The antioxidant function of coenzyme A: a renaissance of a key metabolic cofactor

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Reactive oxygen species (ROS) are cellular metabolites that participate in various signaling and metabolic pathways. However, imbalanced levels of ROS can lead to oxidative stress and damage to cellular macromolecules: DNA, proteins and lipids. Cells overcome oxidative stress by using different enzymatic and nonenzymatic antioxidant systems. In recent years we discovered novel antioxidant function of a key cellular metabolite, coenzyme A (CoA). We demonstrated that during oxidative stress CoA can form a mixed-disulfide bond with protein cysteine thiols termed as protein CoAlation. Using a combination of anti-CoA monoclonal antibodies and LC-MS/MS methodology we showed that established cell lines, single cell and multicellular organisms contain increased level of CoAlated proteins upon exposure to oxidative or metabolic stress. Our research on protein CoAlation has shown that it is a widespread and reversible post-translational modification. More than 2200 prokaryotic and eukaryotic proteins have been found to be CoAlated. To date, we found that under oxidative stress protein CoAlation protect cysteine residues from hyperoxidation and in addition modulate the activity of modified proteins by inducing significant conformational changes. CoAlation of S. aureus GAPDH, aurora kinase A, peroxiredoxin 5 and metastasis suppressor protein NME1, were shown to reversibly inhibit their function, mediated by covalent modification of their catalytic cysteines or cysteine residues located close to catalytic sites. A study performed on the transcription factor accessory gene regulator AgrA (S. aureus), showed that CoAlation at its Cys199 interfered with its binding to DNA. Overall, these studies show the important cellular role of CoA in regulating the function of proteins and their downstream interacting partners under different cellular stress conditions and uncover CoA as a major antioxidant in both prokaryotic and eukaryotic cells.