Title	Binding of metal ions to proteins sustains our lives : Mechanistic chemistry of biomolecules sheds light on life phenomena on the molecular level
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Author	池田, 亜希子(Ikeda, Akiko)
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The Research

Associate Professor Yoshiaki Furukawa is featured in this issue, whose field of research focuses on mysteries of life phenomena through the metalloprotein formation process.

Binding of metal ions to proteins sustains our lives

Mechanistic chemistry of biomolecules sheds light on life phenomena on the molecular level

With the help of metal ions, proteins control numerous vital reactions. For example, a protein known as superoxide dismutase 1 (SOD1) begins to protect cells against reactive oxygen species only after it has bound copper and zinc ions. However, mutant forms of SOD1 incapable of metal binding form abnormal aggregates, which is considered to be a cause of amyotrophic lateral sclerosis (ALS). By focusing on an *in vivo* process that supplies metal ions to proteins, Dr. Yoshiaki Furukawa strives to shed light on various life phenomena and wishes to apply the results of his research to the prevention of incurable diseases and the development of remedies.

Metal ions indispensable to biological activities

Inside organisms, a variety of metal ions, such as iron, zinc, copper, molybdenum, cobalt, etc., exhibit their functions upon binding to proteins. Each and every one of these ions is indispensable to sustaining our lives. An environmental shift of tremendous magnitude that occurred on Earth in remote antiquity is believed to have much to do with the question why we humans came to need such a wide variety of metal ions.

Dr. Furukawa explains, "For example, hemoglobin, which is contained in our red blood cells, is a protein with an iron (II) ion. Hemoglobin can carry oxygen molecules because an oxygen molecule is bound to the iron (II) ion. Iron (II) ion is considered to be the first metal ion used by living things. This is presumably because this ion was abundant in oceans of the primeval Earth." Proteins that have metal ions (hereinafter metalloproteins) caught Dr. Furukawa's special interest, making him intent on studies of metalloprotein structures and functions.

Concentration of molecular oxygens in the atmosphere increased sharply as photosynthetic cyanobacteria appeared on Earth. As a result, most of the iron (II) ions were oxidized, which later accumulated on the sea bottom as insoluble iron(III) oxide. The use of iron ions suddenly limited, it is assumed that living things adapted themselves to environmental changes by smartly using copper and various other metal ions instead.

Protecting lives against reactive oxygen species by using metal ions

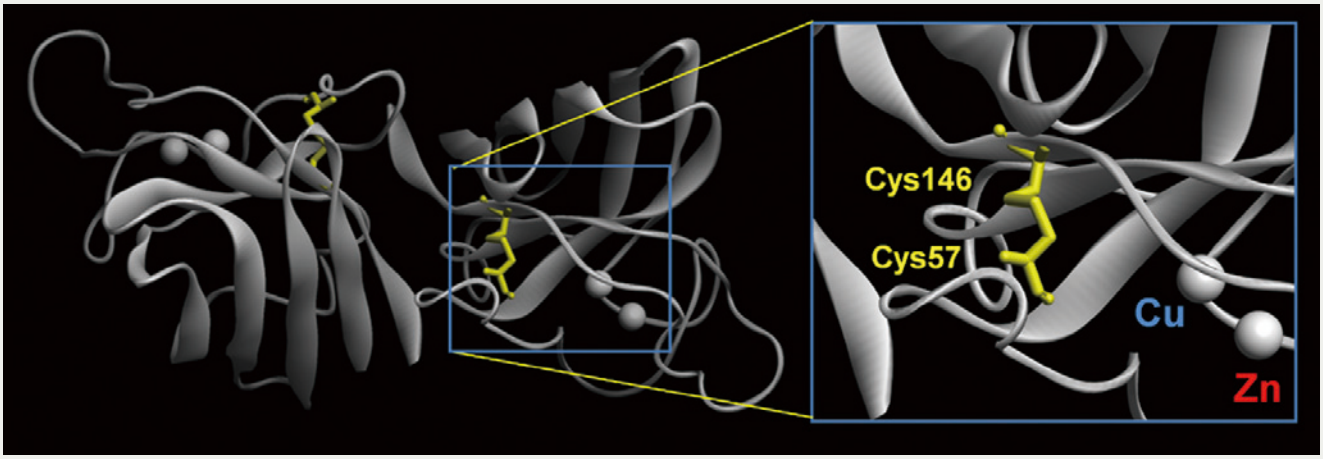
Of all proteins, about one third are said to bind some sort of metal ions. Why do living things need metal ions this much?

