# Investigations of metabolic pathways of Reactive Sulfur Species

**PhD thesis**


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# 1. Introduction

Intracellular redox balance is essential for cellular viability, proliferation, and the regulation of processes ranging from energy metabolism and signal transduction to stress adaptation. Redox imbalance causes oxidative or reductive stress at the cellular level; moreover, several diseases are characterized by an impaired redox state.

Reactive oxidants are continuously generated by intracellular and extracellular sources; therefore, a fine-tuned regulatory system is necessary to buffer redox fluctuations to prevent redox imbalance. Hydrogen sulfide ($H_2S$) was known only as a highly toxic molecule, but has now emerged as a small signaling molecule. Similarly, Reactive Sulfur Species (RSS) have been recognized lately as critical regulators of redox homeostasis. Their chemical versatility, together with their high reactivity, positions them as central components of intracellular redox systems, capable of buffering oxidative stress while simultaneously modulating signaling pathways.

It is important to have robust methods that can measure dynamic changes in the levels of RSS in order to get deeper insights into their biological roles. Their inherent chemical instability and high reactivity, together with the fact that RSS constitute a dynamic interconnected system, make their reliable detection technically challenging. Hence, it is essential to start the detection protocols by "freezing" their dynamic equilibria by converting them into stable and detectable forms, while maintaining cellular speciation.

## 2. Objectives

Reactive sulfur species (RSS) are crucial regulators of cellular functions and intracellular redox balance; however, their inherent chemical instability makes their reliable detection technically challenging.

My first aim was to critically re-evaluate and optimize our current RSS detection protocol, to identify and control key experimental parameters that influence analytical performance and reproducibility, with special focus on preserving persulfide species.

My second objective was to apply the optimized protocol to various biological matrices, including cultured cells, tissue samples, and cell-free plasma, for comprehensive RSS monitoring and to further improve and expand the analytical method to enable time-resolved fluxomic analyses and use this technique to study the metabolism and catabolism of selected RSS and to track their dynamic fluctuations over time in *in vitro* systems.

With the optimized RSS detection protocol, I aimed to investigate the metabolic pathways of RSS in two complex biological systems. In a genetically engineered mouse model in which the livers lack both the Trx and GSH machineries, my objective was to identify the origin of cysteine and assess the contribution of the different cysteine-producing pathways maintaining the redox homeostasis.

The methods that I optimized were also used to explore the roles of protein persulfide species in the formation of pancreatic ductal adenocarcinoma (PDAC) progression and metastasis.

# 3. Methods

## Metabolomic and fluxomic analyses

### Sample preparation for cells and tissue samples

Thiol and persulfide species were alkylated with β-(4-hydroxyphenyl)ethyl iodoacetamide (HPE-IAM). Briefly, the cells were scraped in 75% methanol (MeOH) containing 5 mM HPE-IAM or the cryopulverized tissue samples were resuspended in it. After sonication, the samples were alkylated at 37°C for 20 min and centrifuged (14 000g; 10 min; 4°C) to remove precipitated protein. The supernatant was acidified with 10% formic acid (FA) and diluted with eluent A (0.1% FA in water) before injection. The samples were kept on ice between each step. The remaining pellets were resuspended in 1% SDS/PBS, sonicated and protein content was measured by BCA assay.

### HPLC-MS/MS method

The high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) measurements were carried out on a Thermo Vanquish UHPLC (ultra-high-performance liquid chromatograph) coupled with a Thermo Q-Exactive Focus Orbitrap MS. Positive ionization mode and higher-energy collisional dissociation were used to detect the metabolites.

The alkylated thiols and persulfides were analyzed on a Phenomenex Kinetex C18 (50 x 2.1 mm, 2.6 µm) column, eluents 0.1% FA/H2O (A) and 0.1% FA/MeOH (B). In the original gradient, 5% B was

linearly increased to 95% in 15 min, then back to 5% in 2 min; the flow rate was 0.3 ml/min, 30°C. In the modified gradient, the initial 5% B was increased to 13%, then to 95% in 2 and 4 min, held there (0.5 min), and back to 5% in 0.1 min. The flow rate was 0.5 ml/min and the column temperature was 40°C.

Thioether and disulfides were measured on a Thermo Scientific Hypercarb (100 x 2.1 mm, 3µm), with eluents of 0.5% FA/H2O (A) and 0.5% FA IPA: ACN 1:1. (B). The gradient was as follows: 0% B increased to 3% in 1.5 min, to 30% in 3.5 min, then to 100% in 1 min, held there for 2 min, and back to the initial 0% in 1 min. The flow rate was 0.2 ml/min, and the column was maintained at 40°C.

