Division of Stem Cell Research
Cell Differentiation

Tackling the mysteries of hematopoietic stem cells Together with research on the blood vessel development, we close in on the truth behind the mechanisms of their origin and maintenance

Scientists have been aware of hematopoietic stem cells (HSCs), a representative type of stem cells, for a relatively long period. But we still do not know where they come from or how they are maintained within the body. Dr. Ogawa seeks to elucidate the nuts and bolts behind HSCs, and to develop regenerative techniques for HSCs that may one day be developed into life-saving clinical applications.

Professor
Minetaro Ogawa
ogawamin@kumamoto-u.ac.jp

Profile

After graduating with a Bachelor' s degree in pharmaceutical chemistry from the Faculty of Pharmaceutical Sciences at Kanazawa University, Dr. Ogawa entered the Graduate School of Pharmaceutical Sciences at the same university, where he obtained his Master' s degree, and later, Doctoral degree by thesis only.
He worked as a research assistant at the Institute of Molecular Embryology and Genetics, Kumamoto University Medical School, as well as Faculty of Medicine, Kyoto University. He held a research fellowship at the Basel Institute for Immunology in Switzerland, then worked as an associate professor at the Graduate School of Medicine, Kyoto University. In 2002, he returned to the Institute of Molecular Embryology and Genetics, Kumamoto University as a professor.

References

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- Tsuji-Tamura, K., Sakamoto, H. and Ogawa, M. ES cell differentiation as a model to study cell biological regulation of vascular development. 'Embryonic Stem Cells: The Hormonal Regulation of Pluripotency and Embryogenesis' ed. Craig Atwood, ISBN 978-953-307-196-1, INTECH, Vienna, Austria, 2011, pp581-606.

The undiscovered origins of HSCs

Hematopoietic stem cells are found within bone marrow, and they are ultimately responsible for blood formation. These cells differentiate into white blood cells, red blood cells, lymphocytes, and all the other types of cell that make up our blood, and further serve to keep the respective levels of those cells at the required constant. They are a representative type of stem cells, long since known to science. "Having said that, we do not actually know where HSCs themselves are generated, nor do we know the sort of control mechanisms in place to keep them self-renewing and maintained within the body," explains Dr. Ogawa.

In developing fetuses, blood formation occurs before the generation of HSCs. In this stage, white blood cells, red blood cells, lymphocytes, and other types of blood cell are produced from endothelial cells; we know that these cells do not pass through HSCs in order to become blood cells. Today, it is possible to produce endothelial cells from embryonic stem (ES) cells, cultured in petri dishes, and then to generate blood cells from the endothelial cells. But those are not really HSCs, of course. Dr. Ogawa is keen to point out that, so far, scientists have only succeeded in producing hemogenic endothelial cells, not true HSCs.

"We know that if you introduce a certain gene into an ES cell, then you end up with something that is 'quite like' an HSC. But that does not mean it is any good at what it is supposed to do, and we also know that these HSC will not differentiate into lymphocytes," explains Dr. Ogawa. "There are still many mysteries to be uncovered about the generation mechanisms of HSCs. One of the core topics of my research is shedding light on these mechanisms and looking to see how they could be put to use in HSC regeneration techniques."

Aiming for HSC generation under crystal-clear conditions

At Dr. Ogawa's laboratory, his team is working on a study of the self-renewal mechanisms of HSCs. It is not possible for HSCs to produce blood cells without there being an adequate supply of HSCs, so these cells implement an iterative process of self-replication, all the while maintaining their pluripotency, before differentiation into blood cells. The team is trying to establish how this self-renewal is controlled to ensure that the body never runs out of its supply of HSCs.

At present, although bone marrow transplantation is conducted as a treatment for leukemia, the process is marred by the lack of matching donors. If it became possible to use ES cells or induced pluripotent stem cells, derived from the patient's own body, to produce HSCs, to use genetic therapy to return these HSCs to a normal state, and to re-introduce them to the patient's body; then the level of treatment available for blood diseases like leukemia would soar. "That is a real motivator for me; we need to figure out and fully understand where these HSCs come from and how they control their self-renewal," says Dr. Ogawa. "The next stage is to develop perfect conditions—carefully developed and chemically defined—under which we can generate 'real' HSCs with real HSC functionality."

