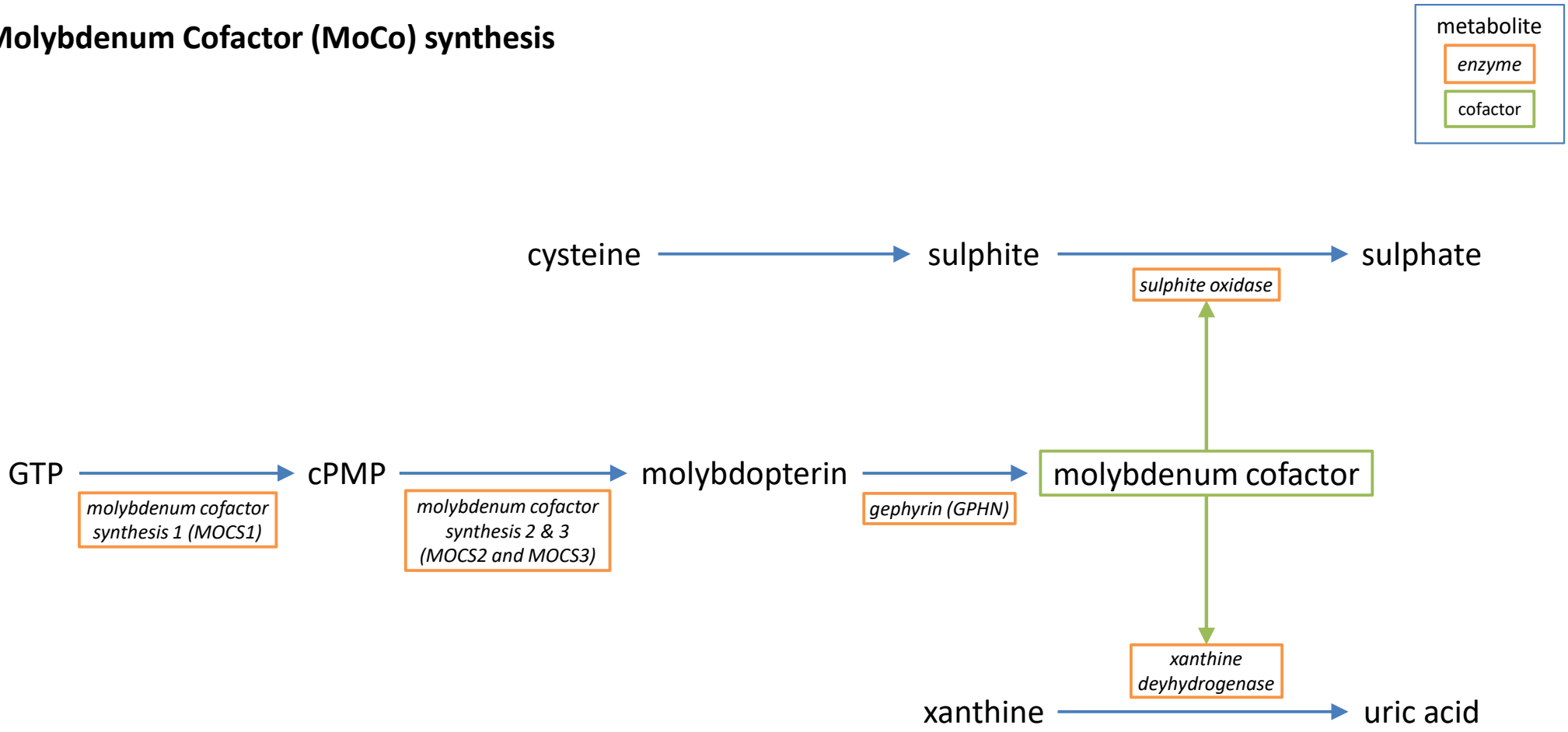
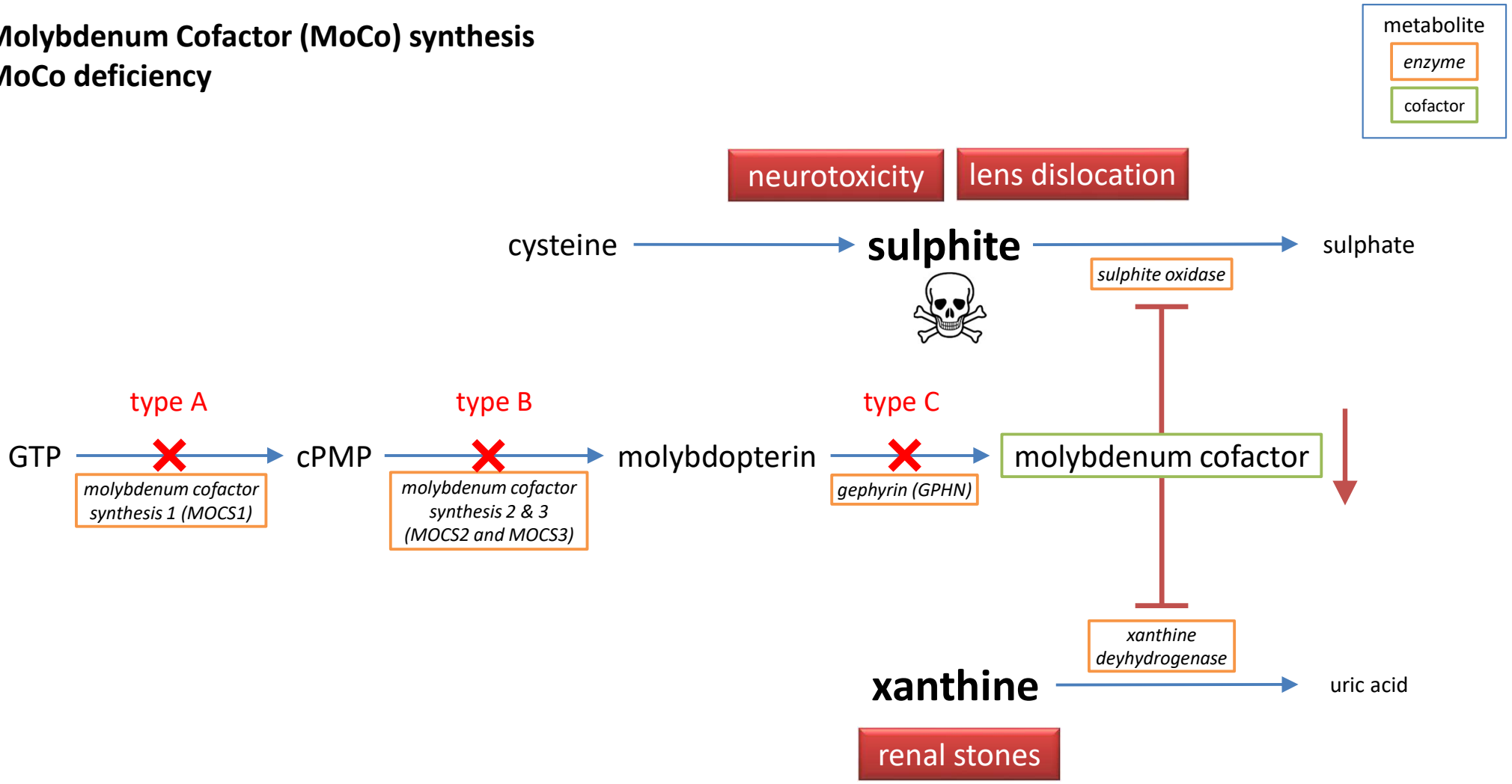
Molybdenum Cofactor (MoCo) synthesis



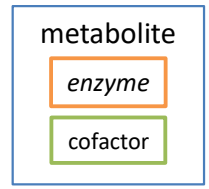
Molybdenum Cofactor (MoCo) synthesis
MoCo deficiency

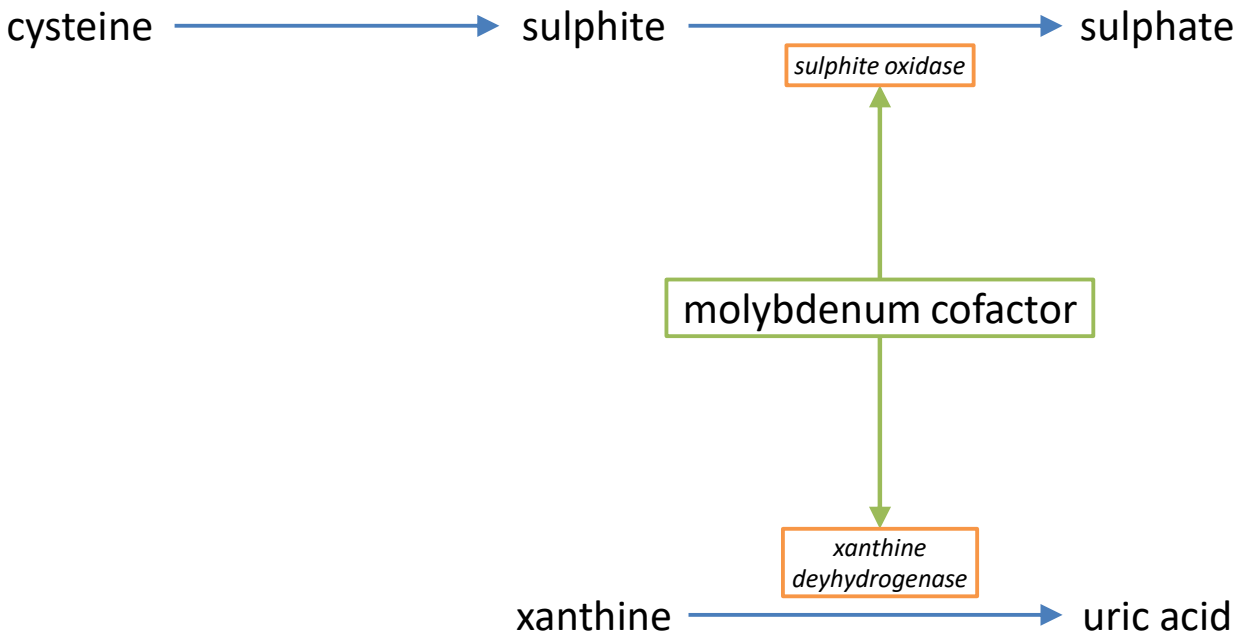


Molybdenum Cofactor (MoCo) synthesis

Animated 1

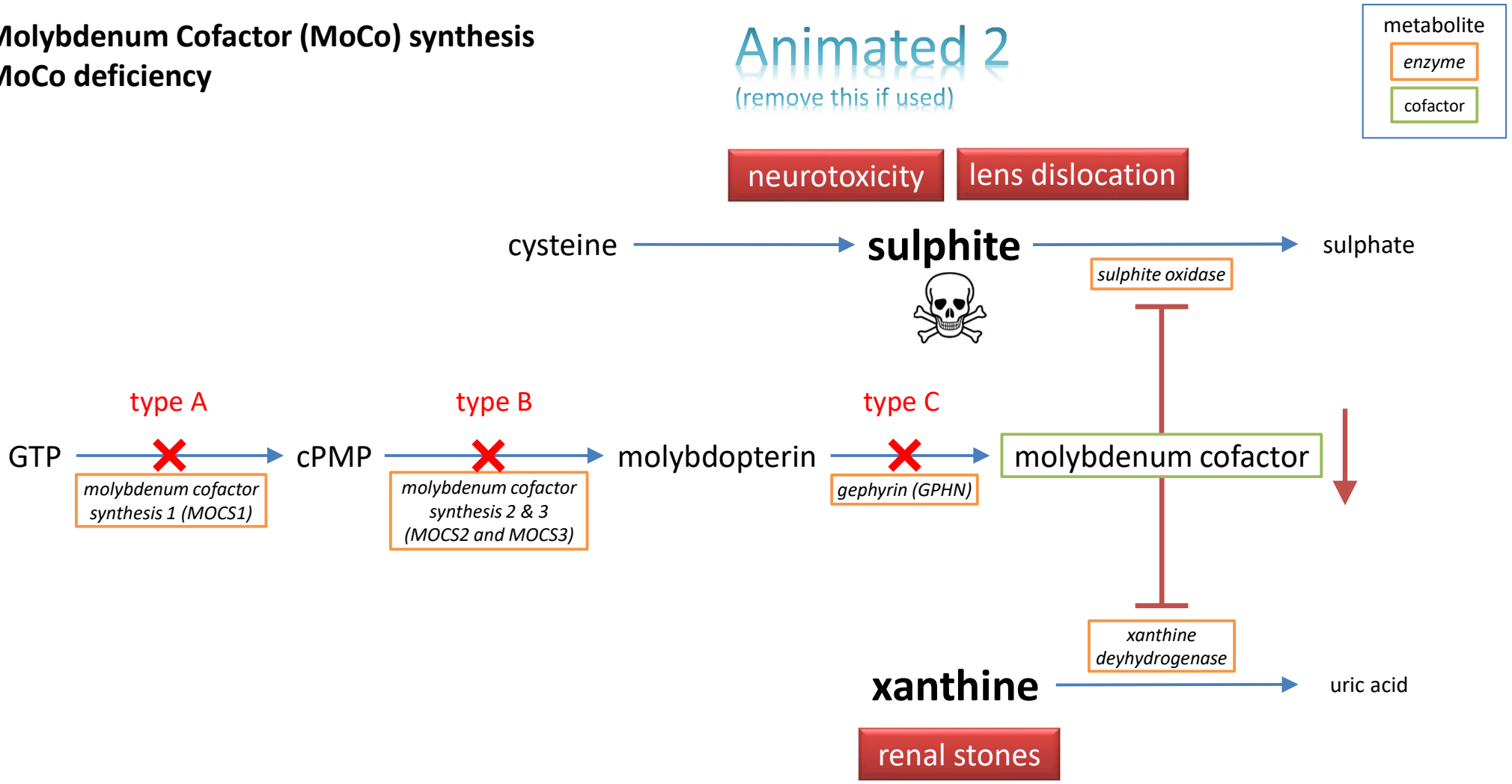
(remove this if used)





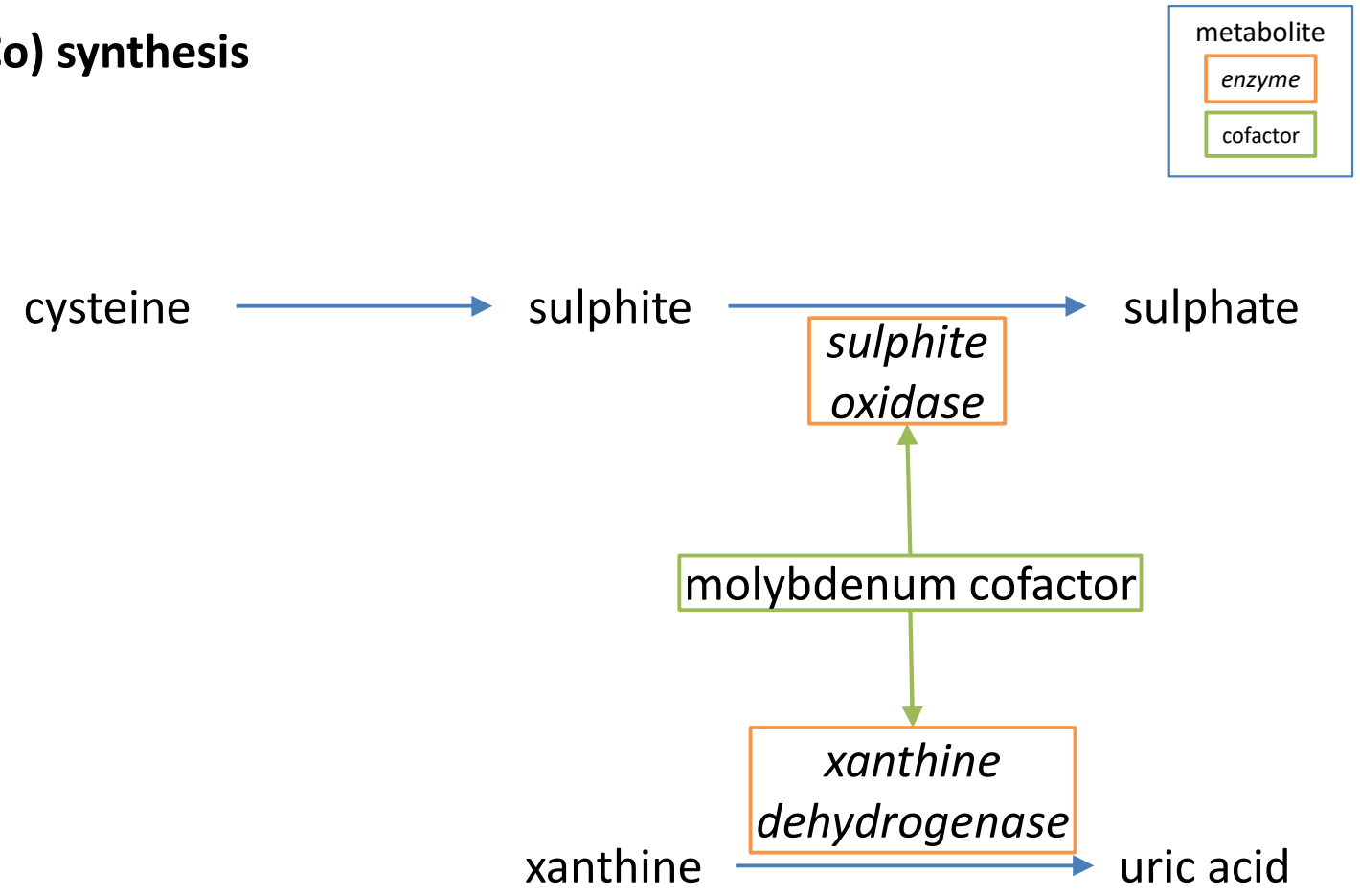
Molybdenum Cofactor (MoCo) synthesis
MoCo deficiency