"Various chemical reactions are taking place inside organisms to sustain their lives. Characters behind these chemical reactions are proteins. Proteins are polymers consisting of amino acids, but proteins as such can produce only limited chemical reactions. By binding metal ions, however, the number of chemical reactions that proteins can afford increases in a single swoop." Metal ions thus came to play vital roles indispensable to maintain highly advanced, sophisticated life phenomena.

The metalloprotein SOD1 (Cu/Zn-superoxide dismutase) that Dr. Furukawa focuses on is an enzyme capable of removing the superoxide O_2^-, a highly toxic reactive oxygen species. Malfunction of SOD1 increases the intracellular concentration of O_2^-, which would damage DNA and/or membranes so much that living things won't be able to live any longer. SOD1 consists of two subunits, each having a structure to which one each of a copper and zinc ion are bound (Fig. 1). The copper ion functions

Fig.1 Structure of SOD1 protein

One each of copper (Cu) ion and zinc (Zn) ion is bound to each of the two subunits. Two cysteine residues (Cys57, Cys146) form a disulfide bond, which serves as something like a "lid" to prevent the Cu and Zn ions from getting dissociated.



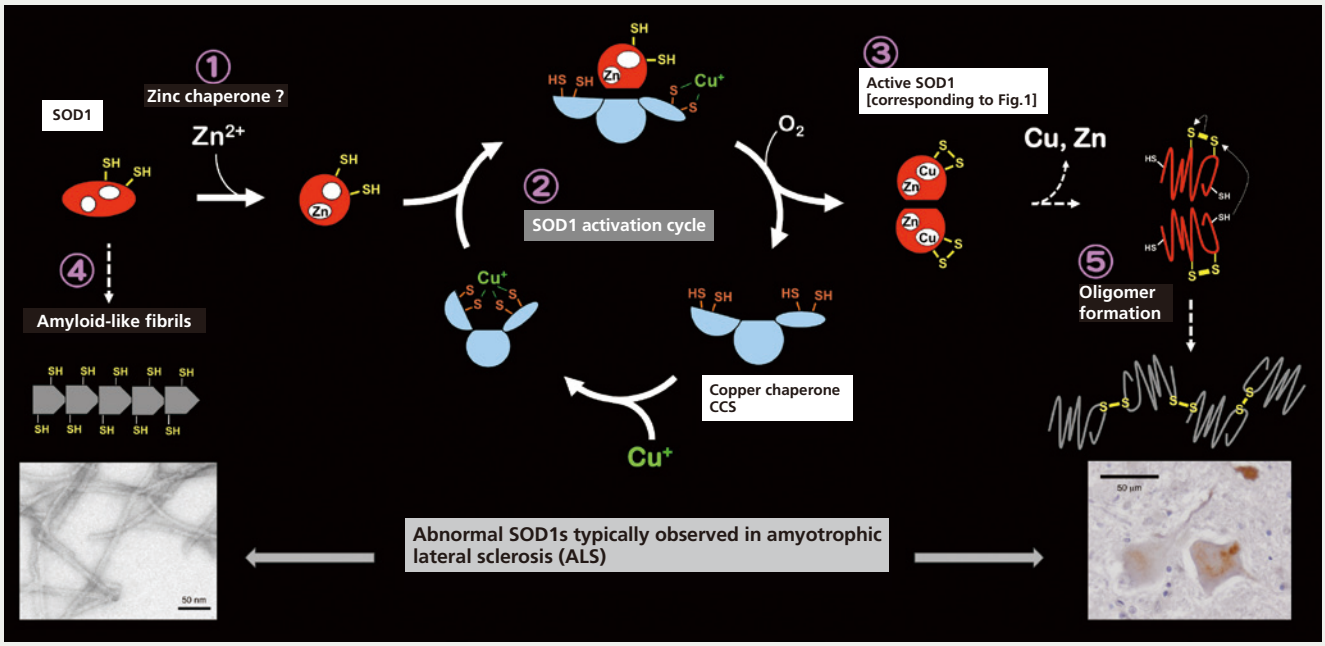


Fig.2 Dr. Furukawa-suggested mechanism of SOD1 activation and aggregation

① SOD1 binds a zinc ion first (mechanism unknown); ② then a copper ion is supplied by a copper chaperone, CCS; ③ SOD1 with enzymatic activity is produced as a result; metal-dissociated SOD1s aggregate into abnormal structures like ④ amyloids (photo: electron microscopic image) and ⑤ oligomers (photo: neurons of an ALS patient, the brown-colored area being oligomer). Dr. Furukawa suggests that this mechanism concerns the development of ALS.

as the active site for removing O_2^- while the zinc ion serves for stabilizing the SOD1 structure. Curiously enough, SOD1 can function within organisms by selectively binding copper and zinc ions only from among the diverse range of metal ions.

How do proteins capture metal ions?

"Living things are unable to create metal ions themselves. Naturally, they have to take in metal ions from food. Since some metal ions are toxic, however, they need to capture specific metal ions only, bring them into their cells, and supply the metal ions to specific proteins. This is a very intriguing phenomenon, but much remains unknown about it," says Dr. Furukawa, admitting that relationships between metal ions and proteins are still shrouded in mystery. It is likely that various biomolecules are scrambling for metal ions within cells, which leads to assumption of the existence of "metallochaperones" tasked with conveying metal ions to specific proteins. Prof. Valeria Culotta of Johns Hopkins University and Prof. Thomas O'Halloran of Northwestern University discovered copper chaperones for the first time in 1997. This accomplishment was followed by recent reports of discovery of iron and nickel chaperones. By the way, the chic-sounding term "chaperone" is a French word originally meaning a senior lady who teaches refined manners to young ladies about to make their debut in society.

