MINIREVIEW PROLOGUE

Introduction to the Thematic Minireview Series on Redox-active Protein Modifications and Signaling*

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The dynamics of redox metabolism necessitate cellular strategies for sensing redox changes and for responding to them. A common mechanism for receiving and transmitting redox changes is via reversible modifications of protein cysteine residues. A plethora of cysteine modifications have been described, including sulfonylation, glutathionylation, and disulfide formation. These post-translational modifications have the potential to alter protein structure and/or function and to modulate cellular processes ranging from division to death and from circadian rhythms to secretion. The focus of this thematic minireview series is cysteine modifications in response to reactive oxygen and nitrogen species.

In the first minireview of this series, Rafael Radi discusses a stealth oxidant, peroxynitrite, which is short-lived and nucleophilic and is generated by the marriage of two radicals, nitric oxide and superoxide radical anion (1). Peroxynitrite accounts for much of the cytotoxicity associated with nitric oxide and superoxide and can furnish secondary radicals such as nitrogen dioxide and carbonate radicals. Among key oxidative modifications promoted by peroxynitrite are protein thiol oxidation and tyrosine nitration.

In the second minireview, Harry Ischiropoulos and co-workers continue the discussion on nitric oxide signaling via reversible cysteine S-nitrosylation, a post-translational modification that modulates protein stability, location, and function (2). Reactive cysteine residues that undergo S-nitrosylation are also vulnerable to other oxidative modifications. The authors discuss S-nitrolylation from a proteomic perspective and the potential consequences of targeting the same cysteines by other modifiers.

Mauro Lo Conte and Kate S. Carroll discuss the role of protein sulfenylation and sulfhydration in the third minireview (3). They discuss how the availability of new reagents has allowed detection of these oxidative modifications in vitro and in cells, and they present examples of the importance of these post-translational modifications in cell signaling pathways.

Claudia M. Cremers and Ursula Jakob discuss reversible disulfide bond formation as a strategy for oxidant sensing in the fourth minireview of this series (4). The importance of buffering against the vagaries of oxidant stressors, including reactive oxygen, nitrogen, and chlorine species, is highlighted. The high concentration of cellular protein thiols and the possibility for reversible formation of disulfides make proteins well suited for mediating regulatory roles in response to changing redox conditions.

A different and reversible cysteine modification, namely glutathionylation, is the subject of the fifth minireview authored by Kenneth D. Tew and co-workers (5). This also is a strategy for protection of cysteines against overoxidation while simultaneously modulating protein structure and/or function. Enzymes are involved in both adding (glutathione transferases) and removing (glutaredoxin) the glutathione moiety and thereby regulating glutathionylation-dependent cell signaling.

Alessandra Stangherlin and Akhilesh B. Reddy discuss the bridge between redox homeostasis and the circadian clock in the sixth minireview (6). Although cellular and organismal oscillations in response to food availability, light, and temperature are well studied, timekeeping via circadian redox state changes in peroxiredoxin is a relatively new discovery. The authors discuss mechanisms for cross-talk between the cellular redox state and the circadian clock, a link found in both prokaryotes and eukaryotes.

In the final minireview, Young-Mi Go and Dean P. Jones take a proteomic look at redox metabolism, which, via reversible and irreversible protein modifications, can impact function at the level of individual proteins and those working in complexes (7). Oxidative modifications, which often involve cysteine residues, have profound physiological consequences ranging from signaling cell cycle progression to determining cell shape.

In summary, these seven minireviews represent the cutting edge of the field of cysteine redox modifications and their roles in signaling. They demonstrate that redox cycles dynamically regulate protein structure and function and thereby cellular functions.

REFERENCES

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