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.

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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