demonstrate laser light emission from conjugated polymer microcavities (*9*). Ho and colleagues show how such mirrors can now be made from the same type of organic polymer layers that form the emissive part of the microcavity structure. Their work will pave the way for new polymer optoelectronic devices.

By making a periodic stack of layers that have alternating high and low refractive indices, one can produce an optical mirror whose high reflectivity arises from the constructive interference between reflections from the individual layer interfaces. By adjusting the periodicity, one can control the wavelength at which reflection occurs (see the figure). That this can be done with polymers is no surprise, because polymers have a range of different refractive indices. The use of such a structure in an LED, however, requires the mirror to also have appropriate charge-transporting properties. The work of Ho *et al.* now shows how this can be achieved.

To control the refractive index of the emissive polymer material, the authors doped it with small silica beads about 5 nm in diameter. The refractive index of silica is typically 1.46, compared with those of many light-emitting conjugated polymers, which are often greater than 2. This feature allowed them to produce refractive indices in the range 1.6 to 2.7 by using doping levels of up to 50% by volume. One might have expected that such a procedure would result in strong optical scattering, a mechanism used for making white paint (*10*). However, the size of beads used by Ho *et al.* is only a small fraction of the wavelength, and therefore the films exhibit minimal extra scattering and have a well-defined refractive index. The new functionality comes not simply from controlling this refractive index, but in combining layers of different refractive indices. Ho and colleagues made their high-reflectivity mirrors by sequentially depositing two polymers, one doped with silica beads, the other not. The resulting microcavity effect of the new organic mirror is perhaps best shown by the reduced-width spectrum that emerges from the device (see the figure).

To overcome problems of reduced electrical conductivity associated with adding the silica beads, the authors adopted a chemical doping strategy. This allowed operational LEDs to be made, however, they require operating voltages 10 times those required by normal organic LEDs and thus have a rather poor power efficiency. Although further studies are clearly needed to make practical microcavity LED devices, this work shows much potential.

Ho and colleagues have shown that the optical and electrical properties of conjugated polymers may be controlled by making use of design at several different length scales. This is the essence of their advance. If the problems of poor electrical conductivity can be overcome, then this approach may lead to a competitive microcavity LED design. Ultimately one might hope that this approach would help to demonstrate electrically pumped lasing, although the issue of charge transport is even more critical here. Ho *et al.*'s use of form to control function is complemented by studies of periodic structuring in the plane of the microcavity that have been successfully used to demonstrate optically pumped lasing in various solid-state organic systems (*11*). With an increasing number of aspects of functionality now under our control, we should be better placed to take full advantage of these fascinating materials.

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PERSPECTIVES: BIOMEDICINE

Stopping DNA Replication in Its Tracks

James E. Cleaver

Living organisms have a remarkable capacity to be prepared for every eventuality. All of the genomes sequenced so far contain suites of fascinating genes that sense the presence of DNA damage, signal that things have gone awry, and correct the DNA lesion. The mechanisms that serve to restore damaged DNA and get cells on their way include nucleotide, base, and mismatch repair, recombinational repair, direct reversal, and cell cycle checkpoints.

The first connection between DNA damage, repair, and human pathology came with the identification of the human cancer syndrome xeroderma pigmentosum (XP) (*1*). Relative to people without this autosomal recessive disease, XP patients are 1000 times as susceptible to sunlight-induced melanoma and nonmelanoma skin cancers. Cells from XP patients cannot carry out nucleotide excision repair (NER), in which nucleotides damaged by ultraviolet (UV) light are removed, and this results in the accumulation of errors as the damaged DNA tries to replicate itself (*2*). But there is one awkward fact that has remained to sully the association between DNA damage, repair, and cancer in XP: About 25% of clinically diagnosed XP patients do not have NER defects and their cells are barely UV sensitive. These patients are known as XP variants (XP-V) and do not seem to fit with the other seven genetic complementation groups (XP-A through XP-G), in which the affected genes are all involved in NER (*3*). Many laboratories have hunted for the XP-V gene without success, and the reason for the susceptibility of XP-V patients to UV-induced skin cancers has remained unclear. A defect in replication of damaged DNA was suspected, but the mechanism was unknown (*4*). Now Johnson *et al.* reporting on page 263 of this issue (*5*), and Masutani *et al.*, reporting in a recent issue of *Nature* (*6*), reveal the identity of the XP-V gene.

