could contribute to the stabilization of additional factors that would not have been detected through in vitro screening, which does not accurately model the tumor microenvironment. Notably, NDRG3 was not reported to be a VHL substrate by Zhang *et al.* Future efforts could undertake this screening approach in hypoxic cells, allowing protein modifications downstream of lactate accumulation. This would more closely reflect advanced disease, including tumor hypoxia.

A current challenge concerns the stratification of patients into subgroups that will likely benefit from targeted therapies. Recent progress has been made in identifying individuals with ccRCC likely to respond to immune checkpoint blockade approaches on the basis of polybromo 1 (*PBRM1*) gene loss (*11*). However, selecting patients for specific small-molecule inhibitors remains difficult. Genomic and preclinical data suggest inhibition of HIF2α would be efficacious in treating most ccRCC patients. However, in practice, HIF2α inhibition does not work on some tumors, even if they express HIF2α, and resistance develops in tumors that were initially sensitive to the treatment (*12*). Emerging strategies have focused on identifying consistent targetable metabolic adaptations in ccRCC that might benefit a larger patient population, regardless of the genetic background of primary tumors (*13*). This has revealed multiple metabolic enzymes that are universally lost in ccRCC that could be reexpressed using epigenetic drugs. The identification of biomarkers, such as ZHX2, may represent a way to stratify patients whose tumors are sensitive to combinatorial therapies and delineate new clinically actionable pathways in ccRCC, such as NF-κB signaling. However, like most transcription factors, NF-κB remains difficult to pharmacologically inhibit.

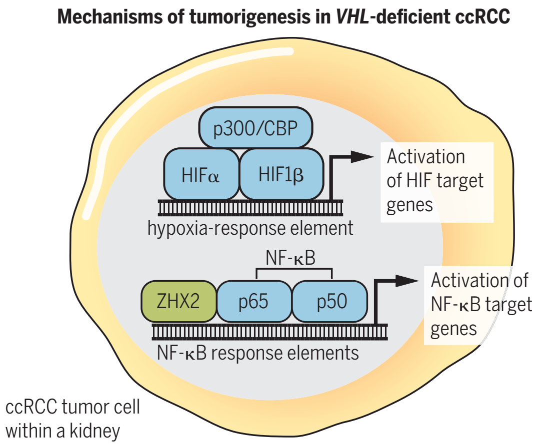
The work of Zhang *et al.* raises additional questions, including, what other factors regulate ZHX2 protein stability? It is likely that ZHX2 is dynamically regulated, in part, through a non–VHL-dependent mechanism, as the amounts of ZHX2 protein did not always correlate with HIFα abundance nor were they eliminated following reinstatement of VHL. Furthermore, as ZHX2 is expressed, to some degree, in the renal epithelium of patients with *VHL* mutations, does this transcription factor function in healthy kidney tissue before ccRCC development?

As ZHX2 and HIF2α regulate distinct target genes in ccRCC, it is likely that they have complementary roles in tumorigenesis (see the figure). Additionally, the key pathways and mechanisms responsible for promoting ccRCC growth downstream of NF-κB were not elucidated. Cell-growth phenotypes downstream of ZHX2 depletion need to be investigated, given that rescue of ZHX2 loss was incomplete. It will also be interesting to evaluate ZHX2 overexpression and its consequences in larger patient cohorts.

In hepatocellular carcinoma and Hodgkin's lymphoma, ZHX2 is a tumor suppressor that transcriptionally represses the expression of cyclins A and E, among other targets (*14*, *15*). This contrasts with its role in ccRCC, where ZHX2 promotes tumorigenesis through its positive role in NF-κB–target gene expression. Elucidating cell-type–specific patterns of genomic occupancy and functions of ZHX2 across cancer types is an appealing future direction. These studies highlight the importance of lineage specificity in determining whether a given factor has an oncogenic or tumor suppressive role. ■

ZHX2 promotes tumorigenesis

ZHX2 and HIFα transcription factors escape degradation in *VHL*-deficient kidney cancer. The factors accumulate, bind to specific DNA motifs, and activate genes that promote tumor growth. p300 and CREB-binding protein (CBP) are transcriptional coactivators.