## HPLC-MS/MS measurements for protein persulfides

To detect protein persulfides, cells were scraped in RIPA buffer containing 5 mM HPE-IAM. After sonication and centrifugation (14 000g, 10 min, RT) supernatants were desalted with spin columns (Zeba spin columns, 7K MWCO, 0.5 ml). Protein content was measured in the flow-through using the BCA assay. 100 mM HPE-IAM in DMSO was reintroduced to the samples, and protein concentration was brought to 1 mg/ml. For digestion, pronase (final concentration: 3 mg/ml) was used in a 35 mM Na-acetate buffer (pH 5.0) at 37°C for 1h 10% trichloric acid was added, and the undigested proteins were precipitated. The HPLC-MS/MS method for cysteine and cysteine-persulfide were the same as described in section 4.2.2.

## Mouse experiments

All mouse protocols were reviewed and approved by the Montana State University Institutional Animal Care and Use Committee (MSU IACUC; approval numbers 2018- 118-01, 2019-50-97, 2021-118-01, 2021-118-IA, 2022-50-IA, or 2023-225-IA) or the University of Veterinary Medicine Budapest, Hungary (UVMB), Animal Research Ethics Committee (approval numbers PE/EA/00744-6/2022 and PE/EA/00977-6/2023). All mice were kept in forced-air HEPA-filtered caging systems and were specific pathogen-free (SPF). All mouse harvests were performed between 9:30 and 11:30 to minimize the circadian effects; experimental mice were 8 weeks to 8 months old.

TR/GR-null mice are full-body knockouts for glutathione reductase (GR) and liver-specific disruption of TrxR1 and Trx.

## Liver lysate experiments

Cryohomogenized liver powder was rehomogenized in lysis buffer (50 mM HEPES, pH 7.4; 150 mM KCl; 0.1% CHAPS, protease inhibitor cocktail [Sigma 04693159001]), sonicated and centrifuged (14 000g, 10 min, 4°C). Protein concentration was measured by the BCA assay kit. The final protein concentration was 2-4 mg/ml. The lysate samples were kept on ice, and PAG was added prior to the initiation of the reaction at a final concentration of 1 mM. For the lysates, a 10x MasteMix (5 mM [$^{34}S_2$]-CSSC, 2 mM PLP, and/or 1 mM NADPH) was added, and the mixture was incubated at 25°C to complete the reaction. After 30 min, the reaction was stopped by adding ice-cold

75% MeOH containing 5 mM HPE-IAM, and the alkylation and HPLC-MS/MS analyses were carried out as described above.

### Recombinant Cse reaction

The recombinant Cse (0.5 μM) reaction was carried out in the same buffer as described above. The protein was kept on ice, and 10x Master Mix (2 mM PLP and 5 mM [$^{13}C_6$, $^{15}N_2$]-CSSC) was added, then the mixture was transferred to 25°C, and samples were taken at the indicated time points. Ice-cold 75% MeOH containing 5 mM HPE-IAM was added to stop the reaction; the alkylation and metabolomic analyses were carried out as described above.

## Statistical analyses

Statistical analyses and graphical representation were performed with GraphPad Prism software. Student's T-test was used for pairwise comparisons for all figures, unless indicated otherwise. For liver lysate experiments, one-way ANOVA with Tukey's correction was used. Significance was assigned as * for $p < 0.05$; ** for $p < 0.01$, $p > 0.05$ is indicated as ns (not significant, $p > 0.05$), where it is relevant.

## 4. Results

The HPE-IAM-based LMW and HMW persulfide detection protocol, has become widely used for detecting RSS; however, the critical steps in sample preparation have not been well studied. Moreover, some alkylation parameters differ across studies without any explanation (from 20 min to 60 min). For this reason, we reinvestigated critical steps of the LMW sample preparation protocol and the experimental setup of the HPLC-MS/MS method.

We found that cell confluency, an often-overlooked parameter, can critically influence measurement outcomes. Cbs and Cse activites were highly influenced by cell density. Both enzymes promote cell proliferation and under overly confluent conditions, their expression diminishes, which likely accounts for the decreased persulfide levels we measured in overly confluent cultures. To investigate the RSS producing functions of these enzymes or the dynamics of the cellular RSS pool, it is important to maintain consistent cell confluency throughout their studies, ideally around 80-90% ($4x10^5$ cell/ml).

