Metabolite Regulators of Life Processes

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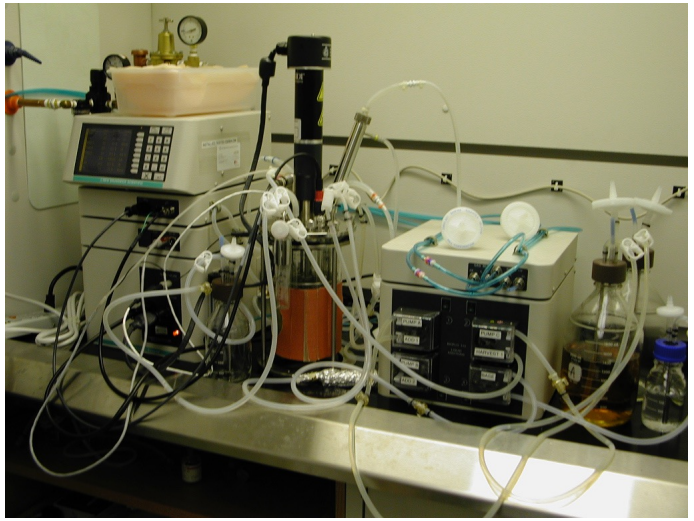
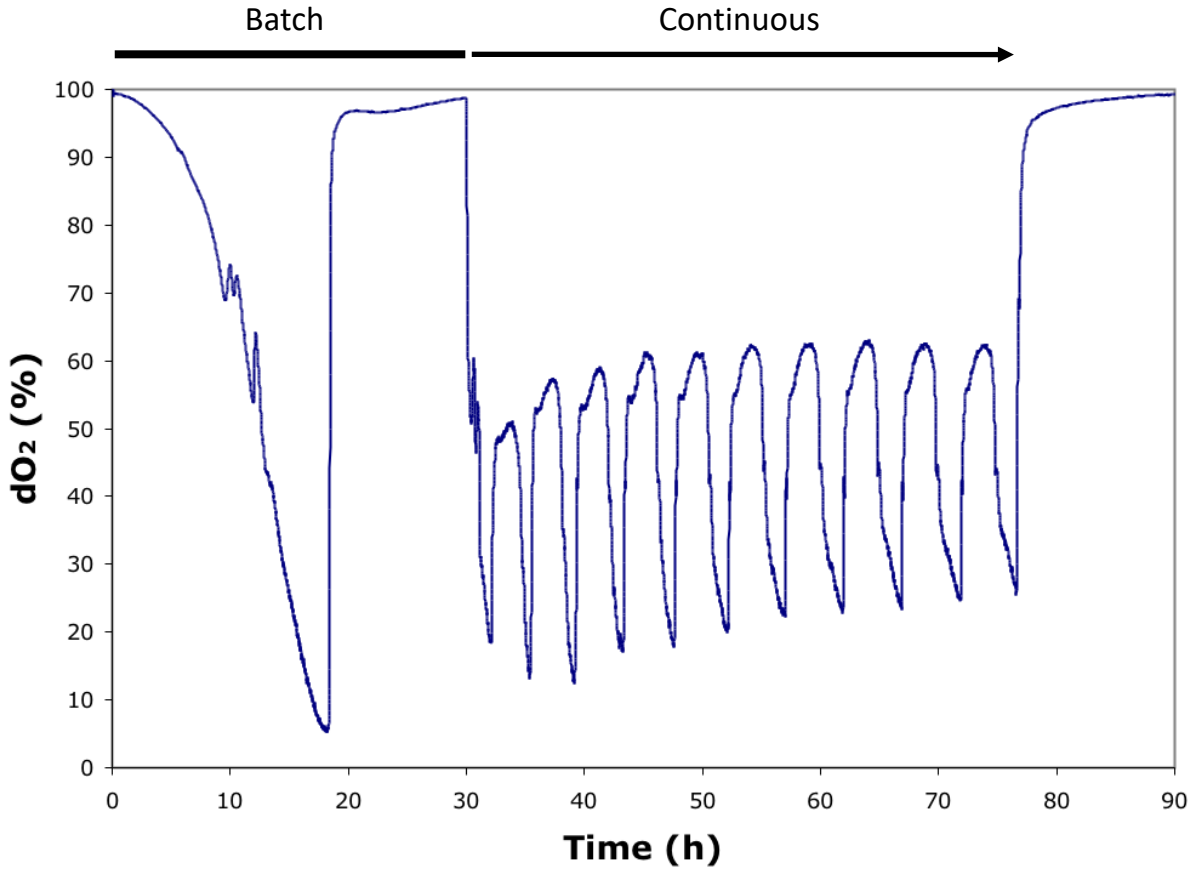
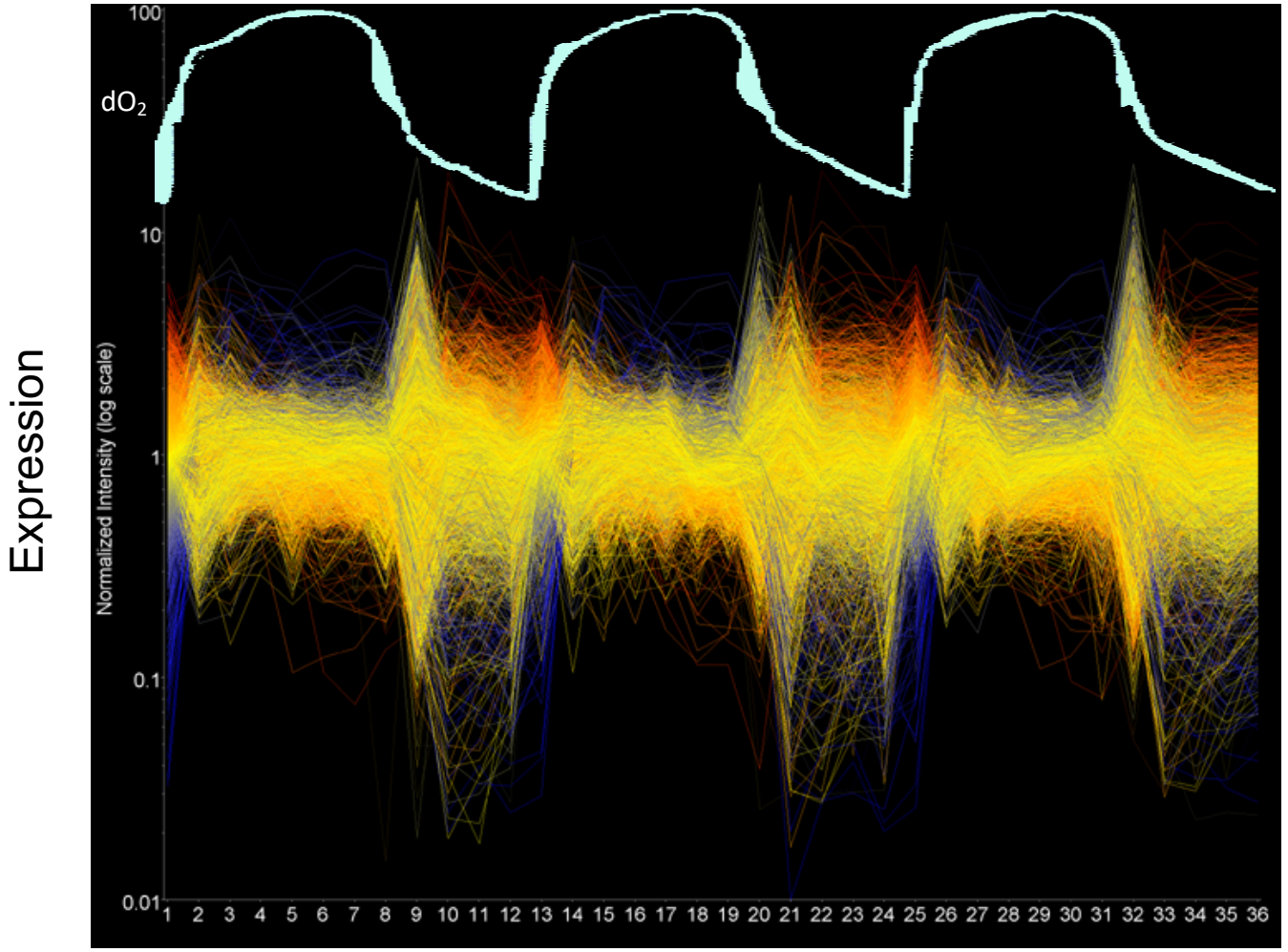
Metabolic cycles exhibited by budding yeast cells in a chemostat

