

Healthcare industry BW

Stem cell research

The role of stem cell dormancy in regeneration and cancer

Scientists at the HI-STEM stem cell institute in Heidelberg have shown that the stem cells responsible for replenishing blood cells have the greatest potential of self-renewal of any other stem cells. However, they are normally in a dormant state, and only become active upon exposure to certain stress factors. This protects the genomes of the stem cells from damage that causes leukaemias. The researchers have shown that an oncogene called MYC controls the stem cells' transition from dormancy to active self-renewal. Vitamin A counteracts activation of the oncogene by inflammatory factors. Myc gene expression is controlled by a modular gene enhancer cluster. In leukaemia stem cells, this cluster is deregulated and the MYC concentration elevated.



Visiting HI-STEM. From the left/standing: Prof. Dr. Michael Baumann, Chairman and Scientific Director of the DKFZ, Prof. Dr. Andreas Trumpp, CEO of HI-STEM gGmbH, and Dietmar Hopp, founder of the Dietmar Hopp Foundation.
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Adult stem cells that have the ability to undergo life-long self-renewal are responsible for replenishing the terminally differentiated cells of our organs and tissues. The prospect of using this regeneration potential to cure the most serious diseases puts stem cell research at the centre of scientific, clinical and public interest. For decades, the transplantation of bone marrow and haematopoietic stem cells has been an established method for treating blood cancer (leukaemias and lymphomas) and is used many thousands of times a year in Germany. Stem cells can also play a key role in the development and growth of cancer and cancer metastases. Andreas Trumpp, a renowned stem cell researcher from Heidelberg explained that “many cancers are caused by pathologically altered stem cells. Cancer stem cells play a role in the spread of cancer in the body and in making the cancer insensitive to standard therapies.”

Both aspects – stem cells as bearers of hope and harbingers of disease – are the subject of intensive research at the Heidelberg Institute for Stem Cell Technology and Experimental Medicine HI-STEM, which was founded by Trumpp in 2008 with the support of the Dietmar Hopp Foundation and the German Cancer Research Center (DKFZ). HI-STEM gGmbH is located at the DKFZ in Heidelberg, where Trumpp also heads up the Division of Stem Cells and Cancer.

Stem cells between dormancy and activation

In its ten-year existence, HI-STEM has become a leading centre of international stem cell research with over 50 employees who have been instrumental in developing the centre's cancer stem cell concept into one of the pillars of oncological research. (BIOPRO has reported on this on several occasions). Trumpp and his team have shown that among the haematopoietic stem cells (HSCs) responsible for the formation and replacement of blood cells, those with the greatest potential for self-renewal and differentiation usually experience a kind of deep sleep in a “stem cell niche” in the bone marrow. They become active, divide and thereby increase the pool of new stem cells and progenitor cells only when enhanced by certain inflammatory and stress factors such as lipopolysaccharides in bacterial infections and interferons in viral infections or cell loss caused by chemotherapy. All types of blood cells can be formed billions of times from these stem

cells.

The researchers from Heidelberg have discovered that the transcription factor MYC plays a crucial role in the transition of HSCs into a dormant state and their subsequent awakening. MYC is an oncogene that plays a critical role in many different cancers. By knocking out the c-Myc and N-Myc genes in embryonic stem cells, the researchers were able to show that although MYC controls stem cell dormancy and general metabolic activity, it does not control the identity of the pluripotent stem cell. This could for example mean that single dormant and refractory cancer stem cells can survive for a long time in organs without losing their identity or potential. Local inflammatory reactions could wake up such cells, reactivate MYC and unleash their potential to eventually grow into a metastasis.

Vitamin A deficiency leads to the loss of haematopoietic stem cells

In a study published in 2017, Trumpp and his co-workers – in collaboration with scientists from the European Bioinformatics Institute in Cambridge, UK – demonstrated that retinoic acid, a vitamin A derivative, regulates the transition between active and dormant HSCs (dHSCs). In order to investigate the properties and behaviour of these dHSCs in situ, the researchers established a specific transgenic mouse model (Gprc5C reporter mouse) with enhanced green fluorescent protein (EGFP) that enables the researchers to identify and isolate dHSCs based on their fluorescence. The first author of the study, Dr. Nina Cabezas-Wallscheid, reported that vitamin A-retinoic acid counteracts stress factor-dependent dHSC activation by limiting protein translation and MYC concentration. “If reporter mice are fed a vitamin A-free diet for a prolonged period, this leads to the loss of stem cells,” said the scientist who has since moved from Heidelberg to Freiburg where she now heads up a group of researchers at the Max Planck Institute of Immunobiology and Epigenetics. “Without retinoic acid, the activated HSCs can no longer return to a dormant state and instead mature into specialised blood cells,” Dr. Nina Cabezas-Wallscheid concluded. In September 2017, Cabezas-Wallscheid was awarded a prestigious ERC Starting Grant from the European Research Council that enables her to further advance her research group’s work on dHSCs.