For SOD1, a copper chaperone called CCS supplies copper ions. Dr. Furukawa found that SOD1 receives copper ions from CCS via the cycle shown in Fig. 2, and figured out that such copper ions protect the body against toxic reactive oxygen species. Furthermore, Dr. Furukawa determined that failure of this cycle hampers the supply of copper ions from CCS to SOD1. If that is the case, SOD1 cannot function as an enzyme and maintain its proper structure, causing numerous SOD1 molecules to aggregate – an abnormal phenomenon. Yet, Dr. Furukawa confesses he is still totally in the dark about how SOD1 captures a zinc ion. His challenge continues toward identifying the world's first "zinc chaperone."

Failure of metal binding causes neurodegenerative diseases

"What I'd like to know is how proteins secure metal ions. The importance of this process can be clearly understood from the fact that proteins that failed to bind metal ions are observed in various diseases," remarks Dr. Furukawa. While he asserts that his research is purely directed to basic studies, his research also attracts the attention of the medical circles given that SOD1 aggregates are a phenomenon observed in some amyotrophic lateral sclerosis (ALS) patients.

ALS is an incurable disease, with which nerves (motor neurons) that control body muscles are affected. This, in turn, causes muscles necessary for moving legs or breathing to atrophy. Many cases of hereditary ALS involve mutations in the SOD1-coding gene. As of now, more than 150 kinds of mutations have been reported in SOD1-coding gene.

What's more, mutant SOD1s are found aggregating in motor neurons of the ALS patients. By controlling the binding of copper and zinc ions to SOD1, Dr. Furukawa succeeded in a test tube experiment to reproduce the process of SOD1 aggregation that develops within motor neurons of ALS patients.

"The question yet to be solved is whether SOD1 aggregation causes ALS or whether the development of ALS causes SOD1 to aggregate. This is the point we need to watch for. Even if we have successfully identified a substance that controls SOD1 aggregation, therefore, we cannot definitely say it will become an ALS remedy," says Dr. Furukawa cautiously. Nevertheless, he continues to publish his own research results, convinced that clarifying the detailed mechanism of metal ion-controlled SOD1 activation and aggregation will eventually lead to a full understanding of ALS.

We may see the day come before long, when Dr. Furukawa's genuine interest in metalloproteins will lead to the discovery of an innovative drug for this incurable disease.

(Reporter & text writer : Akiko Ikeda)