGENES

Monkey business

Everyone has heard of using immunotherapy to try to treat cancer, but could some vaccines actually have caused cancer? Millions of people were infected with the oncogenic simian virus-40 (SV40) when they received a contaminated polio vaccine over 40 years ago. SV40 is able to transform cells *in vitro* and induce tumours in animals, so what were its effects on these people? Two papers in the 9 March issue of *The Lancet* associate this virus with non-Hodgkin's lymphoma. Could SV40 underlie the increased incidence of this cancer over the past few decades?

SV40 causes B-cell lymphomas in animals and has lymphotropic tendencies in humans, so Regis Vilchez *et al.* and Narayan Shivapurkar *et al.* set out on separate investigations to see if it is associated with human lymphoma. SV40 is a DNA polyomavirus that expresses the large T-antigen, which binds and inactivates p53 and RB, leading to cellular transformation. The two research groups screened various human tissue types for the presence of SV40 large T-antigen DNA sequences.

Both Vilchez *et al.* and Shivapurkar *et al.* reached similar conclusions, reporting that SV40 large T-antigen DNA sequences could be detected in 42% and 43% of non-Hodgkin's lymphoma samples, respectively. Viral DNA was only found in a small percentage of Hodgkin's lymphoma, breast or colon cancer samples, and was not observed in lymphoid tissue that was taken from people without cancer. Both groups detected viral DNA most frequently in diffuse large B-cell lymphoma samples, indicating that mature B cells might be more susceptible than precursors to the transforming ability of SV40.

The main source of known human exposure to SV40 occurred between 1955 and 1963, when millions of Americans were immunized with SV40-contaminated polio vaccines. The vaccine was prepared from kidney cells of rhesus monkeys that were naturally

GENOMIC INSTABILITY

Caught short

An intact DNA-damage-response pathway is required to protect against tumorigenesis, and mutation of some genes that are known to be involved in the DNA-damage checkpoint causes cancer-predisposition syndromes; for example, *ATM* and *NBS1* cause ataxia telangiectasia and Nijmegen breakage syndrome, respectively. *MRE11* is also involved in this pathway, and is mutated in the ataxia-telangiectasia-like disorder (ATLD), but, until now, its role in cancer development has been unknown. In the March issue of *EMBO Reports*, Giuseppe Giannini *et al.* show that *MRE11* is specifically mutated in mismatch-repair-deficient cancers, which impairs their response to DNA damage.

To determine whether *MRE11* is mutated in human cancers, a 5′ fragment of the *MRE11* transcript was amplified by polymerase chain reaction from a range of cell lines. Low levels of this fragment, and another product — a transcript that is deleted for exon 5 and encodes a truncated protein product — were obtained from several colorectal cancer cell lines, as well as a prostate cancer and an endometrial carcinoma cell line. These cell lines are all deficient in mismatch repair; so does this deficiency cause the *MRE11* mutations?

Sequencing the mutated *MRE11* gene revealed that the splice site 5′ to exon 5 contained deletions of one or two of the 11 thymine bases that are normally found — a mutation type that is frequently found in mismatch-repair-deficient cells. This reduces the efficiency of the splicing signal, which accounts for both the truncated product and the reduced expression of the wild-type product. Similar mutations were also found in mismatch-repair-deficient — but not mismatch-repair-proficient — primary colorectal cancers. The expression of both the mRNA and protein was also very low, indicating that the transcript might be degraded.

MRE11 forms a complex with NBS1 and RAD50 (the M–N–R complex). NBS1 is phosphorylated by ATM following DNA damage, which is required for the S-phase checkpoint and relocalization of the M–N–R complex to sites of DNA repair. So how is this process affected by mutations in *MRE11*? Expression of NBS1 and RAD50 is reduced in mismatch-repair-deficient cancer cells — a phenotype also observed in ATLD cells — and, following exposure to ionizing radiation, cells are resistant to both DNA synthesis inhibition and relocalization of the M–N–R complex to sites of repair. MRE11 is therefore an important target for mutation in mismatch-repair-deficient cancer cells.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Giannini, G. *et al*. Human MRE11 is inactivated in mismatch repair-deficient cancers. *EMBO Rep.* **3**, 248–254 (2002)

WEB SITE

Encyclopedia of Life Sciences: http://www.els.net
human mismatch repair: defects and predisposition to cancer

infected with the virus, which was unknown at the time. Five of the SV40-positive non-Hodgkin's lymphoma patients in the study of Vilchez *et al*. were born after the contaminated poliovirus vaccine was administered, indicating other mechanisms of viral transmission.