XP-V cells are unable to replicate the leading strand of their DNA past pyrimidine dimers, which are formed as photoproducts after UV exposure (see the figure, top panel) (*7*). Photoproducts located on the lagging strand only interrupt formation of very small DNA fragments (Okazaki fragments, about 100 nucleotides in length) such that DNA replication is able to proceed. Continued synthesis of the lagging strand induces an asymmetrical replication fork that results in extended single-stranded regions of the leading strand parental DNA. These regions resemble the DNA structures formed by degradation and resynthesis during correction of DNA mismatches, and this is reminiscent of the connection between NER of transcribed strands and mismatch repair. These single-strand gaps have long been recognized, and kinetic experiments show that they are eventually filled in (even in the UV-exposed XP-V cells) by mechanisms that involve either bypass of

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the photoproducts (*4*) or recombination between sister chromatids (a process that can be suppressed by p53 activation) (*8*). But two major questions remain unanswered: Which gene products are involved in bypass of pyrimidine dimers, and how do they relate to the common symptoms of susceptibility to skin cancers found in all XP patients?

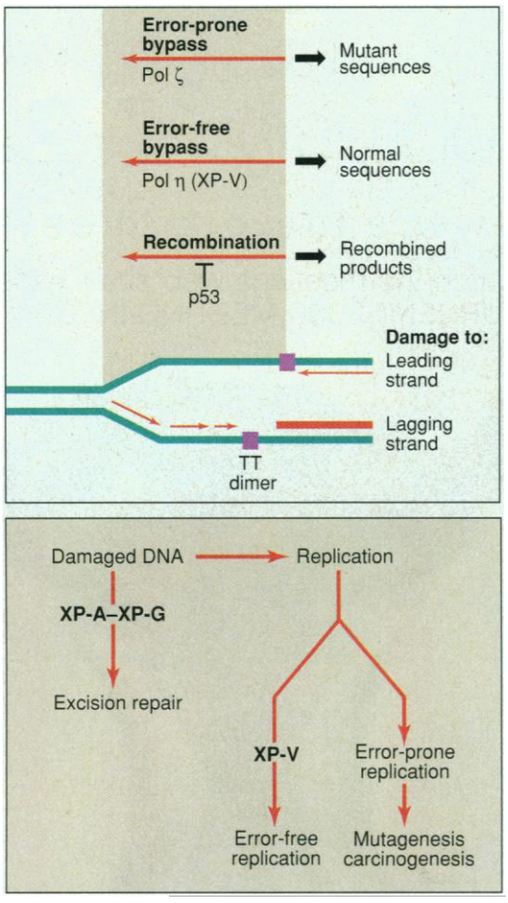
The Rad6 epistasis group of the yeast *Saccharomyces cerevisiae* is a family of genes involved in a DNA replication pathway that is activated by UV-induced DNA damage. This pathway is associated with two members of a new class of bypass DNA polymerase, η and ζ. Polymerase ζ (Pol ζ) is an error-prone polymerase (the product of the *REV3/7* genes) that frequently inserts incorrect bases opposite pyrimidine dimers (*9*). This polymerase is functional in XP-V cells. In contrast, Pol η, the product of the *RAD30* gene, is remarkably faithful, correctly inserting adenines opposite UV-induced TT pyrimidine dimers (*10, 11*). According to the Johnson and Masutani reports, it is Pol η that is defective in XP-V cells.