We found that lower temperatures during sample preparation, including cell lysis, are favorable for protecting persulfide species from degradation. Furthermore, scraping the cells on ice preserves LMW persulfide levels. Alkylation parameters have a significant effect on the speciation of the detected RSS species; therefore, these parameters also need to be tightly controlled. Data suggest that higher temperatures (45°C) likely degrade persulfide species, causing them to be falsely detected as thiols. Alkylation at a lower temperature

(37°C) is slower but better preserves CSSH species. Our temperature/time optimization indicated that at 37°C with HPE-AIM, 20 min is enough to reach complete derivatization. Longer times, however, increase the detected amount of $H_2S$; saturation isn't reached after 60 min. As our group published before, the detection of $H_2S$ with derivatization utilizing a protocol is problematic due to the liberation of $H_2S$ from biological sulfide reserves. It requires strict timing for the alkylation and, because the HPE-IAM based protocol also gives information on $H_2S$ levels, we emphasize that precise timing of the alkylation step is a critical requirement for reproducible results. We propose that 20 min at 37°C achieves representative alkylation of thiols, persulfides, and $H_2S$, so we have used these parameters as our standard protocol across experiments. It is also noteworthy that extended alkylation times allow alkylation of not only thiol species but also amino groups, a frequent side reaction when using iodoacetamide derivatives. The alkylation time can be tightly controlled by effective quenching by acidification and keeping the samples at 4°C. Our data revealed that alkylation is ineffective at 4°C; hence, storing the samples on ice between each step will ensure that unwanted reactions (alkylation) during sample preparation will not occur. Moreover, temperature control of the HPLC autosampler at 4°C ensures sample stability prior to injection. Nevertheless, prompt measurement of the samples is favored to avoid RSS degradation. To address this, we optimized our HPLC-MS/MS method to reduce the time samples spend in the autosampler.

The optimized method enables us to measure LMW and HMW persulfides in various biological samples and obtain reliable data. Mass spectrometric detection also enables us to use stable-isotope-labeled amino acids and perform time-resolved fluxomic analyses to investigate the contributions of different metabolic pathways.

We used the optimized HPE-IAM based method and integrated fluxomic analyses in several studies: for example, this method revealed that, under TRP14 deficiency, the transsulfuration pathway becomes more active to support the CSH demand.

We performed steady-state metabolomic analyses on disulfide reductase-deficient mouse livers and found elevated levels of CSSC, CSH, GSH, and even CSSH. These data suggested that the existence of alternative efficient CSH-producing pathway(s) exists in these mutant livers. To uncover the origin of the CSH, we had to develop an *in vivo* model system that allows us to monitor sulfur metabolism.

Performing stable isotope tracing in *in vivo* studies is complex, and the method of administering the isotopically labeled amino acids is crucial. While in *in vitro* studies, administering the isotopically labeled amino acids can be as simple as adding to or changing the media, in *in vivo* studies it is not so straightforward. To obtain reliable and reproducible results, our group established a protocol, where the isotopically labeled amino acid was administered via a jugular catheter, enabling a continuous infusion rather than a single high-dose administration. Jugular catheterization coupled with our HPLC-

MS/MS method indeed provided a robust, reliable platform for investigating the *in vivo* metabolic pathways of RSS.

Administration of [$^{34}$S]-labeled Methionine allowed us to follow the labeled sulfur through the transsulfuration pathway in both genotypes. We found that, although the canonical CSH producing activity is slightly elevated, this pathway cannot fully account for CSH production in TR/GR-null mouse livers.

Using [$^{13}C_6$,$^{15}N_2$]-CSSC, we revealed that, despite TR/GR-null mice being unable to reduce the S-S bond in CSSC, they can still obtain CSH from CSSC. Importantly, the redoxins, particularly TRP14, as well as other thioredoxins and glutaredoxins, are not the only enzymes that can use CSSC as a substrate. Cbs and Cse can also use CSSC as a substrate to produce CSSH; accordingly, we detected an elevated level of labeled CSSH in the TR/GR-null mouse livers compared to WT. These reactions are PLP-dependent, so we used AOAA to inhibit PLP-dependent enzymes and investigate their significance.

AOAA was either administered to mice for steady-state metabolomics or used in tracing studies. Resting metabolomic analyses revealed that CSSH levels decreased in response to AOAA treatment in both genotypes, whereas CSH levels decreased only in the mutants. These findings were confirmed using labeled [$^{13}C_6$,$^{15}N_2$]-CSSC with AOAA. The inhibitor treatment caused a significant decrease in the ratio and labeled levels of CSSH in both genotypes; however, labeled CSH and its ratio decreased only in TR/GR-null livers. These experiments

confirmed that CSH production in TR/GR-null but not in WT mice is PLP-dependent.

