Scientists discover molecular communication network in human stem cells

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Scientists at A*STAR's Genome Institute of Singapore (GIS) and the Max Planck Institute for Molecular Genetics (MPIMG) in Berlin (Germany) have discovered a molecular network in human embryonic stem cells (hESCs) that integrates cell communication signals to keep the cell in its stem cell state. These findings were reported in the June 2013 issue of *Molecular Cell*.

Human embryonic stem cells have the remarkable property that they can form all human cell types. Scientists around the world study these cells to be able to use them for medical applications in the future. Many factors are required for stem cells to keep their special state, amongst others the use of cell communication pathways.

Cell communication is of key importance in multicellular organisms. For example, the coordinated development of tissues in the embryo to become any specific organ requires that cells receive signals and respond accordingly. If there are errors in the signals, the cell will respond differently, possibly leading to diseases such as cancer. The communication signals which are used in hESCs activate a chain of reactions (called the extracellular regulated kinase (ERK) pathway) within each cell, causing the cell to respond by activating genetic information.

Scientists at the GIS and MPIMG studied which genetic information is activated in the cell, and thereby discovered a network for molecular communication in hESCs. They mapped the kinase interactions across the entire genome, and discovered that ERK2, a protein that belongs to the ERK signaling family, targets important sites such as non-coding genes and histones, cell cycle, metabolism and also stem cell-specific genes.

The ERK signaling pathway involves an additional protein, ELK1 which interacts with ERK2 to activate the genetic information. Interestingly, the team also discovered that ELK1 has a second, totally opposite function. At genomic sites which are not targeted by ERK signaling, ELK1 silences genetic information, thereby keeping the cell in its undifferentiated state. The authors propose a model that integrates this bi-directional control to keep the cell in the stem cell state.

These findings are particularly relevant for stem cell research, but they might also help research in other related fields.

First author Dr Jonathan Göke from Stem Cell and Developmental Biology at the GIS said, "The ERK signaling pathway has been known for many years, but this is the first time we are able to see the full spectrum of the response in the genome of stem cells. We have found many biological processes that are associated with this signaling pathway, but we also found new and unexpected patterns such as this dual mode of ELK1. It will be interesting to see how this communication network changes in other cells, tissues, or in disease."

"A remarkable feature of this study is, how the information was extracted by computational means from the experimental data," said Prof Martin Vingron from MPIMG and co-author of this study.

Prof Ng Huck Hui added, "This is an important study because it describes the cell's signaling networks and its integration into the general regulatory network. Understanding the biology of embryonic stem cells is a first step to understanding the capabilities and caveats of stem cells in future medical applications."

More information: Goke, J. et al. Genome-wide Kinase-Chromatin Interactions Reveal the Regulatory Network of ERK Signaling in Human Embryonic Stem Cells, *Molecular Cell*, June 2013.

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