Deciphering molecular mysteries: New insights into metabolites that control aging and disease

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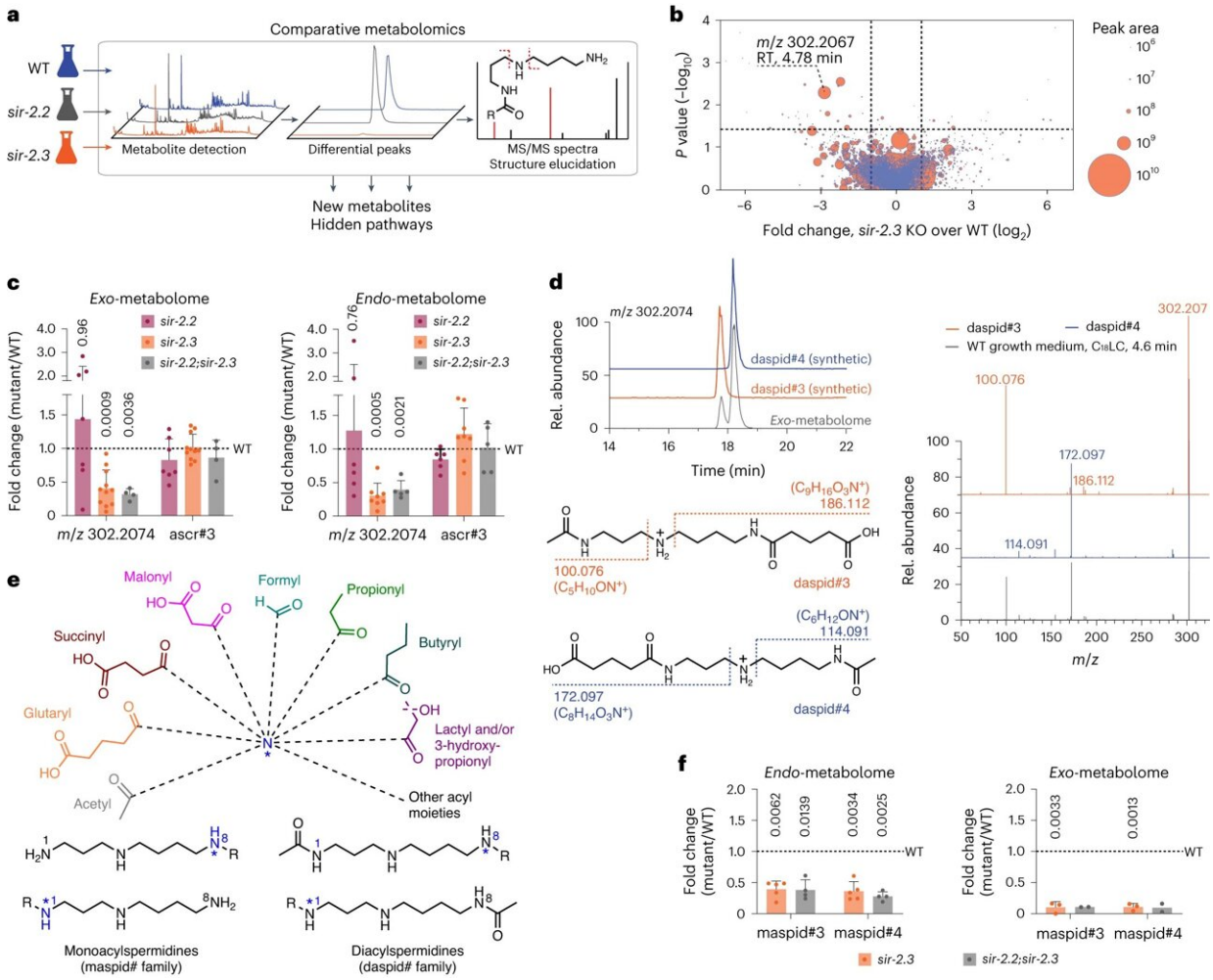