To get deeper insights into which metabolic pathways are responsible for this effect, we conducted a more comprehensive evaluation of the CSSC-CSSH reaction, using [$^{34}S_2$]-C**SS**C (M+4 C**SS**C). The major aim of this experiment was to capture the double-labeled M+4 CSSH species, which should be the first intermediate in the enzymatic reaction when CSSC is used as a substrate for Cse and Cbs. Mice were infused with M+4 C**SS**C, and thiol and persulfide species were monitored. The mutant mice had higher CSH levels than WT mice, which correlates with our previous results. Examining the CSSH persulfides, we were able to detect only one-sulfur-labeled M+2 C**S**SH, and this was detected only in the mutant livers; M+4 C**SS**H wasn't detectable in the livers of either genotype. But the M+2 C**S**SH, where the inner sulfur is labeled, suggested that the labeled M+2 C**S**H must be formed in the first step, and the persulfidation occurs afterward. M+4 C**SS**H is a highly reactive and labile intermediate; we concluded that this was due to the fast decomposition in an *in vivo* environment.

We examined different *in vitro* systems to validate the CSSC-CSSH-CSH reactions. First, primary hepatocytes were isolated from both genotypes, and fluxomic analyses were performed using M+4 CSSC. Isolated TR/GR-null hepatocytes were viable and metabolically active; they obtained more M+2 C**S**H from M+4 C**SS**C than did the WT hepatocytes. In this system, we were able to measure M+2 C**S**SH

and M+4 C**SS**H. The M+2 C**S**SH showed the same pattern as *in vivo* studies: elevated enrichment in TR/GR-null cells. Interestingly, M+4 C**SS**H levels were lower in mutant cells than in WT cells; we suggest this may be due to increased turnover in mutant cells.

We were able to capture this labile species in isolated hepatocytes; moreover, we applied a specific inhibitor to further investigate the roles of Cbs and Cse in CSH production in TR/GR-null cells. At first, we used AOAA as a semi-selective inhibitor of PLP-dependent enzymes, but in hepatocytes, we further narrowed it to a Cse-selective inhibitor, PAG. Isotopic labeling with inhibitor treatment confirmed that Cse is the main enzyme in M+4 C**SS**H production from M+4 C**SS**C in both genotypes. In the labeled M+2 C**S**H, the PAG treatment resulted in a significant decrease in mutant cells but not in WT cells. These results confirmed that CSH production in the TR/GR-null genotype is Cse-mediated, via CSSH as an intermediate.

TR and GR use NADPH as a source of electrons; Cse and Cbs need PLP as a cofactor for their activities. Therefore, we performed an *in vitro* experiment to test the cofactor dependency of CSH production in the genotypes. We used liver lysates and added M+4 C**SS**C to induce the enzymatic reactions. M+4 C**SS**H and pyruvate were produced only in the reaction mixtures with PLP, and PAG treatment inhibited their production. This confirmed that the C-S bond cleavage in CSSC is Cse-mediated. Accumulation of these two analytes did not differ much across genotypes. However, in CSH, a different pattern emerged. In WT livers, NADPH-dependent reactions were the main

CSH producing pathways, whereas in the TR/GR-null lysates, CSH was produced only when PLP was added. This experiment corroborates our prediction that CSH production in WT is NADPH- and disulfide-bond-reduction-dependent, whereas in TR/GR-null livers it is PLP-dependent and occurs via C-S bond cleavage. These data also indicate that NADPH-dependent CSH formation is the more efficient pathway; but, in primary hepatocytes and *in vivo*, C-S bond cleavage reaction is the sole mechanism for CSH production in TR/GR-null hepatocytes.

Reaction 1 (WT): $CSSC \xrightarrow{Trp14,\ TR,\ NADPH} 2\ CSH$

Reaction 2 (TR/GR-null): $CSSC \xrightarrow{Cse,PLP} CSSH \rightarrow\rightarrow CSH$

This experiment also suggested that the formation of CSH from CSSH is not an enzymatic reaction, as no other cofactors were needed for the conversion of CSSH to CSH. We tested this prediction using recombinant Cse, where only the enzyme, PLP, and [$^{13}C_6$,$^{15}N_2$]-CSSC were present. [$^{13}C_3$,$^{15}N$]-CSSH and [$^{13}C_3$]-pyruvate levels started to increase immediately after the addition of the cofactor and the substrate, while the appearance of [$^{13}C_3$,$^{15}N$]-CSH was delayed. These data confirmed two major points: i) CSSH is a precursor of CSH, and ii) the transformation from CSSH into CSH is not an enzymatic reaction.