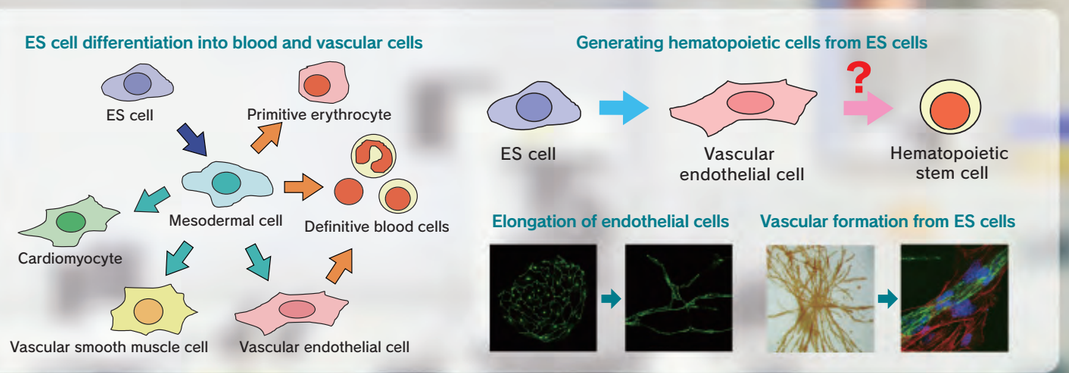
This determination to uncover the secrets behind the origins of HSCs, and then to take that knowledge and use it for the betterment of medicine, is an excellent example of the commitment seen in so many biologists engaged in basic research.

Toward the truth behind blood vessel formation mechanisms

Elsewhere, Dr. Ogawa and his team are looking at cell-shape control mechanisms in vascular endothelial cells, with a particular focus on Foxo1 as a transcription factor that plays an important role in vascular formation.

When ***Foxo1***-deficient ES cells are cultured and used to produce blood vessels in a petri dish, the resulting endothelial cells show abnormalities in shape. They are unable to regulate their shape through elongation, and instead take on abnormal forms. The ***Foxo1***-deficient mouse model resulted in embryonic lethality as a result of abnormalities in blood vessel formation. "This indicated that Foxo1 has a role to play in regulating the expression of other genes related to the elongating function of vascular endothelial cells," explains Dr. Ogawa. "We then looked at what other genes control ***Foxo1***, and discovered a candidate gene that encodes an enzyme that worked to balance the phosphorylation of certain proteins. Without Foxo1, the candidate gene may not be expressed, which means that this same gene must be one of the genes related to regulation of the morphology of cells. Dr. Ogawa and his team have also established that if this gene is inserted into ***Foxo1***-deficient endothelial cells, the cells will regain the ability to elongate normally. Their work in this area continues.

Blood vessels form normally when vascular endothelial cells assemble with vascular smooth muscle cells, but when ***Foxo1*** has been knocked out, the endothelial cells and smooth muscle cells fail to assemble, remaining separate instead. Dr. Ogawa and his team believe that this is because Foxo1 controls the gene that would otherwise facilitate the assembly of the two cells types; their work continued in an effort to prove this hypothesis.



Teaching Staff

Assistant Professor

Hiroshi Sakamoto

I am currently conducting stem cell research using hematopoietic stem cells. I am always keen to adopt the latest technology into my research and combine it with more traditional methodological approaches with the aim of developing new ideas and concepts in stem cell research.

Assistant Professor

Kiyomi Tamura

My main research topic is the clarification of mechanisms of blood vessel formation. Blood vessel formation is very closely linked to the advancement of a number of diseases, including cancer and chronic inflammation. I am trying to establish what mechanisms are in place to regulate blood vessel formation, and ways in which we might be able to regenerate and control blood vessels. I hope that this research will contribute to the development of therapies for such diseases.