The critical function of miR-146b against hematopoietic malignancy

Hiroshi Asahara
MD,Ph.D.,Professor
Department of Systems BioMedicine, Graduate School of Medical and Dental Sciences, TMDU

Takahiro Mitsumura
MD,Ph.D.,Specially Appointed Assistant Professor
Department of Respiratory Medicine, Graduate School of Medical and Dental Sciences, TMDU

THE NON-CODING RNA molecule miRNA 146a (miR-146a) was originally identified as an NF-κB-induced miRNA capable of repressing NF-κB activity. Further, miR-146a-deficient (knockout [KO]) mice showed autoimmunity, such as T-cell-mediated multiorgan inflammation.

A homolog of miR-146a, miRNA 146b has the same seed sequence as that of miR-146a and can also repress TRAF6 and IRAK1 expression. Therefore, miR-146b may also play a critical role in preventing tumor development. It was reported that reduced expression of miR-146b was observed in various types of tumors, such as breast cancer, glioma, gallbladder cancer, and large B-cell lymphoma. In addition, it has been reported that overexpression of miR-146b suppresses malignancy in lymphoma, leukemia, breast cancer, and gliomas. However, the physiological roles of miR-146b and the functional differences between miR-146a and miR-146b in the context of tumorigenesis remain elusive.

In this study, we generated miR-146b-knockout (KO) and miR-146a-KO mice by genome editing and found that both strains developed hematopoietic malignancies such as B-cell lymphoma and acute myeloid leukemia during aging. However, the B-cell lymphomas observed in miR-146a-and miR-146b-KO mice were histologically different in their morphology, and the malignancy rate was lower in miR-146b mice than miR-146a mice. Upon mitogenic stimulation, the expression of miR-146a and miR-146b was increased, but miR-146b expression was lower than that of miR-146a. Using a previously developed screening system for microRNA targets, we observed that miR-146a and miR-146b could target the same mRNAs, including TRAF6, and inhibit subsequent NF-κB activity. Consistent with these findings, both miR-146a-and miR-146b-KO B cells showed a high proliferative capacity. Taken together, sustained NF-κB activation in miR-146b KO mice could lead to the development of hematopoietic malignancy with aging. The results of this miRNA study are expected to contribute to the elucidation of the pathological conditions of hematopoietic cancers and development of new therapy for these diseases.

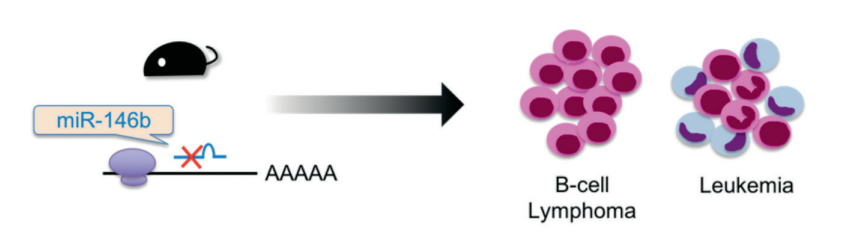

Fig.1: miR-146b knockout (KO) mice developed hematopoietic malignancy.

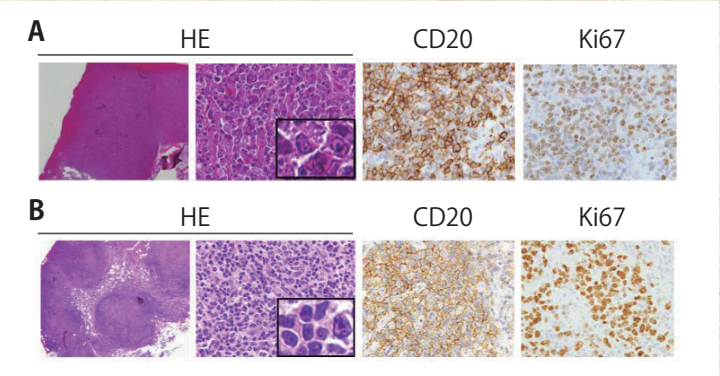

Fig.2: B-cell lymphomas developed in the lymph nodes of miR-146a and miR-146b KO mice.
A: Lymphoma observed in the lymph nodes of miR-146a KO mice.
B: Lymphoma observed in the lymph nodes of miR-146b KO mice.

The article "Ablation of miR-146b in mice causes hematopoietic malignancy" is published in Blood Advances at doi: 10.1182/bloodadvances.2018017954.

