that apoptosis resulting from *Rb* inactivation in the lens also depends on functional p53.

Embryos that are genotypically *Rb*^{-/-}, *p53*^{-/-}, or those doubly transgenic for E7 and E6 expression in the lens (to abrogate *Rb* and p53 function, respectively), display dramatically reduced apoptosis in lens fibre cells^{1,2}. Fibre cells continue to proliferate because they are released from the *Rb* growth restriction, suggesting that p53 is required as a tumour suppressor to respond to aberrant loss of *Rb* by implementing cell death.

Because of the embryonic lethal phenotype, the issue of whether continued cell proliferation in the absence of apoptosis leads to increased tumorigenicity cannot be addressed in *Rb*^{-/-} mice. Adult mice with lens-specific E7 and E6 expression, however, develop lens tumours, whereas mice transgenic for E7 and E6 alone, do not¹. The cooperativity between the loss of *Rb* and p53 in oncogenesis can be explained by the requirement that cell proliferation and apoptosis accompanying *Rb* loss must be coupled to the loss of the apoptotic activity of p53. Cell proliferation can be sustained only in the absence of the p53 safeguard mechanism to eliminate cells engaged in untimely DNA synthesis or cell-cycle progression during terminal differentiation. With p53 function intact, the loss of *Rb* is held in check by the apoptotic response mechanism controlled by p53.

On the one hand, it is understandable that deregulated cell proliferation upon *Rb* loss during terminal differentiation would have profound effects in development⁶⁻⁸, as *Rb* is apparently essential for exit from the cell cycle. On the other, the loss of the p53 safeguard alone is not immediately detrimental to the differentiation process¹⁷ until a second event (such as an *Rb* mutation) occurs, in which case aberrant cell proliferation can be tolerated and tumour formation initiated.

As the mechanism of regulation of apoptosis becomes clearer, it is interesting to note that *Rb* and p53 both interact functionally at the level of the cell cycle (see figure). Control of E2F by *Rb* can regulate passage from G0/G1 and into S phase¹⁰. Transcriptional activation of the

WAF1 (also known as p21, Cip1 and Sdi1) cell-cycle-dependent kinase inhibitor (CdkI) by p53 can inhibit several cell-cycle-dependent kinases (Cdk) and cell-cycle progression¹⁸⁻²¹. With *Rb* function intact, cell proliferation can be arrested in differentiating cells by functional sequestration of E2F by *Rb*. As p53 can promote growth arrest as well, its presence may be redundant and therefore not apparent. p53 may also be inactive as long as *Rb* function is intact. In the absence of *Rb*, created by genetic loss of *Rb* gene function or through the expression of E7 or E1A, which interact with *Rb* at the protein level, E2F activation stimulates cellular DNA synthesis.

p53, however, can inhibit cell-cycle progression through CdkI inhibition of other Cdk/cyclin complexes, and this failure to stop growth properly as a result of conflicting growth signals may produce apoptosis. Alternatively, p53 may become activated in response to *Rb* loss, perhaps through the generation of DNA damage, and implement apoptosis independently of transcriptional transactivation of cell-cycle regulatory genes²². The HPV E6 and adenovirus E1B 55K proteins can block apoptosis in the situation of *Rb* loss and p53 activation through direct interference with p53 (refs 4, 5), whereas Bcl-2 and the adenovirus E1B 19K protein override apoptosis indirectly^{16,15}. Without both *Rb* and p53, E2F activation stimulates cell proliferation, which is unobstructed in the absence of p53, permitting tumour formation.

Although it is attractive to link cell-cycle control and apoptosis because a checkpoint for abnormal cell growth is then automatically in place, it is still possible that p53 may implement the apoptotic programme by a mechanism that has nothing to do with the cell cycle. Nonetheless, the involvement of tumour suppressors in the regulation of apoptosis in normal differentiation is now firmly established and should provide fertile ground for future work. □

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Light and shade

FOR many white-skinned people, a suntan is the height of chic. Sadly, it has a fearsome sting at the end of a very long tail. The same solar ultraviolet light that provokes the tan also slowly attacks and degrades the collagen fibres of the dermis beneath it. After many years of exposure, the dermis loses its taut elasticity, and folds into wrinkles. Some people are so afraid of facial wrinkles that they try to avoid sunlight altogether. They wear sunblock creams all the time, summer and winter, to screen out the ultraviolet and stave off the encroaching creases. Daedalus is now resolving the whole dilemma.

He points out that many substances absorb light and re-emit it at twice the frequency. Some are natural organics, such as urea and β -carotene, but certain 5-nitropyridine derivatives show the effect more strongly. For good results the molecules must be correctly ordered: either in a crystal lattice or within a Langmuir-Blodgett film. So DREADCO cosmetics are formulating a skin cream around lipid-soluble 5-nitropyridine derivatives. It will carry the second-harmonic generator molecules into the epidermis, where they will be absorbed and aligned by the ordered lipid membranes of the melanocyte cells.

The user will then be able to tan in ordinary daylight. The second-harmonic generator will absorb this light, and fluoresce at twice the frequency — neatly in the ultraviolet. The weak fluorescence, generated within the melanocytes themselves, will trigger them as effectively as the fiercest solar ultraviolet beating down from outside. They will synthesize melanin copiously to defend the skin against this seemingly ferocious radiative assault. In fact the stimulation will be entirely local, and no other skin structures will be irradiated at all.

DREADCO's 'Fluorotan' cream will provoke a tan in the duldest or most overcast weather, or even in a British November fog. It will act as a sort of pre-emptive inoculation against solar ultraviolet light. When real sunlight comes along, the user will be pre-tanned, indeed over tanned, for the occasion. His epidermis, already fully charged with skin-defending melanin, will ward off both the threat of skin cancer and the wrinkles of old age.

Occasional reapplications of Fluorotan will keep this smart, safe, protective tan permanently in place. It will even work under sunblock cream (which is transparent in the visible). Elegant in youth, and safe from the corrugations of age, the user will enjoy the best of both worlds. David Jones

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