



National University Corporation Gifu University
National University Corporation Kyoto University

The three-dimensional structure of the interleukin-18 complex was elucidated and it progresses drug development for intractable immune neurological diseases.

<Summary>

The department of Pediatrics, Graduate School of Medicine, and the United Graduate School of Drug Discovery and Medical Information Sciences in Gifu University, ahead of other countries, elucidated the three-dimensional structure of a complex in which interleukin-18 (IL-18) binds to the receptor. This work was performed in collaboration with the Laboratory of Structural Physiology, Department of Biophysics, Graduate School of Science and the Laboratory of Biomolecular Function Chemistry, and Graduate School of Engineering in Kyoto University. New drug development will be greatly advanced by elucidation of this complex structure at atomic resolution. The results of this research are open to the public at “Nature Communications” published on December 15, 2014.

<Background>

The human body has a function to protect the body from infection by inducing a substance called cytokines when bacteria and viruses invade. IL-18 is one of many cytokines. It strongly induces inflammation and works to exclude pathogens, however, its excess production causes the onset and exacerbation of multiple diseases including intractable immune neurological diseases such as rheumatoid arthritis. Although biologics including antibodies have already been clinically applied as medical agents for interleukin activation, a small molecule drug that can get into cell membranes and the nucleus with a small molecular weight has not been developed well. Although inhibitory agents for IL-18 are hoped to be developed, because of its extreme technical difficulty, a three molecule complex structure, IL-18 and 2 types of receptors, and its detailed activation mechanism, which are an important basis of drug development, were not clear for about 20 years, from the beginning of research to today.

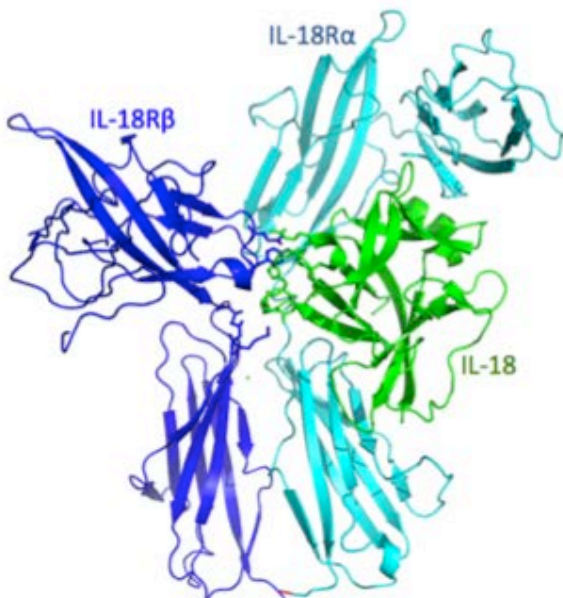
<Research content>

Our research group synthesized IL-18 protein and IL-18 receptor protein using gene-recombination technology and revealed the three-dimensional structure of the

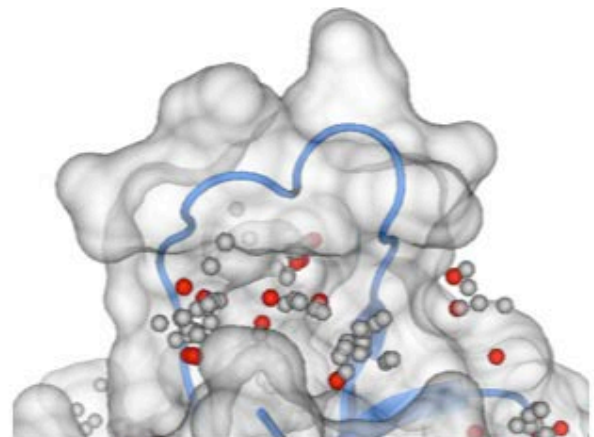
complex at atomic resolution using the X-ray crystallography technology. From this, we found that IL-18 (green) bound to IL-18 receptor α (light blue) as it was surrounded by the receptor, and IL-18 receptor β (blue) lay side by side with IL-18 receptor α and bound to IL-18 (figure below left). In addition, we also measured the effects of amino acids located on the interaction surface between IL-18 and IL-18 receptor β using the solution NMR method, surface plasmon analysis, and the cell function experiment approach, and revealed that several amino acids located on each IL-18 side and on the IL-18 receptor β side had important roles in their interaction. These results clarified, for the first time in the world, detailed IL-18 signal transduction that was previously left unexplained.

