Detecting the Elusive: Selective Capture of a Transient Sulfenic Acid Species

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Sulfenic acids are an unstable intermediate of thiol oxidation, the first product of an assembly line of cascading oxidation that may eventually result in the creation of a sulphone\(^1\). Sulfenic acids are known to exist in proteins, the result of post-translational oxidation of cysteine residues. Central to redox signaling, these modifiable cysteines serve as biological sensors by which a cell can evaluate and respond to levels of oxidative stress. Their heightened presence in oxidative stress diseases such as cancer makes them an attractive area of research, with the hope of exploiting the sulfenic acid-modified cysteine residues for drug targeting and development.

With this in mind, previous work has been conducted utilizing a dimedone-based probe to identify proteins with sulfenic acid modifications\(^2\). These probes exploit the chemoselective nucleophilic addition reaction between dimedone and a sulfenic acid. The resulting thioether can be modified further through direct conjugation reactions to biotin or to fluorophores. Using this method, sulfenic acids have been identified in proteins with a diverse array of functions, ranging from metabolism to vesicle trafficking, suggesting further roles for sulfenic acids outside redox signaling and homeostasis.

Currently, our lab is optimizing a novel procedure for the selective capture of a transient sulfenic acid species using dimedone. Because sulfenic acids have dual electrophilic and nucleophilic properties, they are able to react to form disulfides, participate in nucleophilic attacks, and are prone to further oxidation. Thus, the major challenge of our work is finding the “sweet spot” for our reaction conditions where sufficient oxidant is present to generate the desired sulfenic acid and allow for its capture. While still very much a work in progress, intriguing recent developments suggest an alternative mode of sulfenic acid capture proceeding through a sulfenic acid tautomerization from a sulfenyl to a sulfinyl species, resulting in a tricyclic as well as the more classic thioether capture product\(^3\).

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