Vitamin A deficiency is detrimental to blood stem cells

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Lack of vitamin A in the body has a detrimental effect on the hematopoietic system in the bone marrow. The deficiency causes a loss of important blood stem cells, scientists from the German Cancer Research Center (DKFZ) and the Heidelberg Institute of Stem Cell Research and Experimental Medicine (HI-STEM) now report in the latest issue of the journal *Cell*. These findings will open up new prospects in cancer therapy.

Many specialized cells, such as in the skin, gut or blood, have a lifespan of only a few days. Therefore, steady replenishment of these cells is indispensable. They arise from so-called "adult" stem cells that divide continuously. In addition, there is a group of very special stem cells in the bone marrow that were first discovered in 2008 by a research team led by Andreas Trumpp, who is a division head at the DKFZ and director of HI-STEM. These cells remain in a kind of dormancy most of the time and only become active in an emergency such as bacterial or viral infections, heavy blood loss, or in the wake of chemotherapy. Once their work is done, the body sends its most potent stem cells back to sleep. The scientists assume that this protects them from dangerous mutations that may lead to leukemia.

The mechanisms that activate these special stem cells or make them go back to sleep after their work is done have remained elusive until now. The scientists have now identified retinoic acid, a vitamin A metabolite, as a crucial factor in this process. If this substance is absent, active stem cells are unable to return to a dormant state and mature into specialized

blood cells instead. This means that they are lost as a reservoir. This was shown in studies with specially bred mice whose dormant stem cells are green fluorescent. "If we feed these mice on a vitamin A deficient diet for some time, this leads to a loss of the stem cells," said Nina Cabezas-Wallscheid, who is the first author of the publication. "Thus, we can prove for the first time that vitamin A has a direct impact on blood stem cells."

This finding not only enhances our understanding of the development of blood cells, it also sheds new light on prior studies that demonstrate that vitamin A deficiency impairs the immune system. "This shows how vitally important it is to have a sufficient intake of vitamin A from a balanced diet," Cabezas-Wallscheid emphasized. The body cannot produce its own vitamin A.

The scientists also have hopes for new prospects in cancer treatment. There is evidence that cancer cells, like healthy stem cells, also rest in a state of dormancy. When dormant, their metabolism is almost completely shut down—and this makes them resistant to chemotherapy. "Once we understand in detail how vitamin A or retinoic acid, respectively, sends normal and malignant stem cells into dormancy, we can try to turn the tables," explained Trumpp. "If we could make cancer cells temporarily enter an active state, we could thus make them vulnerable to modern therapies."

In addition, in collaboration with colleagues from the European Bioinformatics Institute in Cambridge, the team performed genome-wide analyses of single cells and discovered that the transition from dormant to active stem cells and then on to progenitor cells is a continuous one and follows a different path for each individual cell. So far, scientists had assumed that specific cell types develop step by step in a defined pattern. This finding revolutionizes the previous concept of how cell differentiation in the body takes place.

More information: Nina Cabezas-Wallscheid et al, Vitamin A-Retinoic Acid Signaling Regulates Hematopoietic Stem Cell Dormancy, *Cell* (2017). DOI: 10.1016/j.cell.2017.04.018

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