GRAPHIC: N. DESAI/SCIENCE

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CLIMATE

The seasonal fingerprint of climate change

Satellite data provide evidence for human impacts on the seasonal temperature cycle

By **William J. Randel**

The identification of anthropogenically forced climate change from observational data is challenging. Climate-change effects over the time scale of decades are relatively small compared to natural variability but become progressively larger and influential as time proceeds. Detection of an evolving forced climate signal in observational data is often based on identifying characteristic space-time patterns; this approach is referred to as fingerprint or optimal detection studies. On page 245 of this issue, Santer *et al.* (*1*) identify a previously undetected fingerprint in the mid-latitude seasonal temperature cycle of temperature sensed by satellites over the past four decades. The work adds to the rigorous evidence for human influence on observed atmospheric changes.

In optimal detection studies, fingerprint patterns—for example, the spatial variations of surface warming—are derived from historical climate model simulations driven by greenhouse gas increases and other realistic forcings such as those from atmospheric aerosols and large volcanoes. The modeled and observed patterns are then compared in a robust statistical framework; significance is tested against the background of natural climate variability derived from unforced model simulations. Such analyses have provided conclusive evidence of climate-change signals in observed surface and upper-air temperatures, ocean heat content, the hydrologic cycle, and other quantities (*2*).

Reliable observations of near-global surface temperature extend for ~150 years, but continuous satellite measurements cover only about 40 years, which is a challenge for isolating emergent climate signals in atmospheric temperatures. A previous fingerprint study

Atmospheric Chemistry Observations and Modeling Laboratory, National Center for Atmospheric Research, Boulder, CO 80307, USA. Email: randel@ucar.edu

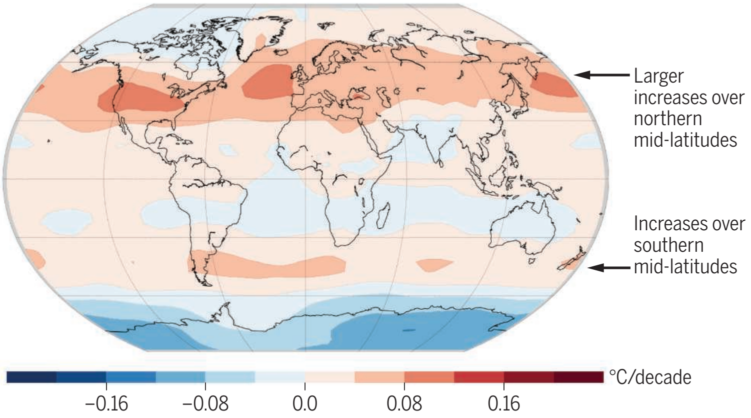
used satellite measurements to identify the characteristic vertical structure of warming in the troposphere (below 10 to 15 km) and cooling in the stratosphere (up to 50 km); this structure is a predicted response to increasing greenhouse gases (*3*). Changing stratospheric ozone concentrations also influence stratospheric temperatures (*4*). Annual-mean, long-term temperatures have risen in the troposphere for most of the globe north of ~60°S, and, although most models warm faster than observations over the full satellite record, as shown by Santer *et al.*, the statistical signature is highly significant.

Santer *et al.* now focus on the seasonal variation of tropospheric warming and show that this warming becomes systematically stronger in mid-latitudes during summer; the warming amplifies the background seasonal cycle. This pattern is seen in both hemispheres, but the amplification is larger and spans a broader latitude range in the Northern Hemisphere, where the strongest signals occur over the continents (see the figure).

