

## Editorial:

Mueller, Jonathan Wolf; Collier, Abby C.; Gesteira, Tarsis F

DOI:

[10.3389/fmolb.2022.912700](https://doi.org/10.3389/fmolb.2022.912700)

License:

Creative Commons: Attribution (CC BY)

*Document Version*

Publisher's PDF, also known as Version of record

*Citation for published version (Harvard):*

Mueller, JW, Collier, AC & Gesteira, TF 2022, 'Editorial: Sulfation pathways – there and back again', *Frontiers in Molecular Bioscience*, vol. 9, 912700. <https://doi.org/10.3389/fmolb.2022.912700>

[Link to publication on Research at Birmingham portal](#)

### General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

### Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.



# Editorial: Sulfation Pathways—There and Back Again

Jon Wolf Mueller<sup>1\*</sup>, Abby C. Collier<sup>2\*</sup> and Tarsis F. Gesteira<sup>3\*</sup>

<sup>1</sup>Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, United Kingdom, <sup>2</sup>Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada, <sup>3</sup>College of Optometry, University of Houston, Houston, TX, United States

**Keywords:** PAPS synthase, sulfation pathways, protein folding/stability/aggregation, conjugate analytics/mass spectrometry, sulfo-metabolite synthesis/analytics

## Editorial on the Research Topic

### Advances in Sulfation Pathways Research

Sulfation Pathways are understood as the oxidative branch of sulfur metabolism (Günel et al., 2019). Core to sulfation pathways is sulfate activation, the transfer of sulfate to biological acceptor molecules and its dynamic cleavage in a spatially and temporally specific manner. The biochemical problem of sulfate activation is evident even in geological specimens—gypsum may be observed in orthopedic casts, an example of the highly inert sulfate ion (Figure 1). A significant amount of energy is needed to turn biological sulfate into PAPS (3'-phospho-adenosine-5'-phospho-sulfate), the active sulfate form.

The many and diverse sulfation acceptor molecules in biology dictate the molecular functions of ubiquitous sulfation pathways. Recent publications have highlighted doubly sulfated steroids (Lightning et al., 2021) as well as sulfo-conjugated vitamin D species (Jenkinson et al., 2022). This Research Topic focused on *Advances in Sulfation Pathways Research* features nine research articles and three reviews, authored by 63 individual scientists, significantly advancing the field of Sulfation Pathways, highlighted within the following paragraphs:

Research into sulfation pathways always relied on state-of-the-art analytical methods. Hence, we are pleased to present novel mass-spectrometry-based ways of profiling sulfated metabolites in urine by Fitzgerald et al. Developing mass spectrometry methods is impossible however without having the respective pure compounds readily at hand. In this regard, Alshehri et al. report a novel sulfation strategy to prepare steroid sulfates and isotopically labeled variations thereof, certainly an innovation with great importance for the field. Whenever coming from a genomic viewpoint, it may be necessary to characterize a sulfation enzyme with regards to its activity. With this in mind, Sun et al. have prepared a manuscript on optimized sulfotransferase assays.

Sulfation impacts greatly on steroidogenesis—sulfated steroids may represent transport forms and/or modulate downstream processing (Foster and Mueller, 2018). Two studies by Pavlič et al. and De Almeida Da Costa et al. independently provide experimental evidence that endometrial tissues can generate estrogens from circulating steroid sulfates. Sulfation of steroids predominantly occurs within the cytosol and sulfated steroids then need dedicated transporters to enter circulation and for the uptake into target tissues. Karakus et al. provide an in-depth study about the steroid sulfate uptake transporter SOAT (SLC10A6) in adipose tissue that illustrates this well.

When studying sulfated steroids, not only are circulating steroids important, but also sulfated neuro-steroids. This Research Topic features two review articles about steroid sulfation in neurodegenerative diseases by Vitku et al. and during neurodevelopment by Clarke et al. Fascinating topics that will enable exciting discoveries in future, with great potential for the development of novel therapeutics.

## OPEN ACCESS

### Edited and reviewed by:

Cecilia Giulivi,  
University of California, Davis,  
United States

### \*Correspondence:

Jon Wolf Mueller  
j.w.mueller@bham.ac.uk  
Abby C. Collier  
abby.collier@ubc.ca  
Tarsis F. Gesteira  
tgferrei@central.uh.edu

### Specialty section:

This article was submitted to  
Cellular Biochemistry,  
a section of the journal  
Frontiers in Molecular Biosciences

**Received:** 04 April 2022

**Accepted:** 29 April 2022

**Published:** 16 May 2022

### Citation:

Mueller JW, Collier AC and Gesteira TF  
(2022) Editorial: Sulfation  
Pathways—There and Back Again.  
Front. Mol. Biosci. 9:912700.  
doi: 10.3389/fmolb.2022.912700



**FIGURE 1** | Sulfur and a rock of sulfate. A lump of elementary sulfur featuring many shades of sulfuric yellows (front) and a rock of gypsum (rear), also known as  $\text{CaSO}_4 \bullet 2 \text{H}_2\text{O}$ . Both specimens were kindly provided by the Lapworth Museum of Geology, University of Birmingham, for an outreach event (to JWM).

