Medical Xpress

Stripping leukemia-initiating cells of their 'invisibility cloak'

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Two new studies reveal a way to increase the body's appetite for gobbling up the cancer stem cells responsible for acute myeloid leukemia (AML), a form of cancer with a particularly poor survival rate. The key is targeting a protein on the surface of those cells that sends a "don't eat me" signal to the macrophage immune cells that serve as a first line of defense, according to the reports in the July 24th issue of the journal *Cell*.

In essence, says Irving Weissman of Stanford University, that signal sent by a cell-surface protein known as CD47 "is an invisibility cloak for leukemia stem cells." Safe from the macrophages whose job it is to clear pathogens and damaged or aging cells from the bloodstream, the CD47-coated leukemia-producing cells are free to traverse the circulation, navigating macrophage-lined blood vessels of the spleen, liver and marrow, and lodging tumors along the way.

The same signal is also temporarily produced at lower levels by normal blood-forming stem cells when they migrate, said Siddhartha Jaiswal, also of Stanford. "CD47 is the vehicle that allows normal stem cells to move from one bone marrow site to another," he explained. To do that, they too must pass a field of macrophages.

"It's something protective on normal cells that's acquired by these malignant cells," Weissman said. The leukemia stem cells co-opt this ability and take it to an extreme in order to evade macrophage killing.

With their colleagues Ravindra Majeti and Mark Chao at Stanford, the researchers further extended their initial findings in mice to humans in the second study. They found that CD47 is more highly expressed on human acute myeloid leukemia stem cells than on their normal stem cell counterparts. Among adult patients with AML, higher CD47 levels predicted worse overall survival, they report.

Antibodies against CD47 allowed the cancer stem cells to be eaten by macrophages and prevented them from taking hold in mice. Anti-CD47 treatment of mice with human leukemia also cleared the animals of their disease.
The results suggest that the CD47 antibodies, perhaps in combination with others, might serve as the first targeted therapy for AML.

"AML is treated today with high dose chemotherapy and in many cases bone marrow transplants," said Majeti, who is a clinical hematologist. "The truth is that the overall survival is really dismal," with 30 to 40 percent of patients surviving at five years. The situation for those over the age of 65 can be much worse, and, he noted, the disease is one that principally affects the elderly. There is therefore an urgent need to develop novel therapeutic agents with less toxicity, and the antibody therapy might fit the bill, he said.

In addition to the potential for a new antibody-based therapy, the ability to differentiate between leukemia and normal stem cells based on their CD47 levels suggests other alternatives as well. For instance, patients could be treated with very strong chemotherapies or radiation and then rescued with their own purified normal stem cells.

The findings in leukemia may prove relevant to other forms of cancer as well, Weissman said, as they are also known to express CD47. Indeed, Jaiswal noted, CD47 was first described as an ovarian cancer marker.

Source: Cell Press (news : web)