Animated 2
(remove this if used)



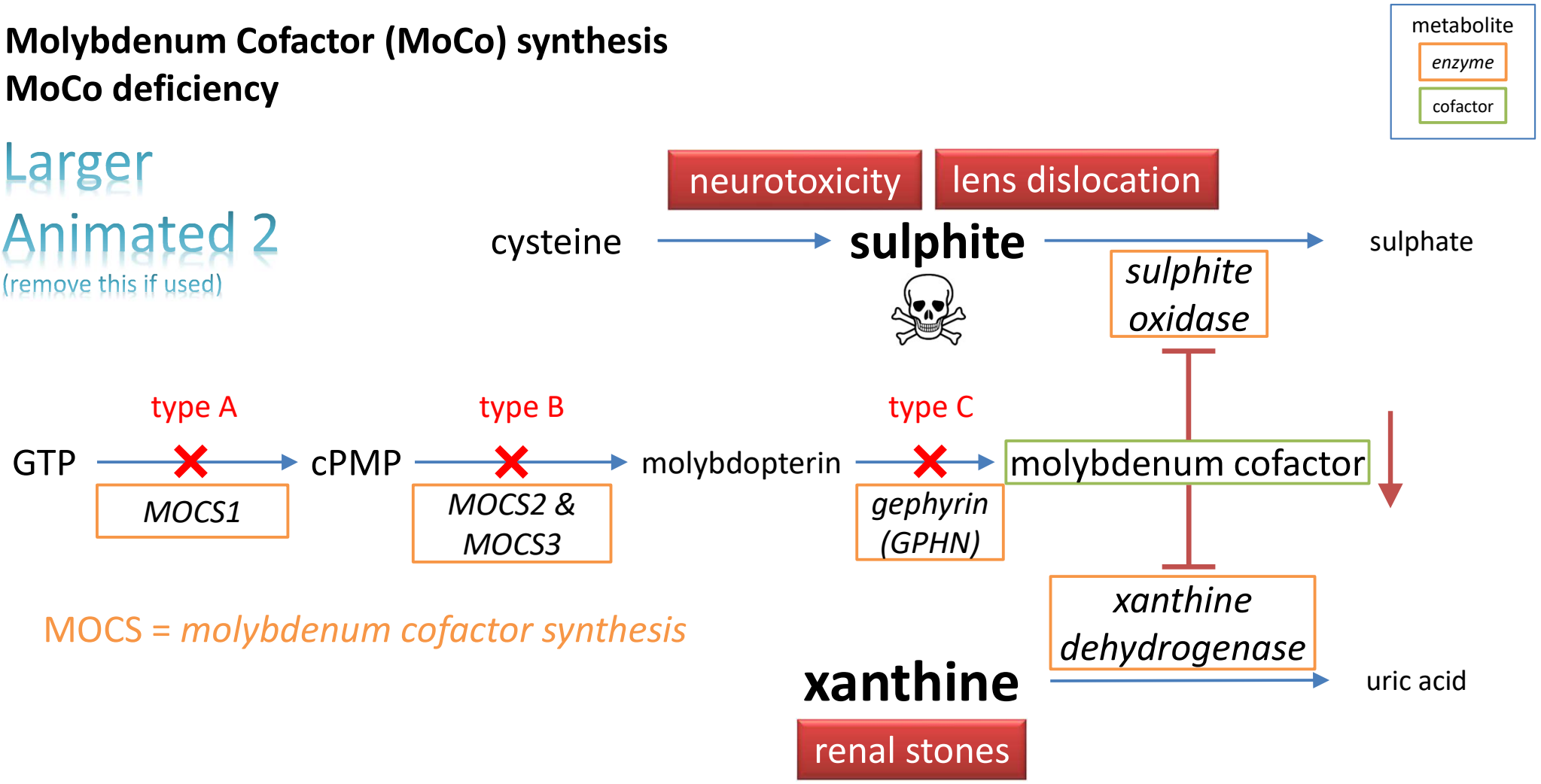
Molybdenum Cofactor (MoCo) synthesis

Larger
Animated 2
(remove this if used)



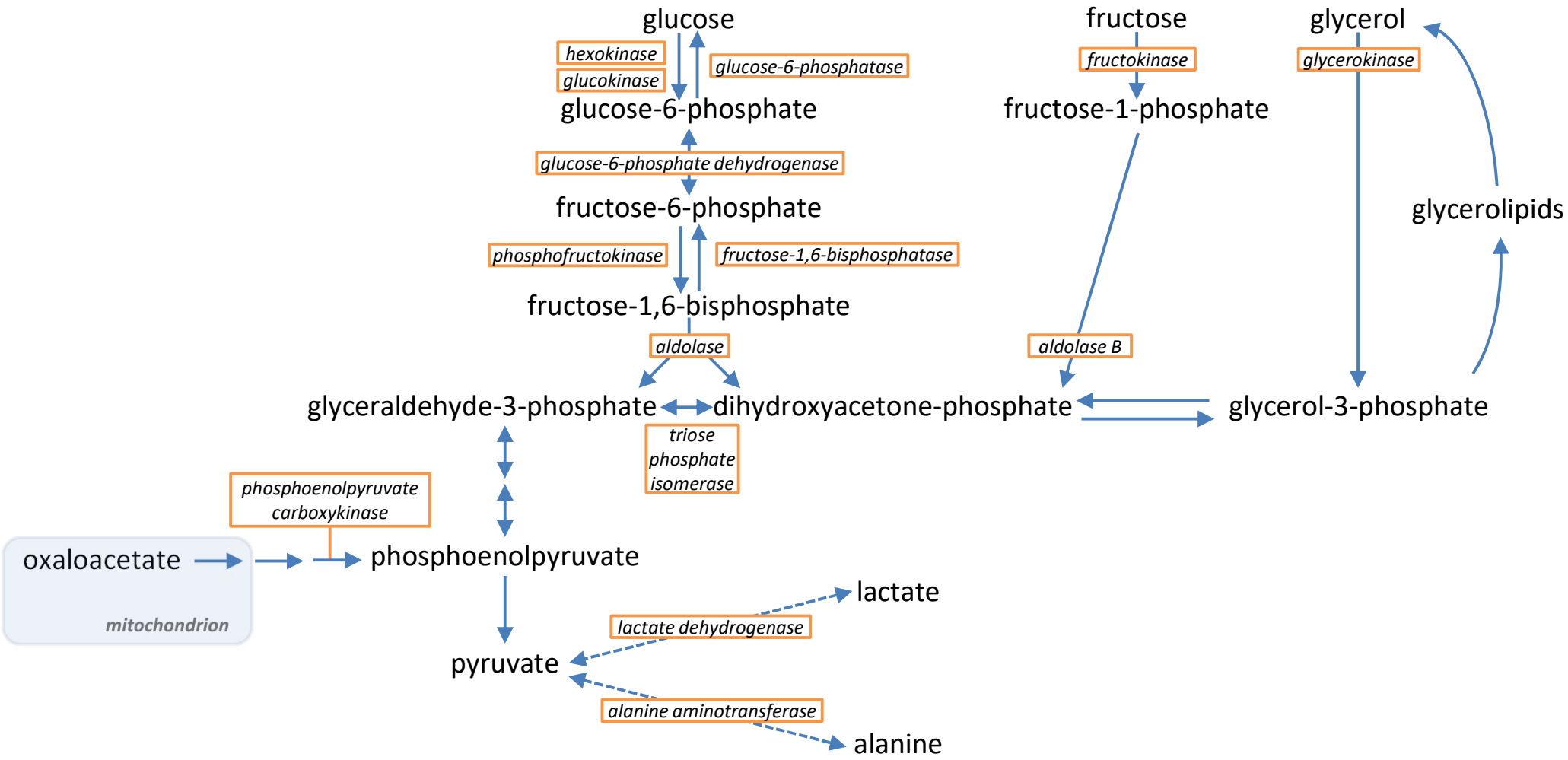
Molybdenum Cofactor (MoCo) synthesis
MoCo deficiency

Larger
Animated 2
(remove this if used)

