

VIROLOGY

HIV Gets By With a Lot of Help From Human Host

HIV is ridiculously simple yet astonishingly complex. The virus contains a mere 9000 bases of RNA—one-millionth the amount of genetic material in a human cell—and a paltry suite of nine genes that code for a measly 15 proteins. Yet this virus can relentlessly nibble at immune cells until the entire system collapses, opening the door for a vast array of illnesses and, ultimately, death. For HIV to do its damage, however, it must repeatedly infect new cells and copy itself, a feat that requires help from its human host. And as a startling paper published online (www.sciencemag.org/cgi/content/abstract/1152725) by *Science* this week explains, that's where HIV's complexity becomes abundantly apparent. The findings also spotlight intriguing, novel drug targets. "This is destined to be one of the key HIV papers of this decade, if not longer," says Robert Gallo, who heads the Institute of Human Virology in Baltimore, Maryland, and did landmark studies that tied HIV to AIDS.

Using cutting-edge molecular techniques, a team led by geneticist Stephen Elledge at Brigham and Women's Hospital in Boston found that the virus relies on 273 human proteins to do its dirty work. These so-called HIV dependency factors (HDFs)—only 36 of which researchers had previously identified—enable the virus to attach to immune cells, wiggle in, shed the protein coat that surrounds its RNA, convert that to DNA, shuttle the genetic material into the nucleus, transcribe genes into amino acids, and then assemble proteins, sprinkle them with sugars, and help newly minted HIVs bud through the surface, where they then go on to find their own cellular prey. "Some viruses carry their houses on their backs, and other viruses invade other people's houses and take over," says Elledge, who had never done an HIV study before but was attracted by the virus's small size. "HIV is more of the latter, and it requires lots and lots of different host functions."

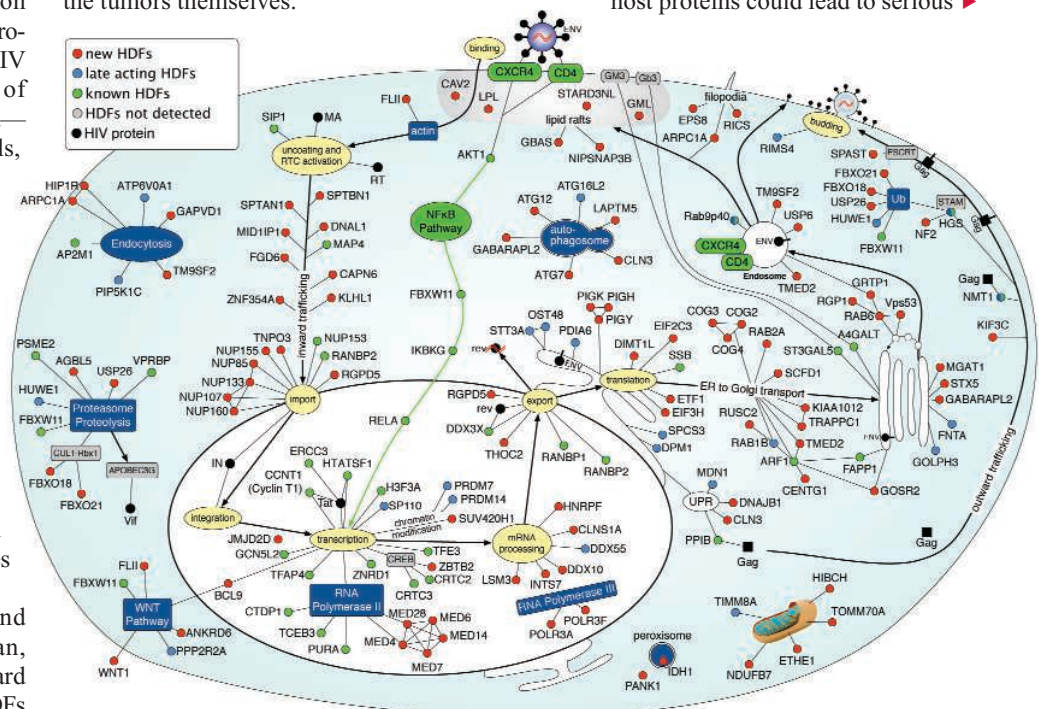
Elledge, postdoc Abraham Brass, and co-workers—including Judy Lieberman, director of the Division of AIDS at Harvard Medical School in Boston—found these HDFs by using libraries of recently discovered small interfering RNAs (siRNAs), which can disrupt

