Subject area: _BIO_

Bio-redox regulation by small molecular diselenide and selenenyl sulfide compounds

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Highlights

Here, we report on synthesis and application of novel mimics of protein disulfide isomerase and thioredoxin reductase, which contribute to the quality control of nascent proteins and cytosolic redox regulation, respectively.

Abstract

Redox homeostasis of the endoplasmic reticulum (ER) is maintained by various disulfide(SS)-based oxidoreductases. For example, protein disulfide isomerase (PDI) controls SS-formation in nascent proteins along with the oxidative folding in ER. A decrease in PDI activity under ER stress leads to protein misfolding, which is responsible for the progression of various human diseases, such as neurodegenerative diseases, diabetes mellitus, and atherosclerosis. In this presentation, we report that water-soluble cyclic diselenides mimic the multifunctional activity of the PDI family by facilitating oxidative folding, disulfide formation/reduction, and repair of the scrambled disulfide bonds in misfolded proteins[1].

Meanwhile, thioredoxin reductase (TrxR), a selenoprotein containing selenocysteine (Sec)–Cysteine (Cys) sequence as the redox center, plays crucial roles to regulate the cytosolic redox balance. The highly reactive selenolate, which is produced by reduction of selenenyl sulfide (Se-S) linkage formed between Sec and Cyc, can reduce variety of substrates due to the easily accessible of the flexible C-terminal, in which the Se-S active site exists. Here, we synthesized novel water-soluble cyclic selenenyl sulfides as small-molecular model compounds of TrxR and applied those as a catalyst to the TrxR-related reactions, i.e. catalytic reduction of (1) protein SS bonds, (2) a reactive oxygen species, and (3) dihydroxy ascorbic acid. In this presentation, TrxR-like catalytic mechanisms and possibility of pharmaceutical application of the synthesized compounds will be discussed from experimental and theoretical results.

1 K. Arai, et al., Diselenides with Novel Oxidoreductase and Isomerase Activities, *ChemBioChem*, 2018, **19**, 207.