Summary : Tokyo Medical and Dental University (TMDU) researchers used knockout mouse models created by gene editing to reveal that the miRNA miR-146b, like miR-146a, is involved in the development of cancers, with each having similar but not identical effects. The knockout mice showed high rates of B-cell lymphoma and acute myeloid leukemia, which was associated with the absence of miRNA causing NF-κB overactivation. These insights should help in the fight against cancers involving miRNA dysregulation.

How does estrogen protect bones? Unraveling a pathway to menopausal bone loss

TOKYO–OSTEOPOROSIS IS a condition in which bones become weak and prone to fractures. Fractures typically occur in the wrist, spine, or hip, and can often lead to permanently impaired mobility. Women over 50 are at a high risk of developing osteoporosis, which may be due to the loss of estrogen that occurs after menopause. While studies have linked estrogen levels to bone health, the exact details of this connection are not entirely clear. Researchers at Tokyo Medical and Dental University (TMDU) describe a new molecular link between estrogen and bone aging, which may eventually lead to new strategies to treat postmenopausal osteoporosis.

Bone is a complex tissue, consisting of a matrix of proteins and minerals that give it the flexibility and strength to support body movement. Bone also contains several types of specialized cells, including osteocytes, that help to maintain this matrix. Over a person's lifetime, many factors can affect how healthy bone structure is maintained. One of these factors is the female sex hormone, estrogen.

"Over the last few decades, we've learned that estrogen plays an important role in maintaining a functional bone matrix," corresponding authors Tomoki Nakashima and Hiroshi Takayanagi explain. "Exactly how estrogen does this, though, is not fully understood. Our laboratory recently discovered that bone matrix is maintained by a protein called Sema3A, which is secreted by osteocytes. This led us to suspect that there might be a mechanistic relationship between estrogen and Sema3A."

Sema3A does indeed appear to be linked to estrogen: the researchers found that blood serum levels of the protein decrease in premenopausal women as they get older— and drop even further once women reach menopause. But how, at the biological level, are estrogen and Sema3A related? And what is Sema3A doing in bone tissue?

To answer these questions, the researchers turned to mice. When mice are given an ovariectomy (that is, when their ovaries are removed), the loss of estrogen causes their bone mass to decrease. This can be prevented, however, by giving the mice an extra supply of the hormone. The team took advantage of this to explore the function of Sema3A.

"When we genetically removed Sema3A from the osteoblast lineage cells (including osteocytes) of mice, we found that intravenous estrogen no longer prevented bones from deteriorating after an ovariectomy," lead author Mikihito Hayashi describes. "In addition, we found that Sema3A sets off a chain of signaling events that promote the survival of osteocytes in these mice. This suggests that Sema3A serves as a key mechanistic link between estrogen and bone maintenance .

We believe that, as women lose estrogen with age and Sema3A levels drop off, osteocytes begin to die and bone loses the ability to maintain its supportive structure."

The researchers hope that the discovery of Sema3A as a major player in bone health and the signaling molecules it controls in bone may offer new therapeutic approaches to treating osteoporosis.

Tomoki Nakashima
Ph.D., Professor
Department of Cell Signaling, Graduate School of Medical and Dental Sciences, TMDU

The article, "Autoregulation of osteocyte Sema3A orchestrates estrogen action and counteracts bone aging" was published in Cell Metabolism at DOI: 10.1016/j.cmet.2018.12.021.

Summary : Women who have reached menopause are at a greater risk of developing osteoporosis, which can lead to bone fractures and long-term impairment of mobility. Studies have suggested a link between reduced bone density and low estrogen levels due to menopause, but the basis for this link is unclear. Researchers at Tokyo Medical and Dental University found that the protein Sema3A plays a key role in maintaining healthy bones, suggesting a new therapeutic avenue to treat osteoporosis.

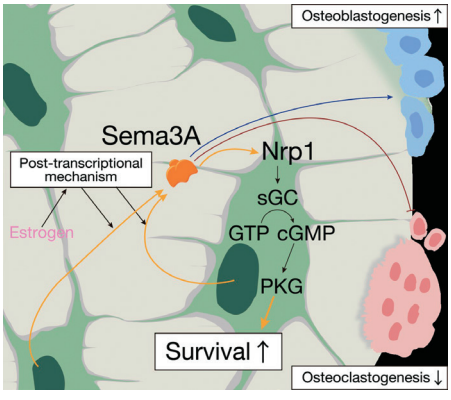

Fig.1: **Autoregulation of osteocyte Sema3A in bone homeostasis**
Estrogen induces osteocyte expression of Sema3A, which acts on its receptor on osteocytes to promote survival, resulting in reduced osteoclastic bone resorption and enhanced osteoblastic bone formation. Sema3A-activated sGC—cGMP signaling through Nrp1 protected osteocytes from apoptosis.

