Medical Xpress

miR loss may power maligant transformation in chronic leukemia

July 5 2012

Loss of a particular microRNA in chronic lymphocytic leukemia shuts down normal cell metabolism and turns up alternative mechanisms that enable cancer cells to produce the energy and build the molecules they need to proliferate and invade neighboring tissue.

The findings come from a new study led by researchers at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James).

The study shows that microRNA-125b (miR-125b) by itself regulates many enzymes and other molecules that allow cells to make building blocks needed for their growth and proliferation such as DNA and lipids needed for cell membranes.

It also shows that miR-125b is often lost in chronic lymphocytic leukemia (CLL), and that the loss is associated with higher rates of glucose metabolism. This is a characteristic of cancer cells called the Warburg effect, and it alters how cancer cells use sugar (glucose) to generate energy. This finding suggests that loss of miR-125b is an early step in CLL development.

The findings, published in the journal *Blood*, provide a more comprehensive understanding of how cancer develops and identifies new potential targets for CLL drug development, the researchers say.

"Our findings indicate that miR-125b is downregulated in both

aggressive and indolent forms of CLL, and that this downregulation is associated with metabolic adaptation to cancer transformation," says principal investigator and corresponding author Dr. Carlo Croce, director of Ohio State's Human Cancer Genetics program and a member of the OSUCCC – James Molecular Biology and Cancer Genetics program.

"By identifying the metabolites that are changed, as we have here, we can propose to use drugs that target them and perhaps control the leukemia," Croce says.

Scientists have known for some time that, as normal cells become cancer cells, different metabolic pathways are switched on and support the enhanced growth and energy needs that malignant cells require. This study reveals one new way that that can happen.

"The power of microRNAs is that they simultaneously control the expression of many genes, usually by suppressing them," says co-corresponding author Esmerina Tili, who is also first author and a post-doctoral researcher in Croce's laboratory.

"We believe miR-125b is a master regulator of cell metabolism, and that its loss enhances metabolism and leads to a transformed state," Tili says. "As the level of miR-125b goes down in CLL cells, the levels of many of the molecules it controls go up, enabling rapid cell growth."

These molecules, along with miR-125b itself, warrant further investigation as possible targets for new drugs to control CLL progression, she says.

"Cancer is a complex disease," Croce says. "The more we know about the changes that occur when cells become malignant, the better therapies we can design."