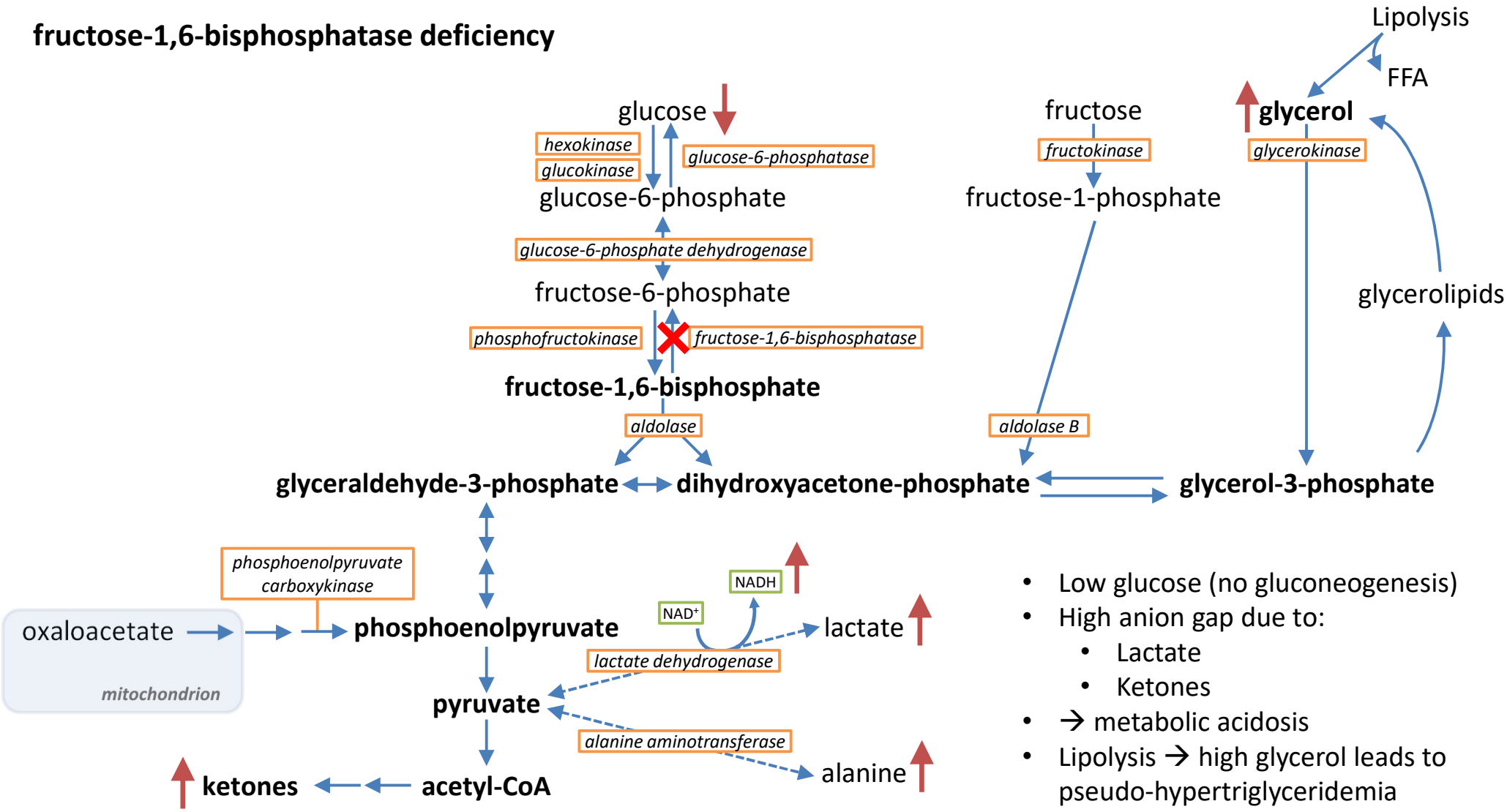


MOCS = *molybdenum cofactor synthesis*

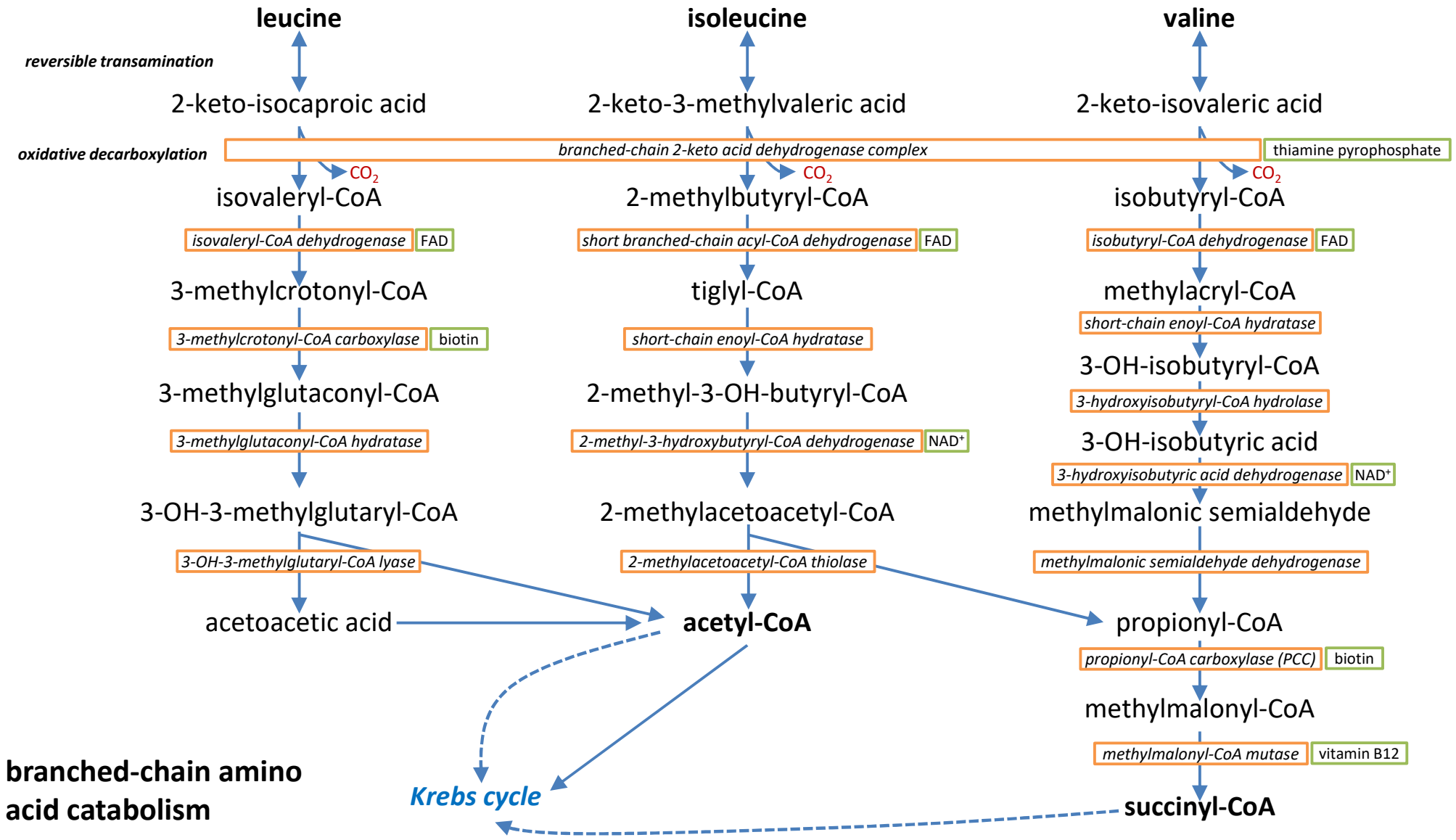
glucose/fructose/glycerol catabolism

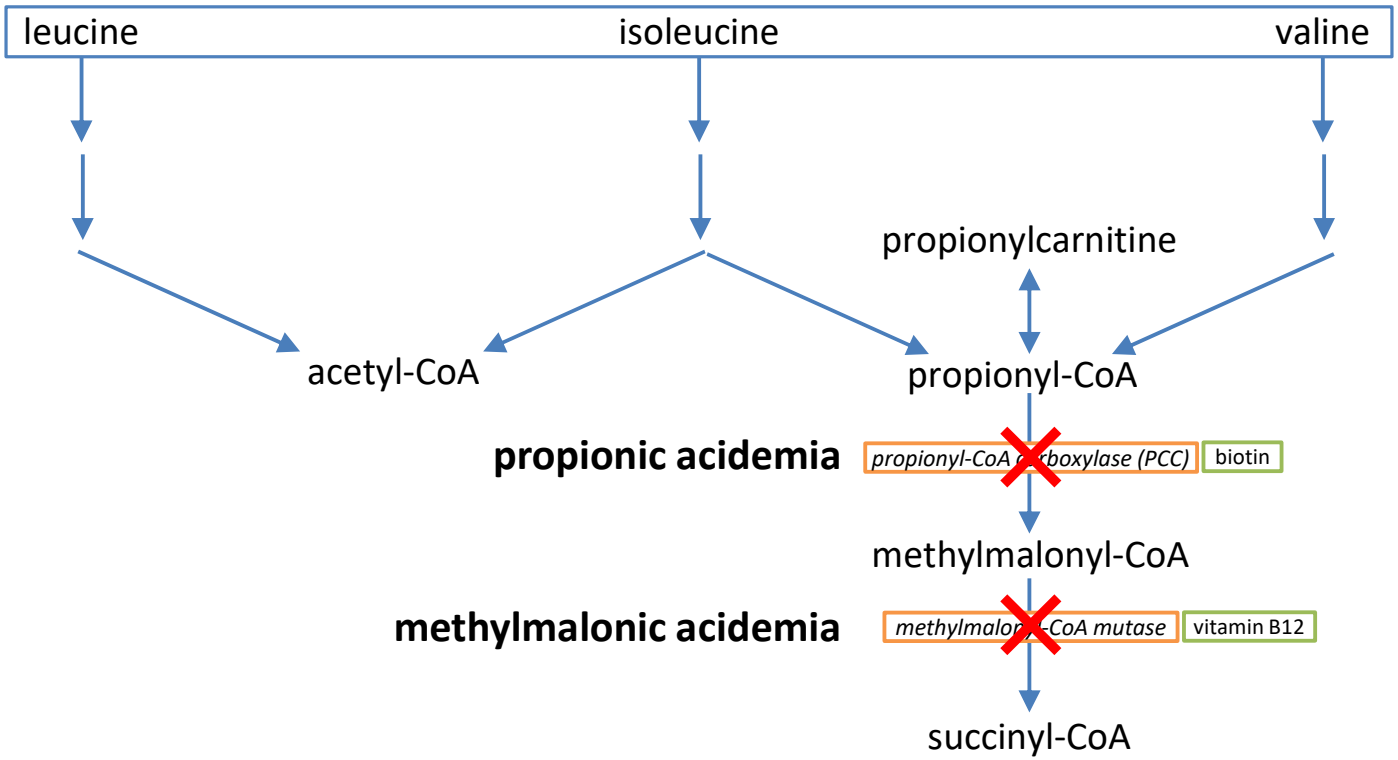


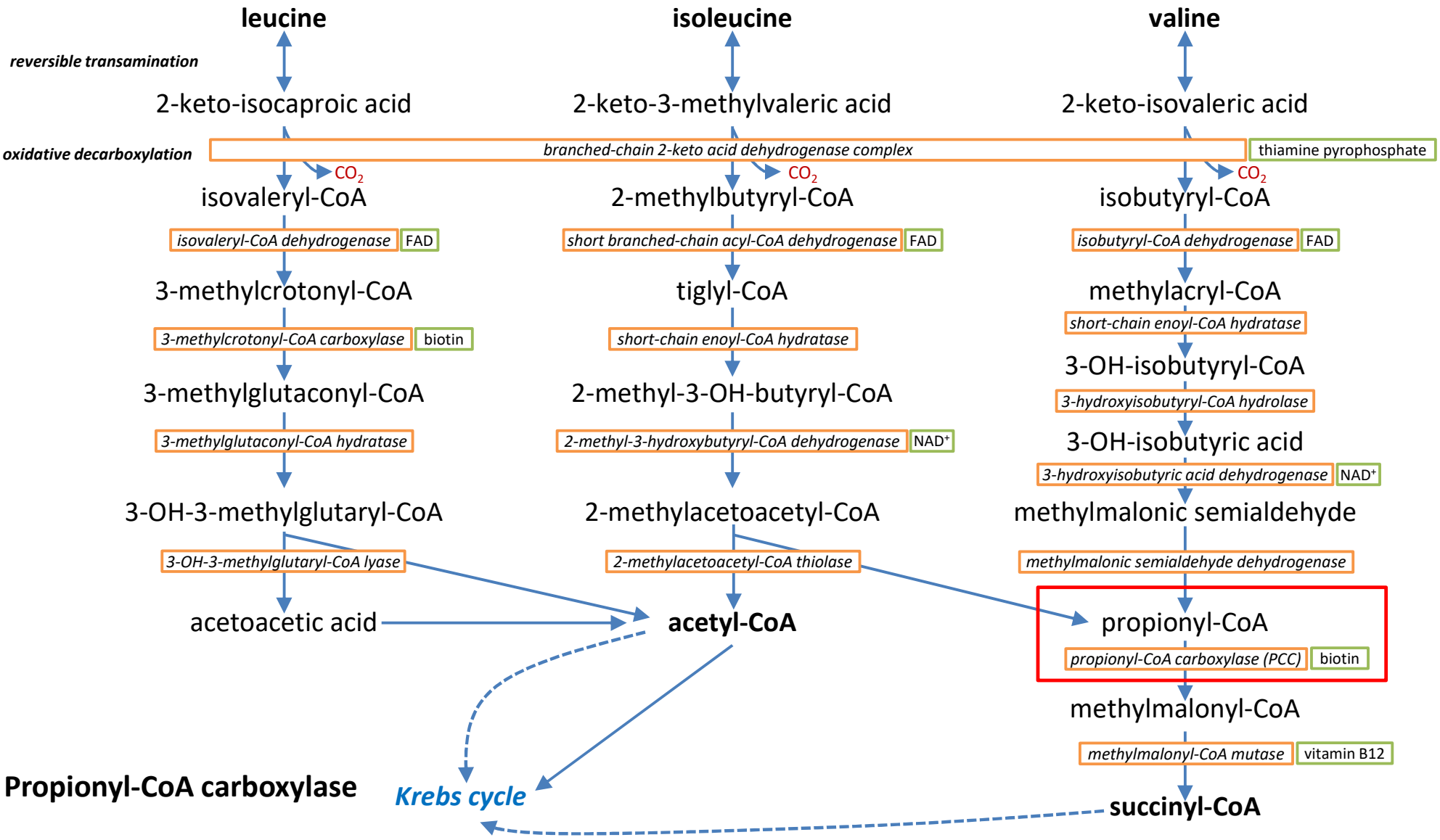
fructose-1,6-bisphosphatase deficiency

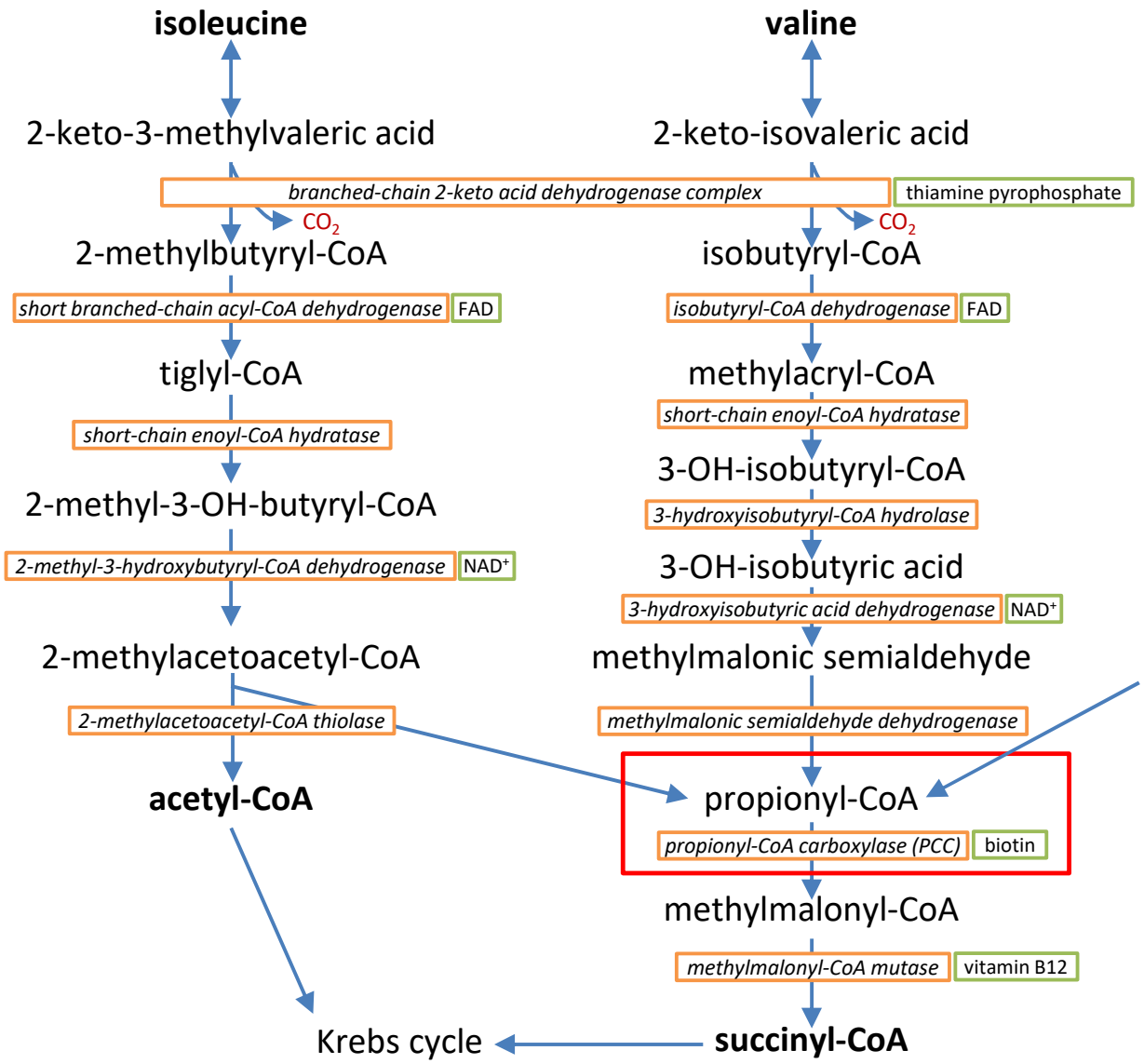


- Low glucose (no gluconeogenesis)
- High anion gap due to:
  - Lactate
  - Ketones
- → metabolic acidosis
- Lipolysis → high glycerol leads to pseudo-hypertriglyceridemia


leucine
isoleucine
valine
reversible transamination
2-keto-isocaproic acid
2-keto-3-methylvaleric acid
2-keto-isovaleric acid
oxidative decarboxylation
branched-chain 2-keto acid dehydrogenase complex
thiamine pyrophosphate
CO2
CO2
CO2
isovaleryl-CoA
2-methylbutyryl-CoA
isobutyryl-CoA
isovaleryl-CoA dehydrogenase
FAD
short branched-chain acyl-CoA dehydrogenase
FAD
isobutyryl-CoA dehydrogenase
FAD
3-methylcrotonyl-CoA
tiglyl-CoA
methylacryl-CoA
3-methylcrotonyl-CoA carboxylase
biotin
short-chain enoyl-CoA hydratase
short-chain enoyl-CoA hydratase
3-OH-isobutyryl-CoA
3-methylglutaconyl-CoA
2-methyl-3-OH-butyryl-CoA
3-hydroxyisobutyryl-CoA hydrolase
3-methylglutaconyl-CoA hydratase
2-methyl-3-hydroxybutyryl-CoA dehydrogenase
NAD+
3-OH-isobutyric acid
3-hydroxyisobutyric acid dehydrogenase
NAD+
3-OH-3-methylglutaryl-CoA
2-methylacetoacetyl-CoA
methylmalonic semialdehyde
3-OH-3-methylglutaryl-CoA lyase
2-methylacetoacetyl-CoA thiolase
methylmalonic semialdehyde dehydrogenase
acetoacetic acid
acetyl-CoA
propionyl-CoA
propionyl-CoA carboxylase (PCC)
biotin
methylmalonyl-CoA
methylmalonyl-CoA mutase
vitamin B12
succinyl-CoA
Krebs cycle
branched-chain amino acid catabolism


leucine
isoleucine
valine
propionylcarnitine
acetyl-CoA
propionyl-CoA
propionic acidemia
propionyl-CoA carboxylase (PCC)
biotin
methylmalonyl-CoA
methylmalonic acidemia
methylmalonyl-CoA mutase
vitamin B12
succinyl-CoA

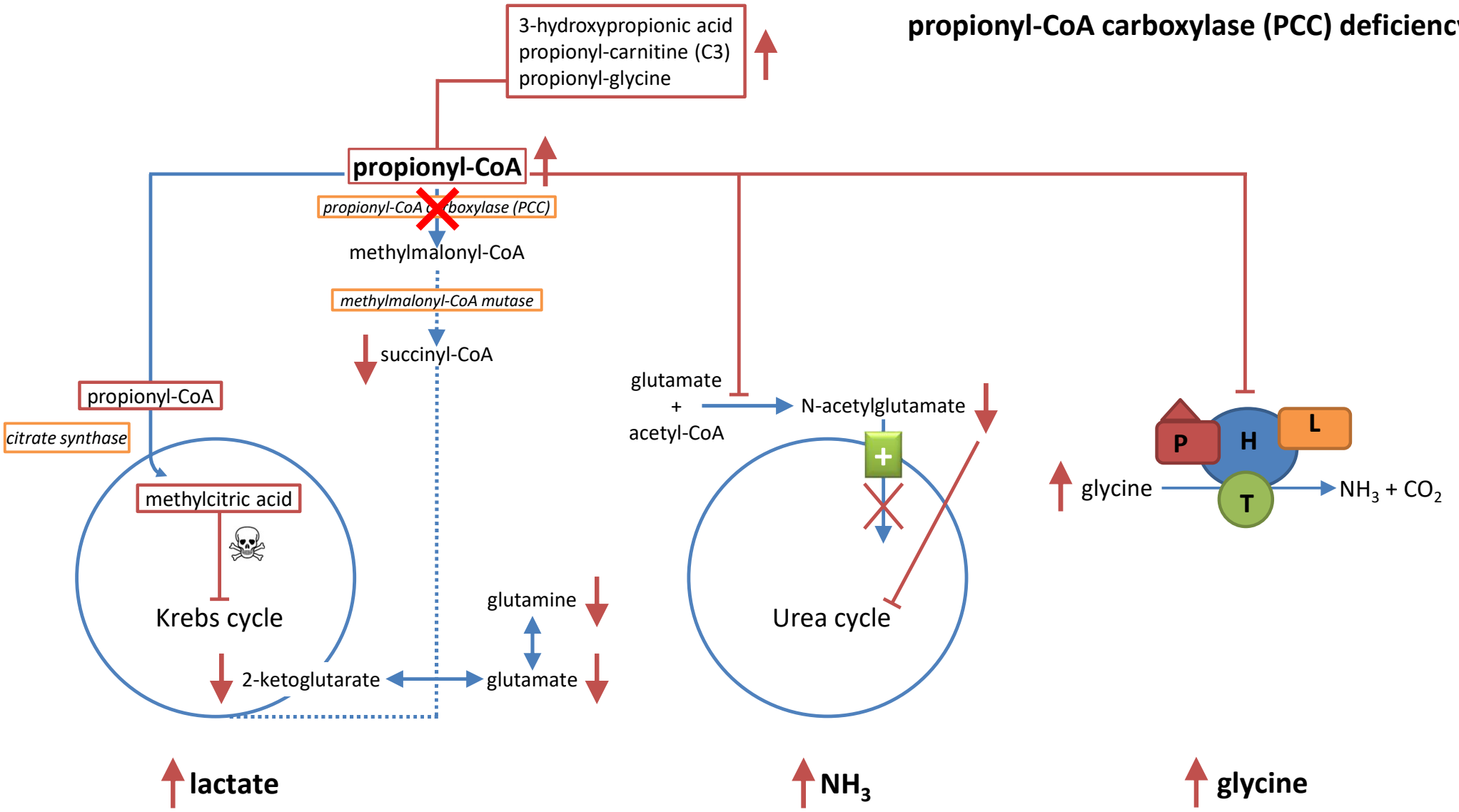

leucine
isoleucine
valine
reversible transamination
2-keto-isocaproic acid
2-keto-3-methylvaleric acid
2-keto-isovaleric acid
oxidative decarboxylation
branched-chain 2-keto acid dehydrogenase complex
thiamine pyrophosphate
CO2
CO2
CO2
isovaleryl-CoA
2-methylbutyryl-CoA
isobutyryl-CoA
isovaleryl-CoA dehydrogenase
FAD
short branched-chain acyl-CoA dehydrogenase
FAD
isobutyryl-CoA dehydrogenase
FAD
3-methylcrotonyl-CoA
tiglyl-CoA
methylacryl-CoA
3-methylcrotonyl-CoA carboxylase
biotin
short-chain enoyl-CoA hydratase
short-chain enoyl-CoA hydratase
3-OH-isobutyryl-CoA
3-methylglutaconyl-CoA
2-methyl-3-OH-butyryl-CoA
3-hydroxyisobutyryl-CoA hydrolase
3-methylglutaconyl-CoA hydratase
2-methyl-3-hydroxybutyryl-CoA dehydrogenase
NAD+
3-OH-isobutyric acid
3-hydroxyisobutyric acid dehydrogenase
NAD+
3-OH-3-methylglutaryl-CoA
2-methylacetoacetyl-CoA
methylmalonic semialdehyde
3-OH-3-methylglutaryl-CoA lyase
2-methylacetoacetyl-CoA thiolase
methylmalonic semialdehyde dehydrogenase
acetoacetic acid
acetyl-CoA
propionyl-CoA
propionyl-CoA carboxylase (PCC)
biotin
methylmalonyl-CoA
methylmalonyl-CoA mutase
vitamin B12
succinyl-CoA
Propionyl-CoA carboxylase
Krebs cycle

