GLOBAL CHANGE

A looming Arctic ozone hole?

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INCREASING concentrations of greenhouse carbon dioxide in the atmosphere may expose us to the possibility of an Arctic version of the Antarctic 'ozone hole', a hazard we have avoided so far because of the special atmospheric conditions of the Northern Hemisphere. But calculations by Austin, Butchart and Shine, on page 221 of this issue[1], show that the changes to be expected from the almost inevitable doubling of CO_2 levels[2] may undo that protection.

The 1985 discovery of a very large springtime loss of lower-stratospheric ozone over Antarctica was a turning point in atmospheric chemistry. Considering that this ozone hole was totally unpredicted, it is impressive that its essence was explained so quickly. Successful merging of ground-based and satellite measurements, polar aircraft expeditions and atmospheric modelling was crucial to our current understanding.

This understanding is centred about a remarkable set of chemical processes initiated by the formation of polar stratospheric clouds (PSCs), composed of water ice and nitric acid trihydrate, in the deep of polar winter[3]. The main chemical cause of ozone destruction results from catalytic cycles involving chlorine and bromine liberated from chemically inert reservoir molecules by heterogeneous reactions on the PSC surfaces. But PSC formation depends very sensitively on the temperature in the polar night, itself controlled, in essence, by infrared cooling and by stratospheric dynamical activity (essentially the upward propagation of meteorological disturbances from the troposphere). With higher disturbance levels, the polar temperatures become warmer. Ozone losses are much smaller over the Arctic than over the Antarctic because the Northern Hemisphere is dynamically much more active than the Southern Hemisphere.

But will this always be so? Austin *et al.* note that the stratosphere is expected to become cooler owing both to CO_2 increases and to long-term ozone decreases[4,5]. This should increase the likelihood of PSCs forming over the Arctic because the saturation vapour pressure of gas-phase water and nitric acid are strong exponential functions of temperature. With extensive PSCs, increased chlorine- and bromine-driven ozone destruction can be expected over the Arctic region.

The threat of an ozone hole over the heavily populated Northern Hemisphere will undoubtedly stimulate a lot of concern, probably more than the already present Antarctic hole. How reliable is the prediction? Austin *et al.* have almost certainly done the best that can be achieved at present. For more reliable calculations we will probably need at least five year's further intensive research into the pertinent atmospheric chemistry and dynamics.

The stratospheric cooling effect of added CO_2 described by Austin *et al.* is beyond doubt. It depends only on the straightforward physics of infrared radiative transfer. Also the ozone reductions that have already occurred in the lower stratosphere have the effect of introducing their own amplifying feedback[6]. That is, ozone reduction induces cooling (less solar ultraviolet is absorbed), which produces more PSCs, liberating more chlorine and bromine... . Austin *et al.* suspect that this is potentially the predominant process. How it will play out in the real world awaits improved modelling and a better understanding of the governing physical processes.

Additional complications arise in the details of ozone chemical processes acting at and near the edge of the stratospheric vortex that forms in the Arctic winter. The net efficiency of Arctic ozone-destroying chemistry could be substantially influenced by the process of shredding and tearing off strips and chunks of chemically processed air by disturbances impinging on the vortex edge[7]. But with modelling of these processes still in its infancy, the quantitative effects are currently beyond calculation.

Long-term increases in the water-vapour content of the stratosphere could make an Arctic ozone hole more likely. The stratosphere's internal source of water vapour is oxidation of methane, the concentration of which is currently increasing by a little less than 1 per cent a year[2]. Increasing amounts of water vapour mean a higher condensation temperature for PSC formation. But water is also imported into the stratosphere from the troposphere in equatorial regions, passing through the cold tropopause on the way. Climate models with increasing greenhouse gases predict a warming of that region[2], so that less water vapour should be trapped out by the cold as tropospheric air passes through. On the other hand, observations suggest that the tropical tropopause has actually cooled over the past two decades[2], possibly because of polar ozone reduction penetrating to the lower-latitude tropopause region[8].

A subtle, but potentially significant factor not considered by Austin *et al.* is the effect tropospheric climate change might have on the dynamical forcing of the stratosphere. Currently, there are two perspectives on this. My view is that a greenhouse-warmed troposphere would probably reduce the amplitude of tropospheric weather disturbances. This is because the simulated reduced meridional temperature contrast near the Earth's surface and increased tropospheric water vapour content in our doubled-CO_2 calculations together reduce the amplitude of tropospheric planetary waves. In addition, increased CO_2 amounts increase the rate at which radiative transfer brings perturbed stratospheric temperature back to radiative balance. Both of these effects would increase the cooling of the Arctic polar vortex.