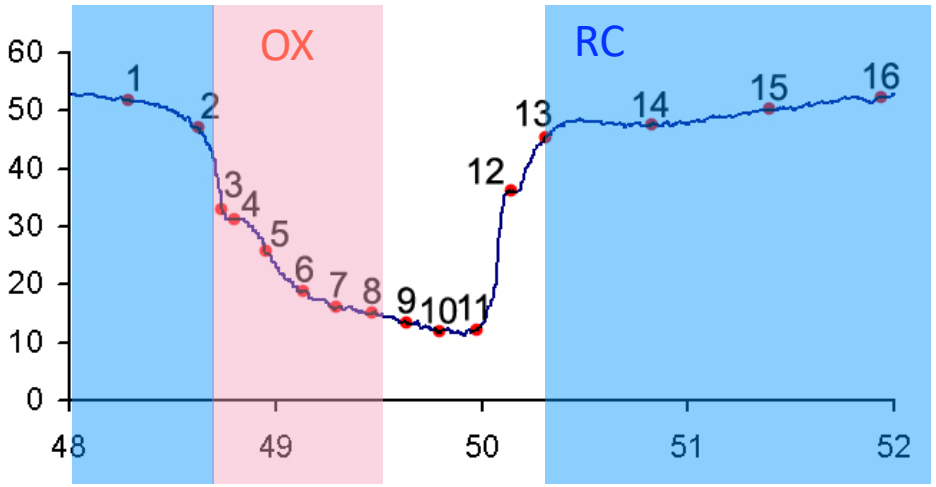




Periodic gene expression during a yeast metabolic cycle



Growth vs. survival genes are reciprocally expressed – how?

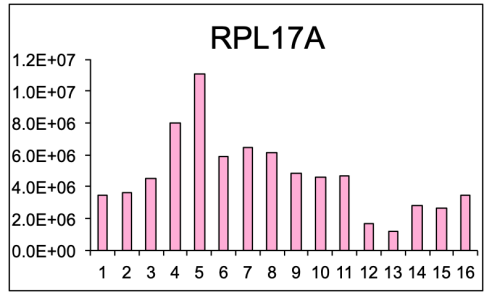


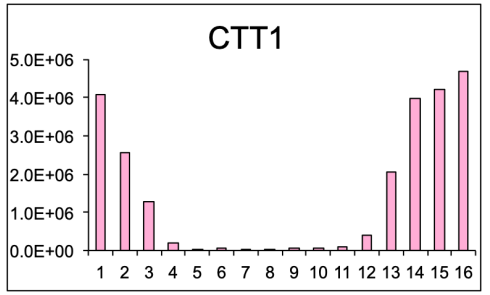
ribosome biogenesis
rRNA processing
protein translation
amino acid biosynthesis
(1000+)

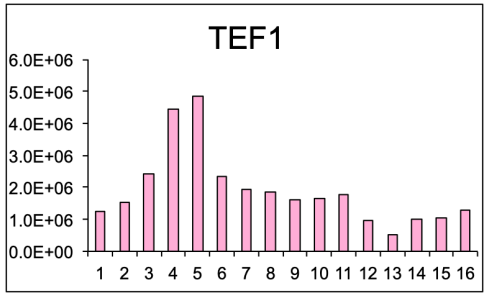
heat shock proteins
ubiquitin/proteasome
autophagy
vacuole
detox enzymes
(1500+)

