Unique role for blood formation gene identified

September 12 2007

All blood cell production in adults depends on the steady work of a vital gene that if lost results in early bone marrow failure, Dartmouth Medical School cancer geneticists have found. Their research reveals an unexpected role for the gene in sustaining the adult blood-forming system, and opens novel strategies for targeting the gene, which is often involved in a type of childhood leukemia.

“We have identified a new pathway that is essential for blood stem cell turnover,“ said team leader Dr. Patricia Ernst, assistant professor of genetics and member of the Norris Cotton Cancer Center. The pathway could be exploited for treating a rare but aggressive infant leukemia, she added. These findings were reported in the September issue of *Cell Stem Cell*.

The investigators created a mouse model to track the function of a gene called MLL, which stands for Mixed Lineage Leukemia. The gene acts in bone marrow stem cells and controls key aspects of their growth to generate all the mature blood cells. If disrupted, it cannot work properly, and leukemia can ensue.

“MLL is the most commonly affected gene in childhood leukemia in children under a year of age; this particular type of leukemia has one of the worst success rates with the existing cancer therapies,” said Ernst, who first helped clarify the role of MLL as a postdoctoral fellow at Harvard.

Many childhood leukemias result from mutations called translocations, where gene pieces on chromosomes accidentally relocate and misalign. In infant leukemia, the chromosome containing the MLL gene breaks within MLL and ends up fused to a different gene. MLL fusion genes likely co-opt normal MLL functions in blood cells, leading to the overproduction of white cells and leukemia.

Previous studies indicated that MLL is critical for embryonic blood stem cell development, but its role for the adult system was unknown. In their mouse model, the researchers found that bone marrow failure occurred as early as 14 days after they induced the experimental loss of MLL, demonstrating the crucial role of MLL as "necessary for both the development and maintenance of the body's blood supply," according to the researchers.

"We have shown that the adult blood-forming system depends on the continuous actions of MLL," Ernst said. Moreover, with the mouse model the scientists established to define normal MLL functions, they can begin exploring how to craft new anti-cancer treatments, she pointed out. "We and other groups can start designing targeted therapies that inhibit cancerous forms of MLL that occur in childhood leukemia and do not affect normal MLL function, which, based on our studies in mice, would be fatal for the patient."

Source: Dartmouth Medical School