<Future directions>

Our research group has previously conducted the development of an inhibitory drug for IL-18 signal transduction based on its conformation, and some candidate molecules have already been identified. These most recent results have made it possible to design drugs specifically for the activation site at an atomic scale, the same scale as for a drug molecule. This research is likely to accelerate clinical applications and it is expected to connect to the development of new treatment methods for various intractable immune neurological diseases in the future.



Revealed 3D structure of the complex
(Green: IL-18, Light blue: receptor α , Blue: receptor β)



Inhibitory drug development using a conformation
(Designing a drug that obstructs the binding site)

<Information about research paper>

Title: The structural basis for receptor recognition of human interleukin-18

Name of academic journal: Nature communications

Authors: Department of Pediatrics, Graduate School of Medicine, Gifu University Takeshi Kimura*, Takahiro Yamamoto, Hidenori Ohnishi**, Zenichiro Kato
The United Graduate School of Drug Discovery and Medical Information Sciences Zenichiro Kato
Graduate School of Science, Kyoto University Hidehito Tochio**
Graduate School of Engineering, Kyoto University Naotaka Tsutsumi*, Mariko Ariyoshi, Masahiro Shirakawa
Graduate School of Medical Life Science, Yokohama City University Kyouhei Arita
Argonne National Laboratory in the U.S. Xiaobing Zuo
Heisei College of Health Sciences Naomi Kondo
Faculty of Pharmaceutical Sciences, Hokkaido University Katsumi Maenaka
Research Institute of Green Science and Technology, Shizuoka University Enoch Y Park
*First author, **Corresponding author

<Glossary>

- Cytokine: One of the bioactive proteins released from cells. It works as an intracellular signaling molecule.
- Interleukin: One of many cytokines. It especially indicates bioactive proteins produced by immunocompetent cells such as lymphocytes and macrophages, etc. A bioactive protein is a protein that regulates various biological reactions by acting on the human body. It is involved in specific reactions and a minute amount is enough to have a reaction.
- Resolution: Although it is normally expressed as numbers to describe the fineness of data that can display and input images in a device handling images such as a computer monitor and a digital camera, etc., in this article it is used to express the degree of minuteness, to what extent how finely a subject is observed. Atomic Resolution means minute observation as the extent that locations of atoms can be precisely distinguished one by one.
- Rheumatoid arthritis: A disease causing swelling, pain and deformation of joints due to an immune abnormality. IL-18 is known to be an aggravating factor for the symptoms. Aggravation is a change of symptoms for the worse. It means an originally bad condition becomes further deteriorated.
- Small molecule drug: A drug with a small molecular weight whose range is about 300 to 500 Da. It can get into cell membranes and even into the nucleus. When it can be chemically synthesized, bulk production becomes possible and the price can be reduced.
- X-ray crystallography: One of the methods to determine protein shape (3D structure). X-rays are irradiated to a target protein crystal and locations of atoms are determined based on the scattered X-rays. By knowing the 3D structure, a mechanism expressing the properties that the protein possesses can be understood.

[Contact information]

(Regarding research)

Department of Pediatrics, Graduate School of Medicine, Gifu University Hidenori Ohnishi

TEL: +81-(0)58-230-6386 FAX: +81-(0)58-236-6387 E-mail: ohnishih@gifu-u.ac.jp

Laboratory of Structural Physiology, Department of Biophysics, Graduate School of Science, Kyoto University Hidehito Tochio

TEL: +81-(0)75-753-4215 FAX: +81-(0)75-753-4218 E-mail: tochio@mb.biophys.kyoto-u.ac.jp

(Publicists)

Public Relations Office, General Affairs Division, General Affairs & Planning Department, Gifu University

TEL: +81-(0)58-293-2009 FAX: +81-(0)58-293-2021 E-mail: kohositu@gifu-u.ac.jp

Public Relations and Social Cooperation Promotion Office, Foreign Affairs Department, Kyoto University

TEL: +81-(0)75-753-2071 FAX: +81-(0)75-753-2094 E-mail: kohho52@mail2.adm.kyoto-u.ac.jp