15th International Conference on the Chemistry of Se &Te
Universidade Federal de Santa Catarina, Florianópolis – Brazil
Nov 28 - Dec 02, 2022 – Hotel Jurerê Beath Village – www.iccst15.com.br

Aliphatic Diselenides as a Potential Manipulator for Proteostasis

Kenta Arai [a,*]

[a] Department of Chemistry, School of Science, Tokai University, Kitakaname, Hiratsuka-shi, Kanagawa 259-1292, Japan
*** Corresponding Email: k-arai4470@tokai-u.jp**

Quality of proteins in the endoplasmic reticulum (ER), where nascent polypeptides gain a unique 3D structure, is maintained by various ER-resident enzymes, such as protein disulfide isomerase (PDI). PDI not only catalyzes SS-formation and SS-isomerization between cysteine residues by its oxidoreductase activity but also suppress protein aggregation by its molecular chaperon activity during oxidative protein folding. Because dysfunction of PDI under ER stress leads to protein misfolding, development of a chemical tool to control the protein quality possesses clinical values from the viewpoint of the treatment of human misfolding diseases such as neurodegenerative disorders.

In this study, we synthesized cyclic diselenide-based compounds as candidates of alternative molecules of PDI. Oxidative folding assay using ribonuclease A (RNase A) as a model protein clearly showed that a catalytic amount of compounds dramatically accelerates the folding reaction of reduced RNase A to the native state. Subsequently, we designed basic amino acid conjugates, which were inspired by the redox active center of PDI (i.e. CGHC sequence), and applied those as the oxidative folding catalyst. Interestingly, application of the compounds to the oxidative folding of hen egg-white lysozyme revealed that conjugation of the basic amino acids, especially histidine (His), to one of synthesized compounds improves the capacity as the PDI-like redox catalyst. Surprisingly, furthermore, these compounds also showed remarkable suppression capacity against protein aggregation. These results suggest that cyclic diselenide compounds would be promising in applications to artificial *proteostasis* control. We are now evaluating the use of these compounds as folding additives by using different substrate proteins and investigating their possible use for medicinal applications.