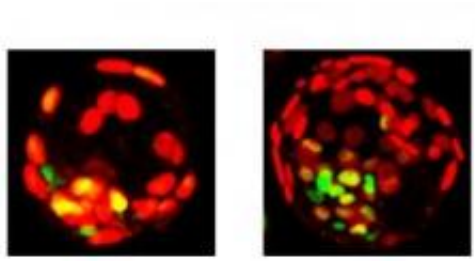
Unearthing King Tet: Key protein influences stem cell fate

July 18 2010



Shown are two mouse embryos at the blastocyst stage. The left is a control embryo and the right is an embryo where Tet1 is depleted at one of the two cells at two-cell stage. Credit: Image provided by Zhang Laboratory at UNC.

Take a skin cell from a patient with Type 1 diabetes. Strip out everything that made it a skin cell, then reprogram it to grow into a colony of pancreatic beta cells. Implant these into your patient and voilà! She's producing her own insulin like a pro.

This type of personalized therapy is the ultimate goal of most stem cell research. But to reliably achieve that goal for treating diabetes and other diseases, there's a whole network of genes, proteins and miniscule chemical reactions to decipher first.

Findings published today in the journal *Nature* put us a step closer to untangling that web. UNC biochemist Yi Zhang, PhD and his team have

discovered that a protein called Tet 1 helps stem cells renew themselves and stay pluripotent—able to become any type of cell in the body.

"This may be one component of a cocktail to reprogram a specialized cell to "go back" to the undifferentiated, embryonic stem cell state," said Zhang, Kenan distinguished professor of biochemistry and biophysics and an investigator of the Howard Hughes Medical Institute. "Then you can differentiate it into whatever cell type you want." He is also a member of the UNC Lineberger Comprehensive Cancer Center.

Both humans and mice have Tet proteins. Observing how Tet proteins operate in colonies of mouse embryonic stem cells, Zhang's team found that the proteins activate a gene called Nanog, which helps stem cells reproduce themselves and keep their pluripotency.

"There are many genes that are important for maintaining embryonic stem cells' status," said Zhang. "We will not understand the whole thing until we identify all the important parts of the network. From that standpoint, we have uncovered another factor in the network."

In addition to observing cell colonies, the team examined the effects of Tet1 protein in "real life" by seeing how a mouse embryo would develop if the Tet1 protein was depleted. They found that when Tet1 is depleted in one cell of the two-cell embryo, cells derived from the Tet1 depleted cells are prone to become trophoblast cells, instead of inner cell mass, from which the pluripotent stem cells are derived.

The Tet1 protein appears to act as an enzyme to maintain the Nanog gene at an active state. When the gene is turned on, the cell maintains its identity as a stem cell. When it's turned off, the cell starts to lose its "stemness". Tet1 performs its function by regulating a modification on DNA, one kind of epigenetic modification. Effects like this are known as epigenetic changes, and they're the reason that various types of cells in

the body perform different functions even though they're all powered by the same genetic code. It's all about which genes are activated—and when.

"The more we understand the machinery that modifies DNA, we'll understand more about cell fate determination," said Zhang. Ultimately, with enough information about Tet proteins and other factors, "we will be able to use that knowledge to reprogram cells—to change their function," he said.

Provided by University of North Carolina School of Medicine