"Hematopoietic Cell Autonomous Disruption of Hematopoiesis in a Germline Loss-of-function Mouse Model of RUNX1-FPD."

Marc Raaijmakers, M.D., Ph.D.
Professor of Hematology, Department of Hematology
Erasmus MC Cancer Institute

Key Points:

- A genetically modified mouse with very low levels of RUNX1 protein only in the blood cells (as opposed to other types of cells) has a low number of platelets. It also has more myeloid cells (a type of white blood cell) and a problem with producing lymphoid cells (another type of white blood cell - remember that white blood cells make up the immune system).

- In another genetically modified mouse, one with low levels of RUNX1 protein in only non-blood cells in the bone marrow, there are no blood system abnormalities such as overproduction of myeloid cells or low platelet counts present.

- Removing RUNX1 protein from non-blood cell types within the bone marrow does not cause blood issues, indicating that the loss of RUNX1 protein in blood cells is the culprit, and therefore treatments need to address the low RUNX1 levels in blood cells specifically.
The Research Project

How *RUNX1* gene mutations can lead to blood issues and then (potentially) to blood cancer is still not completely understood. Additionally, it is unclear whether other types of cells in the body, beyond blood cells, may contribute to the development of blood cancer (in case it’s helpful, click here to see a short video on the biology of RUNX1-FPD).

Because RUNX1 protein is also involved in bone formation and maintenance, Dr. Raaijmakers and his team, led by Dr. Martijn Ernst, wanted to explore the potential role of the bone marrow in the issues that RUNX1-FPD patients have within their blood. They wished to ascertain whether the issues were caused by the *RUNX1* gene not working correctly in blood cells alone, or if the cells in the bone marrow (which also have RUNX1 mutations in patients) may also contribute to the problem.

The team studied two mouse models with a genetic mutation that can reduce RUNX1 protein levels in:

1. Blood cells alone and no other cell types, and in
2. Non-blood cells only that live in the bone marrow

These mouse models enabled them to better examine the role of RUNX1 in blood cells and in the cells surrounding blood cells in the bone marrow microenvironment (the immediate surroundings within the bone marrow where these non-blood cells exist; like an ecosystem in nature, these cells are members of this ecosystem).

Specifically, the research focused on bone marrow mesenchymal stromal cells (BMSCs), which play a crucial role in blood cell production. Previous research in another type of blood disorder showed that specific genetic changes in BMSCs can lead to blood cell abnormalities and even the development of blood cancers in mice, even when the genetic changes were absent in the blood cells themselves.

The Research Results

Through transplant experiments and careful investigations, Dr. Ernst and the team discovered that the bone marrow microenvironment itself does not significantly contribute to the blood issues seen in RUNX1-FPD, (at least in these mouse models).

Instead, the primary cause appears confined to lower levels of RUNX1 in blood cells alone. This is in line with the observation that those RUNX1-FPD patients who have had stem cell transplants no longer experience platelet issues or an increased risk of blood
cancer, despite still having RUNX1 mutations in non-blood cells in the rest of their bodies.

Importantly, the blood system is complex. There are many different types of blood cells traveling throughout the body and you can find blood cells in every single organ, so it is not unreasonable to think that RUNX1-mutated blood cells can directly impact many different tissue types. Additionally, how each of the different cell types within an organ (which are also RUNX1-mutated in patients) interacts with RUNX1-mutated blood cells is still an open question.

As has been shown in other RUNX1 mouse models, the team observed that just altering one copy of the RUNX1 gene in blood cells alone is not enough to cause blood cancer in mice. Additional mutations (genetic changes) are required.

Therefore, it is crucial to recognize that while RUNX1 mutations are associated with an increased cancer risk, they are not the sole determinant for cancer development. This fits with what we understand in humans as well. We observe that those who develop blood cancers acquire multiple mutations in their blood.