Tiny RNA shown to cause multiple types of leukemia

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(PhysOrg.com) -- Whitehead Institute researchers have shown in mouse models that overexpression of the microRNA 125b (miR-125b) can independently cause leukemia and accelerate the disease's progression. Their results are published in this week's online edition of the *Proceedings of the National Academy of Sciences* (*PNAS*).

"MicroRNAs are elevated in many cancers, but in humans and mice, can upregulation of a microRNA actually cause the cancer? That's the question," says Whitehead Institute Founding Member Harvey Lodish. "This 22 nucleotide RNA, one of the smallest RNAs in the body, apparently causes leukemia when it's overexpressed."

According to estimates from the National Cancer Institute, more than 43,000 people in the United States will be diagnosed with some form of leukemia in 2010 and approximately 22,000 will die from the disease. In leukemia, one type of blood cell divides in an uncontrolled fashion in the bone marrow, crowding out other blood cells and frequently causing lowered immunity, anemia, and organ damage.

Leukemias are differentiated by the cell type that hyperproliferates, be it a cell from the lymphoid lineage (B or T-cell) or the myeloid lineage that give rise to red cells, platelets or myeloid cells.

Like other cancers, leukemia is caused by genetic mutations that alter how cells divide, proliferate, or mature. Some leukemia-causing mutations, like the BCR-ABL gene fusion, are relatively well-studied,

but little is known about many leukemia-causing mutations.

In the PNAS paper, first author Marina Bousquet examined a less-studied mutation that leads to miR-125b overexpression in some leukemia patients.

MicroRNAs, like miR-125b, are very short pieces of RNA that normally fine-tune the activity of their target genes. Some miR-125b targets have already been described, including genes involved in the P53 pathway. These targets, which were found by Lodish's former graduate student, Minh Le, are involved with programmed cell death (apoptosis).

Mutations can cause this fine-tuning mechanism to malfunction. In the case of the mutation studied by Bousquet, miR-125b is cranked up to 90 times its normal expression.

To see if this overexpression could actually cause leukemia on its own, Bousquet injected into mice fetal liver cells that overexpressed miR-125b. After 16 weeks, the mice showed extremely high miR-125b production. Between 12 and 29 weeks after the transplantation, half of the mice died from one of three types of leukemia: myeloproliferative neoplasm, B-cell acute lymphoblastic leukemia, or T-cell acute lymphoblastic leukemia.

"Because miR-125b can lead to different kinds of leukemia, it's a major cancer-causing miR," says Bousquet. "It's also interesting that overexpression of miR-125b is seen in patients with B-cell lymphoblastic leukemia and myeloid leukemia, so I'm pretty sure we can find overexpression in other leukemias."

After establishing that miR-125b overexpression can cause different leukemias, Bousquet tested whether miR-125b overexpression can also accelerate disease progression. Into mice without any bone marrow, she

transplanted bone marrow cells that had either the BCR-ABL mutation or the BCR-ABL mutation with a miR-125b overproduction mutation. The mice with both mutations had a median survival of 21 days, compared with 35 days for the BCR-ABL-only control group, a statistically significant difference.

The two experiments show that miR-125b overexpression can be both the primary cause for leukemia and be a secondary agent that hastens its progression.

Although many of miR-125b's target genes have not yet been identified, Bousquet says they are probably involved in proliferation, and cell maturation.

"This is the problem with microRNAs – each miR has many targets," says Bousquet, who will be investigating these targets further. "I would say there is not one good target, but I assume I will find a combination of targets."

Once identified, Bousquet hopes that miR-125b or its gene targets could be exploited therapeutically. Lodish, however remains skeptical.

"We know that miR-125b could trigger leukemia," says Lodish. "But what we don't know is once the cancer has progressed, whether you still need miR-125b. If established leukemia doesn't require miR-125b overexpression, then targeting the microRNA would have little effect."

More information: "MicroRNA miR-125b causes leukemia" *PNAS*, online the week of November 29, 2010.

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