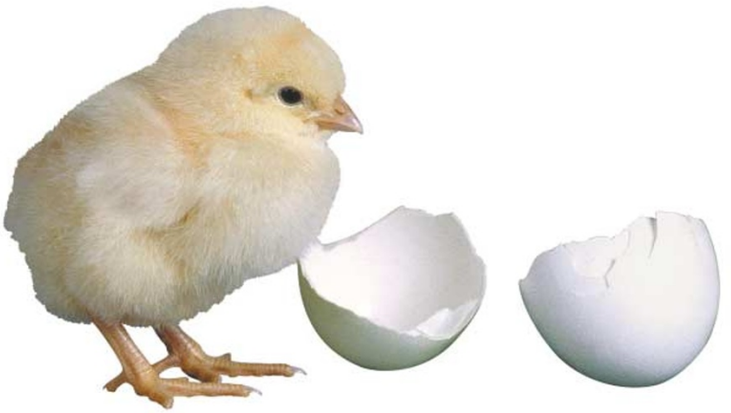
GENOMIC INSTABILITY

What came first?



Colorectal cancer is genetically well defined, and is known to progress through a defined series of stages, but what is the initial event that sets cells along this tumorigenic pathway? Mutation of the *APC* tumour-suppressor gene is certainly an early event, and chromosomal instability (CIN) is also thought to be a driving force of tumorigenesis, but whether CIN occurs early in tumorigenesis — perhaps even causing loss of heterozygosity of the second *APC* allele — is, at present, unknown. Martin Nowak *et al.*, reporting in *Proceedings of the National Academy of Sciences*, have now devised a stochastic mathematical model to investigate this question.

They started by considering the six states, with respect to *APC* inactivation and CIN, that any cell in the colonic crypt could be in. Cells could have none, one or two functional *APC* alleles, in the presence or absence of CIN. They then determined how, and with what rate, a cell could progress from one state to the next by considering parameters such as mutation rate, loss of heterozygosity rate in normal and CIN cells, reproductive rate of $APC^{-/-}$ and CIN cells, and the number of dominant CIN genes.

They calculated the probability that the system reaches the state X_2 (*APC* inactivation occurs in the absence of CIN) or Y_2 (*APC* inactivation occurs in the presence of CIN) first, and therefore whether CIN could cause inactivation of the second *APC* allele. For the second scenario to occur, the number of CIN genes must exceed a certain threshold value. This number depends on several factors, including the selective cost of CIN and the effective number of stem cells per crypt. For a wide range of realistic parameter values, the crucial number of CIN genes is as low as 1–10.

So, under certain conditions, and if the number of dominantly acting CIN genes in the human genome exceeds a certain number, it should be possible for CIN to inactivate the first tumour-suppressor gene in colorectal cancer. The more time-consuming process — confirming this hypothesis — remains to be undertaken.

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References and links

ORIGINAL RESEARCH PAPER Nowak, M. A. *et al.* The role of chromosomal instability in tumor initiation. *Proc. Natl Acad. Sci. USA* 21 Nov 2002 [epub ahead of print]

FURTHER READING Fodde, R. *et al. APC*, signal transduction and genetic instability in colorectal cancer. *Nature Rev. Cancer* **1**, 55–67 (2001)

TRIAL WATCH

Infectious enthusiasm

The sexually transmitted human papillomavirus (HPV) is associated with 50% of cervical cancer cases and is considered to be a potent human carcinogen. In the *New England Journal of Medicine,* Laura Koutsky and colleagues show that a vaccine that prevents persistent HPV16 infection can also reduce the incidence of cervical cancer.

In this double-blind study, 768 women of ages 16–23 received three doses of an HPV16 vaccine that consists of virus-like particles — viral coats without the DNA component. A total of 765 other women received a placebo control and the women were followed for a median of 17.4 months after completing the vaccination regimen.

Some 41 cases of HPV16 infection occurred in the placebo group, and these included nine cases of virus-related cervical intraepithelial neoplasia. Amazingly, none of the women that received the vaccine developed persistent HPV16 infections or virus-associated cervical neoplasia. The vaccine is therefore 100% effective in protecting women from HPV16 and preinvasive cancer. It was also well-tolerated and the immunized women generated high levels of antibodies against the virus.

HPV vaccines are urgently needed, as cervical cancer ranks second as a cause of cancer-related deaths in women. More than 450,000 cases are diagnosed each year worldwide, and therapeutic approaches are limited. Although the incidence of this cancer has been reduced by screening, 50% of cervical cancers that occur in the United States develop in women who have been screened. Furthermore, many women in developing countries do not have access to screening programmes. A safe and effective HPV vaccine could therefore overcome these obstacles to cervical cancer prevention. There is no evidence, however, that this vaccine will reverse cervical cancer once it has developed.

Nearly 20 different types of HPV have been associated with cervical cancer, and Koutsky *et al.* show that vaccination against one will not protect against another. Similar vaccination approaches might be developed to prevent the spread of these other viruses. The task is not as overwhelming as it seems, as only five HPVs — types 16, 18, 31, 33 and 45 — are responsible for most cervical cancer cases. In an accompanying editorial, Christopher P. Crum (Brigham and Women's Hospital, Boston) predicts that widespread vaccination against these five strains could reduce the number of cervical cancer deaths by 95%.

ORIGINAL RESEARCH PAPER Koutsky, L. A. *et al.* A controlled trial of a human papillomavirus type 16 vaccine. *N. Engl. J. Med.* **21**, 1645–1650 (2002)