Protein paves the way for correct stem cell differentiation

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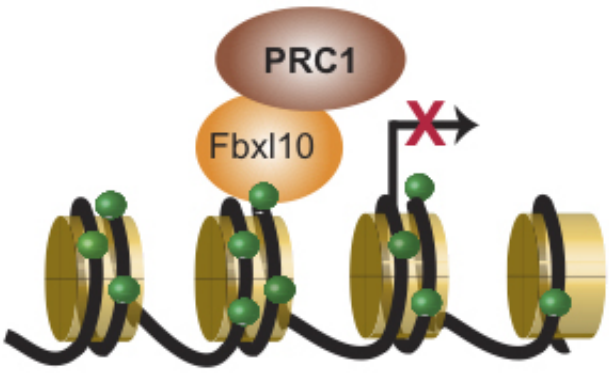

Fbxl10 allows PRC1 to bind to the DNA structure and enables PRC1 to silence the gene. Credit: Xudong Wu

A single embryonic stem cell can develop into more than 200 specialized cell types that make up our body. This maturation process is called differentiation and is tightly regulated. If the regulation is lost, specialized cells cannot develop correctly during development. In adulthood, the specialized cells may forget their identity and develop into cancer cells. Research from BRIC, University of Copenhagen, has identified a crucial role of the molecule Fbxl10 in differentiation of embryonic stem cells and suggests the molecule as a new potential target for cancer therapy.

"Our new results show that this molecule is required for the function of one of the most important molecular switches that constantly regulates the activity of our genes. If Fbxl10 is not present in embryonic stem cells , the cells cannot differentiate properly and this can lead to developmental defects", says Professor Kristian Helin, who heads the research group behind the new findings.

Fbxl10 recruits and activates genetic switches

The Polycomb protein complexes PRC1 and PRC2 are some of the most important genetics switches, which control the fate of individual cells through negative regulation of gene activity. The mechanism by which PRCs are recruited to DNA has been elusive as they are not capable of binding DNA directly. The new results from the Helin research group provide a mechanism for how the PRCs are recruited to the genes that are to be silent.

"Our results show that Fbxl10 is essential for recruiting PRC1 to genes that are to be silenced in embryonic stem cells. Fbxl10 binds directly to DNA and to PRC1, and this way it serves to bring PRC1 to specific genes. When PRC1 is bound to DNA it can modify the DNA associated proteins, which lead to silencing of the gene to which it binds", says postdoc Xudong Wu, who has led the experimental part of the investigation.

Fbxl10 is a potential target for cancer therapy

Timing of gene activity is not only crucial during development, but has to be maintained throughout the lifespan of any cell. Some genes are active at a certain times, but inactive at other times.. Here PRC1 comes into play. PRC1 is dynamically recruited to and dissociated from genes according to the needs of our organism. When cancer strikes, this tight

regulation of gene activity is often lost and the cells are locked in a less differentiated stage. This loss of differentiation and the accumulation of other mutations allow the cancer cells to undergo indefinite self-renewal through endless cell divisions, an ability that normal differentiated cells are prohibited from through tight gene regulation.

"Given the emerging relationship between cancer and stem cells, our findings may implicate that an aberrant activity of Fbxl10 can disturb PRC function and promote a lack of differentiation in our cells. This makes it worth studying whether blocking the function of Fbxl10 could be a strategy for tumour therapy", says Xudong Wu.

And that is exactly what the researchers want to try. In collaboration with the biotech company EpiTherapeutics, the researchers want to develop inhibitors to Fbxl10 as a potential novel therapy for cancer.

The results are published in the journal *Molecular Cell* on February 7, 2013: Wu et al.: Fbxl10/Kdm2b Recruits Polycomb Repressive Complex 1 to CpG Islands and Regulates H2A Ubiquitylation.

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Provided by University of Copenhagen