Johnson *et al.* (*5*) cloned the human homolog of the yeast *RAD30* gene, *hRAD30*, and showed that cell lines derived from XP-V patients carried truncation mutations in this gene. Ironically, but indicative of the importance of this problem, the XP-V gene was simultaneously identified by a different route. Masutani *et al.* (*6*) developed an in vitro assay for measuring DNA replication in cells sustaining UV-induced DNA damage. They isolated, purified, and cloned an activity that restored the ability of XP-V cells to replicate their DNA by bypassing pyrimidine dimers. Both groups identified the human homolog, *hRAD30*, as the XP-V gene and found inactivating mutations in cells from all XP-V patients. The *hRAD30* gene falls into a common class with *UMUC/D* and *DinB* of *Escherichia coli*, which both encode error-free bypass polymerases. But there is still one more mystery. The human genome carries two Rad30 homologs—*hRAD30A*, the XP-V gene, and *hRAD30B*, which has a similar sequence and is expressed at high levels in the testis but does not appear to be involved in XP-V (*12*).

In their next set of experiments, the investigators will no doubt correct the phenotype of XP-V cells by engineering them to express the *hRAD30* gene. Despite intense efforts by many groups (including my own), the XP-V gene did not yield to cloning by functional complementation (that is, transfecting a library of expressed genes into XP-V cells, strongly selecting with UV irradiation and the sensitizer, caffeine, and recovering cDNAs that correct the XP-V phenotype). False positives were many, and strong positive complementation produced unstable clones. This hints that perhaps the biological functions of both Pol η and Pol ζ need to be tightly regulated, and that overexpression could be as bad as absence. Functional complementation has been used successfully to clone *XP-C*, *CSA* (the gene involved in Cockayne's syndrome), and several of the Fanconi's anemia genes.

Elucidating the regulation and functions of these two polymerases should be a fascinating pastime. Why does a cell need to encode, express, and regulate two additional polymerases when the regular DNA polymerases could have been imbued with these properties? Is there an economic cost to replicating damaged templates that necessitates the separation of this process from normal DNA replication? And why are pyrimidine dimers on the leading strand more likely to block DNA replication than those on the lagging strand? Are human bypass polymerases induced by DNA damage like their counterparts in other species? What is the substrate range for accurate replication, bearing in mind that Pol η replicates dimers and AAAF-guanine adducts but not the 6-4 UV photoproduct? Does the error-prone Pol ζ participate, for example, in hypermutation of immunoglobulin genes (in which specific DNA sequences undergo point mutations to increase immunoglobulin diversity)? Would individuals with mutations in the Pol ζ gene be resistant to UV-induced cancers?

The cloning of the XP-V gene will open up new possibilities for research into DNA replication and repair and for finding ways to treat XP patients. XP itself can now be envisaged as arising through a common pathway that starts from either unrepaired DNA damage (XP-A through G) or from the absence of Pol η (XP-V). Both conditions provide increased substrates for error generation by Pol ζ (see the figure, bottom panel). Thus, Pol ζ assumes importance as the felon underlying genomic instability in UV-damaged cells, and may constitute a target for the design of small-molecule inhibitors that could prevent the formation of cancers.



XP-V solved. Replication of UV-damaged DNA (**top**). UV-induced photoproducts on the leading strand of DNA halt DNA replication. However, photoproducts on the lagging strand only prevent completion of small Okazaki fragments so that DNA replication can proceed. This results in progression of the replication fork leaving a long section of unreplicated leading strand. Under these circumstances, continuation of replication requires the activities of either Pol η, an error-free bypass polymerase that resynthesizes a correct DNA sequence, or Pol ζ, an error-prone and mutagenic bypass polymerase. There is a common pathway of carcinogenesis in the different types of xeroderma pigmentosum (XP) (**bottom**). Complementation groups XP-A through G have cells that lack excision-repair capabilities, and XP-V cells do not have the error-free Pol η. Both situations provide increased substrates for the error-prone Pol ζ, resulting in the synthesis of DNA containing errors.

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