

Novel integrative approach sheds light on embryonic stem cell identity

By Simone Otto

Just as every human has a unique personality, every cell type expresses a unique set of proteins necessary to its identity. In a new study published in the April issue of the journal *Proceedings of the National Academy of Sciences*, researchers at NIEHS reported a novel computational approach to identify genes associated with embryonic stem cell (ESC) identity.

Senthilkumar Cinghu, Ph.D., visiting fellow in the NIEHS Systems Biology Group (SBG), is lead author of the study.

(<http://www.ncbi.nlm.nih.gov/pubmed/24711389>)

"Identification and characterization of genes that maintain ESC identity is a key first step toward using ESCs as models for stem cell transplantation therapies and toxicity tests," he said.

Illuminating ESC regulation

ESCs are pluripotent, meaning they have the power to become any cell in the adult human body. During development, ESCs must be able to divide rapidly and repeatedly without acquiring mutations associated with oxidative stress, as happens in adult cells. According to the authors, this research illuminates a novel regulatory mechanism that facilitates rapid proliferation of ESCs without compromising genomic stability.

"Ever-increasing evidence, supporting the possible hijacking of stem cell self-renewal pathways by cancer stem cells, makes it all the more important to identify, characterize, and understand the pathways that control ES cell identity," said **Raja Jothi, Ph.D.**, lead researcher on the study and head of SBG.

Assigning ranks to genes

Sailu Yellaboina, Ph.D.,

(<http://www.crraoaimscs.org/faculty/sailu-yellaboinas/>)

former visiting fellow in SGB, led the effort to develop a computational approach for systematic integration of published gene expression data, to rank-order genes based on their likelihood of defining a cell type of interest. This approach favors genes that are consistently reported in many studies to be highly expressed in ESCs - the cell type of interest in this study - and significantly down-regulated during the normal course of ESC differentiation.

"You're basically leveraging the evidence from a number of data sets and the consistency of data sets to make a reasonably good set of predictions," explained Jothi.

Many genes ranked as most important to determining ESC identity were also members of protein complexes known to be important in ESCs, whereas genes from complexes known to be important for cell differentiation ranked near the bottom of the order.

Nucleolin is an important shield against oxidative stress

The most exciting result was the unexpectedly high rankings of many genes that had never been implicated in ESC biology. **Guang Hu, Ph.D.**, head of the NIEHS Stem Cell Biology Group, joined forces with Jothi and his team to validate over a dozen novel ESC regulators, including Nucleolin, a gene whose expression is particularly high in cancer cells. The researchers revealed the essential role of Nucleolin in ESC homeostasis, for its role in shielding against oxidative stress induced by redox imbalance, which can induce ESC differentiation (see image below).

"Given the similarities between ESCs and cancer cells, we expect our findings to set the stage for understanding not only tumorigenesis, but also cell fate decisions in cancer stem cells, which are widely believed to possess tumor-initiating capabilities," Jothi said.



"Given that ESC cells and cancer stem cells have similar phenotypic traits, the novel Nucleolin-dependent bistable switch we report in ESC cells [see image below] paves the way for the development of new drug targets for cancer therapy," said Cinghu. (Photo courtesy of Steve McCaw)



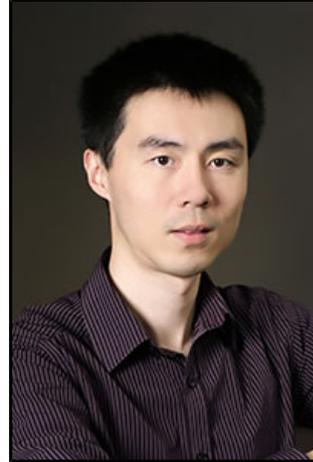
"ESCs are an excellent model for developing new therapies toward regenerative medicine, as well as testing new drugs, especially when there is no good animal model for the disease being studied. Any progress in these areas requires identification and characterization of key genes regulating the homeostatic balance between self-renewal and differentiation in ES cells," said Jothi. (Photo courtesy of Steve McCaw)

Citation: Cinghu S, Yellaboina S, Freudenberg JM, Ghosh S, Zheng X, Oldfield AJ, Lackford BL, Zaykin DV, Hu G, Jothi R. (<http://www.ncbi.nlm.nih.gov/pubmed/24711389>) 2014. Integrative framework for identification of key cell identity genes uncovers determinants of ES cell identity and homeostasis. Proc Natl Acad Sci U S A 111(16):E1581-E1590.

