Cervical cancer

Papillomavirus and p53

Harald zur Hausen

Certain types of human papillomavirus (HPV) are linked with most cases of cervical cancer, and also with vulval, penile and perianal cancers[1,2]. Although viral oncogenes are obviously pivotal in the development of cancer, merely expressing them is not enough — either for immortalization of cultured human cells, or for malignant conversion. Rather, additional modifications in specific cellular genes are needed, and, on page 229 of this issue, Storey and colleagues[3] describe one such modification that predisposes to HPV-linked cervical cancer.

Almost ten years ago, a fresh perspective was brought on the possible mechanisms by which papillomaviruses contribute to cancer, when two HPV oncoproteins, E6 and E7, were shown to interact with two cellular proteins — p53 and retinoblastoma, respectively[4,5]. Both p53 and retinoblastoma had previously been shown to interact with oncoproteins of other DNA tumour viruses, including SV40 and some adenoviruses. After interaction with E6, p53 was found to be degraded[6], and, because p53 is one of the most important cellular proteins in guarding repair processes and maintaining chromosomal stability, this could explain why mutational changes are observed in human cells that are immortalized in culture by HPV.

In human populations, the *p53* gene is polymorphic at amino acid 72 of the protein that it encodes — that is, p53 may contain either a proline or an arginine residue at this position. So far, no correlation has been made between either of these forms and specific human tumours (with the possible exception of lung cancer in non-smokers). But Storey *et al.* now reveal that the arginine form of p53 is more susceptible to degradation by the HPV E6 protein than is the proline form. Moreover, patients with HPV-associated cervical cancer are much more likely to contain the arginine form of p53 compared with the rest of the population. The authors conclude that patients with two copies of the arginine form have a sevenfold higher risk of developing cervical cancer than people with the proline form. Interestingly, a high percentage of skin squamous-cell carcinomas have been reported[7,8] to contain HPV DNA, and these show an even greater prevalence of the arginine p53 modification.

If the arginine form of p53 binds more effectively to E6, it will be degraded (and hence inactivated) more rapidly, leading to increased mutation rates and chromosomal instability. Conversely, in the presence of E6, more functional activity should be maintained with the proline form of p53. Residual p53 activity has been shown in some cervical carcinoma cell lines that contain HPV, and it would be interesting to see whether these lines contain the arginine or the proline form of p53.

The results of Storey and colleagues support the theory that cellular genes must be modified for HPV-linked carcinogenesis to occur[9]. There is likely to be a gradual accumulation of specific cellular changes during malignant progression, and evidence for this includes the long latency for tumour development after primary infection, the observed monoclonality of anogenital tumours that contain HPV, and the absence of tumour-specific modifications in the viral oncogenes. A pronounced mutator phenotype — probably mediated here by increased degradation of p53 — would facilitate accumulation of changes, increasing the risk and reducing the time required for malignant progression.

The involvement of genetic factors in HPV-linked carcinogenesis has been postulated in the past[10], but careful epidemiological studies have been missing until now. In part, this is due to the high prevalence of HPV in all populations studied so far. Now that the functional consequences of the binding of E6 and E7 to polymorphic cellular proteins have been identified, we should be able to study the molecular genetics of affected populations.

In the future, other cellular genes that actively impair viral oncoproteins or suppress their transcription in non-transformed proliferating cells will probably be identified — indeed, the first candidates are already emerging[2]. Failure or inactivation of these proteins will divert cells that carry HPV genomes down pathways to malignancy. Such discoveries will broaden our currently narrow perspective on the molecular genetics of HPV-linked cancers and, although Storey *et al.* have made an interesting and unexpected start, HPV research is still full of surprises. □

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1. IARC *The Evaluation of Carcinogenic Risks in Humans* Vol. 64 (Human Papillomaviruses, IARC, Lyon, 1995).
2. zur Hausen, H. *Biochim. Biophys. Acta* **1288,** F55–F78 (1996).
3. Storey, A. *et al. Nature* **393,** 229–234 (1998).
4. Dyson, N., Levine, A. J., Münger, K. & Harlow, E. *Science* **243,** 934–937 (1989).
5. Werness, B. A., Levine, A. J. & Howley, P. M. *Science* **248,** 76–79 (1990).
6. Scheffner, M., Werness, B. A., Huibregtse, J. M., Levine, J. M. & Howley, P. M. *Cell* **63,** 1129–1136 (1990).
7. Shamanin, V. *et al. J. Natl Cancer Inst.* **88,** 802–811 (1996).
8. de Villiers, E. M. *Biomed. Pharmacother.* **52,** 26–33 (1998).
9. zur Hausen, H. *Lancet* **343,** 955–957 (1994).
10. zur Hausen, H. & de Villiers, E. M. *Annu. Rev. Microbiol.* **48,** 427–447 (1994).

Daedalus

Silent flight

Combustion is a disorganized molecular process. Its product molecules fly around vigorously at random, as hot gas. A heat engine, usually a complex and inefficient piece of machinery, can extract a little of this energy as useful work.

Daedalus is now seeking a better way. In a common model of enzyme action, the reagent molecules sit neatly on the active site of the enzyme, in just the right positions to react. When the last bond of the product molecule is formed, the molecule changes shape, no longer fits, and springs off the enzyme surface, leaving the site free for further reagent molecules. This spring, says Daedalus, must represent a large part of the energy of the reaction. And it is not liberated as heat, but as molecular velocity in a specific direction. Only later, as the product molecule slams into others nearby, is it degraded to heat.

So DREADCO chemists are seeking the equivalent phenomenon on surfaces that catalyse combustion. A well-ordered surface might well fire off the final CO_2 or H_2O molecules vigorously and directedly, as they take their final shape and cease to fit the surface. In a low-density gas environment, they would travel some distance before hitting any other molecule. The catalytic surface would feel the full reaction force of their departure.

The obvious application is to aircraft propulsion. So the researchers are taking their most promising catalytic materials, and vacuum-evaporating them onto model gliders. The evaporation directions are cunningly chosen so that the deposited catalytic crystallites acquire exactly the right orientation to the local wing surface. Each glider is then being flown in a dilute, non-explosive mixture of air with a fuel gas, such as hydrogen or ethylene. With the right catalyst, the products of surface combustion will not be disengaged as hot gas, but will be ejected directionally downwards and backwards. Their reaction will give lift and thrust. In its novel atmosphere, the glider will speed and soar indefinitely.

A realistic aircraft, however, has to fly in pure air on liquid fuel. The fuel will be pumped through porous regions on the catalytic surfaces, to diffuse over them as a monolayer. The new craft will be propelled by its whole surface. It will be utterly silent, free of heavy and expensive engines, and powered with greater than Carnot efficiency. It will transform aviation. Sadly, its owners will have to forego the usual tasteless painted colour-schemes.

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