

An unexpected way to cause leukemia

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Leukaemia – cancer of blood or bone marrow – is caused by mutations that allow defective blood cells to accumulate and displace healthy blood. To devise effective therapies it is crucial to know which mutations cause leukaemia and which cell type gives rise to leukaemic cells.

Researchers from the European Molecular Biology Laboratory (EMBL) in Italy, the EMBL-European Bioinformatics Institute, UK, and the Universities of Harvard, USA, and Lund, Sweden, have now used genetic engineering to introduce a mutation found in human leukaemia patients into mice. In the current issue of *Cancer Cell* they report that the mutation causes leukaemia by triggering innate genetic programmes that allow white blood cells to proliferate uncontrollably. The findings have implications for the way leukaemia should be treated.

Blood is generated from a small number of multipotent stem cells that divide, differentiate and give rise to the many different cell types that make up the blood. At the same time they also maintain the pool of stem cells through a process called self-renewal. While differentiating, cells acquire specific properties and functions, but lose the capacity to selfrenew in the way stem cells do. Mutations interfering with this process and promoting uncontrolled proliferation of certain blood cells can lead to leukaemia. Researchers of the group of Claus Nerlov at EMBL's Mouse Biology Unit now prove that a mutation in a protein called C/EBPa causes acute myeloid leukaemia (AML), a type of leukaemia affecting one lineage of white blood cells, in mice.



"10 percent of all patients suffering from AML have this mutation, but we could never be sure if it causes the disease. By precisely reproducing the human mutation in the mouse we now proved a causative relation," says Peggy Kirstetter, who carried out the research in Nerlov's lab.

Instead of promoting uncontrolled proliferation of malignant blood stem cells, as often assumed as the cause of leukaemia, the mutation acts on already partially differentiated cells. It reprogrammes these cells to selfrenew and to produce countless dysfunctional daughter cells, which displace the healthy blood cells, eventually leading to the inability to transport oxygen around in the body.

"This is the first time that non-stem cell myeloid leukaemia has been generated within a healthy blood system. The findings will have profound implications for our understanding of the development and treatment of leukaemias," says Nerlov.

Scientists always thought that the mutation was the crucial step leading to leukaemia that should be targeted by drugs. Nerlov and colleagues identified a genetic programme activated in self-renewing leukemic cells, which is shared with similar leukaemias caused by other types of mutations. The findings suggest that the cellular changes that lead to selfrenewal are mutation-independent. To develop drugs with a more general efficacy it may therefore be more efficient to target the molecules and pathways shared between different cancer stem cells.

Source: European Molecular Biology Laboratory

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