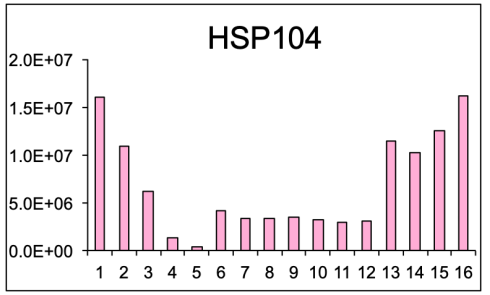
Growth genes

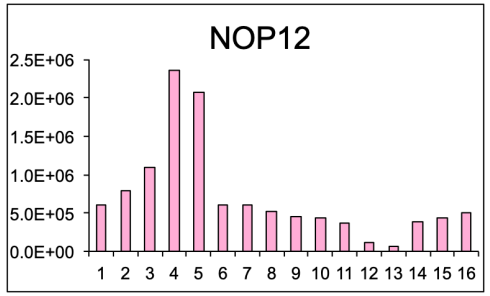
Survival genes

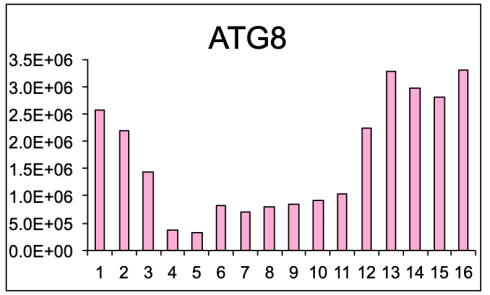




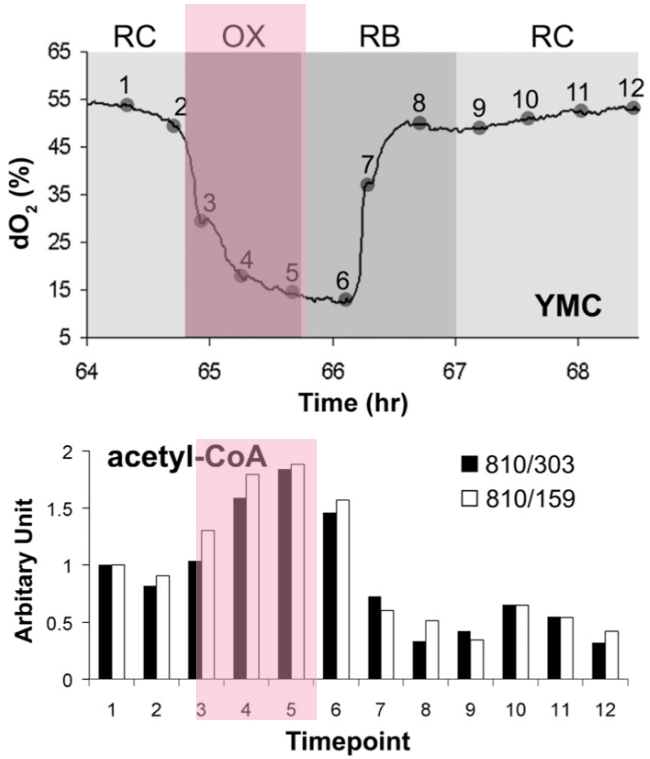


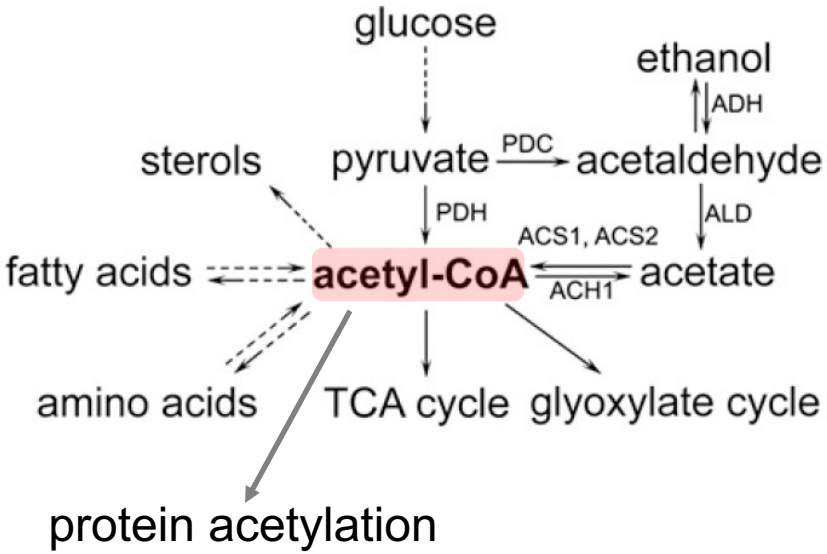




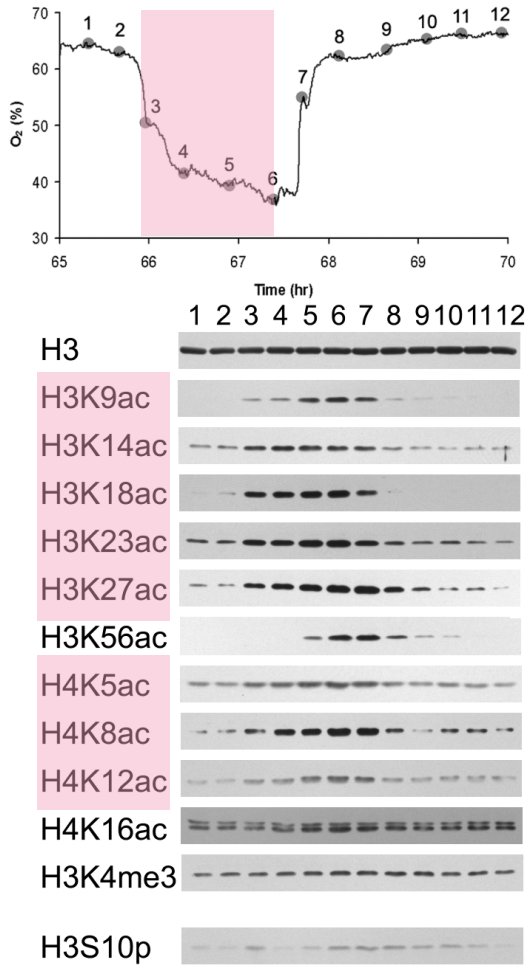


Intracellular levels of acetyl-CoA oscillate during metabolic cycles

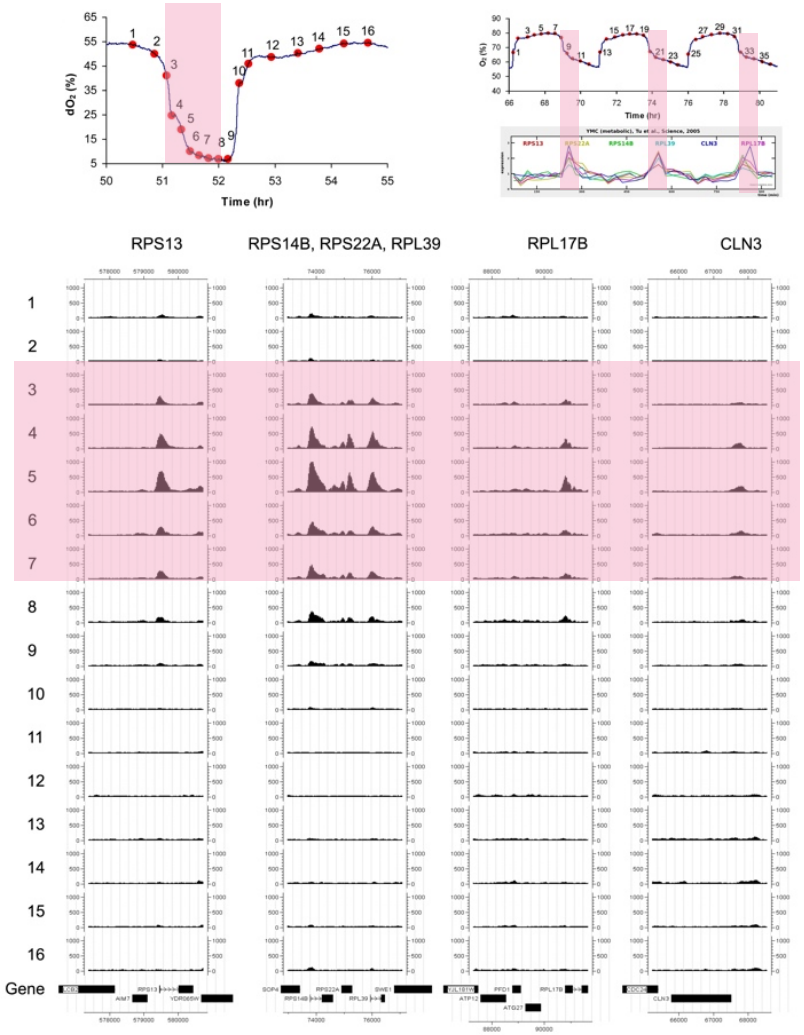




