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Redox-based mitochondrial signaling regulated by a nitrated nucleotide via post-translational modification of mitochondrial heat shock proteins

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Abstract

It is recently well accepted that reactive oxygen species, reactive nitrogen oxides and their secondary electrophilic metabolites are not simply act as toxic substances, but also play important roles in regulation of redox-based signal transduction through modifications of protein thiols of sensor and effector proteins. In this context, mitochondrion is an important target for protein thiol modifications because redox status of mitochondrion is maintained more reducing than other organella. 8-Nitro-cGMP (8-nitroguanosine 3′,5′-cyclic monophosphate) is a nitrated derivative of cGMP that is formed under inflammatory conditions. This nitrated nucleotide can function as a unique electrophilic second messenger in regulation of redox signaling by inducing a post-translational modification of protein thiols via cGMP adduction (protein *S*-guanylation). Here we developed a new mass spectrometry (MS)-based proteomic method—*S*-guanylation proteomics—to identify endogenously formed *S*-guanyled mitochondrial proteins. We found that mitochondrial heat shock proteins including mortalin and 60-kDa heat shock protein (HSP60) were susceptible for protein *S*-guanylation during immunological stimulation. Mortalin and HSP60 were recently reported to regulate mitochondrial permeability transition pore (mPTP) opening, at least partly, by interacting with cyclophilin D, an mPTP component. Our data revealed that immunological stimulation and 8-nitro-cGMP treatment induced mPTP opening in a cyclophilin D-dependent manner. Taken together, our *S*-guanylation proteomics determined that mitochondrial heat shock proteins may be novel targets for redox modification via protein *S*-guanylation that participates in mPTP regulation and mitochondrial redox signaling.

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