

NIEHS research helps unlock one of the secrets of stem cells

By Ernie Hood

What makes stem cells so special? The quest to answer that seemingly simple question has spawned thousands of basic scientific studies at labs across the world in recent years. Last month, the NIEHS [Stem Cell Biology Group](#) in the Laboratory of Molecular Carcinogenesis published the results of a new study that help explain the molecular basis of self-renewal and differentiation in embryonic stem cells (ESCs).

The [paper](#),

(<http://www.ncbi.nlm.nih.gov/pubmed/24315442>)

"The THO complex regulates pluripotency gene mRNA export and controls embryonic stem cell self-renewal and somatic cell reprogramming," appeared in the Dec. 5 edition of the journal *Cell Stem Cell*.

ESCs can give rise to many different cell types commonly found in the adult body. Because of that potential, they are of great interest to both biomolecular researchers and regenerative medicine scientists. At any given time, ESCs face a choice between differentiation, when they respond to specific developmental cues to transform into specific cell types, and self-renewal, when they divide but retain their stem cell status.

Although the transcriptional regulation of ESC self-renewal and pluripotency - the capability to differentiate into one of many cell types - has been extensively investigated, post-transcriptional mechanisms have been poorly understood, until now. Using advanced experimental technologies, the NIEHS group led by Guang Hu, Ph.D., discovered a protein complex that apparently exerts post-transcriptional regulation of gene expression in ESCs.

The THO complex as a rheostat

The THO protein complex has long been known as a housekeeping complex involved in mRNA export, but its role in regulating ESCs has only now come to light, after Hu and his team assayed genes across the entire mouse genome. "In addition to this general housekeeping role, we showed that the THO complex also has a regulatory function in that it preferentially regulates a subset of genes that are uniquely important for ESCs," said Hu.

As Hu explained, transcriptional control is like a set of light switches, where genes can be turned on or off. However, a post-transcriptional regulator, such as the THO complex, acts as a rheostat, or variable resistor, allowing refined control without fully turning on or off the switch. "The THO complex provides a non-committal way to allow the cells to respond to environmental cues, so they can either choose the fate of differentiating to a particular cell type or maintain the stem cell state without fully committing, as the complex regulates the mRNA export without impacting transcription itself," he said.

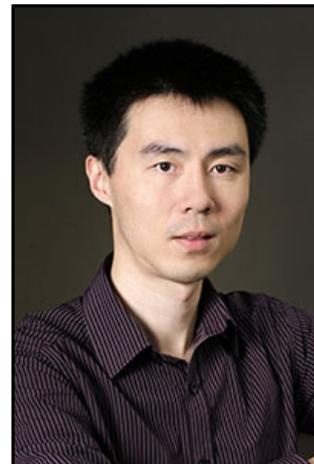
Potential applications

Aside from the significant contribution this discovery makes to the basic understanding of mechanistic processes in ESCs, it may eventually lead to new cell-based therapies, based on manipulating the THO complex to generate induced pluripotent stem cells. It could also spawn new approaches in regenerative medicine, by fostering the manipulation of cell fate in the culture dish, to make various cell types for specific therapeutic purposes

Characterizing the network or pathway is another key objective. "At this moment, we don't know why the THO complex can specifically recognize and regulate these ESC-specific genes, but you would imagine that, at some point, this post-transcription regulation must talk to the transcription regulation, so that there is no conflict between the two," said Hu.

Mouse experiments confirm relevance

The NIEHS [Reproductive Medicine Group](#), led by Carmen Williams, M.D., Ph.D., also contributed to the research, by



"ESCs need to respond to developmental cues in the proper way, but the exact connection between which cue goes through which pathway, to link to which particular mechanism, to flip on the switch or the rheostat, is a key question that most people are still trying to answer," said Hu. "We have not uncovered that particular link in the connection with the THO complex yet, but we are actively searching for it." (Photo courtesy of Steve McCaw)



Williams is also a lead researcher in the Laboratory of Reproductive and Developmental Toxicology. She has been at NIEHS since 2007. (Photo courtesy of Steve McCaw)

conducting experiments involving mouse preimplantation embryos, which showed that THO proteins are needed for proper embryo development to the blastocyst stage, when the embryo is beginning to generate pluripotent stem cells. "This finding means that Guang's experiments in ES cells are actually relevant to the physiological situation *in vivo*, rather than applying only to cultured cells," she explained.

Citation: Wang L, Miao YL, Zheng X, Lackford B, Zhou B, Han L, Yao C, Ward JM, Burkholder A, Lipchina I, Fargo DC, Hochedlinger K, Shi Y, Williams CJ, Hu G.

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