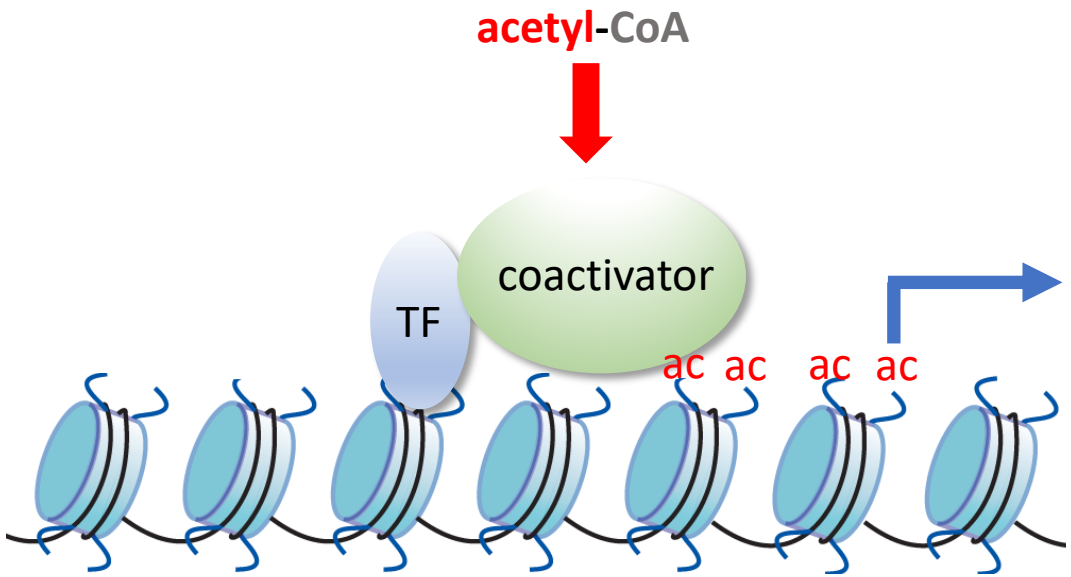
Oscillations of histone acetylation, in tune with acetyl-CoA



A surge in acetyl-CoA induces histone acetylation at growth-promoting genes

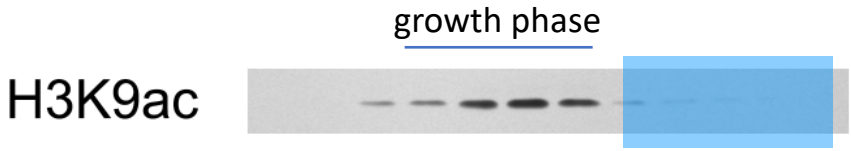


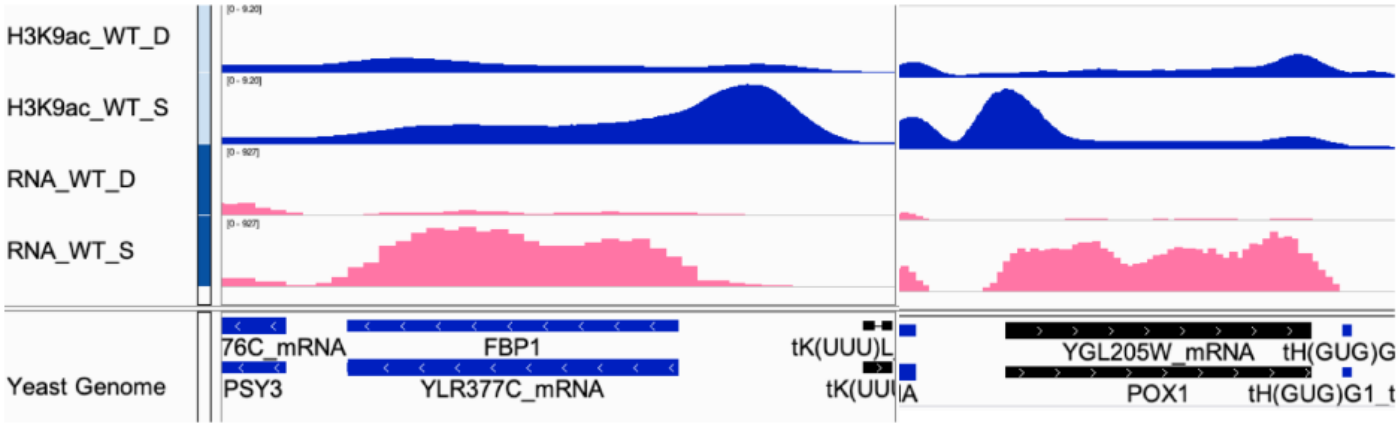
Acetyl-CoA as a driver of gene expression



Epigenetics <-> Metabolism

What happens to histone acetylation during glucose starvation/low acetyl-CoA?