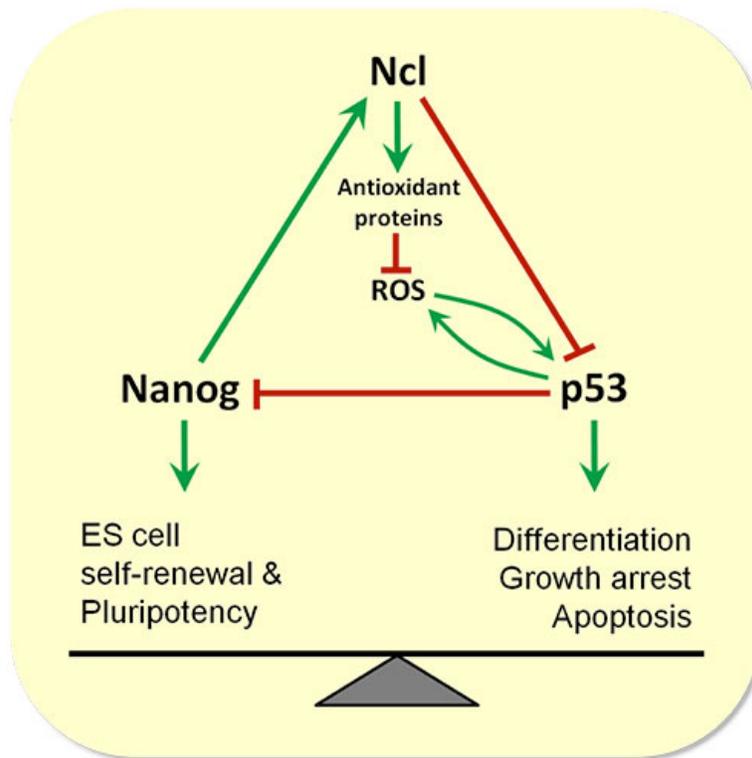
(Simone Otto, Ph.D., is an Intramural Research and Training Award fellow in the NIEHS Ion Physiology Channel Group.)



Yellaboina, an equal contributor with Cinghu in the study, recently left NIEHS to become an associate professor at the C.R. Rao Advanced Institute of Mathematics, Statistics, and Computer Science at the University of Hyderabad in India. (Photo courtesy of Steve McCaw)



The research of Hu and his group seeks to facilitate the development of stem cell therapies, and contribute to understanding how environmental factors can affect human embryogenesis and early development. (Photo courtesy of Steve McCaw)



Proposed model for Nucleolin (Ncl)-mediated regulation of the homeostatic balance between self-renewal and differentiation in ESCs, called an Ncl-dependent Nanog-p53 bistable switch. The balance may be disturbed by depletion of Ncl, leading to reactive oxygen species (ROS)-induced p53 activation and subsequent self-renewal defects and differentiation. The transcriptional regulation of Ncl by Nanog, a master ESC regulator protein, restrains p53, which, when activated, suppresses Nanog. This reciprocity may control the homeostatic balance between ESC self-renewal and cell differentiation. (Photo courtesy of Cinghu et al. 2014)

The Environmental Factor is produced monthly by the [National Institute of Environmental Health Sciences \(NIEHS\)](http://www.niehs.nih.gov/) (<http://www.niehs.nih.gov/>)

, Office of Communications and Public Liaison. The content is not copyrighted, and it can be reprinted without permission. If you use parts of Environmental Factor in your publication, we ask that you provide us with a copy for our records. We welcome your [comments and suggestions](#). (bruskec@niehs.nih.gov)

This page URL: NIEHS website: <http://www.niehs.nih.gov/>
 Email the Web Manager at webmanager@niehs.nih.gov