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Oxidative stress, methionine oxidation, and calmodulin structure and function

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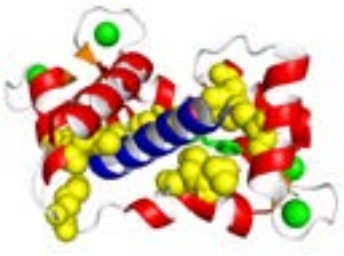
Statement of the Problem: Oxidation of methionine residues in proteins to methionine sulfoxide is a prevalent, reversible post-translational modification. Changes in protein structure and function accompany oxidation due to polarity and steric differences between methionine and the sulfoxide. We are investigating the consequences of methionine oxidation in the regulatory protein calmodulin (CaM), a key calcium signal transducer with nine methionine residues, in hydrophobic pockets of its opposing globular domains, which interact with target proteins. CaM with oxidized methionine residues accumulates under conditions of oxidative stress, and because of its central role in biology, it is important to understand the functional effects of these alterations and their physical origins.

Methodology: Methionine residues in CaM are easily oxidized *in vitro* with hydrogen peroxide. To study the effects of oxidation of specific methionine residues, leucine was substituted for methionine at remaining sites. A combination of functional assays, single molecule studies, and NMR spectroscopy were used to assess functional and structural consequences of methionine oxidation.

Findings: For the best studied case, activation of the plasma membrane Ca-ATPase (PMCA) by CaM, impaired CaM function is due to oxidation of a single C-terminal methionine. Single molecule experiments indicate non-productive binding of oxidized CaM to the PMCA. High resolution NMR studies demonstrate significant structural perturbation in the C-terminal globular domain of oxidized CaM and an inability to anchor the PMCA to this domain.

Conclusion & Significance: The functional effects of methionine oxidation in CaM are highly target dependent, as is the degree to which selective oxidation of particular methionine residues in CaM affects function. The results of CaM activation of the PMCA also indicate that both high-affinity productive and non-productive complexes of oxidized CaM with targets are possible. These facts indicate that a comprehensive understanding of the metabolic consequences of CaM oxidation will be challenging.



Biography

Jeffrey L Urbauer earned Bachelor's and Doctoral degrees in Chemistry from the University of Nebraska-Lincoln. He pursued Postdoctoral studies at the University of Wisconsin-Madison as an NIH Postdoctoral Fellow and at the University of Illinois Urbana-Champaign. He held faculty appointments at the State University of New York at Buffalo, the University of Pennsylvania, and the University of Kansas before joining the faculty in the Department of Chemistry and the Department of Biochemistry and Molecular Biology at the University of Georgia. At the University of Kansas the Mortar Board National College Senior Honor Society awarded him with the Outstanding Educator Award. His research interests include structural biology, protein biophysics and NMR spectroscopy.

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