SL04 Oxidative and electrophilic stresses and their regulator reactive sulfur species

Yoshito KUMAGAI
Faculty of Medicine, University of Tsukuba

Under oxidative stress and inflammation conditions, it is well known that reactive oxygen species (ROS) and nitric oxide (NO) are produced and are able to modify protein thiols associated with cellular redox regulation. Alternatively, a unique concept was also proposed as follows: ROS and NO produced react with small molecules in the body, leading to formation of endogenous electrophiles, which are capable of modifying protein thiols. As a result, endogenous electrophiles act as a signal molecule for activating redox signaling. We are also exposed to a variety of electrophiles such as aromatic hydrocarbon quinones formed during combustion of gasoline, crotonaldehyde in tobacco smoke, methylmercury accumulated in fish, cadmium contaminated in rice, and acrylamide in baked foods on a daily basis, and the molecular target for these electrophiles in the body are macromolecule nucleophiles. There are various redox signaling pathways consisting of sensor proteins with reactive cysteine residues and effector molecules (e.g., kinase and transcription factor) in cells, and the effector molecules are negatively regulated by the sensor proteins in basal condition. We found that environmental electrophiles selectively and covalently modify sensor proteins such as protein tyrosine phosphatase 1B (PTP1B), Kelch-like ECH associated protein 1 (Keap1), heat shock protein 90 (HSP90) and phosphatase and tensin homologue (PTEN), resulting in inhibition of their activities at lower concentrations, thereby activating effector molecules such as epidermal growth factor receptor (EGFR), NF-E2-related factor 2 (Nrf2), heat shock factor 1 (HSF1) and protein kinase B (Akt), respectively. However, activated redox signaling pathways are disrupted by environmental electrophiles at higher concentrations due to nonselective and extensive modification of cellular proteins, leading to cellular toxicity. We therefore suggest that electrophiles have two different aspects in term of redox signaling pathways.

In redox biology field, current consensus is that persulfides (e.g., cysteine persulfide, GSH persulfide) and their polysulfides exhibit high antioxidant capability and nucleophilicity. Of interest, collaboration study with Professor Akaike et al. from Tohoku University revealed that mitochondrial-dependent cysteinyl-tRNA synthetase (CARS2), in addition to its canonical role in protein translation, acts as the principal cysteine persulfide synthases in vivo. It was also shown that not CARS2 and cystathionine γ-lyase (CSE), an enzyme catalyzing formation of cysteine, which is substrate for CARS2 in term of cysteine persulfide formation, play a novel and prominent role in endogenous production of both low molecular weight polysulfides and polysulfidated proteins, corresponding to PerSulfide-Binding Protein (PSBP) that are abundantly detected in cells and in mice. We found that cysteine persulfide, GSH persulfide and even exogenous polysulfide (e.g., Na_2S_4) are able to capture environmental electrophiles such as methylmercury, cadmium and 1,4-naphthoquinone, resulting in formation of their sulfur adducts with less electrophilicity. More importantly, little appreciable activation of redox signaling and toxicity are seen by authentic sulfur adducts of methylmercury, cadmium and 1,4-naphthoquinone. We therefore speculate that persulfides and polysulfides participate in the regulation of redox signal transduction pathways (cell proliferation, detoxification/excretion of electrophiles, quality control of cellular proteins and cell survival) and toxicity during electrophilic stress.