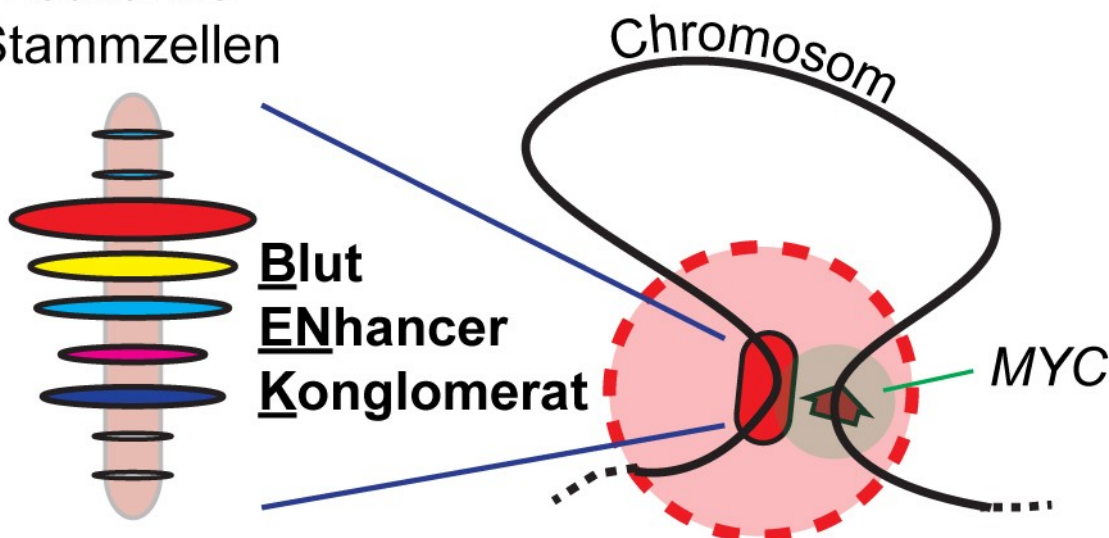
The researchers’ results are consistent with previous observations that vitamin A deficiency impairs the human immune system. The results may also open up new perspectives for cancer treatment on the basis that not only healthy stem cells such as HSCs remain in a dormant state during which their metabolism is largely switched off, but presumably also cancer stem cells. When dormant, cancer stem cells are insensitive to chemotherapy. Andreas Trumpp points out: “If we understand in detail how vitamin A or retinoic acid helps to send normal and malignant stem cells to sleep, we can try to turn the tables. If we were able to cause cancer stem cells to temporarily enter an active state, we could make them vulnerable to modern therapies.” Another possibility would be to cause the cells to become permanently dormant. Both concepts are being driven forward at HI-STEM.



Dr. Nina Cabezas-Wallscheid, formerly at HI-STEM gGmbH, works now at the Max Planck Institute of Immunobiology and Epigenetics in Freiburg.
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A modular gene enhancer that promotes the development of leukaemias

Leukämie- Stammzellen



Schematic showing the region on the chromosome of an AML cancer stem cell where the BENC (blood enhancer cluster) and the Myc gene are located.
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Together with colleagues from the European Molecular Biology Laboratory (EMBL) in Heidelberg and Canadian scientists, Trumpp and his co-workers discovered how the Myc oncogene is regulated in normal HSCs and leukaemia stem cells. The researchers found a cluster consisting of nine gene enhancers that are arranged in individual modules on the chromosome one after the other like a string of pearls. Each of these modules – depending on the type of blood cell – binds certain transcription factors that control Myc gene expression and MYC protein production in a finely balanced interaction. For example, differentiation into blood stem cells and mature B lymphocytes requires very different amounts of MYC protein. Although the Myc gene itself is located at a distance of around 1.7 megabases from the BENC (blood enhancer cluster), looping the DNA brings the two factors into the close spatial vicinity required for them to interact (see

figure).

The researchers demonstrated that BENC is deregulated and Myc-gene activity elevated in leukaemia stem cells, thus speeding up cancer growth. Moreover, they were able to show in an AML (acute myeloid leukaemia) mouse model that leukaemia regressed when BENC was switched off. In addition, some AML patients had several BENC copies while others only had a single enhancer module in the AML stem cells that was specifically active. The amount of MYC was elevated in both cases. This affects the patient's response to therapy and disease prognosis. The survival rate of AML patients therefore correlates with BENC activity. Andreas Trumpp believes that these results could help improve the assessment of AML stem cells in the blood of leukaemia patients. "As the activity of enhancers can be modulated therapeutically, BENC could one day even become a target for novel therapies for this type of blood cancer."

Publications

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