Two additional levels of regulation are suggested by the new work from Wang's group. Specifically, these investigators used high-throughput screening to identify a small molecule, PETCM [α-(trichloromethyl)-4-pyridineethanol], that activates caspase-3 in cell extracts. In elucidating the mechanism of action of this molecule, they identified the oncoprotein prothymosin-α (ProT) and the tumor suppressor putative HLA-DR–associated proteins (PHAPs) as important regulators of caspase-3 activation. These proteins appear to mediate distinct steps in the mitochondrial cell death pathway: ProT blocks formation of the apoptosome, an event inhibited by PETCM. This is supported by the finding that RNA interference directed against ProT activity sensitizes cells to apoptosis and that extracts from ProT-depleted cells no longer respond to PETCM. In contrast, PHAP appears to facilitate apoptosome-mediated caspase-9 activation. More work is required to definitively establish the in vivo significance of the PHAP finding.

This is not the whole story, as the effects of ProT, PHAP, and PETCM on caspase-3 activation in vitro could not be fully recapitulated with purified components, suggesting that additional regulatory molecules are involved. Nonetheless, the premise that ProT and PHAP proteins are regulators of mitochondrial apoptosis provides a strong rationale for the previously described links between these proteins and disease. It is well established that dysregulation of apoptosis can contribute to the pathogenesis of many human disorders; for example, too much cell death can lead to neurodegeneration, and too little can result in cancer (*13*–*16*). Regarding neurodegeneration, the previous finding that PHAP can interact with the protein ataxin-1 suggests that the proapoptotic function of this protein may contribute to the loss of Purkinje cells in spinocerebellar ataxia type 1, a polyglutamine repeat disorder (*17*). This is now the second example illustrating that polyglutamine expansions can directly perturb the apoptotic machinery; the other example is huntingtin, the protein that is aberrant in Huntington's disease (*18*). Even more compelling are the data implicating PHAP and ProT in cancer, although, unlike Bcl-2, the gene loci for PHAPs and ProT have not been definitively linked with human malignancies. PHAP-I has been shown to oppose both *RAS*- and *MYC*-mediated cell transformation, and loss of PHAP-I in cultured cells results in a transformed phenotype, consistent with its ability to stimulate the mitochondrial apoptotic pathway. Conversely, the observation that ProT is a negative regulator of apoptosis is in accord with the finding that it is a transforming oncoprotein in vitro, and that its overexpression is associated with some human cancers.

The prospect of inducing apoptosis selectively in cancer cells is obviously attractive from a therapeutic perspective, and was presumably the rationale for the screen in which PETCM was identified. Notwithstanding, PETCM is unlikely to be of practical therapeutic value because of the high concentrations required for activity in vitro and its putative poor activity against whole cells. Indeed, more work is needed to clarify the molecular mechanisms underlying PETCM activity and to establish whether ProT regulation is truly amenable to intervention by a pharmacologic agent. Other potential strategies for inducing apoptosis include direct activation of procaspases, and the use of small molecule IAP antagonists, and inhibition of NF-κB. Compelling in vivo proof of concept for these approaches is lacking, however, and selectivity for transformed cells remains a huge hurdle.

Regulation of the mitochondrial cell death pathway is even more complex than previously appreciated, and no easily tractable therapeutic targets have yet been identified. Thus, at least in the short run, a strong argument can be made for proceeding with an empirical forward chemical genetics approach and extending the strategy of Wang and colleagues (*5*) to search for pharmacological agents that induce apoptosis only in transformed cells.

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CLIMATE CHANGE

Whither Arctic Climate?

Drew Shindell

In recent years, the Arctic polar vortex—a circumpolar wind in the stratosphere (a layer from 10 to 40 km above Earth's surface) that isolates the cold air within it—has strengthened and become more persistent (*1, 2*). Arctic surface pressure has decreased, leading to strong winter warming in the Northern Hemisphere (*3*). A dramatic reduction in Arctic sea ice (*4*) has been reported. And according to a recent assessment, springtime Arctic column ozone losses have reached 30% in some years of the last decade, with depletion reaching 70% at some altitudes (*5*).

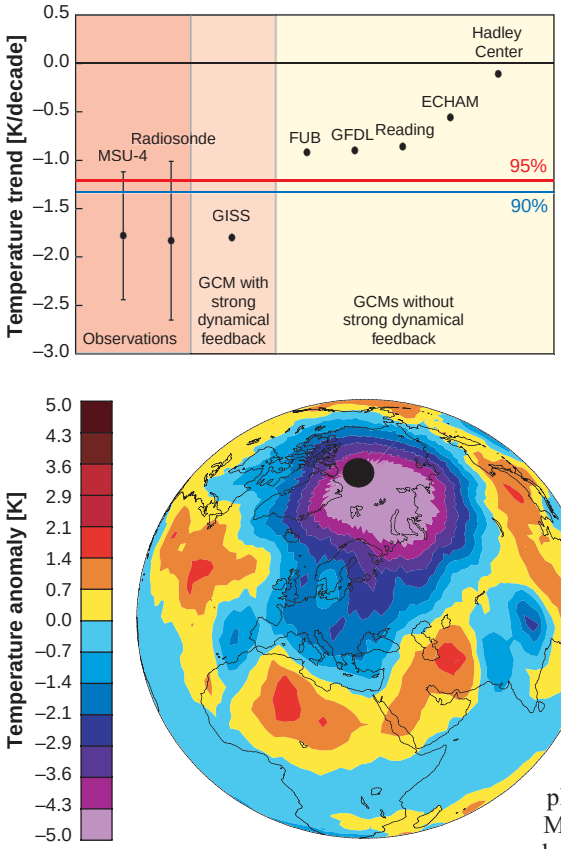
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What is responsible for the observed changes? And are they harbingers of worse times to come? Many model studies have attempted to answer these questions. But comparison with observations shows that models have difficulty reproducing both the trends and the mean state of the Arctic, raising doubt over their ability to elucidate causative connections or predict future trends.