transcription and thereby prevent genes from making their products. Specifically, they took human cells and effectively short-circuited every known gene, one at a time, and then tested whether HIV could establish an infection and copy itself. In all, their genomewide RNA interference screen disrupted more than 21,000 human genes, and by a process of elimination, they isolated the ones that HIV hijacks. "This is an excellent example of siRNA screening," says retrovirologist Warner Greene, who heads the Gladstone Institute of Virology and Immunology at the University of California, San Francisco. "This single paper could guide several interesting graduate student theses in the future."

Gallo says the findings have already led to many new insights, and he shares the study investigators' enthusiasm that these HDFs may make excellent targets for drugs. Elledge compares the strategy to that of much-ballyhooed cancer drugs known as angiogenesis inhibitors, which strangle the blood supply to tumors rather than attack the tumors themselves.

More than two dozen current drugs disable key HIV enzymes. (The U.S. Food and Drug Administration in August for the first time approved an HDF inhibitor, which blocks a receptor the virus docks onto for cell entry called CCR5, but its use is limited to people who have failed to respond to several other drugs.) Although drugs that cripple HIV work powerfully when combined into cocktails, the virus can mutate around each of them, preventing them from binding to their viral targets, eventually leading to drug resistance. Elledge and co-workers contend that HIV would have more difficulty escaping drugs that interfere with HDFs. True, HIV could evolve the capacity to copy itself without one of these factors, but that's a much more difficult task for the virus than mutating to prevent a drug from binding to a viral enzyme. On the flip side, human proteins don't mutate with anywhere near the ease of viruses, which makes it less likely that an HDF would develop drug resistance.

Greene and others caution that targeting host proteins could lead to serious ▶



Complex relationship. HIV (top, purple) relies on more than 200 human proteins to infect immune cells, enter the nucleus, integrate itself into the chromosomes, and then make copies of itself.

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side effects—after all, these HDFs presumably exist to help humans, not the virus. It's also a tall order to discover effective inhibitors against HDFs, says Deborah Nguyen, who with colleagues at the Genomics Institute of the Novartis Research Foundation in San Diego, California, recently published a more limited siRNA study to identify new HIV treatment strategies. “Unfortunately, I think this barrier

won't be crossed for a while,” predicts Nguyen, who says industry's interest in anti-HIV drug R&D is also waning.

Elledge acknowledges the hurdles but counters that many marketed drugs against other diseases target human proteins and provide more benefit than harm. And the hundreds of HDFs his group has identified may play limited roles in human health and development. “Perturbing one may not have

a profound effect on a cell, but it may on HIV,” he says. Yet he agrees that this flood of new data is confusing: “It takes some hard thinking about where to go next.”

Greene says the most immediate challenge is to elucidate the molecular details of how these 273 HDFs interact with HIV. “Currently, the authors can only suggest possible connections,” he says. “But what a great starting point.” **—JON COHEN**

GEOPHYSICS

Daggers Are Drawn Over Revived Cosmic Ray–Climate Link

Last year, climate change scientists thought they had driven a silver stake through the idea that fluctuations in solar activity were behind global warming in the last century. Now, a high-profile team led by geophysicist Vincent Courtillot, director of the Institut de Physique du Globe in Paris, has sought to raise the dead in a paper linking changes in Earth's magnetic field to temperature variations in recent millennia.

The paper, which appeared last year in *Earth and Planetary Science Letters*, has drawn fierce criticism, including a rebuttal in the 15 January issue of *EPSL*, and sparked a rancorous debate on a climate blog. “There is nothing new nor valuable in Courtillot's paper,” asserts Gilles Delaygue, a geochemist at the University Paul Cézanne Aix-Marseille 3. Not so, says Courtillot. “If we are proven to be right, this will seriously backlash on scientists' credibility,” he says.

