complex assembly. Members of each group or subclass have very similar amino-acid sequences when compared with members of the same group or subclass, but there appears to be little sequence similarity between groups. We believe that this grouping of the molecular chaperones is further reinforced by analysis of structural motifs. Members of the hsp70 group and the GroEL subclass each have in common regions of structural similarity that may form coiled-coil domains, whereas this type of structure appears to be missing among the TCP-1 proteins.

Lupas *et al.*[2] first noted that the hsp70 group possesses regions likely to form amphipathic helices similar to those found in proteins that form coiled coils. They designed a computer algorithm which awards high scores to amphipathic helices containing patterns of hydrophilic and hydrophobic amino acids arranged in heptad repeats within a moving window of 28 residues. This algorithm identified more than 200 proteins when tested against GenBank, including the myosins, laminins and the leucine zipper regions of transcriptional regulators. Proteins known not to contain coiled coils, such as globins and immunoglobulins, were never identified by this algorithm.

We applied this algorithm to other members of the hsp70 group with similar results, including two copies of DnaK from the cyanobacterium *Synechococcus* sp. strain PCC 7942 (Synech. sp. PCC 7942) which we have recently sequenced. We extended this analysis to the GroEL subclass (ref. 3) as shown in the figure. Again, members of this subclass are predicted to possess coiled-coil domains. This motif is also shared by highly divergent members of this subclass such as the plastid chaperonin-60 α- and β-polypeptides[4] (GenBank accession numbers M35599 and M35600, data not shown). The coiled-coil domains in all cases are predicted in regions of these proteins which show moderate to low similarity between amino-acid sequences in members of each group or subclass.

By contrast, TCP-1 sequences from mouse and *Drosophila* are not predicted to form this type of structure (GenBank accession numbers P11983 and P12613, data not shown). Analysis of the TF55 member of this subclass revealed two such possible structures each with marginal score quality.

This type of structural analysis further supports the division of the molecular chaperones proposed by Ellis and raises interesting questions about the possible function of coiled-coil domains within two of the three types. We suggest two possibilities for these domains: (1) involvement in the binding of nascent polypeptides; or (2) involvement in the oligomerization of these two types of molecular chaperone.

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Checkpoint policing by p53

SIR — A recent News and Views[1] proffers a seductive model in which the tumour-suppressor protein p53 is integral to a checkpoint that is responsive to DNA damage. Although this model addresses some of the conundrums in our current understanding of p53 action, it leads to a few simple predictions that are not supported by evidence from this or other laboratories.

It is not clear whether the proposal is for p53 to control a G1 checkpoint (thus preventing progress through the 'Start' restriction point) or an S-phase checkpoint, which would allow cells to arrest DNA synthesis when the DNA becomes damaged. We assume that it is the latter as it is implicit in the model that the checkpoint closes down DNA synthesis. The effects of damage to DNA on its replication are complex and depend on the nature of the damaging agent (for example, see ref. 2). For the sake of simplicity we will confine our comments to damage from ionizing radiation. We have previously shown that DNA synthesis is comparably inhibited by ionizing radiation in primary fibroblasts and in fibroblasts transformed by simian virus 40 (SV40)[3]. (The model assumes that loss of p53 function by binding to SV40 T antigen is equivalent to mutational loss of p53.) Further experiments using SV40-transformed cell lines showed that this inhibition was mediated by a *trans*-acting factor[4,5].

Irrespective of whether p53 mediates a G1 or S-phase damage-responsive checkpoint, the proposed model would predict that cycling SV40-transformed cells should, when compared with primary cultures, show increased sensitivity to killing by ionizing radiation. But it has been shown that a series of SV40-transformed human fibroblast lines are, in fact, more resistant to ionizing radiation than the corresponding primary cell strains[6]. When damaged by other agents like ultraviolet radiation, the sensitivity of primary and SV40-transformed lines is very similar. The sensitivity of many tumour and SV40-transformed cell lines to alkylating agents is known to be caused by specific loss of the O6-methylguanine DNA methyltransferase repair enzyme. Thus, although some tumour cell lines may be sensitive to some types of DNA damage, there is no evidence that tumour cells (or SV40-transformed lines) in general are more sensitive to DNA damaging agents than normal cells. We conclude that, although the concept of p53 as a 'molecular policeman' responding to DNA damage is neat and provocative, the wrong suspect may have been apprehended.

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LANE REPLIES — Carr *et al.* argue that I have apprehended the wrong suspect as a 'molecular policeman' because they know of other factors that control sensitivity to alkylating agents, and because they do not find differences in the sensitivity of primary and SV40-transformed cells to ionizing radiation. I have no argument with their first point, and, of course, it is clear from the large number of different mutations that confer sensitivity to genotoxic agents in man and yeast that p53 is not the only factor that 'guards our genome'.

I do, however, maintain the view that inactivation of the p53 pathway is a critical rate-limiting step in the development of neoplasia and that it functions through a checkpoint mechanism. A recent study by Kuerbitz *et al.*[1], extending their earlier work[2], shows clearly that p53 is responsible for a G1 checkpoint control that operates after exposure to low doses of ionizing radiation. These authors demonstrate that the checkpoint is absent in cells that express either no p53 or mutant p53. Critically, they can restore the control by introducing the wildtype p53 gene back into the null cells. The response certainly occurs in physiologically relevant circumstances, as we have recently shown that a dramatic induction of p53 occurs in the basal layer of human skin after mild exposure to solar mimetic ultraviolet radiation[3].