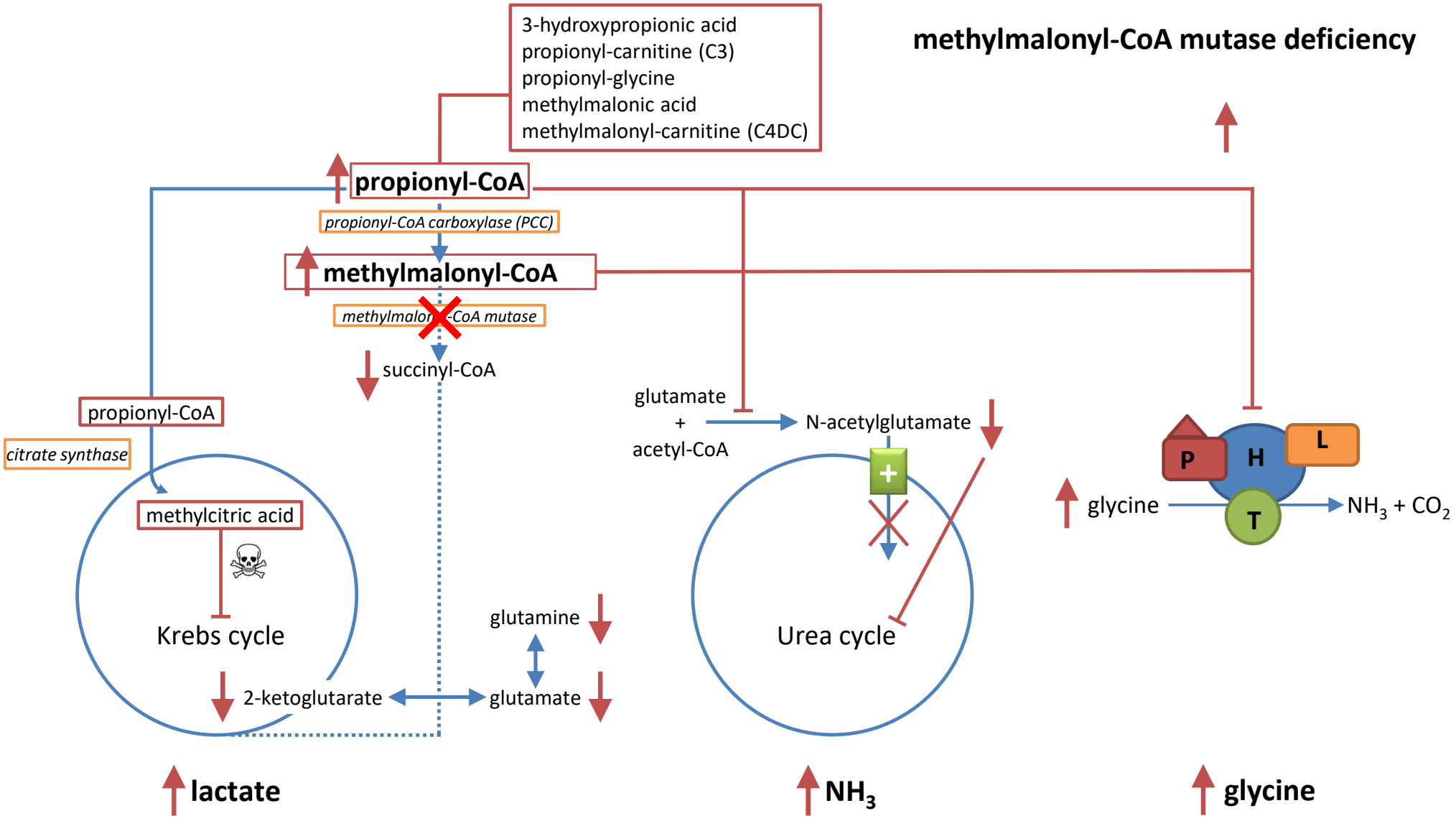


propionyl-CoA carboxylase (PCC)

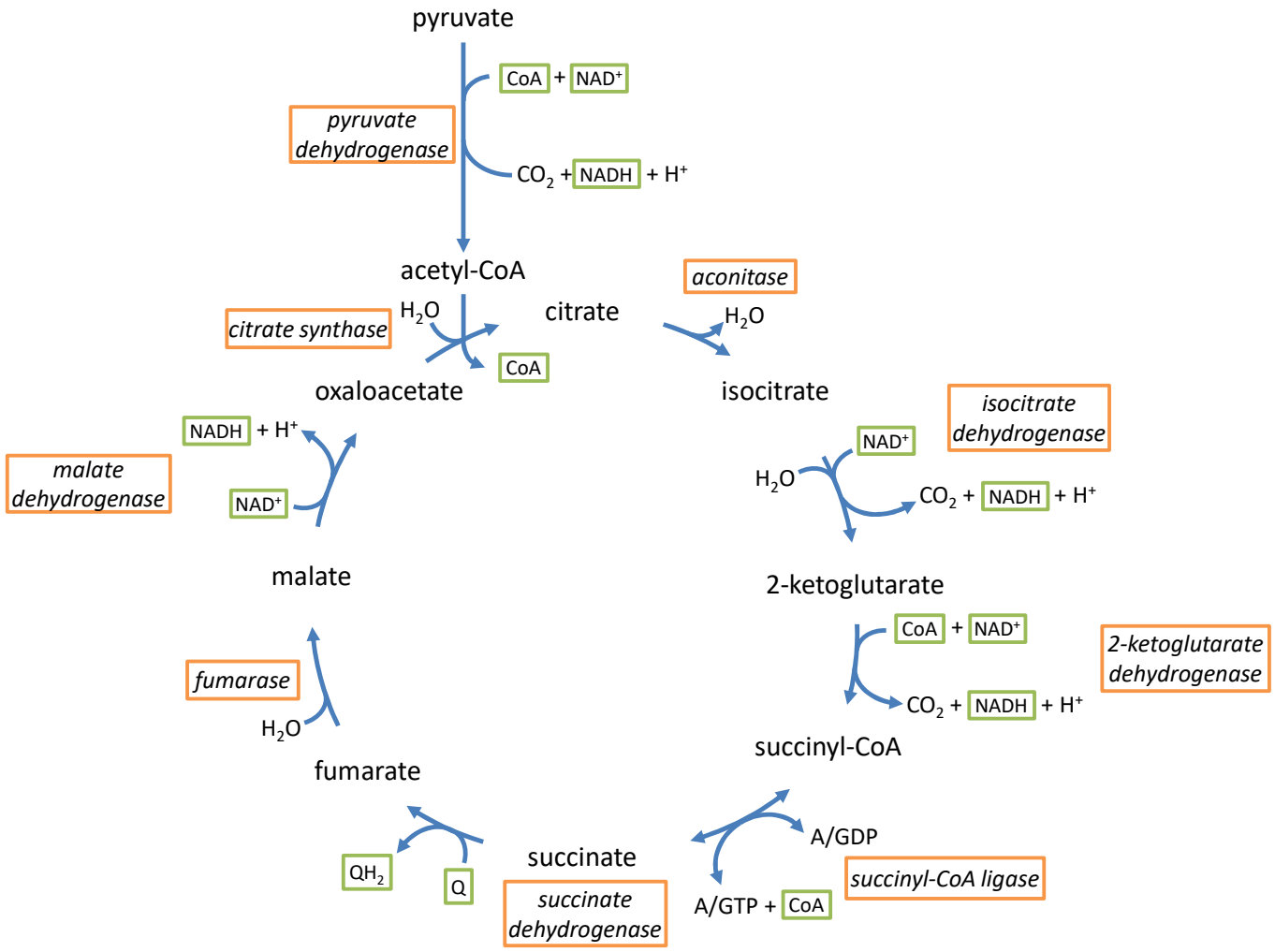
(other) sources of propionic acid/propionyl-CoA

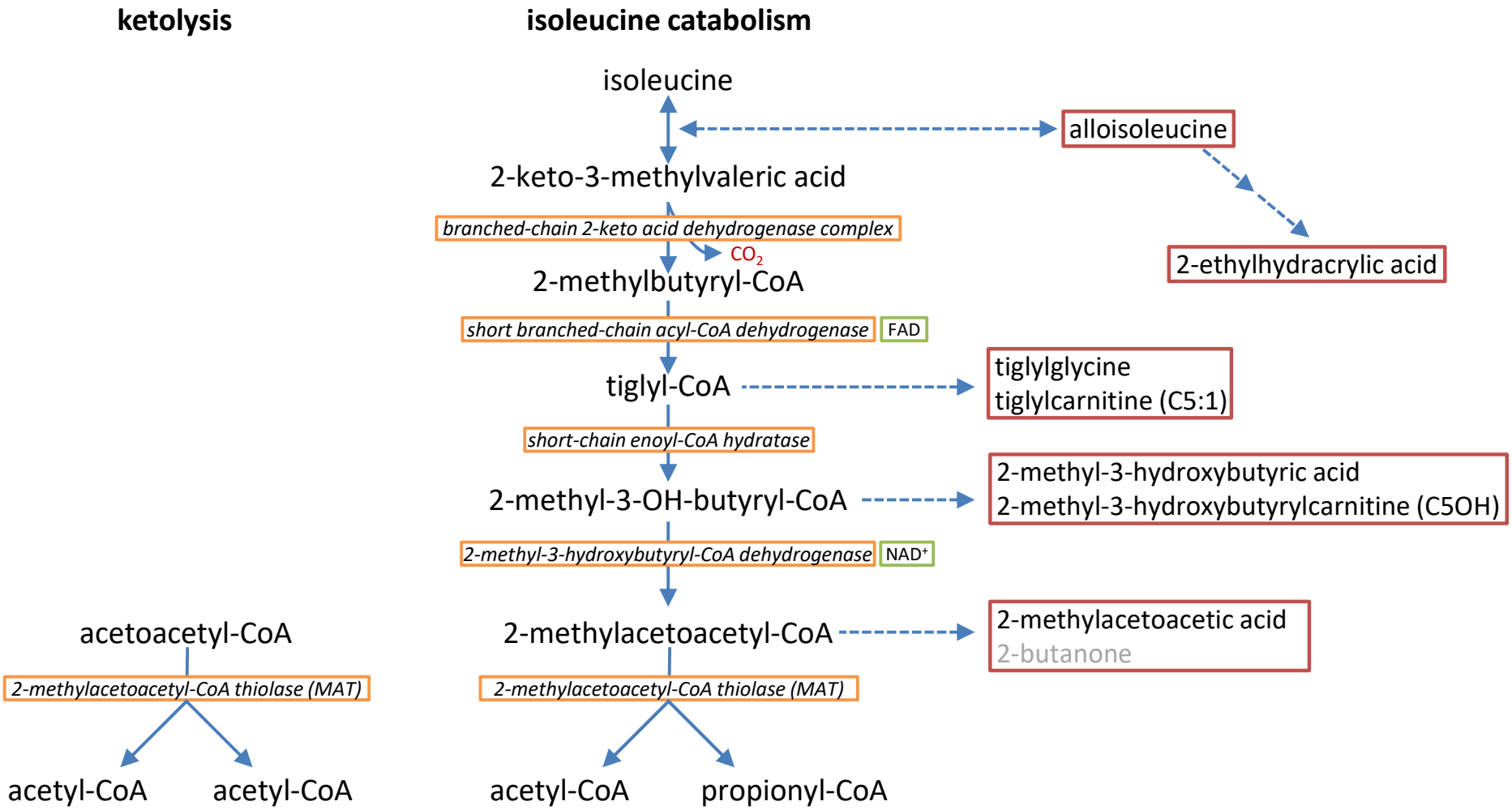
- **V**aline
- **O**dd-chain and branched-chain fatty acids
- **M**ethionine
- **I**soleucine
- **T**hreonine
- bacterial metabolism in the gut


propionyl-CoA carboxylase (PCC) deficiency
3-hydroxypropionic acid
propionyl-carnitine (C3)
propionyl-glycine
propionyl-CoA
propionyl-CoA carboxylase (PCC)
methylmalonyl-CoA
methylmalonyl-CoA mutase
succinyl-CoA
propionyl-CoA
citrate synthase
methylcitric acid
Krebs cycle
2-ketoglutarate
glutamine
glutamate
glutamate
+
acetyl-CoA
N-acetylglutamate
Urea cycle
P
H
L
T
glycine
NH3 + CO2
lactate
NH3
glycine


methylmalonyl-CoA mutase deficiency
3-hydroxypropionic acid
propionyl-carnitine (C3)
propionyl-glycine
methylmalonic acid
methylmalonyl-carnitine (C4DC)
propionyl-CoA
propionyl-CoA carboxylase (PCC)
methylmalonyl-CoA
methylmalonyl-CoA mutase
succinyl-CoA
propionyl-CoA
citrate synthase
methylcitric acid
Krebs cycle
2-ketoglutarate
glutamine
glutamate
glutamate
+
acetyl-CoA
N-acetylglutamate
Urea cycle
P
H
L
T
glycine
NH3 + CO2
lactate
NH3
glycine

