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► **To cite this version:**

Sophie Rahuel-Clermont, Michel Toledano. Parsing protein sulfinic acid switches. *Nature Chemical Biology*, 2018, 14 (11), pp.991-993. 10.1038/s41589-018-0151-z . hal-02075667

HAL Id: hal-02075667

<https://hal.univ-lorraine.fr/hal-02075667>

Submitted on 1 Feb 2022

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1 REDOX REGULATION

2 **PARSING PROTEIN SULFINIC ACID SWITCHES**

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9 **The proteome-wide application of a probe that selectively labels cysteine residues oxidized to the**
10 **sulfinic acid form reveals the mammalian S-sulfinylome and uncovers novel substrates of the**
11 **sulfinyl reductase sulfiredoxin, opening yet unexplored realms of cysteine-based redox**
12 **regulation.**

13 The sulfur atom of the thiol side chain of cysteine (Cys) endows this amino acid with a rich redox
14 chemistry that is exploited in multiple cellular functions. Sulfur chemical reactivity also renders cysteine
15 vulnerable to oxidation to the sulfinic (R-SO₂H) and sulfonic (R-SO₃H) acid forms, which were
16 historically considered to be irreversible oxidative protein damage. The advent of mass spectrometry
17 (MS) allowed the identification of cysteine sulfinic acids in a handful of proteins, in particular the
18 antioxidant peroxiredoxin family (Prx)¹, and then showed that, unexpectedly, the R-SO₂H moiety can
19 be reduced by sulfiredoxin (Srx)². Still, the biological scope of cysteine residue sulfinylation has
20 remained totally unexplored due to a lack of tools for its identification. In a new study, Akter and Fu et
21 al. developed a chemical tool, named DiaAlk, for selectively trapping and tagging sulfinic acids³.
22 Combined with click chemistry and quantitative proteomics, DiaAlk made it possible to reveal the
23 native S-sulfinylome of human cell lines and, remarkably, to identify new Srx substrates.

24 Recognition of the extraordinary protein functionality endowed by cysteine residues has followed
25 the slow pace of biochemical and molecular tool development (Fig. 1). For decades, cysteine has been
26 known as a residue that provides conformational stability to proteins by forming covalent disulfide
27 bonds (R-SS-R') or by coordinating metals, or that serves as catalytic center in various classes of
28 enzymes. Thioredoxin and thioredoxin reductase, which reduce disulfide bonds through thiol-disulfide
29 exchange, were discovered as the hydrogen donor system for ribonucleotide reductase (RNR)⁴. Later
30 discoveries included the regulation of protein function by disulfide bond formation in response to
31 H₂O₂ (ref. 5), by S-nitrosylation (R-SNO) in response to nitric oxide⁶, and the regulated cellular
32 production of H₂O₂ by NADPH oxidases (Noxs) during growth factor signaling⁷. These observations,
33 together with the advent of MS, led to the new concept of cysteine-based redox sensing and signaling⁸.

34 The R-SOH form of the cysteine residue is central in redox sensing and signaling, occurring on
35 multiple proteins in cells stimulated by growth factors, as shown by shotgun redox proteomics. R-
36 SOH, which is formed by the reaction of a nucleophilic cysteine residue with H₂O₂, or by R-SNO
37 hydrolysis, is intrinsically instable, as it readily forms a disulfide by condensation with a proximal
38 thiolate, a sulfenylamide by reaction with a proximal nitrogen, or a sulfinic (R-SO₂H) and then a
39 sulfonic acid (R-SO₃H) by further oxidation. The cysteine sulfinic acid cannot be reduced by common
40 thiol reductases, and its initial identification in very few enzymes meant it was viewed as an exotic
41 modification until its identification in Prxs. Prxs are antioxidants that reduce H₂O₂, thereby forming a
42 catalytic R-SOH, which either condenses into a disulfide reduced by thioredoxin, or is further oxidized
43 to the R-SO₂H form when levels of H₂O₂ are high, inactivating enzyme antioxidant function¹. The
44 finding that sulfinylation is a genetically encoded attribute, occurring in eukaryotes but not
45 prokaryotes⁹, and is reversed by enzymatic reduction by Srx² changed the prevailing view of this
46 modification from an irreversible form of protein damage to an evolutionarily acquired regulatory
47 switch. The S-sulfinic acid switch regulates several cellular functions by its effect on cellular H₂O₂
48 levels¹⁰, and also converts Prxs into a potent protein chaperone during peroxide stress and aging¹¹.
49 Whether the S-sulfinic acid switch regulates other H₂O₂ or NO-responding proteins could not be
50 addressed, until the development of DiaAlk.

51 Using DiaAlk labeling coupled to shotgun MS, Akter and Fu et al. identified a total of 387 S-
52 sulfenylated sites in 296 proteins common to the two cell lines analyzed. They also found that 40% of
53 the S-sulfenylated sites are also present in the S-sulfenylome, consistent with the lineage of these
54 modifications. Interestingly, the S-sulfenylome is much more responsive to exogenous H₂O₂ compared
55 to the S-sulfenylome, consistent with the more facile attack of H₂O₂ on a thiol than on R-SOH. Lastly,
56 by comparing the turnover of R-SO₂H sites between wild type mouse fibroblasts and those lacking Srx,
57 they identified 55 new potential substrates of Srx.

58 These data provide a robust tool to explore a new realm of redox biology, the sulfenylation of
59 cysteine residues at the individual protein and proteome-wide levels. DiaAlk will be invaluable to
60 decipher the role of cysteine sulfinic acid formation as a regulatory switch or as an irreversibly
61 oxidized end product. The low responsiveness of S-sulfenylation to H₂O₂ suggests that these events
62 accumulate during proteins' lifetime, and thus should serve as good markers of chronic oxidative
63 stress. Reduction of S-sulfenylated cysteine residues by sulfiredoxin could be a repair mechanism, or
64 alternatively, indicate the presence of a regulatory switch. S-sulfenylation is probably non-enzymatic,
65 requiring relatively high levels of H₂O₂, other peroxides, or other electrophiles. Its occurrence as a
66 regulatory switch might thus be seen under oxidative stress, or within subcellular compartments
67 accumulating H₂O₂ as is the case for one of the newly identified Srx substrates, the protein tyrosine
68 phosphatase PTPN12. To elucidate the role of the sulfinic acid switches of other new sulfiredoxin
69 substrates such as Parkinson disease protein DJ-1 and actin regulator cofilin, we will have to consider
70 that oxidative stress is part of normal physiology. The newly identified Srx substrates also raise
71 exciting questions about the slow kinetics and specificity of Srx catalysis.¹²

72 **Figure 1. Milestone discoveries in redox biology.** The progression of available tools and
73 approaches has facilitated the expansion of known modifications and functions of cysteine residues.

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101
102 **COMPETING FINANCIAL INTEREST:**

103 There is NO competing interest.