This view contrasts with that presented by a Goddard Institute of Space Studies (GISS) model study, which predicts greater dynamical forcing of the stratosphere in a doubled-CO_2 climate[5]. Suffice it to say that the discrepancy appears to arise from differences in the ways that the calculations treat unresolved convection and gravity-wave processes. If our calculations are correct, reduced dynamical activity would increase the likelihood of an Arctic ozone hole. If the GISS calculations are correct, a process to stave it off may have been identified. Increased dynamical forcing for the winter stratosphere could keep the polar regions warm enough to reduce PSC-induced ozone destruction.

As in many studies of climate change, detection of a trend towards an Arctic ozone hole will not be simple. The Arctic winter varies greatly from year to year. Even with stratospheric cooling, occasional warmer polar winters will buck the trend. Nevertheless, the chances of large ozone-destroying events, like those already known from Antarctica, could be growing.

When might we see such an Arctic ozone hole? As significant Arctic ozone losses have already been identified[9], one could argue that the process is already well underway. Even with the Montreal Protocol, stratospheric chlorine and bromine loading may exceed 1980 values (which were sufficient to trigger the

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3. Solomon, S. *Nature* **347**, 347–354 (1990).
4. Fels, S. B., Mahlman, J. D., Schwarzkopf, M. D. & Sinclair, R. W. *J. atmos. Sci.* **37**, 2265–2297 (1980).
5. Rind, D., Suozzo, R., Balachandren, N. K. & Prather, M. J. *J. atmos. Sci.* **47**, 475–494 (1990).
6. Ramaswamy, V., Schwarzkopf, M. D. & Shine, K. P. *Nature* **355**, 810–812 (1992).
7. Schoeberl, M. R., Lait, L. R., Newman, P. A. & Rosenfield, J. E. *J. geophys. Res.* **97**, 7859 (1992).
8. Mahlman, J. D., Pinto, J. P. & Umscheid, L. J. *J. atmos. Sci.* (submitted).
9. WMO/UNEP *Global Ozone Research and Monitoring Project, Report No 25* (World Meteorological Organization, Geneva, 1992).

Antarctic ozone hole) well into the middle of the twenty-first century[9]. Projections of CO_2 levels suggest a doubling of preindustrial values after the middle of the next century[2]. Beyond that period, chlorine and bromine concentrations will slowly decrease (over a 100-year timescale), while CO_2 levels will probably continue to increase[2]. It remains difficult to pinpoint onset or disappearance dates. Nevertheless, it is safe to assume that the threat of an Arctic ozone hole will be with us for a long time unless CO_2, chlorine and bromine emissions are brought substantially below currently projected levels. □

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TUMORIGENESIS

Suppression with a difference

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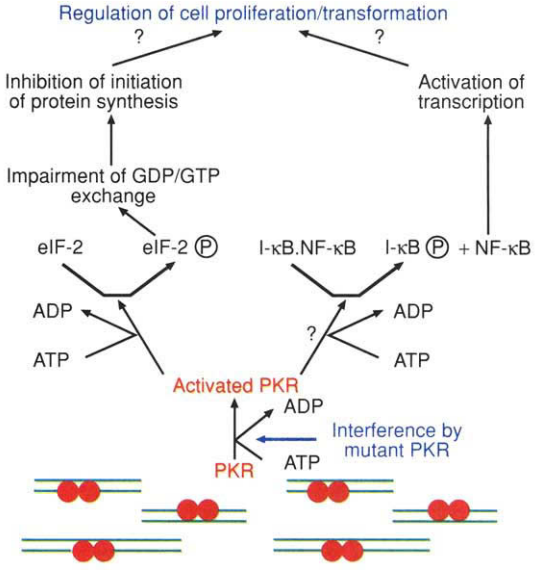
THE concept of tumour suppressor genes (sometimes called anti-oncogenes) is now a familiar one. Mutation or loss of both copies of sequences such as the retinoblastoma (*RB*) or *p53* genes is associated with a number of human cancers[1], suggesting that their protein products keep in check an otherwise uncontrollable ability of cells to proliferate. Although there are several other DNA sequences that are candidates for such genes[2], we still know of far fewer tumour suppressor genes than oncogenes and much less about how their products work. Now, however, there is evidence from two groups[3,4] that a well-characterized protein kinase is a tumour suppressor.