How human actions affect seasonal temperatures

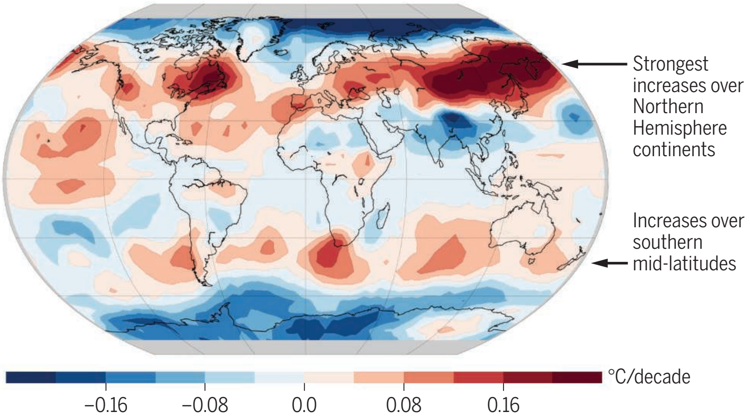
Satellite data for the past 40 years show changes in the mid-latitude temperature cycle in the lower atmosphere, with characteristic structure in both hemispheres. Similar patterns are seen in climate models that include greenhouse gas forcings, but not in models without these forcings.

Climate model average



Changes in the annual temperature cycle derived from an average of 36 different climate models that include greenhouse gas forcing. Results are calculated for simulations covering the period from 1979 to 2016 and sampled similarly to the satellite observations.

Satellite observations



Observed changes in the annual cycle of lower-atmosphere temperature derived from satellite measurements from 1979 to 2016. Red areas correspond to relatively more warming during summer, that is, an increase in annual-cycle amplitude.

GRAPHIC: A. KITTERMAN/*SCIENCE*

The fingerprint pattern against which the observations are evaluated is based on the evolving seasonal cycle in a large group of climate models subjected to anthropogenic and natural forcings. In response to the forcings, the models show a preferential increase in summertime mid-latitude temperatures in both hemispheres (substantially larger in the Northern Hemisphere). This is precisely the signal seen in the observations (see the figure). The pattern correlation of the observed and the simulated signal increases over the satellite data record, and the statistical significance for the changes over four decades is high. The authors duplicate these results in model simulations that include only anthropogenic forcing, thereby demonstrating a human origin. In addition to providing an additional diagnostic of climate change, these results describe a metric—the amplitude of the seasonal cycle—that can be used to evaluate climate model behavior; the different models simulate this response to varying degrees.

The satellite-observed and modeled temperature changes reported by Santer *et al.* are representative of the lower-atmosphere layer averages from ~0 to 10 km. One challenge is to understand the links of these changes to surface climate. Observational studies based on surface temperature measurements during the 20th century show clear evidence for a seasonal variation in surface trends over the continents in both hemispheres, but the largest surface warming occurs in winter, decreasing the background seasonal cycle (*5*, *6*). This change at the surface is opposite to the tropospheric temperature changes identified in Santer *et al.* Analysis of shorter time samples (1981 to 2009, nearly matching the satellite record beginning in 1979) shows mostly insignificant surface changes (*7*), so the connection between changes at the surface and in the free troposphere awaits explanation.

The specific mechanism leading to enhanced tropospheric summertime warming is not well understood. Santer *et al.* suggest that surface-temperature changes are linked to summertime continental drying (*8*), with the resulting effects on water vapor amplifying changes at higher altitudes (*9*). This hypothesis will need further verification. A key aspect of an explanation will need to address the larger and more extensive changes observed in the Northern compared to the Southern Hemisphere.

Santer *et al.*'s findings provide further markers of a substantial human influence on Earth's climate, affecting not only global averages but also local and seasonal changes. As global satellite datasets lengthen in time and cover more parameters, we may expect identification of additional aspects of climate changes in the observational record, including regional and seasonally varying patterns in temperatures and other quantities. It is of crucial importance that the continuity and high quality of satellite observational records are maintained, especially for temperature, water vapor, and precipitation. These analyses will provide further benchmarking opportunities for evaluating and improving climate models. ■

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