the citric acid cycle

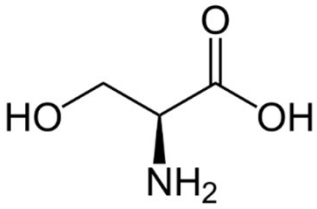


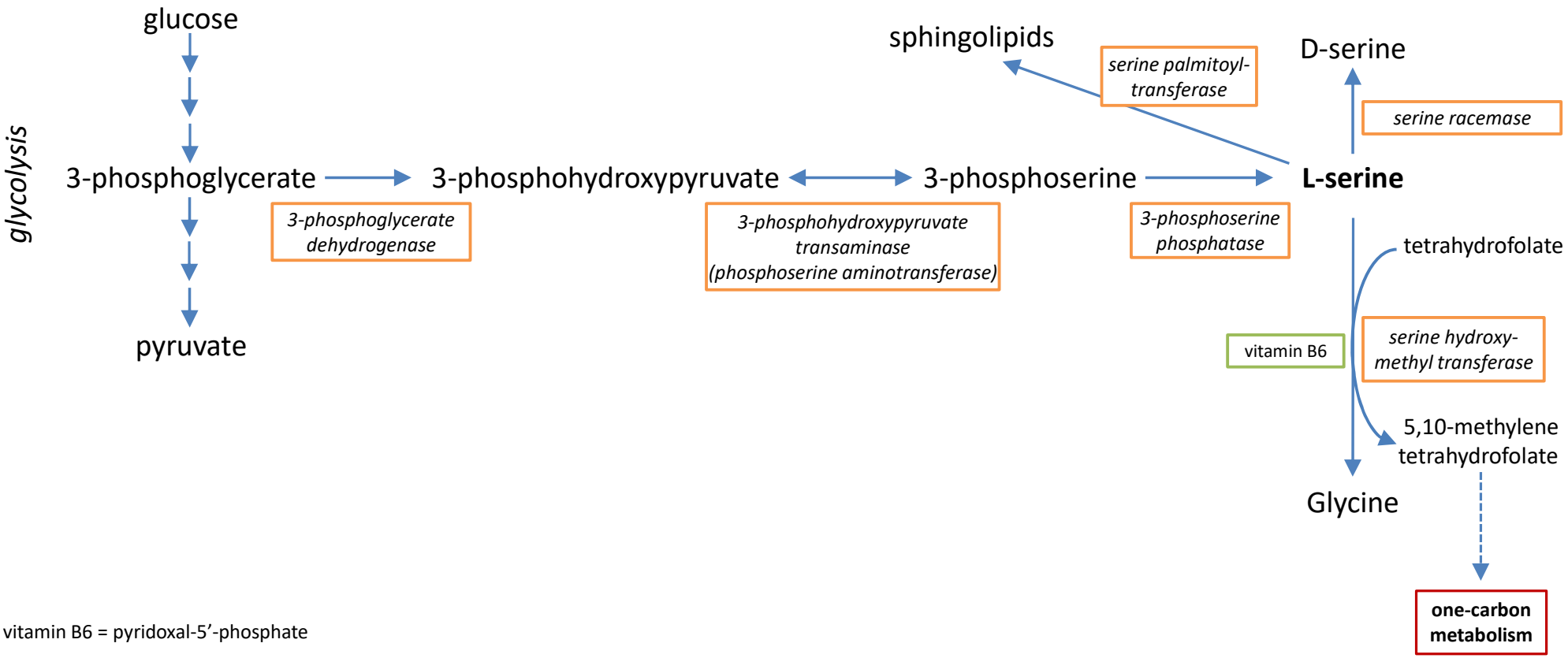


2-methylacetoacetyl-CoA thiolase (MAT) deficiency

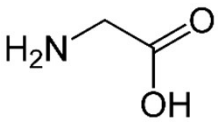
= β-ketothiolase deficiency

serine biosynthesis

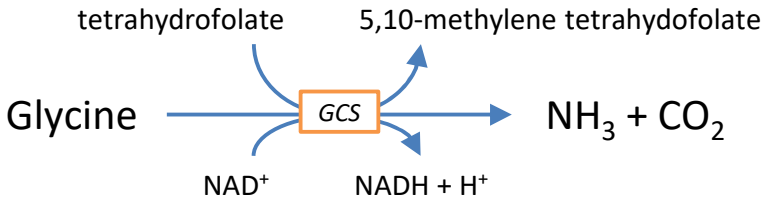


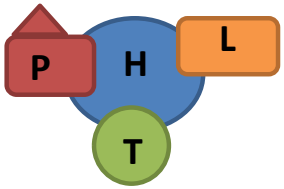


vitamin B6 = pyridoxal-5'-phosphate



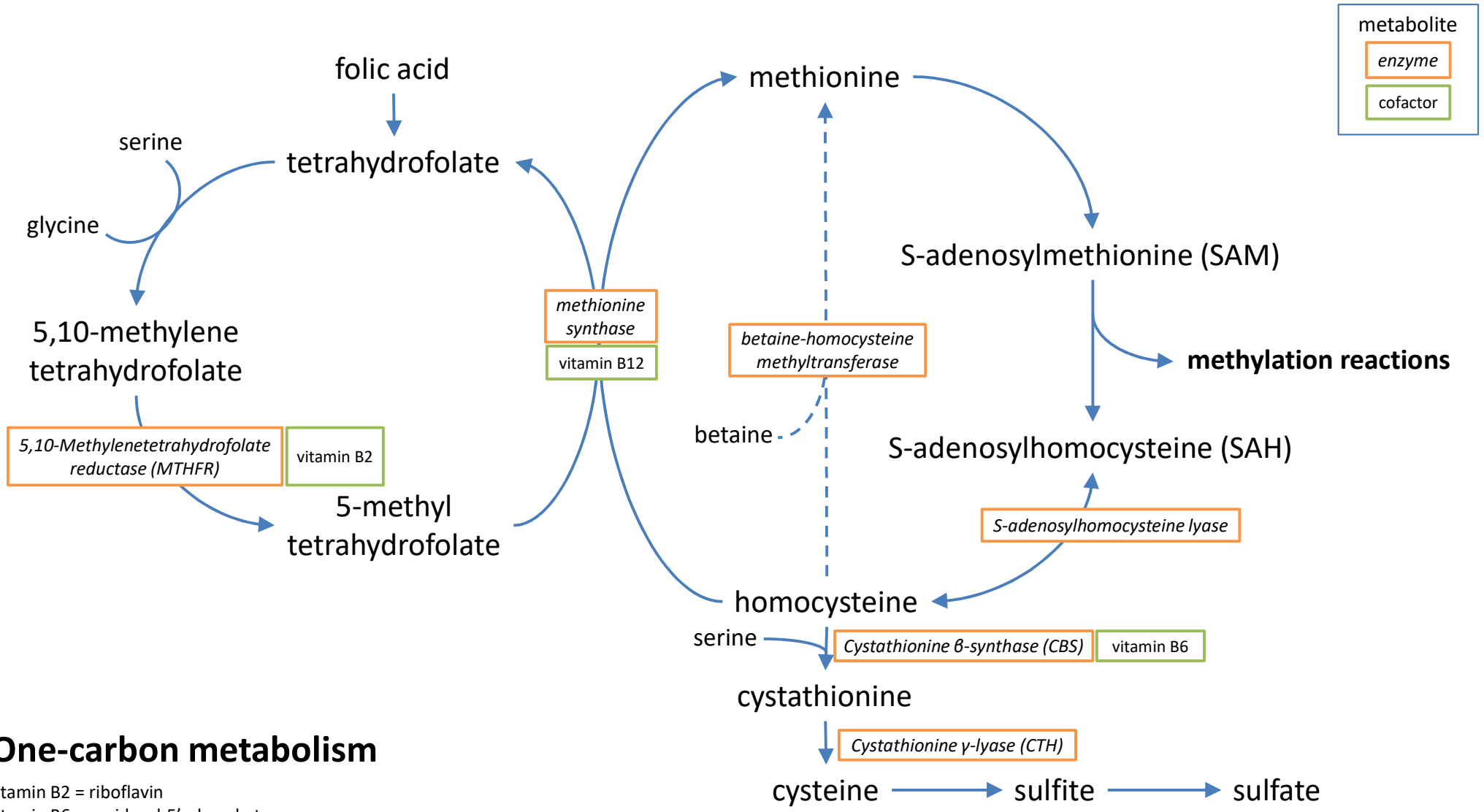
- Synthetic role in:
  - Proteinogenic
  - Creatine
  - Haemoglobin
  - Serine
  - Purines
  - Glycine conjugates





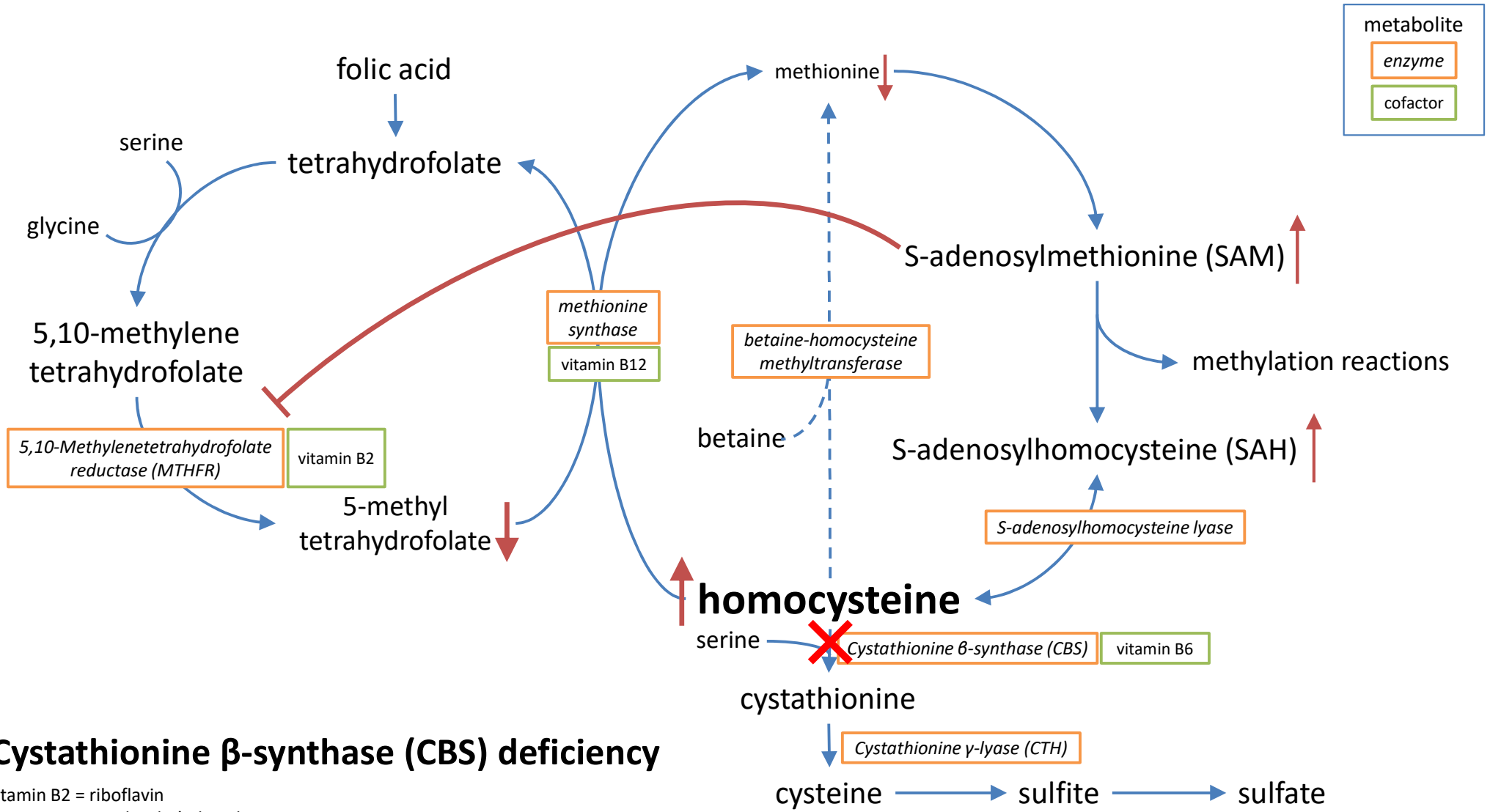
glycine catabolism

- Glycine cleavage system (GCS)
  - **P-protein (*GLDC*)**
    - **P**yridoxal-5'-phosphate-dependent glycine decarboxylase
  - **H-protein (*GCSH*)**
    - Lipoic-acid-containing **H**ydrogen-carrier protein
  - **T-protein (*AMT*)**
    - **T**etrahydrofolate-dependent protein
  - **L-protein (*DLD*)**
    - **L**ipoamide dehydrogenase



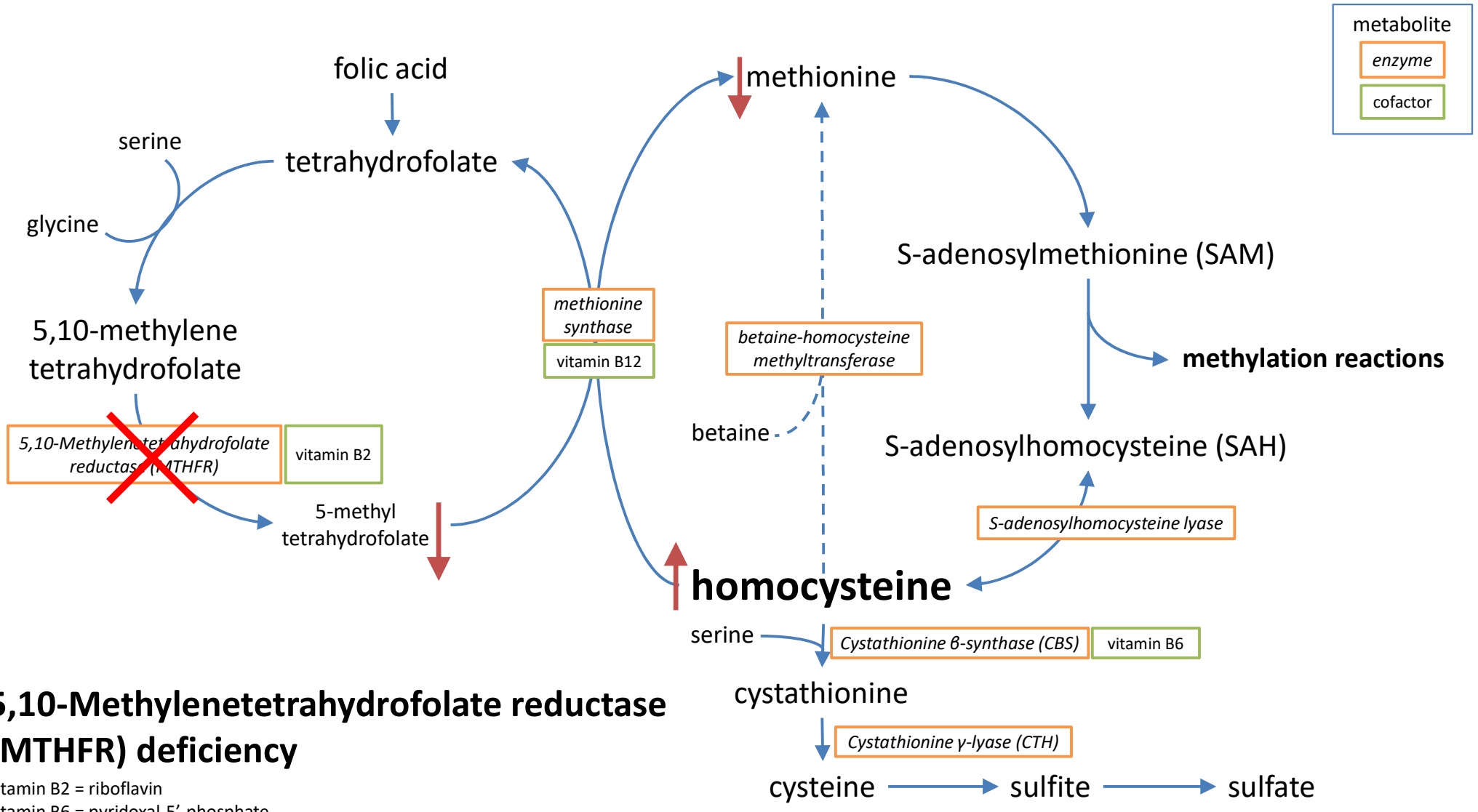
One-carbon metabolism

vitamin B2 = riboflavin
vitamin B6 = pyridoxal-5'-phosphate
vitamin B12 in this cycle = methylcobalamin



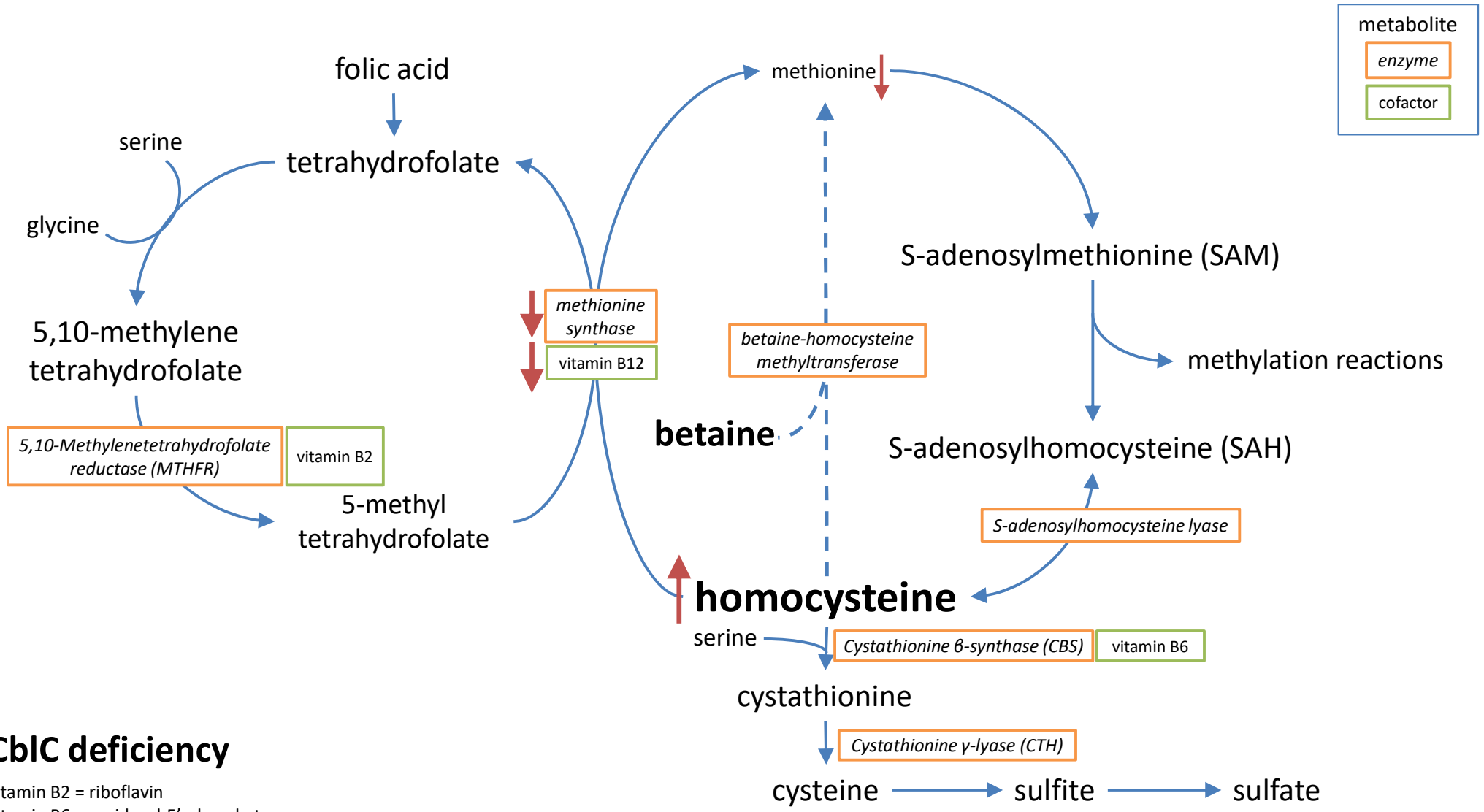
Cystathionine β-synthase (CBS) deficiency

vitamin B2 = riboflavin
vitamin B6 = pyridoxal-5'-phosphate
vitamin B12 in this cycle = methylcobalamin