Comparative metabolomics uncovers decrease in *N*-glutarylspermidines in *sir-2.3* mutants. **a**, Scheme of untargeted comparative metabolomic analysis of sirtuin mutants using HPLC–HRMS/MS. **b**, Untargeted comparative

metabolomics of growth medium of WT and *sir-2.3(ok444)*-mutant *C. elegans*. Bubble sizes reflect peak areas. RT, retention time. $n = 4$. **c**, Fold change of selected metabolites compared to those of WT *C. elegans* in the *exo*-metabolome (left) and the *endo*-metabolome (right). The metabolite feature at an *m*/*z* ratio of 302.2074 (later identified as daspid#3 and daspid#4) was significantly downregulated in *sir-2.3*- and *sir-2.2;sir-2.3*-mutant animals, whereas the ascaroside ascr#3, used as a reference metabolite[23], remained unchanged. *Exo*-metabolome: *sir-2.2*, $n = 7$; *sir-2.3*, $n = 11$; *sir-2.2*;*sir-2.3*, $n = 4$. *Endo*-metabolome: *sir-2.2*, $n = 6$; *sir-2.3*, $n = 8$; *sir-2.2*;*sir-2.3*, $n = 5$. **d**, Separation of daspid#3 and daspid#4 via HILIC HPLC–HRMS and analysis of MS/MS fragmentation. Rel., relative. **e**, *N*-acylspermidines identified in this study, including diacylspermidine (daspid) and monoacylspermidine (maspid) derivatives. **f**, N^8- and N^1-glutarylspermidine (maspid#3 and maspid#4) levels were downregulated in *sir-2.3* and *sir-2.2*;*sir-2.3* mutants compared to WT in the *endo*-metabolome (left) and the *exo*-metabolome (right). *Endo*-metabolome: *sir-2.3*, $n = 5$; *sir-2.2*;*sir-2.3*, $n = 4$. *Exo*-metabolome: *sir-2.3*, $n = 3$; *sir-2.2*;*sir-2.3*, $n = 2$. *n*, number of independent biological experiments. *P* values were calculated by unpaired, two-tailed *t*-tests with Welch correction in **b**. Data are mean ± s.d., and *P* values were calculated using two-sided ratio paired *t*-tests for comparisons relative to WT in **c**,**f**. Credit: *Nature Chemical Biology* (2024). DOI: 10.1038/s41589-023-01511-2

In a significant advancement in the field of biochemistry, scientists at the Boyce Thompson Institute (BTI) and Cornell University have uncovered new insights into a family of metabolites, acylspermidines, that could change how we understand aging and fight diseases.

The study, recently published in *Nature Chemical Biology*, presents an unexpected connection between spermidine, a long-known compound present in all living cells, and sirtuins, an enzyme family that regulates many life-essential functions.

Sirtuins have been the subject of significant attention over the past two

decades. Recent studies indicate that sirtuins play a crucial role in various age-related diseases. As a result, there is growing interest in the link between sirtuins and aging, making them a promising target for therapeutic interventions aimed at improving health span and longevity.

"We were excited to uncover this unexpected branch of cellular metabolism related to sirtuins," says senior author Frank Schroeder, a professor at BTI. "Discovering these previously uncharacterized spermidine derivatives provides insight into the inner workings of this critical pathway and brings us a step closer to understanding the physiological functions of mitochondrial sirtuins."

The researchers took an unbiased approach, comparative metabolomics, a methodology developed by the Schroeder lab for over a decade, to screen for sirtuin-dependent metabolic changes. The study revealed a novel family of metabolites called acylspermidines derived from modifications of diverse proteins, many of which play essential roles in growth and cell survival.

Following the discovery of sirtuin-linked acylspermidines in the simple organism C. elegans, the researchers further demonstrated that the same compounds are also present in mammals (including humans). Lastly, the research team demonstrates the direct impact of these metabolites on lifespan in C. elegans and cell proliferation in mammals.

"Important physiological functions are reflected in many molecular fingerprints, including tens of thousands of small molecule metabolites that remain to be discovered. This work is a step towards uncovering the biological roles and functions of the vast space of chemical dark matter in our bodies," says Bingsen Zhang, a graduate student in the Schroeder lab and first author of the study.

Future research will explore these findings' mechanisms and

pharmacological aspects, particularly how acylspermidines affect lifespan, cell growth, and their potential interactions with other metabolic pathways.

"Nearly 350 years after spermidine was isolated and 100 years after its structure was understood, our work further advances the collective knowledge of the spermidine family, connecting it to other vital biochemical processes, including central energy metabolism and amino acid metabolism," adds Zhang.

More information: Bingsen Zhang et al, Acylspermidines are conserved mitochondrial sirtuin-dependent metabolites, *Nature Chemical Biology* (2024). DOI: 10.1038/s41589-023-01511-2

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