SV40 has previously been associated with solid cancers in humans, including brain tumours, osteosarcomas and malignant mesotheliomas. As it is unlikely that the presence of SV40 large T-antigen alone is sufficient to induce cancer, further work is required to determine exactly how this protein fits into the cascade of transformation events.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Vilchez, R. A. *et al*. Association between simian virus 40 and non-Hodgkin lymphoma. *Lancet* **359**, 817–823 (2002) | Shivapurkar, N. *et al*. Presence of simian virus 40 DNA sequences in human lymphomas. *Lancet* **359**, 851–852 (2002)

FURTHER READING

Malkin, D. Simian virus 40 and non-Hodgkin lymphoma. *Lancet* **359**, 812–813 (2002)

WEB SITES

Adi Gazdar's lab: http://www.swmed.edu/cancer/Labs/Gazdar.htm

Regis Vilchez's department: http://public.bcm.tmc.edu/departments/medicine.html

GENETIC MODELLING

Highs and lows of prediction

Breast cancer — like many forms of cancer — runs in families, and twin-studies indicate that genetics, rather than shared environmental factors, accounts for much of this familial clustering. We've identified a few genes that, when mutated, cause a vastly increased risk of breast cancer, but these genes account for only about 25% of the excess risk seen in families with a high predisposition to breast cancer. In theory, the remaining 75% of this excess risk could be accounted for by a few genes, each contributing a relatively large excess risk, or many genes, each contributing a small excess risk. If the latter case is true, will genetic testing be able to identify women with the highest risk of developing breast cancer? In the March issue of *Nature Genetics*, Paul Pharoah and colleagues argue that it will.

The authors analysed breast cancer occurrence in the relatives of nearly 1,500 individuals with breast cancer, and developed genetic models to fit breast cancer incidence in this population. Two models fit the data well. In the first, a large number of co-dominant alleles accounts for breast cancer susceptibility. Each allele is associated with a small increase in risk, but the effect of more than one allele is multiplicative. In the second model, a single, common recessive allele accounts for breast cancer susceptibility. The authors prefer the polygenic model because it better fits the data in multiple-case families: mothers and siblings have a similar excess risk in these families, which would not be the case if a recessive gene (or genes) accounted for much of the risk.

In the polygenic model, the log of the risk in the population follows a normal distribution. The higher the standard deviation about the mean, the easier it is to discriminate between individuals at high risk and those at low risk. Pharoah and colleagues estimate the standard deviation to be 1.2. If this is the case, the 20% of the population at highest risk is 40 times more likely to develop breast cancer than the 20% at lowest risk.

How does this theoretical ability to identify high-risk individuals compare with the disciminatory power of known risk factors that do not require genotyping? The authors used established risk factors — including age at menarche, number of full-term pregnancies, age at first full-term pregnancy, contraceptive use and family history — to estimate the risk distribution in the population used for the genetic modelling. Again, the distribution was log normal, but this time the standard deviation was only 0.3. This means that the 20% of the population at highest risk is only 3.5-fold more likely to develop breast cancer than the 20% at lowest risk, making it much harder to identify those at the highest risk.

But what if we cannot identify all the genetic factors responsible for the broad risk distribution seen in the polygenic model? Even if only 50% of the factors are known, the model predicts that they are still better at discriminating high- from low-risk individuals than are established non-genetic factors.

So polygenic screening could be an effective way of indentifying those individuals who would benefit most from regular screening and preventive strategies. The next challenge will be to identify these genes. This will be tough, as each gene probably contributes only a tiny proportion of each person's risk, but cancer geneticists can at least console themselves with the thought that their efforts will be of true clinical value.

Cath Brooksbank

References and links

ORIGINAL RESEARCH PAPER Pharoah, P. D. P. *et al. Nature Genet.* 2002 Mar 4; [epub ahead of print].

WEB SITE

Bruce Ponder's lab: http://www.hutchison mrc.cam.ac.uk/Ponder.htm