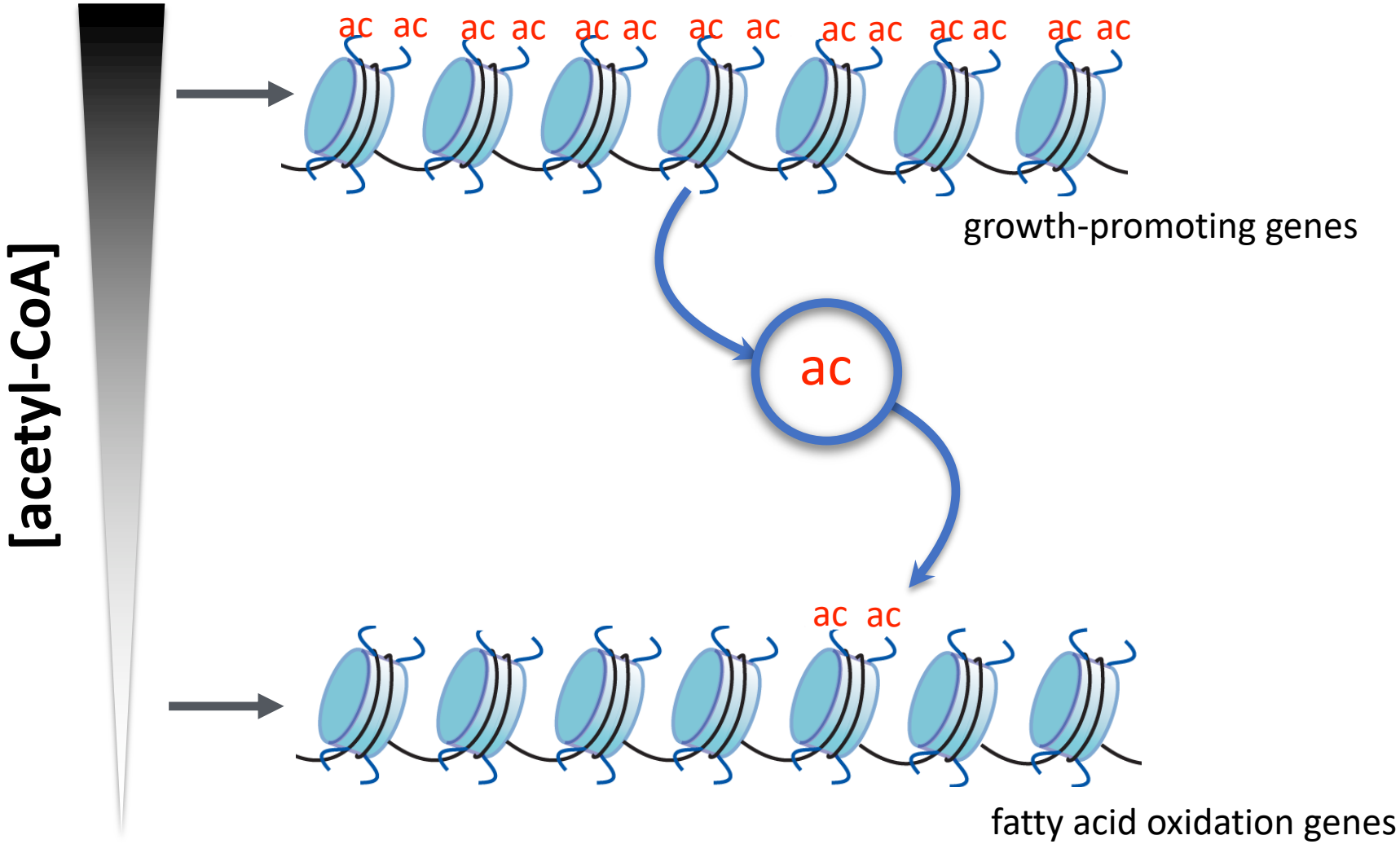




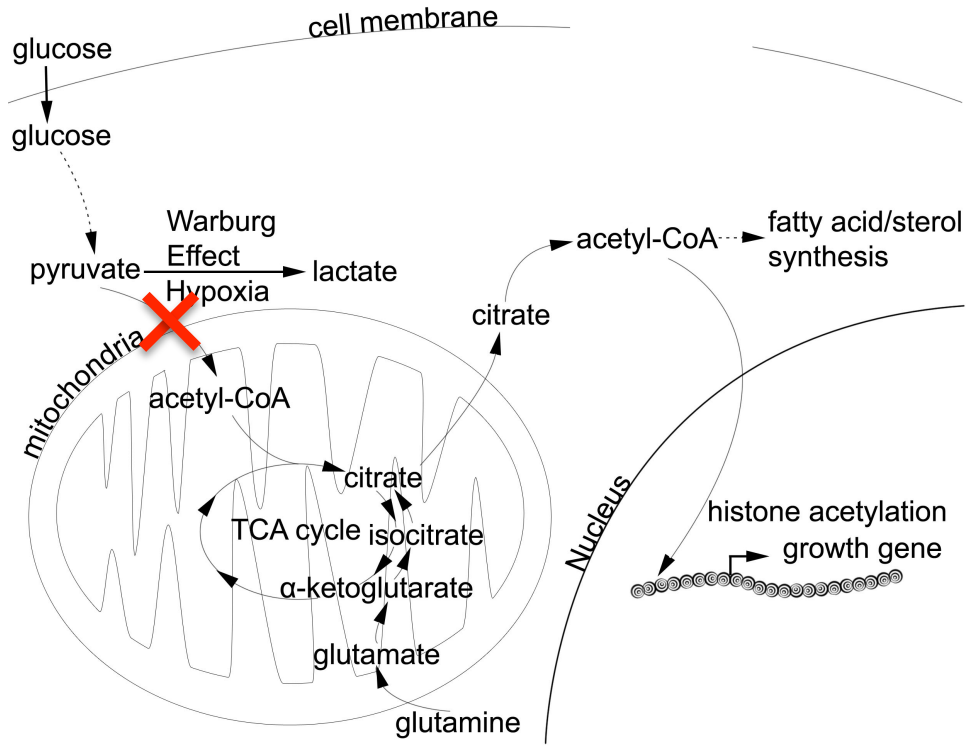
gluconeogenesis

fatty acid oxidation

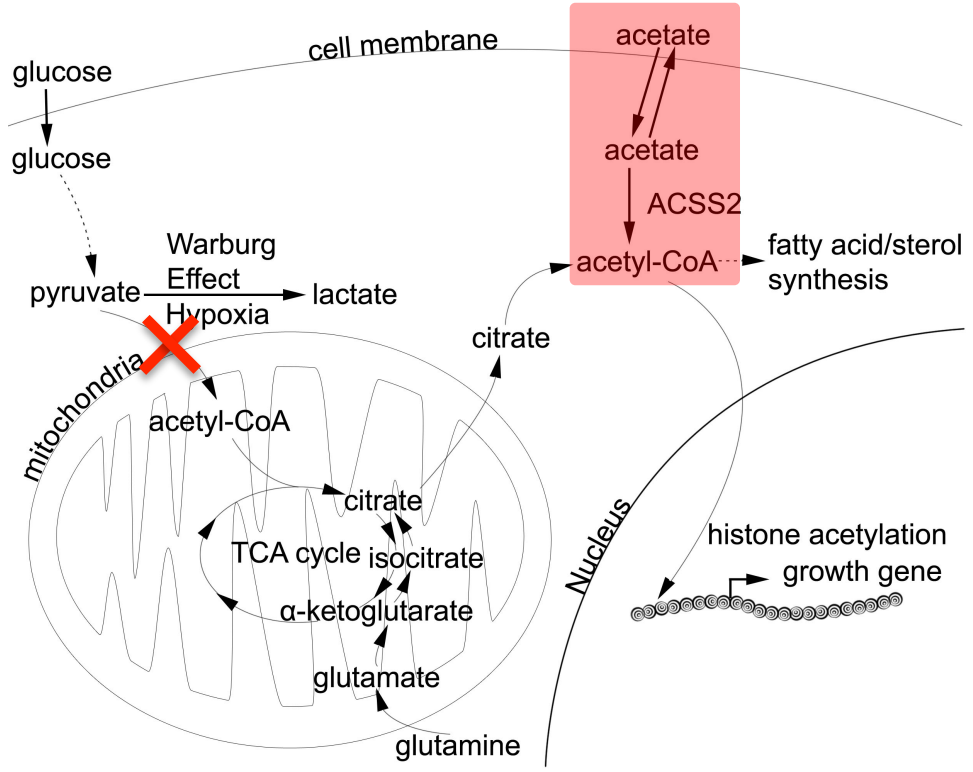
Remaining histone acetylation is targeted to oxidative metabolism genes during glucose starvation



