Novel molecular 'signature' marks DNA of embryonic stem cells

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A team of scientists announced today a critical step on the path of realizing the promise of embryonic stem (ES) cells for medicine. As described in the April 21 issue of Cell, the researchers have discovered unique molecular imprints coupled to DNA in mouse ES cells that help explain the cells' rare ability to form almost any body cell type. These imprints, or "signatures," appear near the master genes that control embryonic development and probably coordinate their activity in the early stages of cell differentiation.

Not only do these findings help to unlock the basis for ES cells' seemingly unlimited potential, they also suggest ways to understand why ordinary cells are so limited in their abilities to repair or replace damaged cells.

"This is an entirely new and unexpected discovery," said Brad Bernstein, lead author of the study, assistant professor at Massachusetts General Hospital and Harvard Medical School, and a researcher in the Chemical Biology program at the Broad Institute. "It has allowed us to glimpse the molecular strategies that cells use to maintain an almost infinite potential, which will have important applications to our understanding of normal biology and disease."

Chromatin–the protein scaffold that surrounds DNA – acts not only as a support for the double helix but also as a kind of gene "gatekeeper." It accomplishes the latter task by selecting which genes to make active or inactive in a cell, based on the nearby chemical tags joined to its

backbone. By examining the chromatin in mouse ES cells across the genome, the scientists discovered an unusual pair of overlapping molecular tags in the chromatin structure, which together comprise what they called a "bivalent domain," reflecting the dual nature of its design. These domains reside in the sections of chromatin that control the most evolutionarily conserved portions of DNA, particularly the key regulatory genes for embryonic development.

"These signatures appear frequently in ES cells, but largely disappear once the cells choose a direction developmentally," said Bernstein. "This suggests they play a significant role in regulating the cells' unique plasticity."

The remarkable design of bivalent domains, which has not been previously described, merges two opposing influences – one that activates genes and another that represses them. When combined in this way, the negative influence seems to prevail and, as a result, the genes positioned near bivalent domains are silenced. However, the activating influence appears to keep the genes poised for later activity. "For genes, this is equivalent to resting one finger on the trigger," said Stuart Schreiber, an author of the Cell paper, the director of the Chemical Biology program at the Broad Institute, and professor at Harvard University. "This approach could be a key strategy for keeping crucial genes quiet, but primed for when they will be most needed."

Although most people think of heredity in terms of DNA and the genes encoded by it, chromatin also carries inherited instructions known as "epigenetic" information. Thus, the chromatin scaffold (including its bivalent domains) forms a sort of molecular memory that, along with DNA, can be transferred from a cell to its descendants. Yet ES cells signify the earliest cellular ancestors, leaving the question of how epigenetic history first begins. The scientists found that bivalent domains coincide with characteristic DNA sequences, indicating that this

molecular memory may originate from the DNA itself. "How the initial epigenetic state is established and then altered during development has implications not only for stem cell biology, but also for cancer and other diseases where epigenetic defects are implicated," Bernstein said.

A related study led by Rick Young, a member of the Whitehead Institute and an associate member of the Broad Institute, appears in the same issue of Cell and describes new control features found in human ES cells.

Source: Broad Institute of MIT and Harvard