Controlling self-renewal of stem cells

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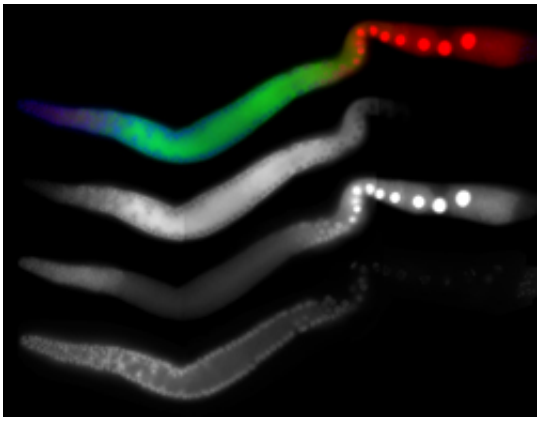

(PhysOrg.com) -- Scientists from the Friedrich Miescher Institute for Biomedical Research (FMI) are the first to establish a direct link between a conserved stem cell factor and the cell cycle regulation in adult stem cells. As published online in the *EMBO Journal*, they demonstrated that the self-renewal of C. elegans germline stem cells requires repression of a cell cycle inhibitor, CKI-2, by a conserved RNA-binding protein, FBF.

The promise of stem cells is two-fold: On one hand, they can differentiate into all the specialised cells in the tissues of the body and thereby guarantee tissue repair; on the other hand, they can self-renew and form new stem cells ensuring -at least in theory- an inexhaustible supply of cells in demand. However, the molecular processes controlling

these traits are still elusive. Thus, a better understanding of stem cell biology is in high demand to be able to deliver eventually on the promise of stem cells in therapy.

From observations scientists have know that stem cells that start to differentiate take longer to divide, their cell cycle is slowed down as if to give the cells enough time to change the program. At the same time, cells that self-renew are pushed through the cell cycle as if to give them no alternative. Despite the growing evidence for the importance of cell-cycle regulation in self-renewal and differentiation, linking critical stem cell factors to the cell cycle regulation in adult stem cells has so far never been possible.

The FMI group leader Rafal Ciosk and his colleagues have now been able to describe for the first time a direct link between proteins controlling stem cell traits and proteins directing the cell cycle. Their results have been published this month online in the EMBO Journal. In their experimental model, the nematode C. elegans, the RNA binding stem cell factor called FBF represses the cell cycle inhibitor CKI-2.This repression is achieved through a direct repression of cki-2 mRNA by FBF. They showed that this mechanism is necessary not only for the self-renewal of stem cells but also to prevent their untimely differentiation. Thus, in the absence of FBF, worms lose their germline stem cells. Once CKI-2 was no longer inhibited in these worms, the cells rushed through the cell cycle and the worms formed germline stem cells again.

"Understanding the processes that determine stem cell characteristics is absolutely critical if we ever want to make use of the full potential of stem cells in therapy. Several lines of evidence have suggested that the decision to self renew or differentiate is closely connected to the cell cycle. We have now been the first to demonstrate this link on a molecular level," comments Ciosk.

More information: Kalchhauser I, et al. (2011) FBF represses the Cip/Kip cell-cycle inhibitor CKI-2 to promote self-renewal of germline stem cells in C. elegans, *EMBO J*. 2011 Aug 5. doi: 10.1038/emboj.2011.263. [Epub ahead of print]

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