5,10-Methylenetetrahydrofolate reductase (MTHFR) deficiency

vitamin B2 = riboflavin
vitamin B6 = pyridoxal-5'-phosphate
vitamin B12 in this cycle = methylcobalamin

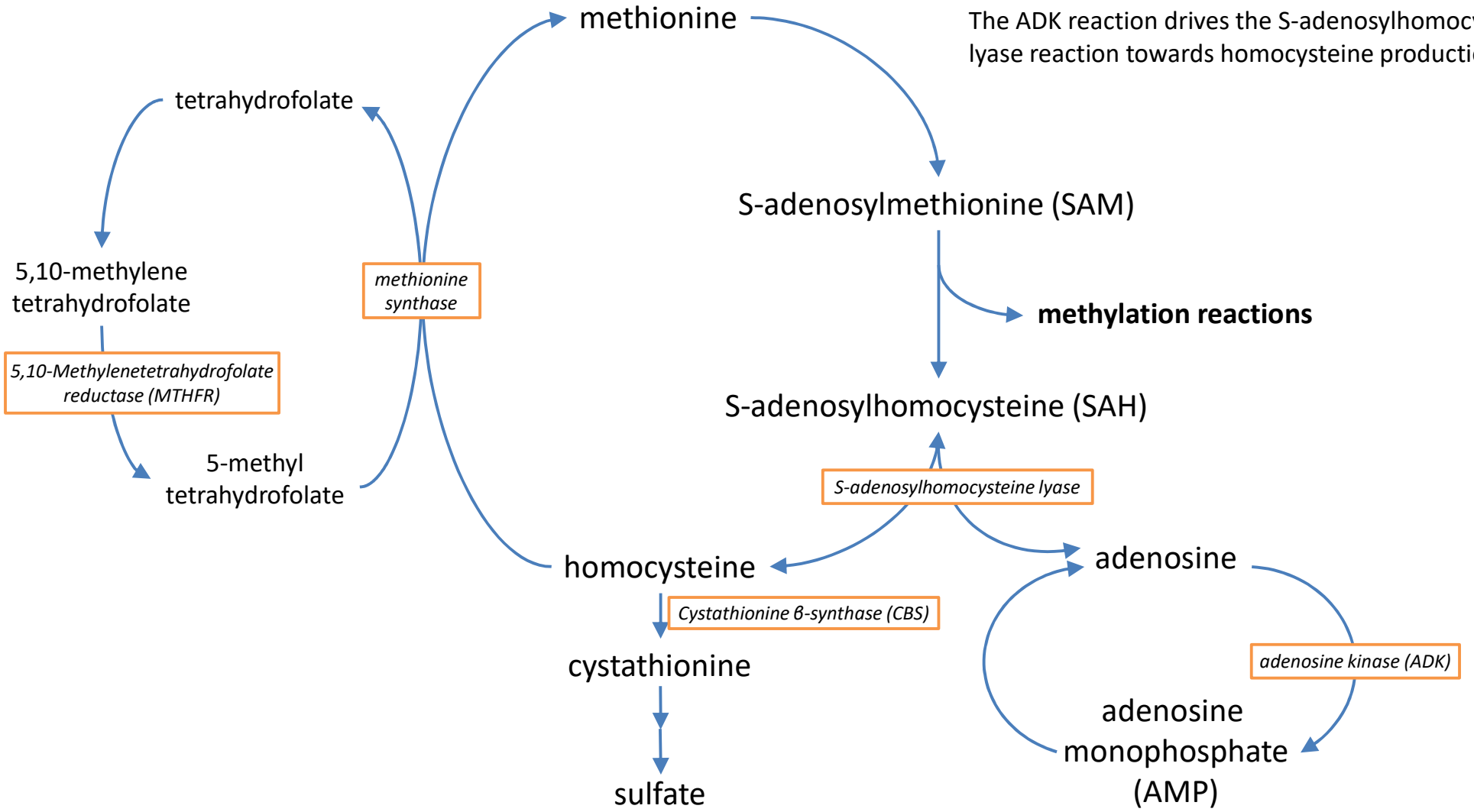


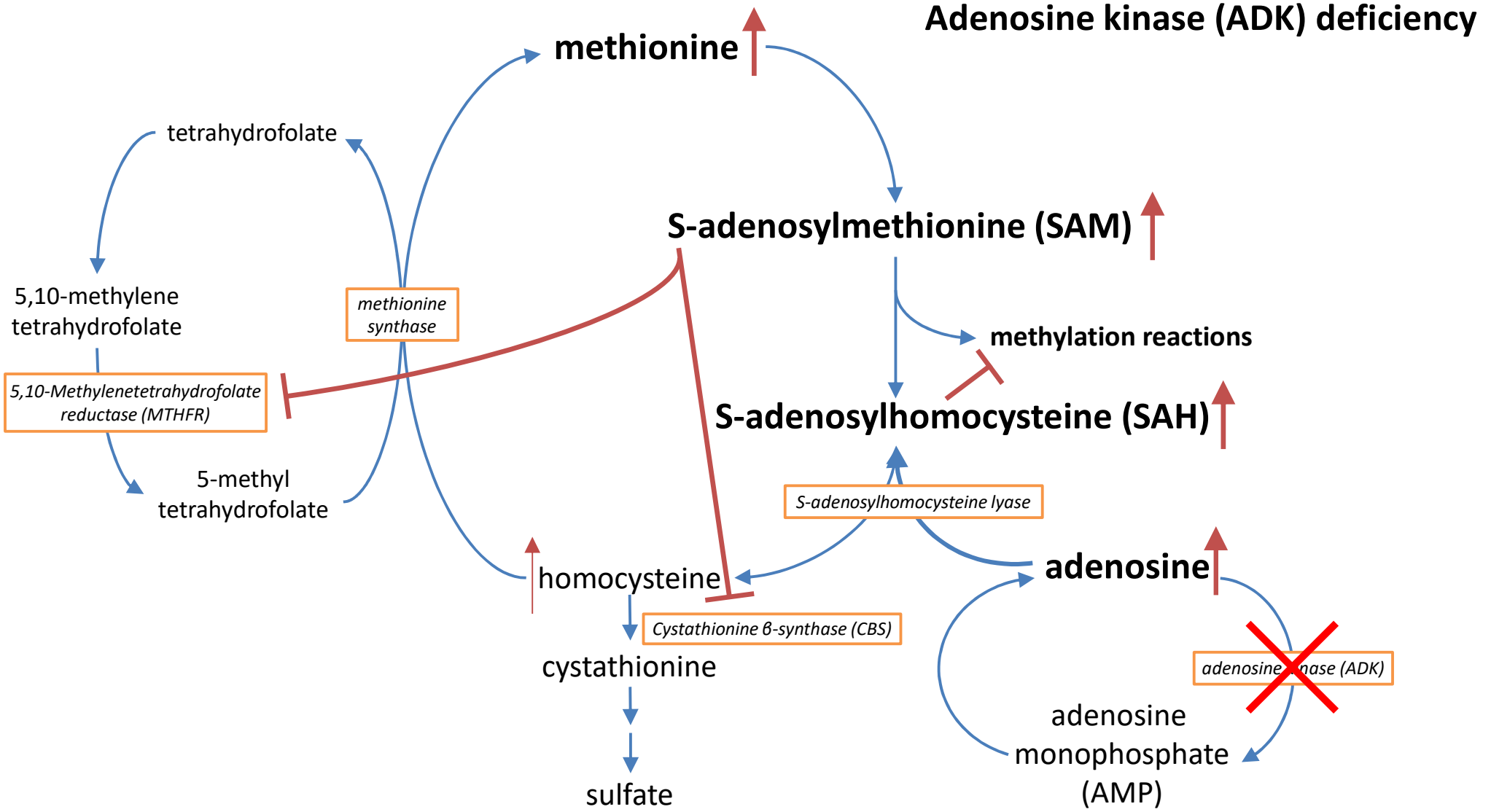
CblC deficiency

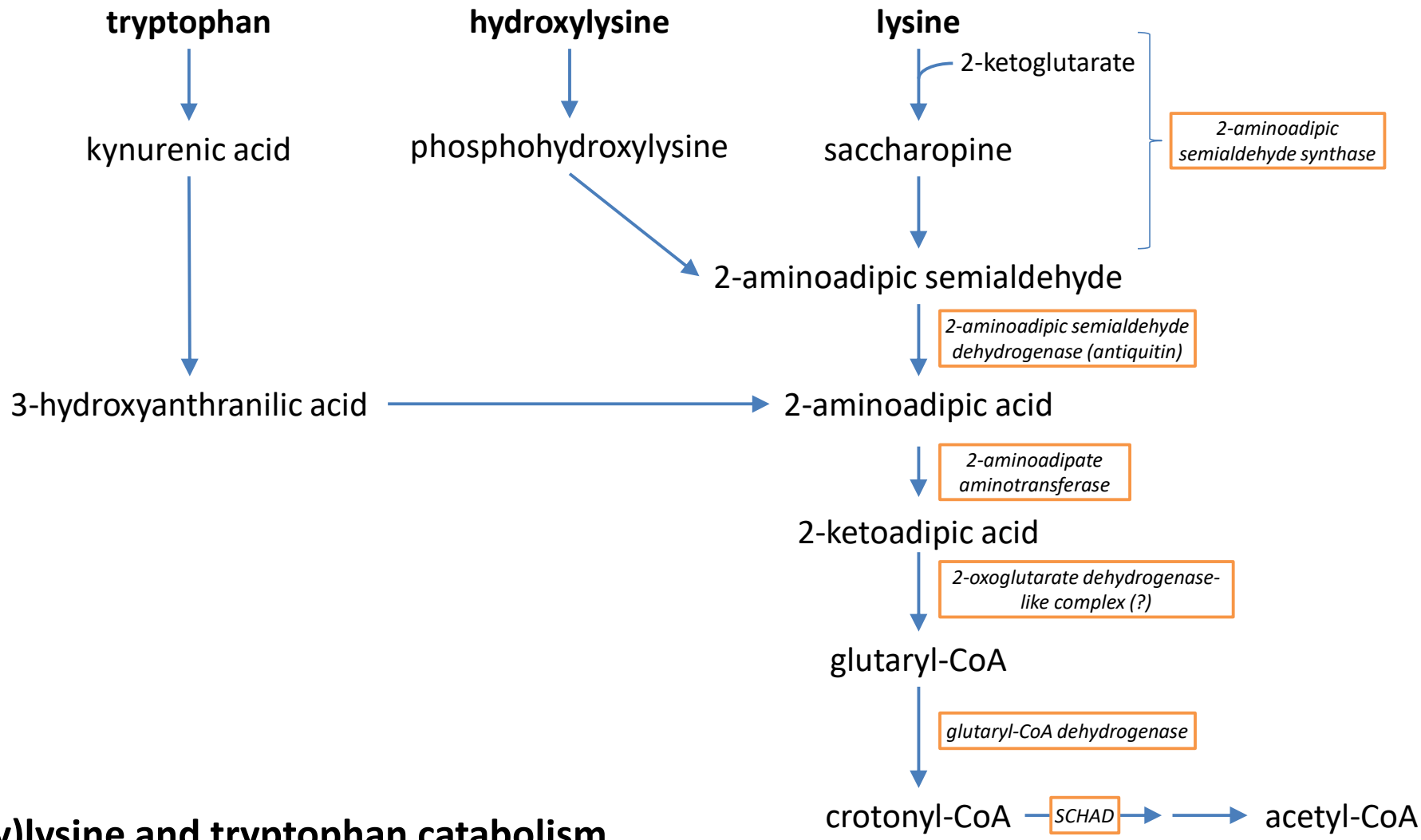
vitamin B2 = riboflavin
vitamin B6 = pyridoxal-5'-phosphate
vitamin B12 in this cycle = methylcobalamin

Adenosine kinase (ADK)

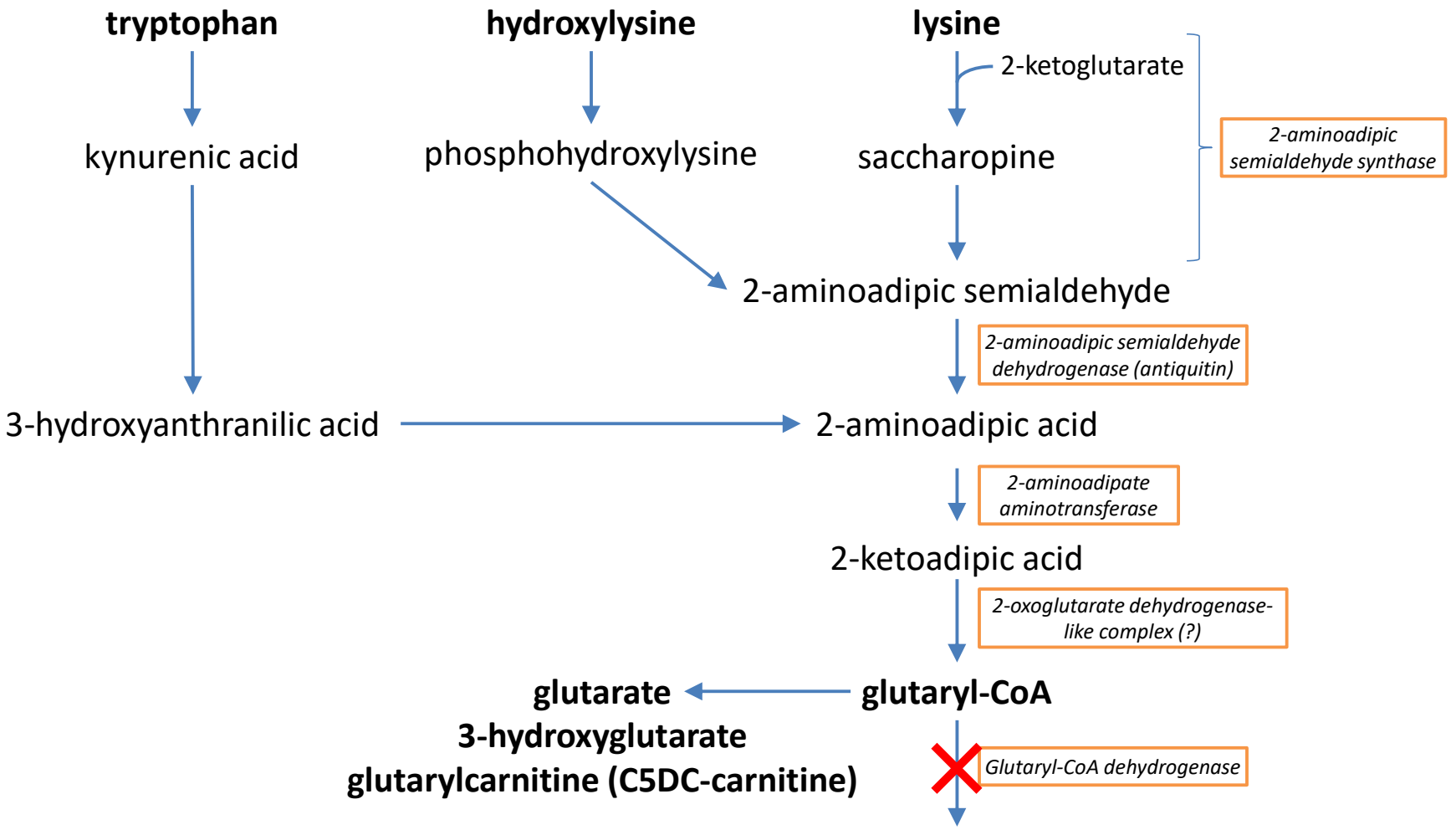
The ADK reaction drives the S-adenosylhomocysteine lyase reaction towards homocysteine production



