Gene-Suppressing Proteins Reveal Secrets of Stem Cells

Scientists have taken a step toward unlocking the mystery of “stemness”: that is, deciphering what makes embryonic stem (ES) cells able to replicate indefinitely and retain the potential to turn into any kind of body cell.

According to papers in Cell and Nature this week, key guardians of stemness are molecules called polycomb group proteins. A team from the Massachusetts Institute of Technology (MIT) and the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, reports that these proteins act in concert with others to repress most of the regulator genes whose proteins turn on key developmental genes. This keeps the ES cell in an undifferentiated state.

Polycomb group proteins are known to play a vital gene-suppressing role in the development of organisms as diverse as fruit flies and humans (Science, 29 April 2005, p. 624). Now, the researchers have tracked this role back to the very earliest stage of development. These proteins are “the founding ingredient for development,” says Rudolf Jaenisch, an author of both studies. “This is a major step forward in efforts to map the regulatory circuitry of embryonic stem cells, which constitutes the founding circuitry of human beings,” adds co-author Richard Young.

In the Cell study, the researchers surveyed all 3 billion base pairs in the human genome and identified every gene that a polycomb group protein, Suz12, binds to in ES cells. They started by treating ES cells so that Suz12 remained bound to its DNA targets even after the cells were broken open. They then dumped the cells’ contents onto a chip containing DNA representing all of the human genome. The DNA sequences affixed to Suz12, which were labeled with a dye, bound to complementary sequences on the chip, revealing their identity. The scientists also report in Nature on a similar study with mouse ES cells using Suz12 and three other polycomb group proteins.

The two efforts identified hundreds of genes targeted by the polycomb group proteins. The vast majority of regulators primed to go into action later in development “are being occupied and repressed by polycomb,” says Young. Many of these silenced regulatory genes are also occupied by the ES cell transcription factors Oct4, Sox2, and Nanog. Both sets of proteins “cooperate in keeping a cell pluripotent and self-renewing,” says Jaenisch.

“These papers are really exciting because they point the way to one of the next levels of stem cell research,” says Princeton University stem cell scientist Thor Lemischka. The new, fuller picture of polycomb group proteins, adds Young, may help scientists guide ES cell gene expression and push cell populations to develop into desired types, such as neurons or insulin-making pancreatic cells.

The same issue of Cell also features a report from the laboratory of Eric Lander at the Broad Institute of Harvard and MIT that highlights the importance of chromatin, the protein package surrounding DNA, in keeping mouse ES cells pluripotent. The scientists, led by Bradley E. Bernstein, found certain chromatin motifs near genes important for development that can repress the genes while at the same time keeping them poised for activation. These chromatin features, which they labeled “bivalent domains,” exert control over many of the same regulatory genes targeted by polycomb proteins.

The three papers “provide a wealth of detailed information” on what keeps ES cells pluripotent, says Vincenzo Pirrotta, a molecular biologist at Rutgers University in Piscataway, New Jersey. The polycomb papers demonstrate that those proteins and ES cell transcription factors bind to “a largely common set of genes.” The Bernstein paper then addresses how genes silenced by these factors ultimately become activated. Together, says Pirrotta, the papers have “defined the important players and the sites of action” that must be studied to get to the root of what it is to be a stem cell.

—CONSTANCE HOLDEN

Anthros Happy: No Bones About It

Because $4 million buys a lot of anthropology research, scientists are celebrating a grant of that size from the European Union to promote research into human origins and anatomical variation in primates. “It’s the largest ever in Europe for a project centered mostly on paleoanthropology,” says Jean-Jacques Hublin of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, a member of the European Virtual Anthropology Network.

The new consortium, launched last month at a meeting in Athens, Greece, will create more than 30 doctoral and postdoctoral positions at 15 participating institutions. The young scientists will learn the latest techniques in 3D imaging, computer modeling, and virtual reconstructions of humans, apes, and their ancestors (Science, 3 June 2005, p. 1404).

