PROTEO
FONCTION | STRUCTURE INGÉNIERIE DES PROTÉINES

CONFÉRENCE

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Landscapes of the endogenous cysteine reactomes: functional protein regulation by S-nitrosylation

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Cysteine residues in proteins can be broadly classified into four functional groups; structural, metal binding, catalytic and regulatory. Regulatory cysteine residues can undergo redox-dependent modifications that impact protein function, stability, and trafficking. Modifications include oxidation to sulfenic acid and covalent adduction of nitric oxide and of glutathione or hydrogen sulfide to form to form S-nitrosocysteine and mixed disulfides respectively. Presently the endogenous redox active cysteine residues and how the different redox modifications are functionally integrated within the proteome are not known. By employing chemical enrichment methodologies followed by mass spectrometric site-specific identification we are acquiring endogenous proteomes of redox-active cysteine residues as well as S-sulfenylated, S-nitrosylated, S-glutathionylated and S-palmitoylated residues. Analysis of data from wild type mouse liver indicates that redox-cysteine modifications (S-sulfenylation, S-nitrosylation and S-glutathionylation) occur predominantly on distinct and non-overlapping proteomes. The biochemical and structural determinants of this apparent selectivity are under investigation. To explore the functional significance of these modifications we studied the biological effects of S-nitrosylation. We report that 25% of the very long chain acyl-CoA dehydrogenase (VLCAD) molecules are S-nitrosylated on a single cysteine residue *in vivo* under physiological conditions. S-nitrosylation lowers the K_M by nearly 5-fold improving the catalytic efficiency (K_{cat}/K_M) of VLCAD by 29-fold. Additional evidence for the functional consequences of S-nitrosylation of VLCAD is obtained in mouse hepatocytes transiently expressing wild-type VLCAD or a point mutant that could not be S- nitrosylated (C238A). Overall, the diverse chemical reactivity of the cysteine sulfur permits multiple modifications that target distinct and separate clusters of cysteine residues in the mouse proteome. This selective modification of cysteine residues significantly expands the biological chemistry by which homeostatic regulation of redox sensing, signaling, protein function, stability, and trafficking is achieved and regulated.

Professeure hôte: Manon Couture

Cordiale bienvenue à toutes et à tous!