Researchers find key step in body's ability to make red blood cells

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Researchers at UT Southwestern Medical Center have uncovered a key step in the creation of new red blood cells in an animal study.

They found that a tiny fragment of ribonucleic acid (RNA), a chemical cousin of DNA, prompts stem cells to mature into red blood cells. The researchers also created an artificial RNA inhibitor to block this process.

Such interventions, if fruitful in humans, might be useful against some cancers and other diseases, such as polycythemia vera, in which the body produces a life-threatening excess of blood cells. Conversely, a drug that boosts red blood cell production might be useful against anemia, blood loss or altitude sickness.

"The important finding is that this microRNA, miR-451, is a powerful natural regulator of red blood cell production," said Dr. Eric Olson, chairman of molecular biology at UT Southwestern and senior author of the study, which appears in the Aug. 1 issue of Genes *& Development.*

"We also showed that a man-made miR-451 inhibitor can reduce miR-451 levels in a mouse and block blood-cell production. We hope that this inhibitor and similarly functioning molecules might lead to new drugs against the fatal disease polycythemia vera, which currently has no therapies," said Dr. Olson, who directs the Nancy B. and Jake L. Hamon Center for Basic Research in Cancer and the Nearburg Family Center for Basic and Clinical Research in Pediatric Oncology.

Red blood cells, which carry oxygen throughout the body, are created in bone marrow from stem cells. The body steps up its production of red blood cells in response to stresses such as anemia, blood loss or low oxygen, but overproduction of the cells increases the risk of stroke and blood clots.

RNA molecules, found throughout cells, perform several jobs. MicroRNAs often bind to and disable other types of RNA, preventing them from carrying out their functions.

Dr. Olson and his colleagues study many different types of microRNAs to determine their functions and to find therapeutic uses of artificial microRNAs.

"miR-451 is found in great abundance in mature red blood cells, but its function was not known," said lead author David Patrick, a graduate student in molecular biology.

In the new study, the scientists created genetically engineered mice that could not make miR-451. The mice had a lowered red blood cell count and also had difficulty creating more red blood cells under conditions that usually stimulate production.

miR-451 works by interacting with another RNA involved in producing a protein called 14-3-3-zeta, which plays a role in the maturation of many types of cells, the researchers found.

The team also treated blood stem cells with an artificial RNA designed to inhibit miR-451. As a result, the number of red blood cells decreased.

Dr. Olson and his colleagues are pursuing a patent on miR-451 inhibitors and studying whether a microRNA-based drug might be useful in treating several blood-related disorders.

More information: "miR-451 protects against erythroid oxidant stress by repressing 14-3-3zeta," Genes and Development, published online July 31, 2010, in print issue on Aug. 1, 2010. doi: 10.1101/gad.1942110.

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