—MICHAEL BALTER

Super-K A-OK

Japan’s Super-Kamiokande neutrino detector is back at full strength, 4.5 years after a shock wave triggered by the implosion of a damaged photomultiplier tube destroyed 7000 of its 11,000 sensors (Science, 23 November 2001, p. 1630). Super-Kamiokande made headlines in 1998 by providing evidence that neutrinos have mass, but manufacturing replacement photomultiplier tubes after the subsequent accident took a while. “There is still a lot of neutrino research to be done,” says Kamioka Observatory Director Yoichiro Suzuki.

—DENNIS NORMILE

Postdocs off the Docket

Two former postdocs at Harvard Medical School in Boston last week admitted that they took research material from their lab without permission, but charges against them were dropped as part of a deal with prosecutors.

The saga began in early 2000, when Jiang Yu Zhu and his wife Kayoko Kimbara shipped reagents from Harvard to the University of Texas, San Antonio, where Zhu had been offered employment (Science, 28 June 2002, p. 2310). Researchers often transfer such materials when they change jobs, but the couple failed to seek permission from their professor, sparking a court case. Prosecutors initially alleged that the couple intended to use the reagents, used in organ-transplant research, to produce a commercial product. After a 2002 arrest, the pair pleaded not guilty. Under a deal with the government, the indictment will be dismissed in a court case. Prosecutors initially alleged that the couple intended to use the reagents, used in organ-transplant research, to produce a commercial product. After a 2002 arrest, the pair pleaded not guilty. Under a deal with the government, the indictment will be dismissed in 1 year if the pair stays out of trouble.

—ANDREW LAWLER
Latest Forecast: Stand By for a Warmer, But Not Scorching, World

While newly climate-conscious news reporters seek signs of apocalyptic change in hungry polar bears and pumped-up hurricanes, evidence-oriented researchers are working to nail down some numbers. They are concerned with climate sensitivity: how much a given increase in atmospheric carbon dioxide will warm the world. If it’s extremely high, continued emissions of greenhouse gases could ignite a climatic firestorm. If it’s very low, they might merely raise the global thermostat a notch or two.

Now two new studies that combine independent lines of evidence agree that climate sensitivity is at least moderately strong—moderate enough so that a really scorching warming appears unlikely. Even with the most conservative assumptions, says climate researcher Chris E. Forest of the Massachusetts Institute of Technology in Cambridge, the studies cool the maximum warming. And the reinforced low end of the range, he says, means continued emissions will fuel a substantial warming in this century.

The new studies use a technique called Bayesian statistics to gauge how adding new information improves past estimates of climate sensitivity. Most previous estimates used only a single line of evidence, such as how climate warmed as greenhouse gases increased during the 20th century or how climate cooled right after the debris from a major volcanic eruption shaded the planet. Lately, such analyses have started with Northern Hemisphere temperatures between 1270 and 1850 extracted from records such as tree rings. In those preindustrial times, volcanoes, the waxing and waning of the sun, and natural variations in greenhouse gases were changing temperature. Hegerl and her colleagues then combined the preindustrial temperature response to those climate forcings with the global response in the 20th century to volcanoes, rising greenhouse gases, and thickening pollutant hazes.

In this week’s issue of Nature, they report a 5% probability that climate sensitivity is less than 1.5°C and a 95% chance that it’s less than 6.2°C. That’s still pretty high, but a far cry from 9°C or 11°C.

In a similar study published on 18 March in Geophysical Research Letters, climate modelers James Annan and Julia Hargreaves of the Frontier Research Center for Global Change in Yokohama, Japan, found the same lower limit of 1.5°C and a 95% upper limit of 4.5°C. They combined published 20th century warming data with records of coolings after recent volcanic eruptions and estimates of chilling in the depths of the last ice age.

“Combining multiple lines of evidence is certainly the way to go,” says Forest. An extremely high climate sensitivity “is probably less likely than we thought a year ago,” agrees climate researcher Reto Knutti of the National Center for Atmospheric Research in Boulder, Colorado. More importantly, “we start to see a much better agreement on the lower bound,” says Knutti. “We can be pretty sure the changes will be substantial” by the end of the century, he says.

—RICHARD A. KERR
Nuke Tests Prove Critical Issue

Science 312 (5772), 351.
DOI: 10.1126/science.312.5772.351c