# Marking of tissue-specific crucial in embryonic stem cells to ensure proper function

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Tissue-specific genes, thought to be dormant or not marked for activation in embryonic stem cells, are indeed marked by transcription factors, with proper marking potentially crucial for the function of tissues derived from stem cells.

The finding in the study by researchers at the Broad Stem Cell Research Center involves a class of genes whose properties previously were thought to be unimportant for stem cell function. Most research has instead focused on genes that regulate a pluripotency network and genes that regulate differentiation of embryonic stem cells into other cell lineages.

The Broad center researchers focused on a third class of genes, those expressed only in defined cell types or tissues, which generally remain silent until long after embryonic stem cells have differentiated into specific cell lineages.

"Although prior models suggested that the cascade of events leading to the activation of tissue-specific genes doesn't begin until embryonic stem cells have differentiated, our findings support a new hypothesis in which the competence of these genes for expression is dependent on specific marks established in the pluripotent state," said Stephen Smale, a professor of microbiology, immunology and molecular genetics and senior author of the study. "If this hypothesis is correct, the proper

marking of tissue-specific genes may be essential for pluripotency and the efficient differentiation of stem cells into clinically usable cell types and tissues."

The study is published in the Dec. 15, 2009 issue of the peer-reviewed journal Genes and Development.

Prior to this study, typical tissue-specific genes were believed to have no critical interactions and exist in a base state in embryonic stem cells, sitting silently in the cell waiting to be "marked" by proteins that set in motion a cascade of molecular events. However, Smale and his team unexpectedly identified protein marks on these genes in stem cells and obtained striking evidence that the absence of these stem cell marks compromises gene expression in stem cell-derived tissues. The finding that these genes were already marked was surprising, Smale said.

"This finding may help us understand what it really means to be pluripotent," Smale said. "True pluripotency may depend on faithful marking in pluripotent stem cells of many or all genes within the human genome."

This could be particularly important for those seeking to use embryonic stem cells or reprogrammed cells, called induced pluripotent stem (iPS) cells, to treat diseases or in regenerative medicine. The stem cell marks may ensure that the end result - a beta cell to treat diabetes, a neuron for Parkinson's disease, or a cardiac cell for heart problems - is a fully functional cell operating at 100 percent of its potential.

"We really do need to pay attention to these genes at the outset," Smale said. "Although silent in stem cells, their properties appear to be very important."