To illustrate how the sun and Earth's magnetic field influence climate, Courtillot's team presented a graph depicting how fluctuations in solar brightness and the strength and orientation of the geomagnetic field shifted up and down in unison with global temperatures during the past century. This was particularly apparent, they claim, from 1940 to 1970, when a decrease in solar brightness and subsequent weakening of the geomagnetic field was followed by a 0.2°C decline in average annual global temperatures. On a millennial scale, they argue, changes in Earth's inner dynamo lead to rapid shifts of our planet's

magnetic dipole. Currently, the magnetic north and south poles are located near the geographic poles, funneling cosmic rays into a bone-dry lower atmosphere. According to the team, when the dipole wanders toward more humid latitudes, more cosmic rays may interact with water vapor in the lower atmosphere, influencing cloud formation.

Their study challenges reports last year from the United Nations Intergovernmental Panel on Climate Change (IPCC), which hold that the primary driver of global warming in the past century is rising atmospheric concentrations of carbon dioxide and other greenhouse gases, largely from industrial and auto emissions. Courtillot is one of a handful of credible scientists who reject IPCC's bottom line. “Magnetic field fluctuations and sun

conclusions nor giving definitive explanations. We are providing new evidences from observations.” He and his team acknowledge that “anomalous warming” in the past 2 decades apparently cannot be linked to solar or geomagnetic activity, although they decline to ascribe it to greenhouse gases.

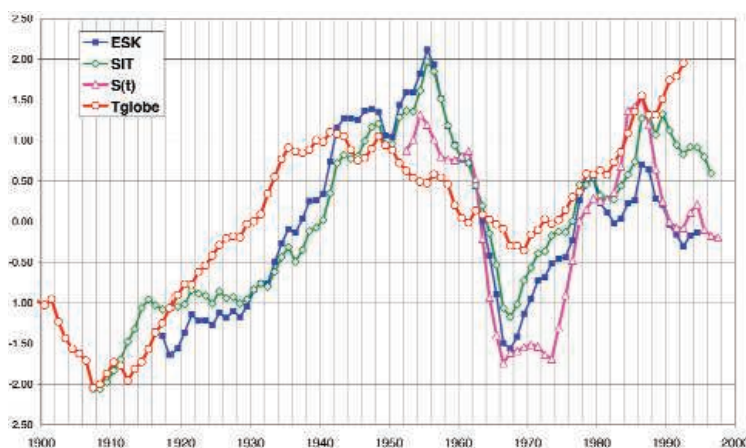
Climate change researchers have set out to strangle the hypothesized climate-geomagnetism connection in its crib. In a comment in *EPSL*, Delaygue and climatologist Edouard Bard of the Collège de France point to flawed analyses of temperature records and other data that they claim undermine the study. Above all, they dismiss the proposed link between solar brightness and cooling in the middle of the 20th century. That cooling, Bard says, is known to be linked to sulfate aerosols, mainly from industrial emissions. “This was an obfuscation of a well-understood phenomenon,” geophysicist Raymond Pierrehumbert of the University of Chicago in Illinois commented on RealClimate.org, a Web site run by climate scientists. Climatologist Phil Jones of the University of East Anglia in Norwich, U.K., adds that there is no need to invoke geomagnetism to explain the temperature record.

This is unlikely to be the last word in the saga. “Many mechanisms that have been debunked have not been debunked at all,” claims Courtillot, who says that he will soon publish two studies arguing that methods used to

measure global temperature need to be revised. Delaygue and many others, however, say that Courtillot's group is doing more harm than good by downplaying the carbon dioxide–climate change link.

—JACOPO PASOTTI

Jacopo Pasotti is a writer in Basel, Switzerland.



More than a coincidence? In this controversial figure, Vincent Courtillot and colleagues argue that variations in Earth's geomagnetic field (ESK and SIT) and solar irradiance are linked to global temperatures in the 20th century, until the advent 2 decades ago of what they call an “anomalous warming.”

pulses fit with global temperature change better than carbon dioxide does,” he asserts, reviving a hypothesis that many scientists believe the IPCC reports had discredited. Knowing they are touching a sore spot, Courtillot cautions: “We are not yet drawing