Alternative sources of acetyl-CoA in mammalian cells



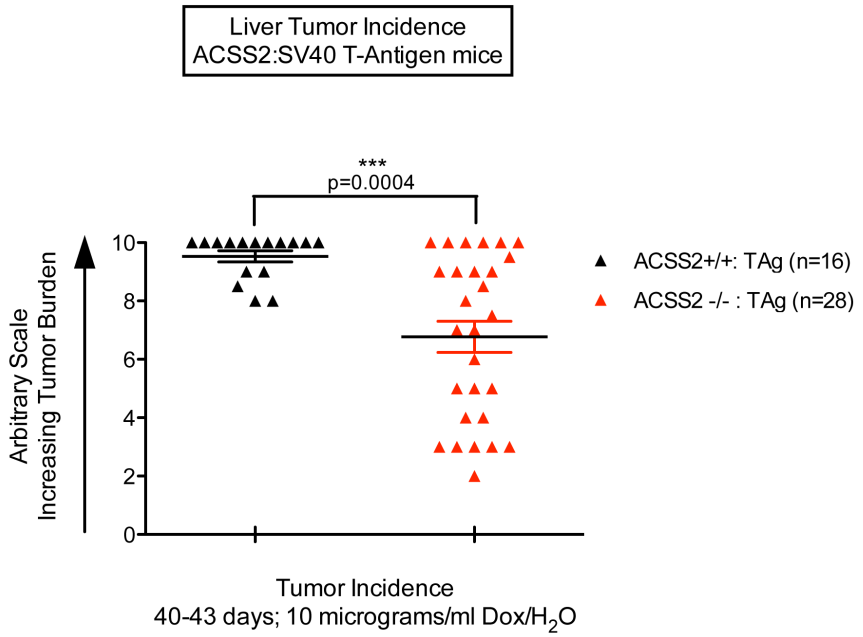
Acetate can be a source of acetyl-CoA in mammalian cells



acetyl-CoA synthetase (ACSS2)

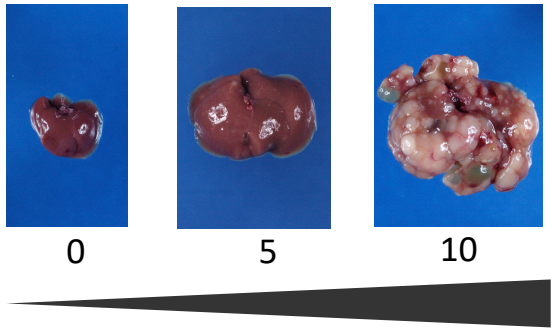
acetate + CoA + ATP ------> acetyl-CoA + AMP + pyrophosphate

Mice lacking acetyl-CoA synthetase develop fewer liver tumors



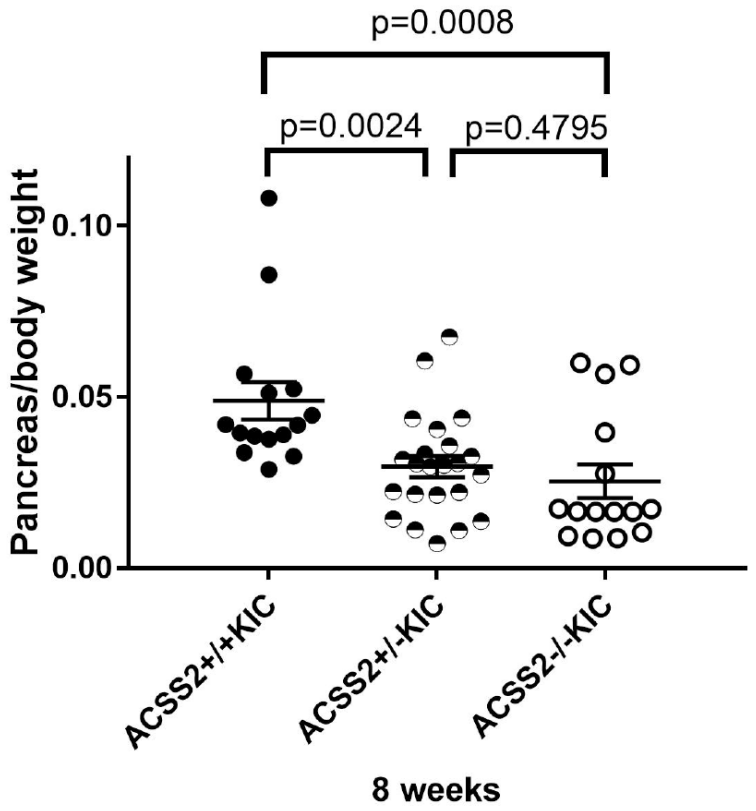
Tumor Burden: Arbitrary Scale

2: Uniform hyperplasia, no visible tumors
4: Uniform hyperplasia with < 10 visible tumors
6: Uniform hyperplasia with >10 visible tumors
8: Uniform hyperplasia with >50 visible tumors
10: Hyperplastic liver replaced by tumors over entire surface

