Judging DNA by its cover

July 23 2012

Stem cells hold great promise for the medicine of the future, but they can also be a cause of disease. When these self-renewing, unspecialized cells fail to differentiate into diverse cell types, they can start dividing uncontrollably, leading to cancer. Already several decades ago, Weizmann Institute scientists were among the first to demonstrate the link between cancer and the faulty differentiation of stem cells. Now a new Weizmann Institute-led study, published in *Molecular Cell*, reveals a potential molecular mechanism behind this link.

The scientists managed to uncover the details of a step in the process of DNA "repackaging" that takes place during embryonic stem cell differentiation. It turns out that for the cells to differentiate properly, certain pieces of the packaging of their DNA must be labeled by a molecular tag called ubiquitin. Such tagging is required for turning on a group of particularly long genes, which enable the stem cell to differentiate. The researchers identified two switches: An enzyme called RNF20 enhances the tagging, whereas a second enzyme, USP44, does the opposite, shutting it down. Furthermore, it appears that both these switches must operate properly for the differentiation process to proceed efficiently. When the scientists interfered with the tagging – either by disabling the "ON" switch RNF20, or by deregulating the activity of the "OFF" switch USP44 – the stem cells failed to differentiate.

These experiments might explain the significance of molecular defects identified in a number of cancers, for example, the abnormally low levels of RNF20 in certain breast and prostate cancers and the excess of USP44 in certain leukemias. Notably, faulty differentiation of stem cells

is often a hallmark of the more aggressive forms of cancer. This research was led by Prof. Moshe Oren of the Molecular Cell Biology Department, with Prof. Eytan Domany of the Physics of Complex Systems Department and Dr. Jacob Hanna of the Molecular Genetics Department. The team included Weizmann Institute's Gilad Fuchs, Efrat Shema, Rita Vesterman, Eran Kotler, Sylvia Wilder, Lior Golomb, Ariel Pribluda and Ester Feldmesser, as well as Zohar Wolchinsky of the Technion – Israel Institute of Technology, Feng Zhang and Xiaochun Yu of the University of Michigan in the US, Mahmood Haj-Yahya and Ashraf Brik of Ben-Gurion University of the Negev, and Daniel Aberdam of the Technion and the University of Nice-Sophia Antipolis in France.

This study belongs to a relatively new direction in cancer research: Rather than focusing on the genes involved, it highlights the role of epigenetics – that is, processes that do not modify the gene code, itself, but affect the way its information is interpreted within the cell. Understanding the epigenetic roots of cancer will advance the search for effective therapies for this disease.

Provided by Weizmann Institute of Science