Hydrogen sulfide mediated deCoAlation of CoAlated Peroxiredoxin 6

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In the realm of redox biology, hydrogen sulfide, once known solely for its toxic attributes, has emerged as a pivotal participant in cellular signaling across diverse cell types. Its predominant mode of action involves interactions with oxidized thiol side chains present in cysteine-containing proteins. Notably, one significant oxidative post-translational modification (oxPTM) of these thiol side chains is persulfidation, a process influenced by hydrogen sulfide (H_2S). Persulfidation profoundly impacts the reactivity of numerous cysteine-containing enzymes and plays a critical role in their protection against oxidative stress. Another important oxPTM is CoAlation. It seems to be a reversible oxidative stress-induced process that can alter the activity and function of the target proteins and is also specific to regulatory cysteine side chains. Coenzyme A (CoA) is indispensable in important cellular processes, such as the synthesis and oxidation of fatty acids, it is involved in Krebs cycle, ketogenesis, biosynthesis of cholesterol and acetylcholine, regulation of gene expression, cellular metabolism through protein acetylation and more.[1]

Peroxiredoxins (Prdxs) are often called the redox sentinels of the cell. They rapidly react with hydrogen peroxide which together with the reducing thioredoxin machinery makes them key defense factors in oxidative stress and central hubs in redox signaling processes. Excessive oxidative conditions could induce irreversible overoxidation of Prdxs and thereby hinder their activities, which may be prevented by persulfidation.[2]

My research focuses on the potential persulfidation reaction in the redox cycle of Peroxiredoxin 6 (Prdx6), a member of the Prdx enzyme family. Within the proposed model, after Prdx6 oxidation, it reacts with a coenzyme A (CoA) molecule (CoAlation), forming a disulfide-bound Prdx6-S_p-SCoA. Subsequent thiol/disulfide exchange reactions with H_2S (deCoAlation) may yield both the thiol and persulfide forms of Prdx6 (Fig. 1). My thesis successfully established that upon the reactions of Prdx6-S_p-SCoA with H_2S, the primary deCoAlation product is Prdx6 persulfide, which may be involved in cellular signaling processes.[3]

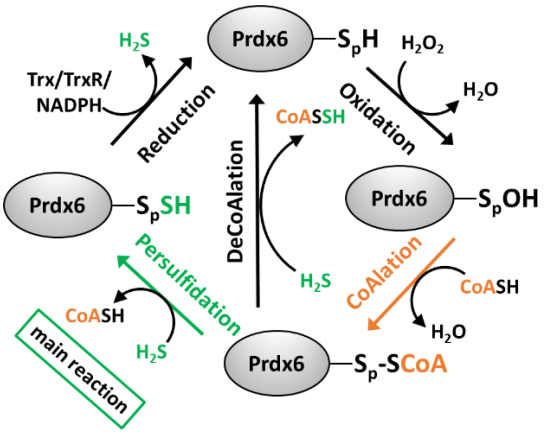

Figure 1: The suggested CoAlation cycle of the human Prdx6

[1] Paul, B., Snyder, S. *Nature Reviews Molecular Cell Biology*, 13, 499–507 (2012)

[2] Dóka, É., Ida, T., Dagnell, M., Abiko, Y., Luong, N. C., Balog, N., Takata, T., Espinosa, B., Nishimura, A., Cheng, Q., Funato, Y., Miki, H., Fukuto, J. M., Prigge, J. R., Schmidt, E. E., Arnér, E. S. J., Kumagai, Y., Akaike, T., Nagy, P., *Science advances*, 6(1), eaax8358 (2020)

[3] Gout, I., *Biochemical Society Transactions*, 46(3), 721-728 (2018)