Ozone depletion may seem an obvious choice for tracking changes in the Arctic and evaluating model performance (*5*). However, Arctic ozone loss is extremely variable and sensitive to a given year's meteorology. In winter, the Arctic vortex is frequently disturbed by sudden stratospheric warmings caused by planetary waves (waves thousands of kilometers in length that are generated primarily by land-sea heating contrasts). As a result, temperatures in the lower stratosphere can increase by tens of degrees over just a few days. Polar ozone depletion is most rapid during a short period in spring when sunlight has returned to the Arctic but temperatures are still cold. A sudden warming in mid-March may shut off nearly all ozone depletion, whereas if the warming takes place 2 weeks later, severe ozone loss may occur.

Temperatures that reflect the seasonal strength of the Arctic vortex are a better indicator of structural changes in the stratosphere. Stratospheric temperatures at 70°N have been monitored from satellites since 1979. Large, statistically significant cooling trends have been reported for spring temperatures (February to April) (*6*). Radiosonde data show similar trends (*7*). At about 15 km altitude (100 hPa) at 70°N, satellite and radiosonde trends agree well (this is not the case at some higher levels).

Stratosphere-resolving models provide



Are stratospheric dynamics changing? (**Top**) Temperature trends from March to May in the lower stratosphere at about 15 km (100 hPa), 70°N, from 1979 to 1998 (*18*). Blue and red lines: 90% and 95% confidence limits, respectively, for the cooling to be equal to or larger than the indicated value. Error bars: traditional confidence interval about the best estimate. (**Bottom**) MSU lower stratospheric temperature anomalies for April 2001 relative to the 1979 to 2001 April mean show a cold, strong polar vortex, in line with the long-term trends (*18*).

some insights into what causes these large cooling trends (see the figure). Taking into account greenhouse gas increases, ozone losses, and—in the case of the ECHAM4, Hadley Center, and GISS models—estimates of increasing stratospheric water vapor, the models all show a cooling in the stratosphere. But the radiative effects of these changes cannot fully explain the temperature differences observed by satellite and radiosondes between the 1980s and 1990s.

Modulation of planetary wave propagation by an enhanced meridional temperature gradient near the tropopause (which separates the stratosphere from the underlying troposphere) could refract waves away from the high-latitude stratosphere. This could provide a positive feedback on the radiative cooling of the Arctic vortex (*8, 9*). Only the simulation with a strong dynamical feedback of this sort (GISS) shows good agreement with the observed cooling rates (see the figure). Dynamic strengthening of the polar vortex thus appears to be required to match observed cooling rates.

However, the GISS model and another general circulation model (GCM) that also finds a strong planetary wave feedback (*10*) have simpler physics and coarser horizontal resolution than several recent modeling studies that found no clear strengthening of the Arctic vortex (*11–13*). A recent model study of the role of the stratosphere in surface climate found no wave feedback, and therefore no dependence of surface trends on whether the stratosphere was included (*14*).

Some differences between the models can be explained by physical reasons. GCMs often cannot reproduce observed polar temperatures well. One recent simulation study began with an Arctic vortex 15 to 20 K colder than observed (*13*); the vortex may have been so strong that it could not be further enhanced. The model used in (*14*) produced a weakening of the polar vortex with time, providing a likely explanation for why it did not produce a positive feedback from planetary waves.

Most differences between models can probably be attributed to uncertainties in the specification of gravity-wave physics. Gravity waves are generated by atmospheric disturbances in the troposphere such as storm fronts, strong wind shears, and flow over mountains. Only recently have sources other than topography been taken into account in many models, and understanding of the generation and propagation of these waves is still poor. Yet they play a key role in determining the structure of the stratosphere, thus affecting the sensitivity of the vortex to dynamical disturbance by planetary waves. Observed springtime temperatures are well correlated with winter wave fluxes (*15*), but models have difficulty matching this correlation precisely, suggesting that wave dynamics are not yet well represented in the models.

It is tempting to have the greatest confidence in the most sophisticated models. But Arctic vortex dynamics are largely driven by planetary-scale waves. Because these waves are thousands of kilometers in length, they can easily be resolved with limited spatial resolution and may not require the most complex physics. Similarly, gravity-wave parameterizations are largely empirical, and it is not clear how important high resolution is in this context.

Simpler mechanistic models or GCM "cores" focusing on specific processes thought to be relevant can also be used to examine this issue. Two such studies (*16, 17*) support a modulation of planetary wave propagation by cooling of the polar lower stratosphere, leading to a strengthening of the vortex and a reduction in Arctic surface pressure, as in some of the GCMs (*8, 10*). Observational evidence supports the modeled trend toward equatorward wave propagation (*2, 9*), which has also been linked to continental winter warming and sea ice changes (*9*). A substantial body of evidence thus suggests that changes in wave propagation have contributed to both the strengthening of the Arctic vortex and the surface changes.

If the dynamical strengthening of the Arctic vortex continues, the Northern Hemisphere continents are likely to continue to warm rapidly during winter, and Arctic ozone recovery may be delayed substantially. However, given the large uncertainties in wave processes and the resulting disagreement between models, observed trends cannot yet be linked to definitive causes.

All models in the figure predict an eventual recovery for Arctic ozone, but it remains unclear when this recovery is likely to begin or what the rate of continental winter warming will be. Only with continual improvements to models, extension and improvement of the observational record, and intensive interaction between the two will we get a better understanding of dynamical feedbacks, and hence a better idea of the likelihood of dramatic future changes in the Arctic.

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