Aspects of sulfation pathways are highly conserved in multicellular organisms. Hence, the review article by Igreja and Sommer about sulfation pathways in nematode development will be of great interest to the community—much is known about the genetics of these pathways, however a lot remains to be uncovered from the metabolism side.

One part of sulfation pathways that differs greatly between species is degradation of the remnants of PAPS-dependent sulfation. 3'-Phospho-adenosine-5'-phosphate seems to be a waste product in humans—it however represents important signaling properties in plants. Ashykhmina et al. studied the divergent functions of this nucleotide in stress signaling, when encountered in different cellular compartments. It remains to be seen, if any of these signaling propensities would also be discovered in human sulfation pathways.

## REFERENCES

Brylski, O., Ebbinghaus, S., and Mueller, J. W. (2019). Melting Down Protein Stability: PAPS Synthase 2 in Patients and in a Cellular Environment. *Front. Mol. Biosci.* 6, 31. doi:10.3389/fmolb.2019.00031

From a synthetic biology perspective, some sulfation proteins have been characterized in their folding and protein stability, reviewed here (Brylski et al., 2019), following on from which Brylski et al. constructed a folding sensor that reports protein integrity *via* Förster resonance energy transfer. This elegant advance allowed measurement of protein unfolding within intact cells. With this approach, Brylski et al. established that cellular ATP levels determine the stability of a nucleotide kinase. The same team of researchers also studied the stability and aggregation behavior of disease-related protein variants of the highly conserved enzyme PAPSS2 (Brylski et al.).

We look towards a bright future in Sulfation Pathways research. New developments may bring insights in novel or overlooked sulfated metabolites. Linking sulfation pathways with other metabolic pathways may also be highly interesting—such as the study of two Golgi-residing heparan sulfate sulfotransferases that cooperatively act on their substrate (Gesteira et al., 2021). By investigation of patients with rare genetic mutations or by using omics and big data approaches, we also may be able to link sulfation pathways to other biological themes; and linking steroid sulfation to adrenal tumors (Mueller et al., 2021) is a first step towards this goal.

There were dedicated meetings on sulfation pathways back in the 1990s. Due to renewed interest and significant advances in the field, such meetings started again. SUPA meetings took place in Greifswald, Germany, in 2015; then continued in Birmingham, United Kingdom, in 2017, and Castle Rauischholzhausen, Germany, in 2019. Accompanying Research Topics on sulfation pathways were published in 2016 (Mueller and Muller, 2016) and 2018 (Mueller and Foster, 2018). We are delighted to present the current Research Topic, looking towards the SUPA 2023 meeting that is being organized already.

## AUTHOR CONTRIBUTIONS

JWM drafted the manuscript. All authors approved the final version of this editorial.

## ACKNOWLEDGMENTS

We cordially thank Annalisa Pastore for introducing us to the publisher Frontiers. We also thank all the listed reviewers as well as several anonymous reviewers for their invaluable input as expert referees.

Foster, P. A., and Mueller, J. W. (2018). Sulfation Pathways: Insights into Steroid Sulfation and Desulfation Pathways. *J. Mol. Endocrinol.* 61 (2), T271–T283. doi:10.1530/JME-18-0086

Gesteira, T. F., Marforio, T. D., Mueller, J. W., Calvaresi, M., and Coulson-Thomas, V. J. (2021). Structural Determinants of Substrate Recognition and Catalysis by Heparan Sulfate Sulfotransferases. *ACS Catal.* 11 (17), 10974–10987. doi:10.1021/acscatal.1c03088

- Günel, S., Hardman, R., Kopriva, S., and Mueller, J. W. (2019). Sulfation Pathways from Red to Green. *J. Biol. Chem.* 294 (33), 12293–12312. doi:10.1074/jbc.REV119.007422
- Jenkinson, C., Desai, R., McLeod, M. D., Mueller, J. W., Hewison, M., and Handelsman, D. J. (2022). Circulating Conjugated and Unconjugated Vitamin D Metabolite Measurements by Liquid Chromatography Mass Spectrometry. *J. Clin. Endocrinol. Metab.* 107 (2), 435–449. doi:10.1210/clinem/dgab708
- Lightning, T. A., Gesteira, T. F., and Mueller, J. W. (2021). Steroid Disulfates - Sulfation Double Trouble. *Mol. Cell. Endocrinol.* 524, 111161. doi:10.1016/j.mce.2021.111161
- Mueller, J. W., and Foster, P. A. (2018). Steroid Sulfation Research Has Come a Long Way. *J. Mol. Endocrinol.* 61 (2), E5–E6. doi:10.1530/JME-18-0109
- Mueller, J. W., Vogg, N., Lightning, T. A., Weigand, I., Ronchi, C. L., Foster, P. A., et al. (2021). Steroid Sulfation in Adrenal Tumors. *J. Clin. Endocrinol. Metab.* 106 (12), 3385–3397. doi:10.1210/clinem/dgab182
- Mueller, J. W., and Muller, S. (2016). Welcome to a SUPA Issue. *Chemico-Biological Interact.* 259 (Pt A), 1. doi:10.1016/j.cbi.2016.11.006

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Mueller, Collier and Gesteira. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.