We validated the above-described *in vitro* findings in mice. Administering PAG to resting animals confirmed that CSSH levels in the liver were Cse-dependent, because they decreased in both

genotypes following PAG treatment; however, as expected, CSH levels decreased only in TR/GR-null livers. We examined the plasma of these animals and found that the inhibitor treatment did not alter plasma CSH levels in either genotype, confirming that CSH production is cell autonomous in liver and that the CSH demand in TR/GR-null cells is not met by CSH generated in other organs.

The Cse C-S bond-cleaving reaction had been described earlier. Those authors suggested that Cse can generate CSSH from CSSC more effectively than Cbs, but they didn't investigate CSH formation afterward. Moreover, the *in vivo* importance of this reaction was called into doubt. Here, we demonstrated the significance of this reaction in a mouse model and confirmed that it can support the CSH demand in hepatocytes under disulfide reductase deficiency. Without isotope tracing, the importance of this pathway could not have been delineated, further strengthening the biological importance of robust RSS measurement technologies.

In another study, we showed that BRAF V600E inhibition therapy in melanoma induces Cse upregulation. Parallel metabolic reprogramming together allows this upregulated Cse to use CSSC as its primary substrate to produce elevated levels of CSSH, which is utilized by the cells to develop resistance to BRAF V600E targeted therapy. Due to treatment in melanoma cells, not only LMW but also protein persulfide species were elevated. For the examination of HMW persulfides, the same HPLC-MS/MS method for free amino acids that we use for LMW metabolites can be applied directly after

total protein digestion with pronase. Using this approach, we investigated the roles of protein persulfides in different cancer model systems. In metastatic PDAC cells, Cbs showed a high expression, especially in T3M4 cells. Silencing Cbs (shCbs) in this cell line hindered metastasis formation in our mouse models; however, it did not alter the tumor size. Further investigation revealed that the STAT3 transcription factor is highly active in these cells and promotes epithelial-to-mesenchymal transition via Wnt signaling, a key step in metastasis. STAT3 can be persulfidated and protected from overoxidation-induced transcriptional activity loss. In the shCbs T3M4 cell line, decreased protein persulfide levels and increased STAT3-dimer were observed. This suggeted that Cbs contributes to STAT3 persulfidation in these cells and protects it from oxidation-induced damage. These data suggest that, if an effective drug targeting Cbs can be developed, it might serve as a therapeutic target in PDAC, leading to a less aggressive tumor phenotype and fewer metastases.

Both LMW and HMW RSS have important biological roles and functions. In this thesis, I critically re-evaluated and improved RSS detection methods, which enabled us to effectively investigate their functions and metabolic pathways in both cellular systems and whole-animal models.

## 5. Conclusions

Intracellular redox balance is essential for cellular viability, proliferation, and regulating processes such as energy metabolism, signal transduction, and stress adaptation. An imbalance in redox homeostasis results in oxidative or reductive stress, which can lead to different diseases. Reactive Sulfur Species (RSS) are vital for maintaining intracellular redox balance, but their detection is challenging due to their high reactivity, which makes them labile. To enable biological studies of RSS, we first optimize and re-evaluate alkylating protocols that preserve their speciation and capture labile persulfide species. The optimized method thereby enabled us to investigate low- and high-molecular weight (LMW and HMW) persulfide species in various biological matrices and to gain deeper, mechanistic insight into their metabolism and biological roles.

The HPE-IAM-based LMW and HMW persulfide detection protocol is widely used due to HPE-IAM's stabilizing effect on these species. We critically re-evaluated this persulfide detection method to improve the reliability and reproducibility of our analyses. Using the improved method with stable isotope-labeled fluxomic analyses, we examined two complex biological systems: a disulfide reductase-deficient mouse model and a pancreatic ductal adenocarcinoma model. We showed that, under disulfide reductase deficiency, a PLP-dependent, Cse-mediated C–S bond-cleaving pathway can be activated, bypassing NADPH-dependent disulfide reduction of CSSC and thereby maintaining CSH homeostasis. Our in vitro and in vivo stable-

isotope-tracing studies provided the first evidence that this pathway is indeed biologically relevant; moreover, it highlighted the metabolic flexibility of sulfur metabolism.

Additionally, we linked the transsulfuration enzyme Cbs to metastasis formation in PDAC tumors through HMW persulfides and demonstrated that posttranslational protein pesulfidation can affect protein activity, thereby initiating epithelial-to-mesenchymal transformation and metastasis formation.

The research outlined in this thesis expands our comprehension of the metabolic pathways of sulfur metabolites and the adaptability of these pathways. We gained a deeper mechanistic understanding of the roles of LMW and HMW persulfide species in sulfur metabolism and redox homeostasis.

# 9 Bibliography of the candidate's publications

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