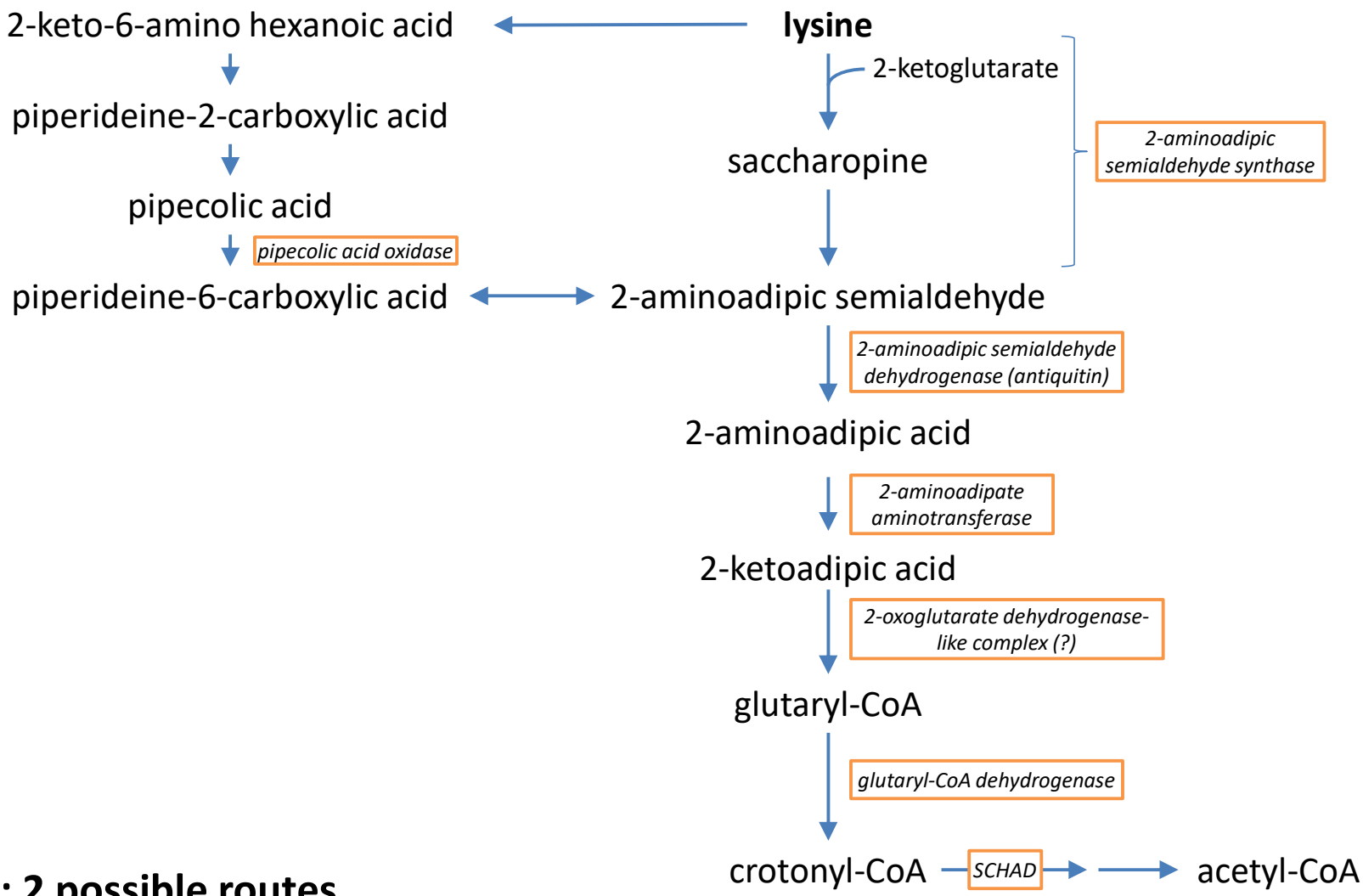

Adenosine kinase (ADK) deficiency
methionine
tetrahydrofolate
S-adenosylmethionine (SAM)
5,10-methylene tetrahydrofolate
methionine synthase
methylation reactions
5,10-Methylenetetrahydrofolate reductase (MTHFR)
S-adenosylhomocysteine (SAH)
5-methyl tetrahydrofolate
S-adenosylhomocysteine lyase
homocysteine
adenosine
Cystathionine β-synthase (CBS)
cystathionine
adenosine kinase (ADK)
adenosine monophosphate (AMP)
sulfate



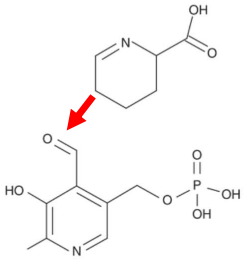
(hydroxy)lysine and tryptophan catabolism

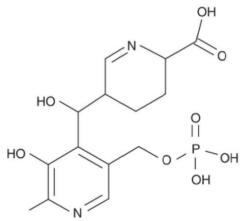


glutaryl-CoA dehydrogenase deficiency (GDH)



lysine catabolism: 2 possible routes





2-aminoadipic semialdehyde dehydrogenase (antiquitin) deficiency

2-keto-6-amino hexanoic acid

piperideine-2-carboxylic acid

pipecolic acid

pipecolic acid oxidase

piperideine-6-carboxylic acid (P6C)

+

vitamin B6 = pyridoxal-5'-phosphate (PLP)

Inactivated vitamin B6

lysine

2-ketoglutarate

saccharopine

2-aminoadipic semialdehyde synthase

2-aminoadipic semialdehyde

2-aminoadipic semialdehyde dehydrogenase (antiquitin)

2-aminoadipic acid

2-aminoadipate aminotransferase

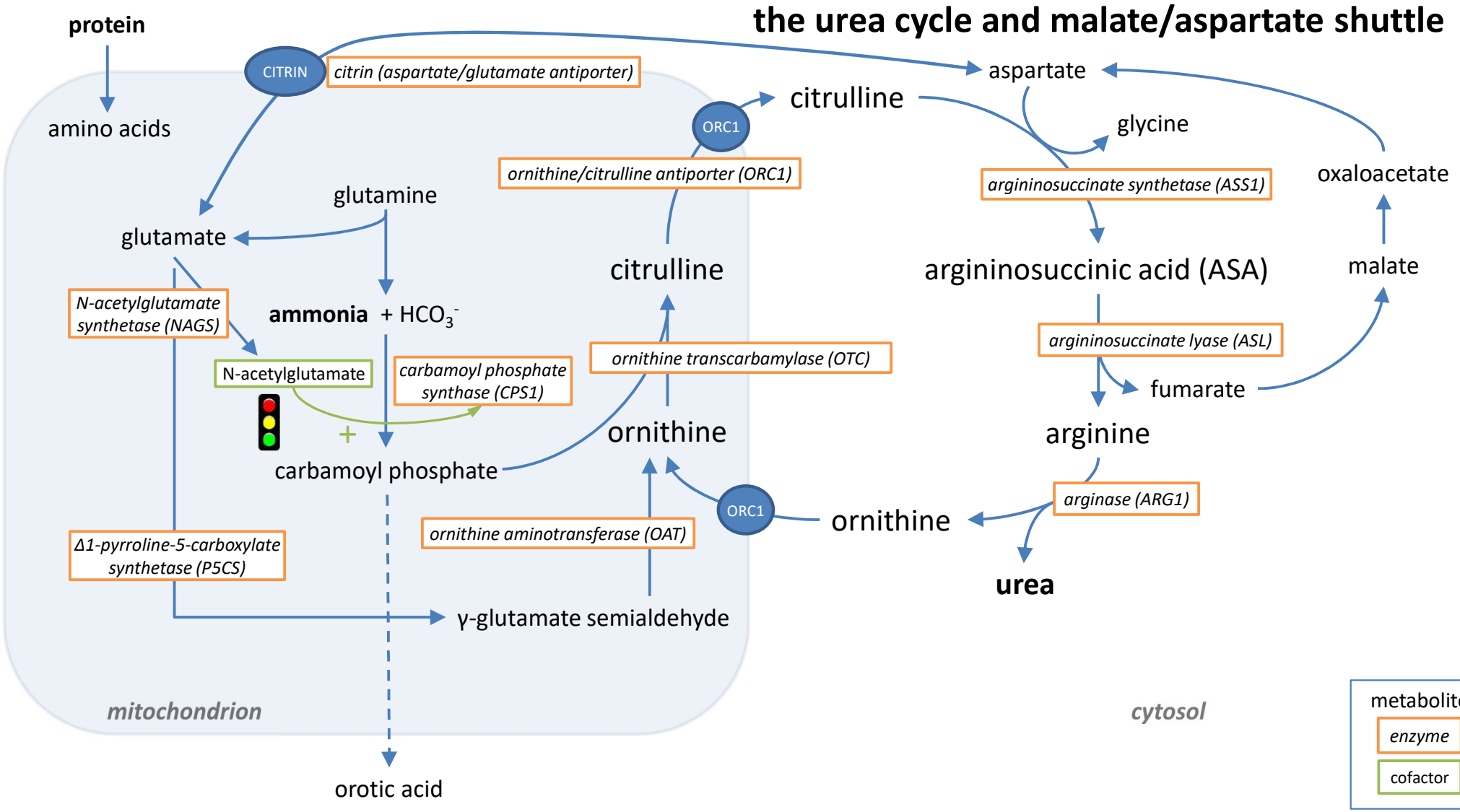
2-ketoadipic acid

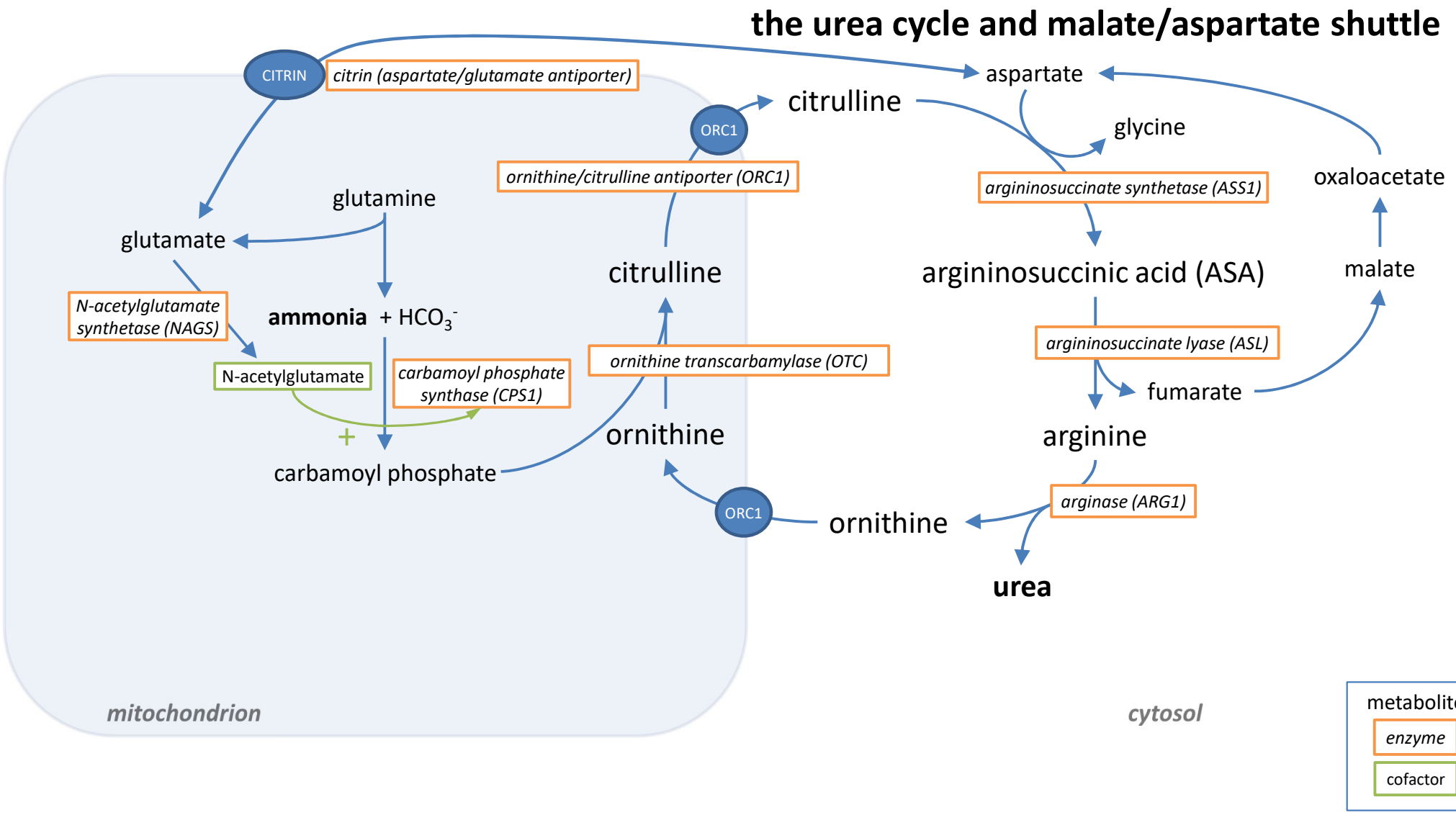
2-oxoglutarate dehydrogenase-like complex (?)