The enzyme in question is the double-stranded RNA (dsRNA)-regulated protein kinase variously known as p68, DAI (for dsRNA-activated inhibitor), dsI, P1 kinase and PK_{ds}. In accord with an informal agreement made by many workers in the field, I will here call it PKR (for RNA-activated protein kinase). The enzyme is inducible by interferons, and is also present at a low level constitutively in many cell types. It has a major role in one of the pathways by which the antiviral effects of the interferons are exerted in infected cells[5] (see figure). The idea is that dsRNA produced during the replicative cycles of a range of viruses activates PKR, which then goes on to inhibit protein synthesis (both viral and cellular) by phosphorylating a subunit of the essential polypeptide chain initiation factor eIF-2. As a result, the exchange of GDP for GTP on eIF-2 (catalysed by another factor) is blocked, chain initiation is impaired and virus replication is thereby inhibited.

So what has this got to do with tumour suppression? The complementary DNA for human PKR was cloned two years ago[6] and several laboratories have since been busily making site-directed mutants and expressing these proteins in a variety of systems. What the new reports show is that 3T3 fibroblasts stably over-expressing forms of inactive PKR are highly tumorigenic when injected into nude mice. The protein kinase was inactivated either by mutation of a single residue involved in the phosphate transfer reaction[4] or by deleting a short stretch of amino acids probably required for substrate recognition[3]. Neither cells transfected with a plasmid encoding the wild-type enzyme nor cells containing the plasmid vector alone were tumorigenic. So it seems likely that the over-expression of inactive PKR interferes with the functioning of wild-type PKR in a dominant negative fashion leading to tumour development.



Possible mechanisms of action of PKR in the control of cell proliferation and transformation. PKR monomers (red) are activated by autophosphorylation following their binding to dsRNA (green; protein dimerization may be required). Active PKR phosphorylates the protein synthesis initiation factor eIF-2 and inhibits translation; it is also possible that PKR phosphorylates I-κB, the inhibitor of the transcription factor NF-κB, causing dissociation of I-κB from NF-κB and activation of the transcription of a number of genes stimulated by NF-κB. Interference with the activation or activity of PKR by mutant forms of the protein kinase may interfere with one or both pathways, leading to tumorigenesis by steps that remain to be determined.

The results are exciting for several reasons. First, they identify a potential tumour suppressor activity that is distinct from those currently known. Both the *RB* and *p53* gene products are believed to function as DNA-binding proteins and/or components of transcription complexes, directly regulating the expression of downstream genes. By contrast, PKR is a cytoplasmic, ribosome-associated protein that apparently acts by regulating translation. Second, the evidence for the involvement of PKR in tumorigenesis may at least partly explain the effects of the interferons as cell-growth inhibitors and anti-tumour agents[7].

Third, we know of a number of viruses that have evolved mechanisms for the inactivation or degradation of endogenous PKR[8]. Such mechanisms include production of small RNA molecules that prevent the activation of the enzyme by dsRNA[9,10], synthesis of proteins that sequester the dsRNA activators[11], and even the production of a decoy protein that looks rather like the enzyme's substrate, the α-subunit of eIF-2 (ref. 12). In the case of viruses that do not kill their host cells but instead produce a mitogenic response or transform the cells to a tumorigenic phenotype, part of the growth-promoting effect might involve the inactivation of PKR by viral gene products. Such an effect, if it occurs in immortalized cells, would be analogous to that of the viral proteins E1a (adenovirus), T antigen (simian virus 40) and E7 (human papillomavirus), which bind to and interfere with the action of the *RB* tumour suppressor protein[1].

How might a high level of mutant PKR interfere with the activity of the endogenous protein kinase? One simple explanation would be that the two proteins compete for binding of limiting amounts of dsRNA activators (the nature of which is largely unknown). Alternatively, given that there is some evidence that PKR exists as a homodimer and that this configuration may be necessary for its activation by autophosphorylation in the presence of dsRNA, the formation of heterodimers between active and inactive enzyme subunits could interfere with the activation process.

Whatever the mode of action of the PKR mutants, it might seem surprising that the elimination of a negative translational control mechanism can lead directly to a tumorigenic phenotype. There is a precedent, however, in that