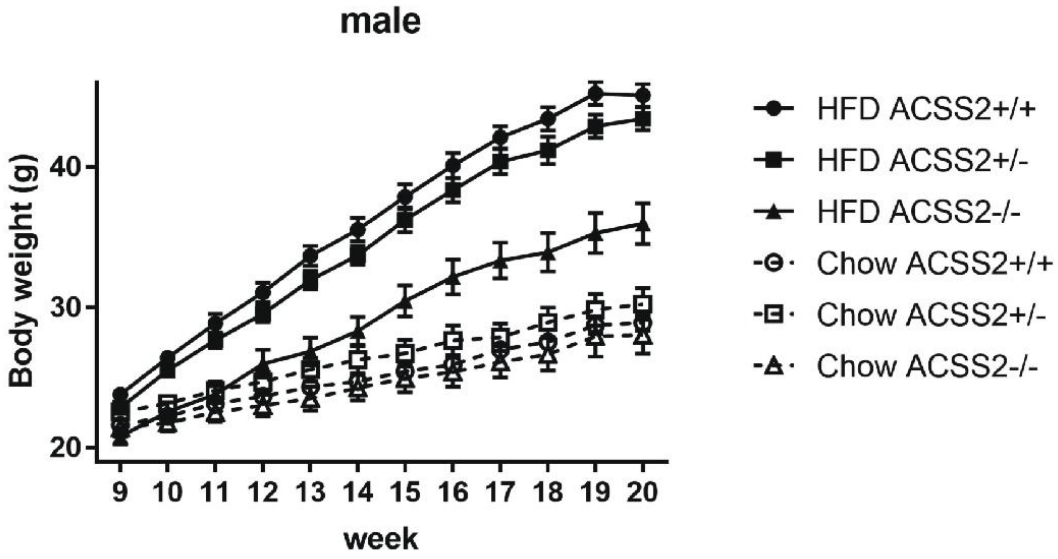


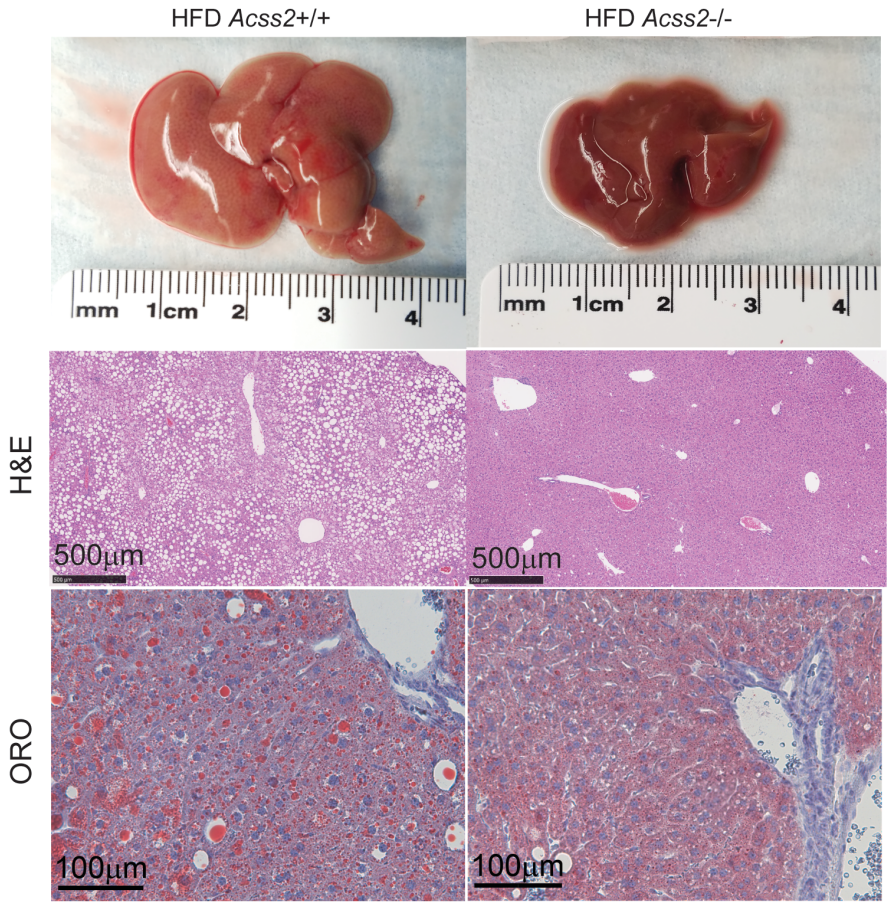
Mice lacking acetyl-CoA synthetase develop fewer pancreatic tumors

LSL-Kras^{G12D}; Cdkn2a$^{f/f}$; p48^{Cre} (KIC)

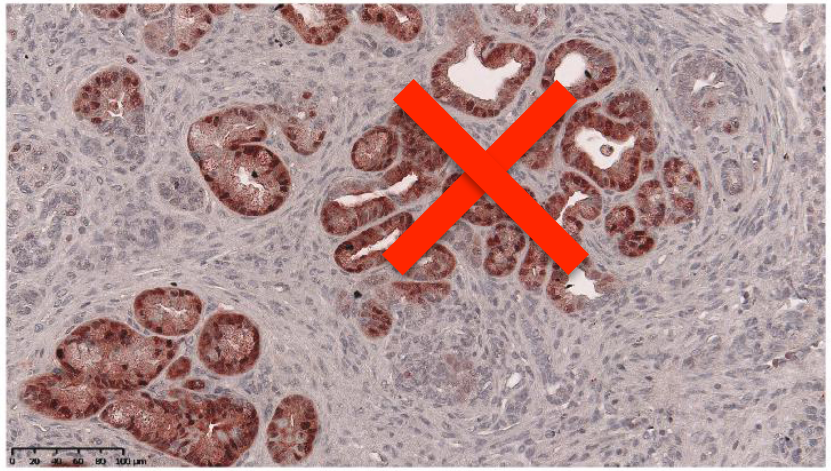


Mice lacking acetyl-CoA synthetase exhibit reduced accumulation of fat in liver

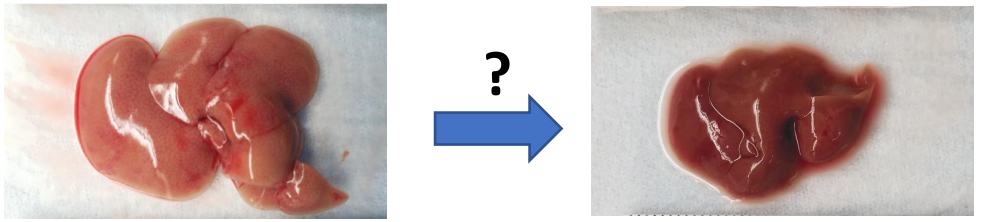




An inhibitor of acetyl-CoA synthetase may have therapeutic utility

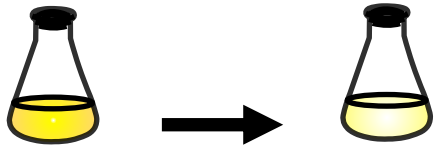


Inhibit PanINs to prevent pancreatic cancer?



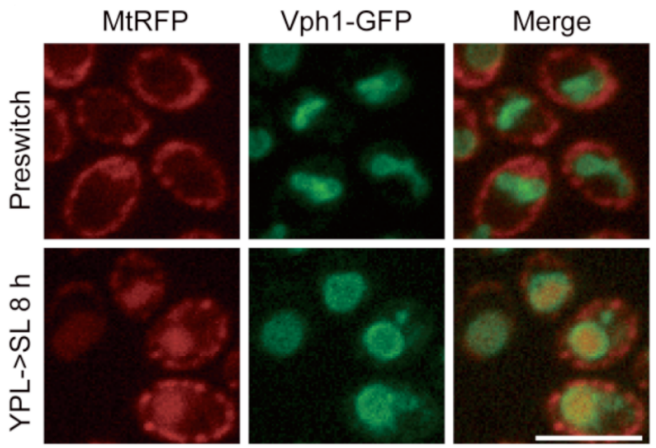
reverse fatty liver disease?

Insufficiency of methionine triggers autophagy

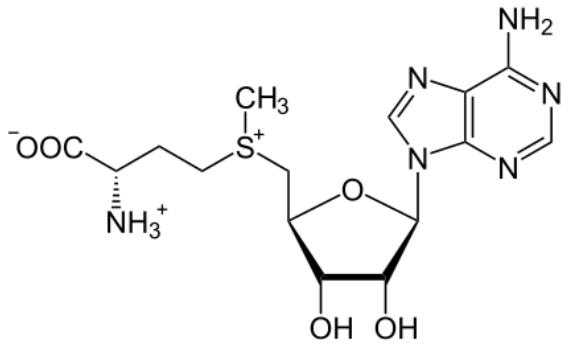


YPL
(rich = +AA)

SL
(minimal = -AA)