"Instant Liver, Just Add Water"? Not Quite, but a Better Way to Grow Multiple Organs

TOKYO, JAPAN – PLURIPOTENT stem cells are specialized cells that can become almost any type of cell or tissue in the body. Because of this potential, they are often used in research to study disease. One way this is done is by coaxing stem cells to form organoids, which resemble organs but can be more easily studied in a laboratory. Researchers centered at Cincinnati Children's Hospital Medical Center (CCHMC) and Tokyo Medical and Dental University(TMDU) have devised a better way to make one particular organoid to aid in studies of the liver, bile duct and pancreas.

"Our focus was on generating a hepato-biliary-pancreatic organoid, which would allow us to better understand how the liver, bile duct, pancreas, and associated tissues form during embryonic development and how they normally function together," explains Takanori Takebe, senior author of the study. "The current technical approaches are fairly limited, though, and the resulting models lack the complexity of true organs."

In the technique pioneered by the research team, human stem cells are used to make small "spheres" of cells that each represent different parts of a developing embryo. The spheres are fused together to create an immature organoid, which is then allowed to mature and grow while suspended in a specially engineered three-dimensional gel. With the new technique, the resulting organoid bears a striking resemblance to a liver, pancreas, and the connecting bile ducts.

"What we are most excited about is the sophistication of the organoid," says Hiroyuki Koike, one of the researchers involved in developing the technique. "We could see branches that directly connected the bile duct to the pancreas. Amazingly, the pancreatic tissue that emerged was able to secrete digestive enzymes through the ducts, similar to how the true organ would function. The complexity of the organoid is really quite remarkable."

The researchers also showed that, by making specific genetic mutations, they can stop the stem cells from becoming a working organoid – demonstrating the potential usefulness of the system to study diseases that arise in these organs.

Takanori Takebe
Professor
Organ and Tissue Neogenesis Consortium, Advanced Multidisciplinary Research Cluster, Institute of Research, TMDU

"There are still a number of challenges in the field with respect to creating a robust multi-organ model system that can be easily manipulated in a research setting," Takebe adds. "The work here shows that it is possible to create such a system using human pluripotent stem cells. This is quite exciting, as it lends credibility to the idea that stem cells might be used to make personalized models to study how organs form and how genetic mutations lead to organ malfunction."

The article,"Modeling human hepato-biliary-pancreatic organogenesis from the foregut-midgut boundary" was published in Nature at DOI: 10.1038/s41586-019-1598-0.

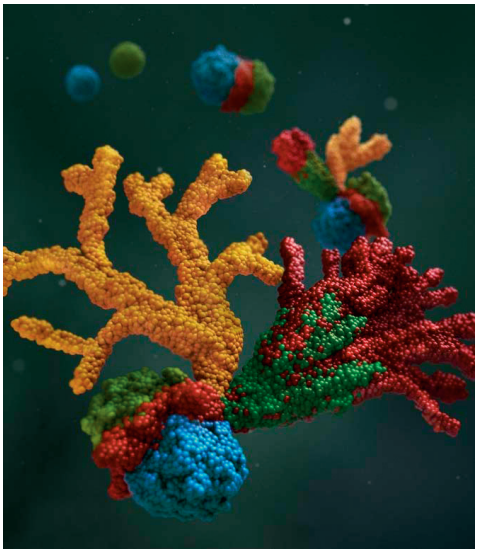

Fig.1: **3D CG of multi-organoid model grown from human stem cells**
Liver: red, Bile duct: green, Pancreas: yellow, Gut: other colors.

Summary: Pluripotent stem cells can be used to make experimental models of organ systems, but current techniques often produce models that bear limited resemblance to true organs. Researchers at Cincinnati Children's Hospital Medical Center (CCHMC) and Tokyo Medical and Dental University (TMDU) developed an improved method to make a sophisticated three-dimensional organoid model of the liver, pancreas, and bile ducts. The model may help researchers understand how these organs form and how genetic mutations can lead to diseases in these organs.