tory processes, the story is probably far more complicated. For example, at least some anti-proliferative activities of p53 rely on another candidate tumour-suppressor gene, *IRF1* (ref. 6). Cooperative activation of the *p21/WAF1* gene is implicated in this case, too. However, the mechanism may be distinct from that described for $p33^{ING1}$, and there may not be direct protein–protein association between p53 and IRF1. Furthermore, p53 can physically associate with yet another tumour-suppressor gene product — the WT1 protein[7]. Perhaps all associates belong to the same team or, maybe, p53 chooses different partners under different circumstances.

What are the practical implications of the new findings? For one, the concentration of $p33^{ING1}$ might determine the extent to which a given tissue can mount an effective p53 response on exposure to stress. This could explain the puzzling observation that, unlike the promiscuous activation of p53 in cultured cells, only a limited number of tissues within a normal organism show strong p53 activation in response to DNA damage. An even smaller number show the expected biological effects[8].

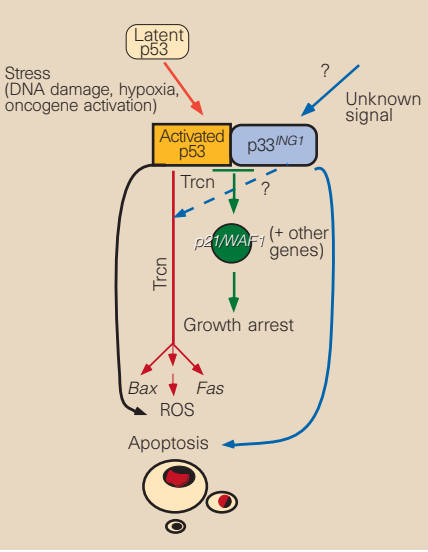

Figure 1 **$p33^{ING1}$ and p53 as mediators of cell fate. p53 can arrest cell proliferation by activating a set of target genes, among which *p21/WAF1* is pivotal. p53 can also induce cell death through apoptosis. This outcome relies, at least in part, on the transcriptional activation (Trcn) of death-promoting genes such as *Bax* and *Fas/ApoI*, and of genes involved in the production of reactive oxygen species (ROS). To exert its cellular effects p53 must first be biochemically activated, typically entailing an increase in cellular levels of p53. As Garkavtsev *et al.*[2] now report, many of p53's activities are carried out in cooperation with $p33^{ING1}$, presumably through a physical interaction between the two proteins. But it is not known which signals modulate the activity of $p33^{ING1}$, and whether p53-mediated apoptosis also requires $p33^{ING1}$.**

The findings of Garkavtsev *et al.*[2] may also relate to the important question of whether p53 is fully functional in the 50 per cent of human tumours that retain a wild-type *p53* gene. Certain types of tumour inactivate their p53 through increased expression of the p53-binding protein Mdm2 (ref. 9). So loss of $p33^{ING1}$ function is another potential mechanism for inactivation of p53 in cancer cells. Moreover, in a limited analysis of three neuroblastoma cell lines, one line harboured a rearranged *ING1* gene resulting in a truncated protein[3]. Many more lines must be analysed before firm conclusions can be drawn, but it is remarkable that neuroblastoma cells often contain high levels of wild-type p53 (ref. 10) — a counter-intuitive behaviour given the highly malignant nature of these cells.

Despite being highly abundant, the p53 in neuroblastoma cells is functionally defective[11] (although this is somewhat controversial). The possibility that these cells carry a defect in $p33^{ING1}$ might explain their unusual immunity to p53. Furthermore, the excess p53 accumulates in the cytoplasm of neuroblastoma cells, rather than in the nucleus, raising the possibility that $p33^{ING1}$ might enable efficient nuclear translocation of p53.

A growing effort is now being invested in developing p53-based cancer gene therapies[12]. If $p33^{ING1}$ is essential for the effective anti-tumour action of p53, we may need to determine the status of $p33^{ING1}$ in every tumour before subjecting the patient to such experimental therapy. There is already reason to suspect that *ING1* may be deleted in some head and neck tumours, which are prime targets for clinical trials in the near future[12]. What is badly lacking now is an extensive assessment of alterations in $p33^{ING1}$ — at the level of the gene as well as the protein — in human cancer. If such alterations are encountered at a significant frequency, we can take it for granted that $p33^{ING1}$ will soon follow in the footsteps of its better-known team-mate and, like p53, will become a hot item in biomedical research. □

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Daedalus

Bacterial diplomacy

No man is an island, said John Donne. Each of us is a community of billions, nearly all of them bacteria. The human skin, gut, mouth, vagina, etc., all harbour complex ecologies of many different micro-organisms, all living in seeming harmony. But how is this harmony maintained between selfish species? Moulds such as *Penicillium* take selfishness to extremes, and attack their bacterial rivals with deadly antibiotics. But more subtle discouragements must be more widespread. Thus, while it is quite easy to contract either syphilis or gonorrhoea, it is much harder to get both. Each disease seems to protect against the other. Similarly, few people carry more than one tapeworm; the first arrival somehow 'warns off' later ones. And invading bacteria are also usually warned off by our permanent flora. Clearly, says Daedalus, the chemical signalling behind our bacterial harmony is a set of gentlemen's agreements rather than gang warfare.

So DREADCO bacteriologists are now studying these agreements. They are culturing simple mixtures of gut and skin organisms, observing their equilibria and isolating the metabolites they produce. A signalling metabolite would be expected to shift the equilibrium of a culture to which it was added in excess, or from which it was rigorously excluded. Gradually the project should build up a library of such signalling metabolites, and discover their scope and mode of action.

The final goal is a new and milder form of antibacterial therapy. Many diseases, from vague inflammations and stomach upsets to sinusitis and genital infections, are upsets of bacterial equilibria. The medics move in with antibiotics, kill off goodies and baddies alike, and leave the field open for a new colonization. With luck it re-establishes the original equilibrium. But how much neater to drop in a nicely chosen mixture of chemical signals, warning the rioters to calm down, telling the persecuted to stand up for their rights, intimidating the foreigners, and thus restoring the equilibrium directly!

Yet Daedalus may have been anticipated. He now wonders if our immune system keeps our benevolent microbial ecologies in balance by multiple chemical signals. If so, all multicellular species may use such signals in their negotiations with bacteria. Hence, possibly, the bafflingly complex multi-component nostrums of the old herbalists and animal-product therapists.

David Jones