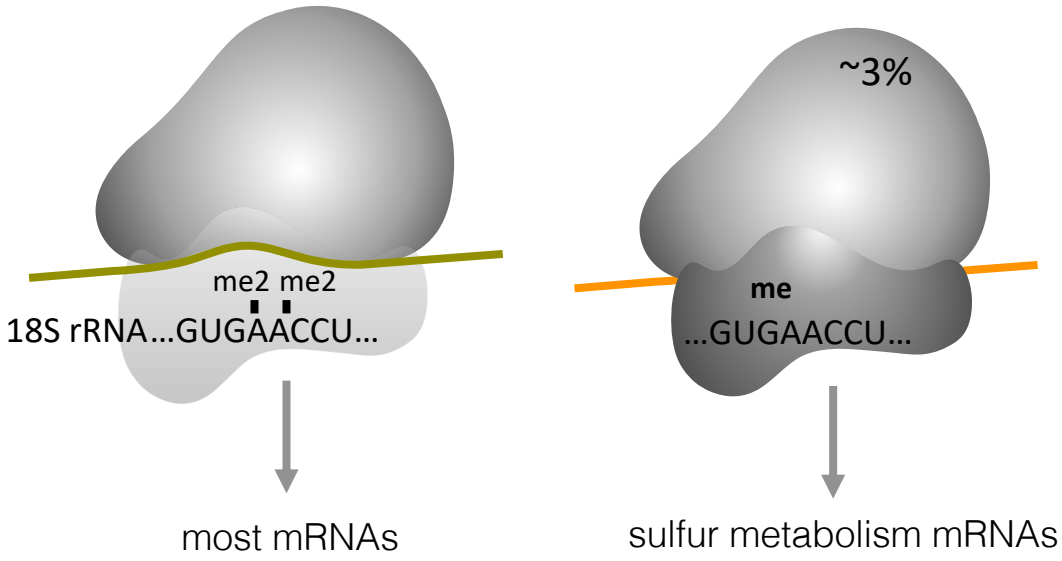


methionine

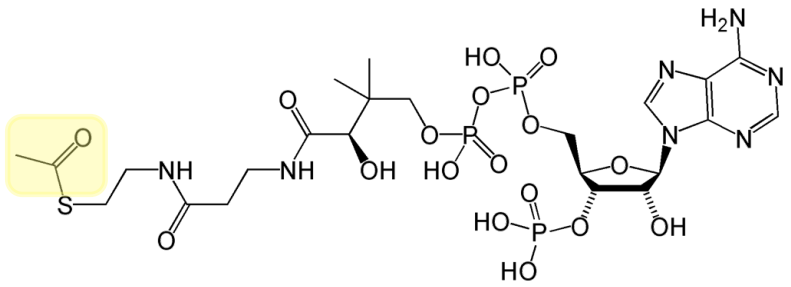


S-adenosylmethionine

Regulation of translation by the number of methyl groups on 18S rRNA



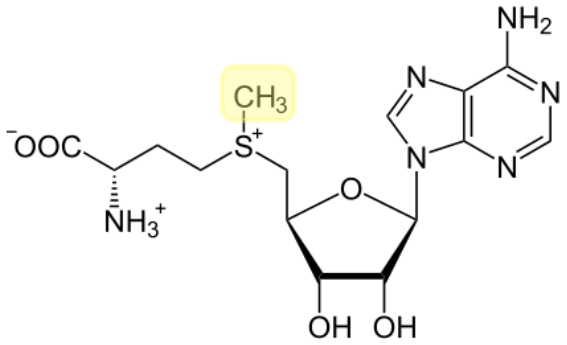
Sentinels of the cellular metabolic state



acetyl-CoA

"two-carbon donor"

signal of carbon source sufficiency

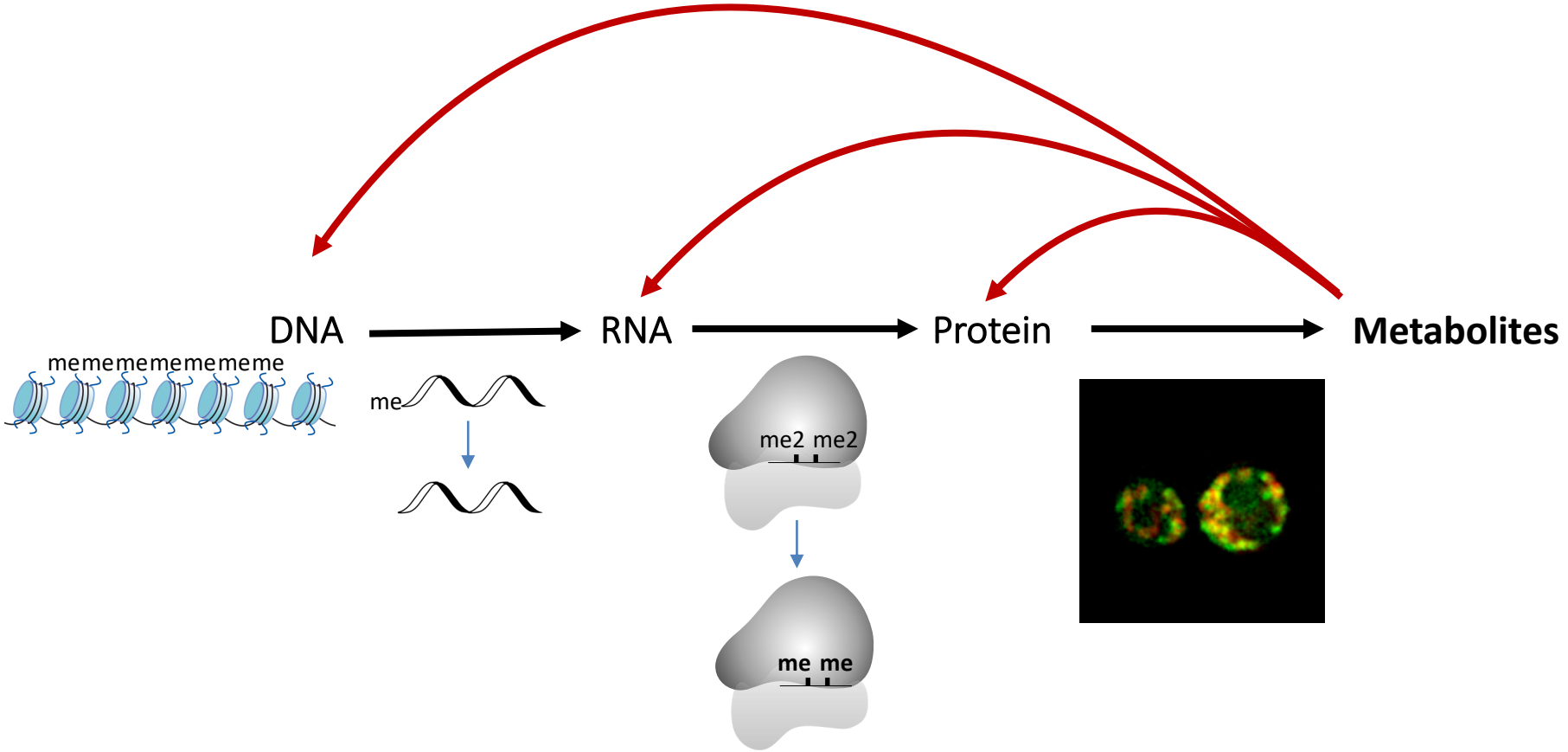


S-adenosylmethionine

"one-carbon donor"

signal of amino acid sufficiency

Metabolites and their underappreciated influence on life processes



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