glutaryl-CoA

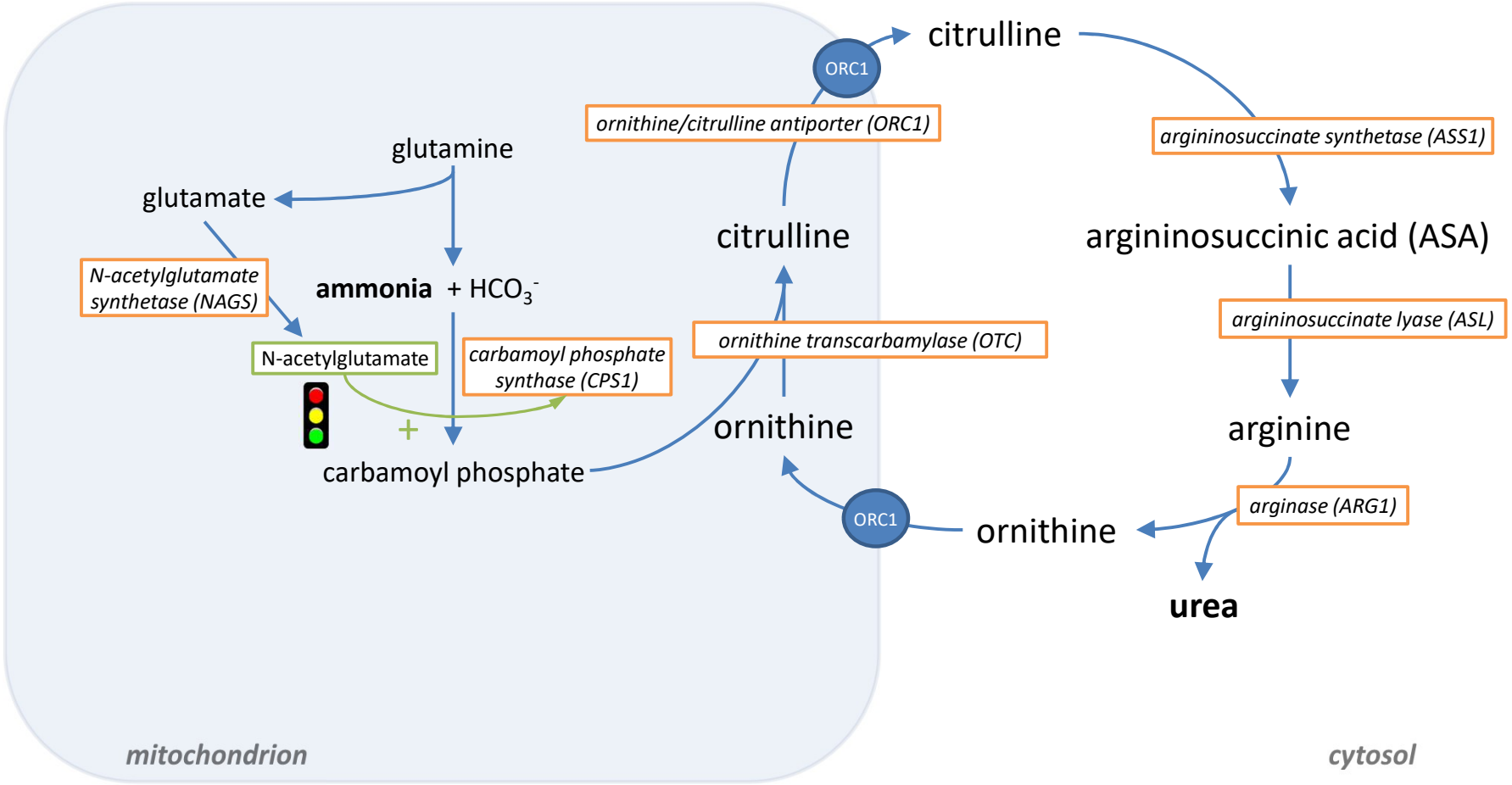
glutaryl-CoA dehydrogenase

crotonyl-CoA — *SCHAD* → acetyl-CoA

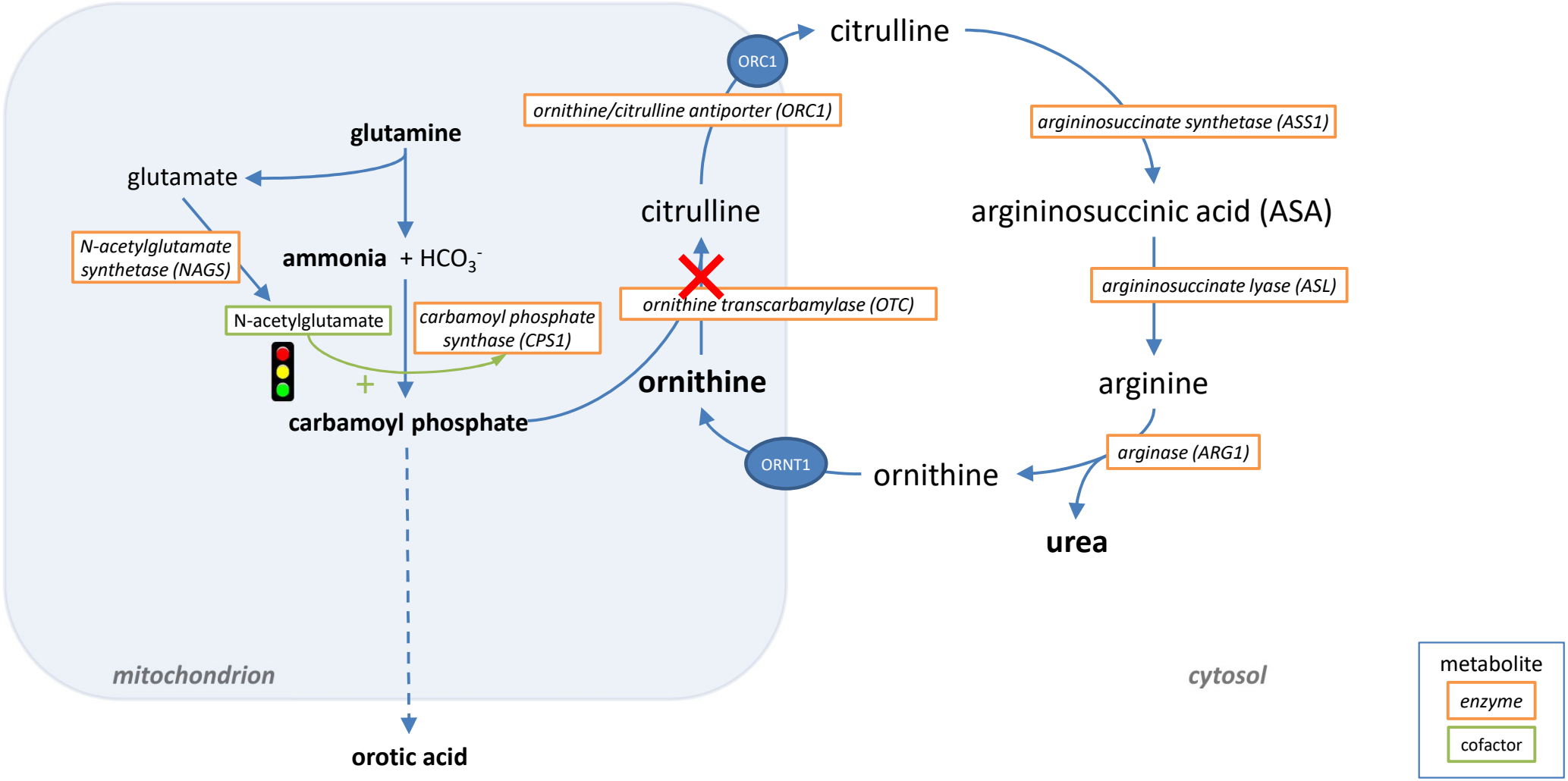

the urea cycle and malate/aspartate shuttle
protein
amino acids
CITRIN
citrin (aspartate/glutamate antiporter)
aspartate
citrulline
ORC1
ornithine/citrulline antiporter (ORC1)
glycine
argininosuccinate synthetase (ASS1)
oxaloacetate
glutamine
glutamate
citrulline
argininosuccinic acid (ASA)
malate
N-acetylglutamate synthetase (NAGS)
ammonia + HCO_3^-
argininosuccinate lyase (ASL)
N-acetylglutamate
carbamoyl phosphate synthase (CPS1)
ornithine transcarbamylase (OTC)
fumarate
ornithine
arginine
carbamoyl phosphate
arginase (ARG1)
ORC1
ornithine
ornithine aminotransferase (OAT)
Δ1-pyrroline-5-carboxylate synthetase (P5CS)
urea
γ-glutamate semialdehyde
mitochondrion
cytosol
orotic acid
metabolite
enzyme
cofactor

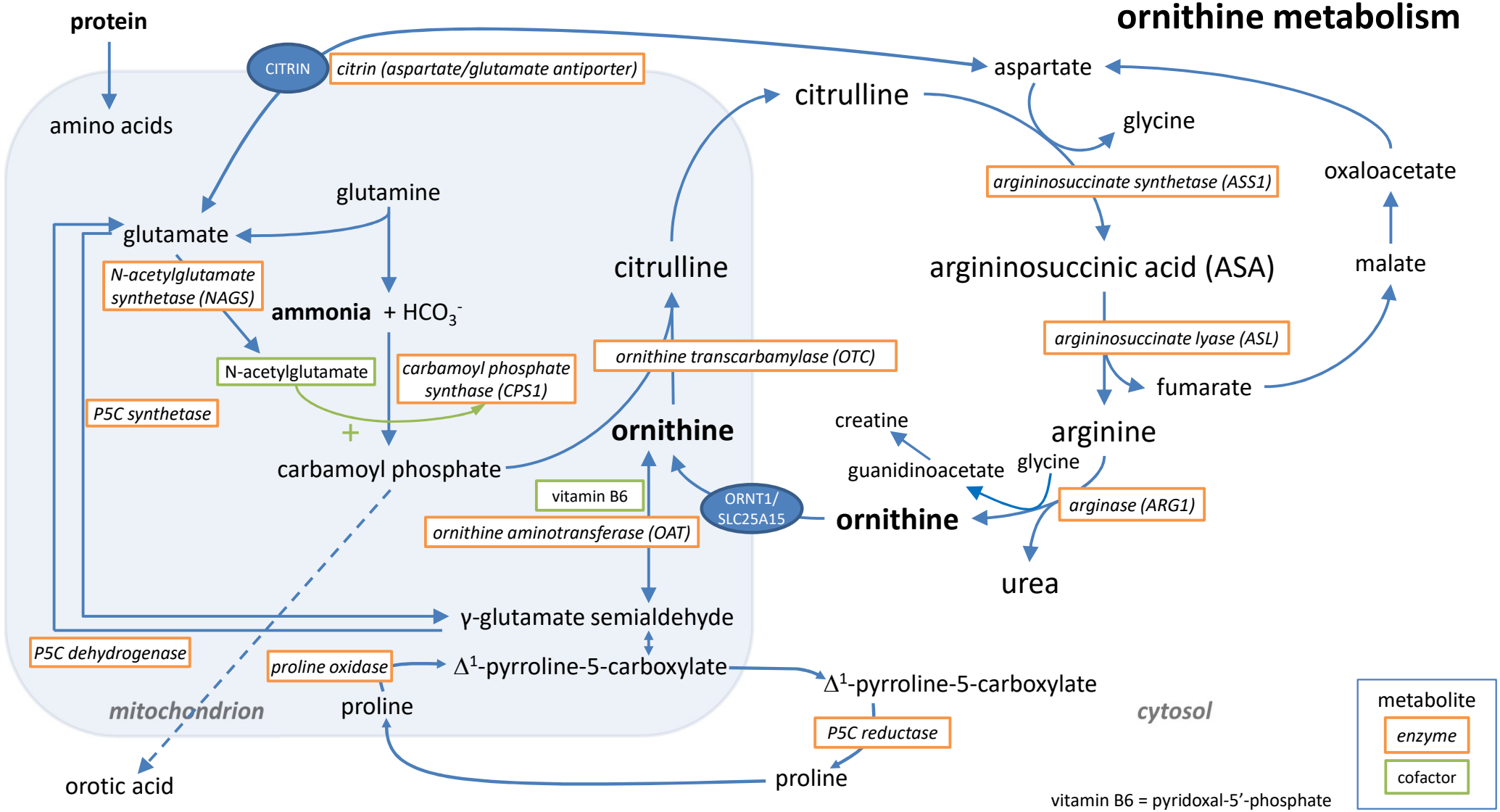

the urea cycle and malate/aspartate shuttle
CITRIN
citrin (aspartate/glutamate antiporter)
aspartate
citrulline
ORC1
ornithine/citrulline antiporter (ORC1)
glycine
argininosuccinate synthetase (ASS1)
oxaloacetate
glutamine
glutamate
citrulline
argininosuccinic acid (ASA)
malate
N-acetylglutamate synthetase (NAGS)
ammonia + HCO_3^-
argininosuccinate lyase (ASL)
N-acetylglutamate
carbamoyl phosphate synthase (CPS1)
ornithine transcarbamylase (OTC)
fumarate
+
ornithine
arginine
carbamoyl phosphate
ORC1
arginase (ARG1)
ornithine
urea
mitochondrion
cytosol
metabolite
enzyme
cofactor

the urea cycle

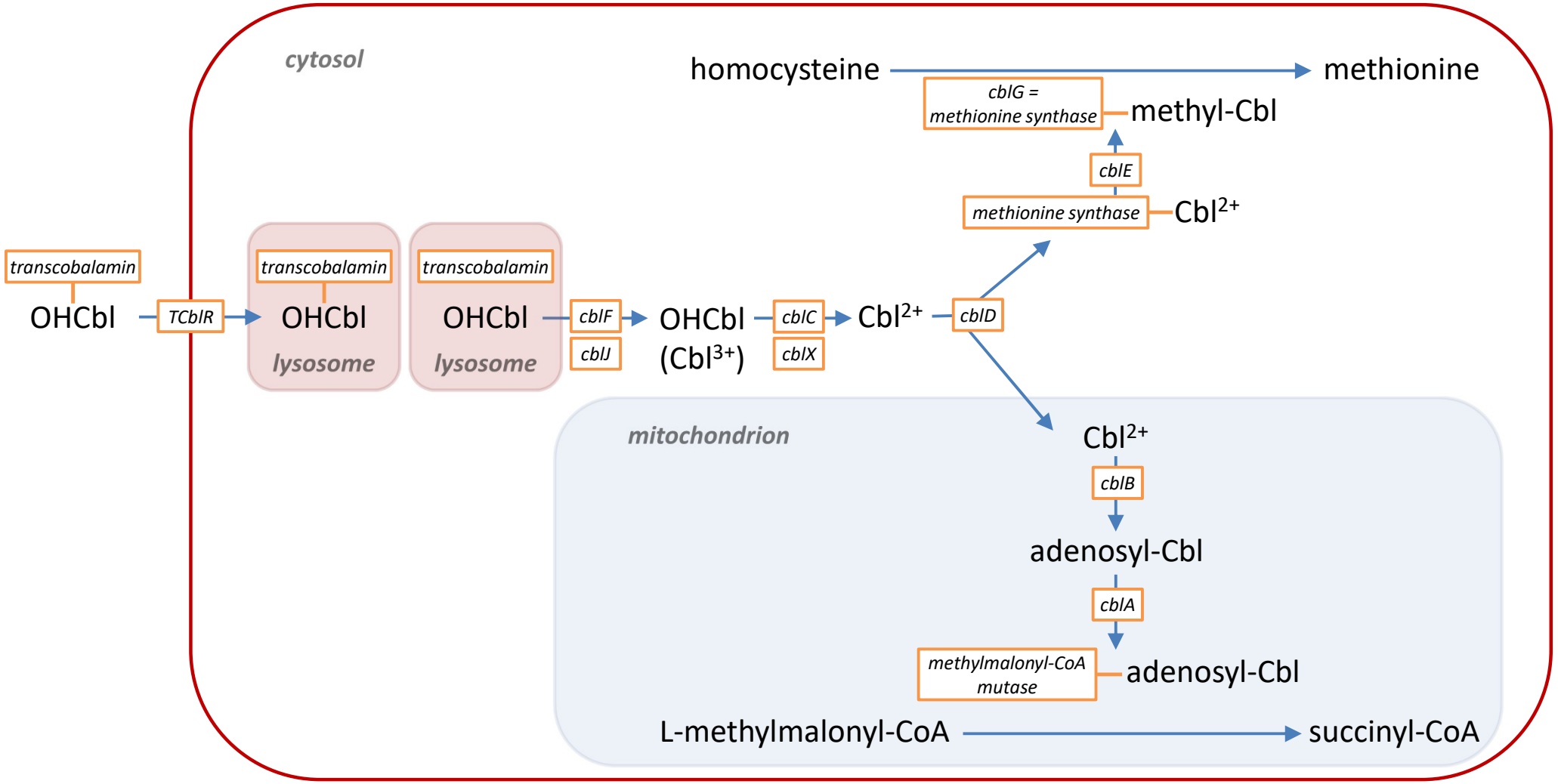


OTC deficiency

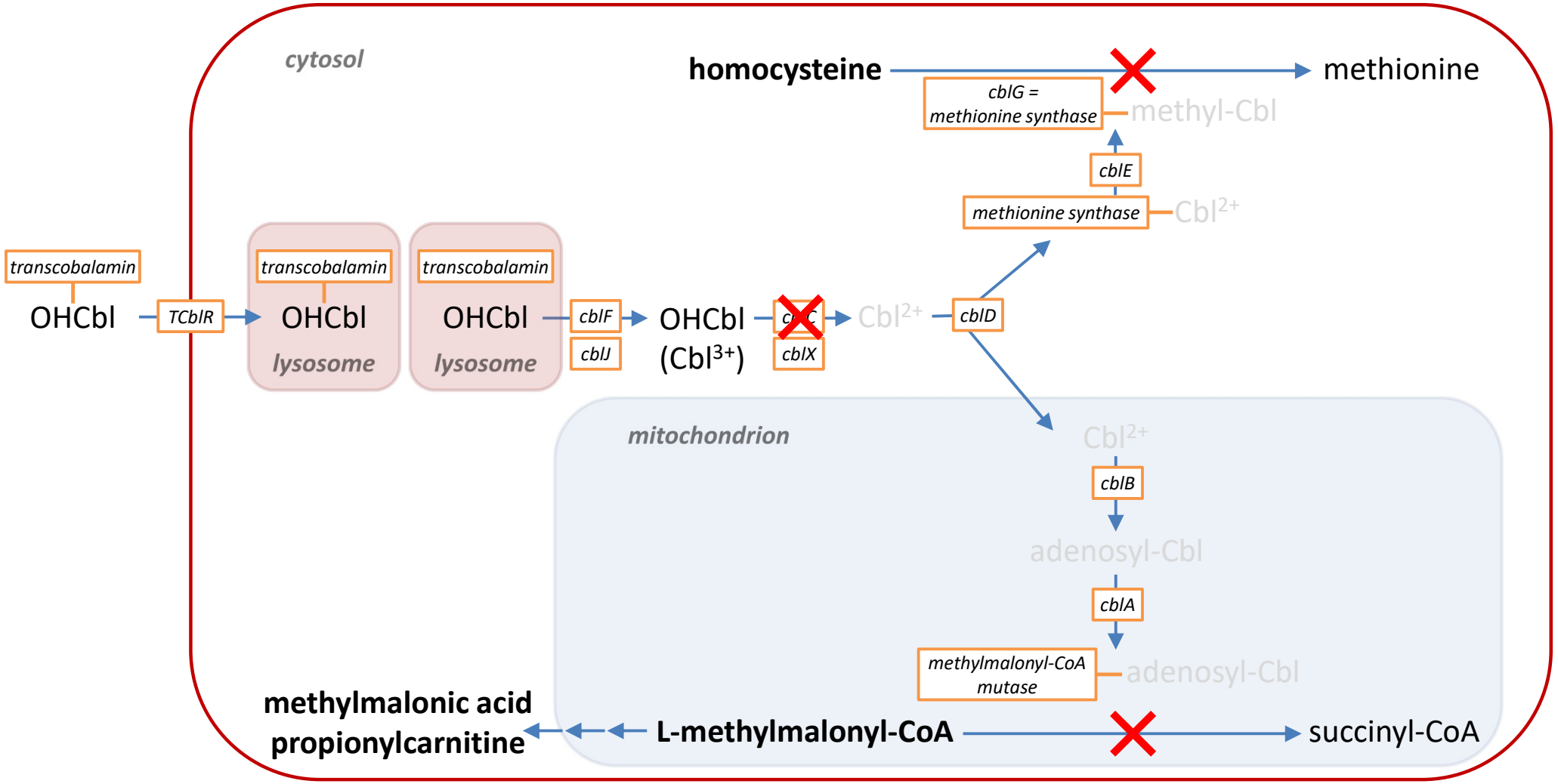



ornithine metabolism
protein
amino acids
CITRIN
citrin (aspartate/glutamate antiporter)
aspartate
citrulline
glycine
argininosuccinate synthetase (ASS1)
oxaloacetate
glutamine
glutamate
N-acetylglutamate synthetase (NAGS)
ammonia + HCO_3^-
citrulline
argininosuccinic acid (ASA)
malate
argininosuccinate lyase (ASL)
N-acetylglutamate
carbamoyl phosphate synthase (CPS1)
ornithine transcarbamylase (OTC)
fumarate
P5C synthetase
creatine
arginine
ornithine
guanidinoacetate
glycine
carbamoyl phosphate
vitamin B6
ORNT1/ SLC25A15
ornithine
arginase (ARG1)
ornithine aminotransferase (OAT)
urea
γ-glutamate semialdehyde
P5C dehydrogenase
proline oxidase
Δ^1-pyrroline-5-carboxylate
Δ^1-pyrroline-5-carboxylate
mitochondrion
proline
cytosol
P5C reductase
proline
orotic acid
metabolite
enzyme
cofactor
vitamin B6 = pyridoxal-5'-phosphate

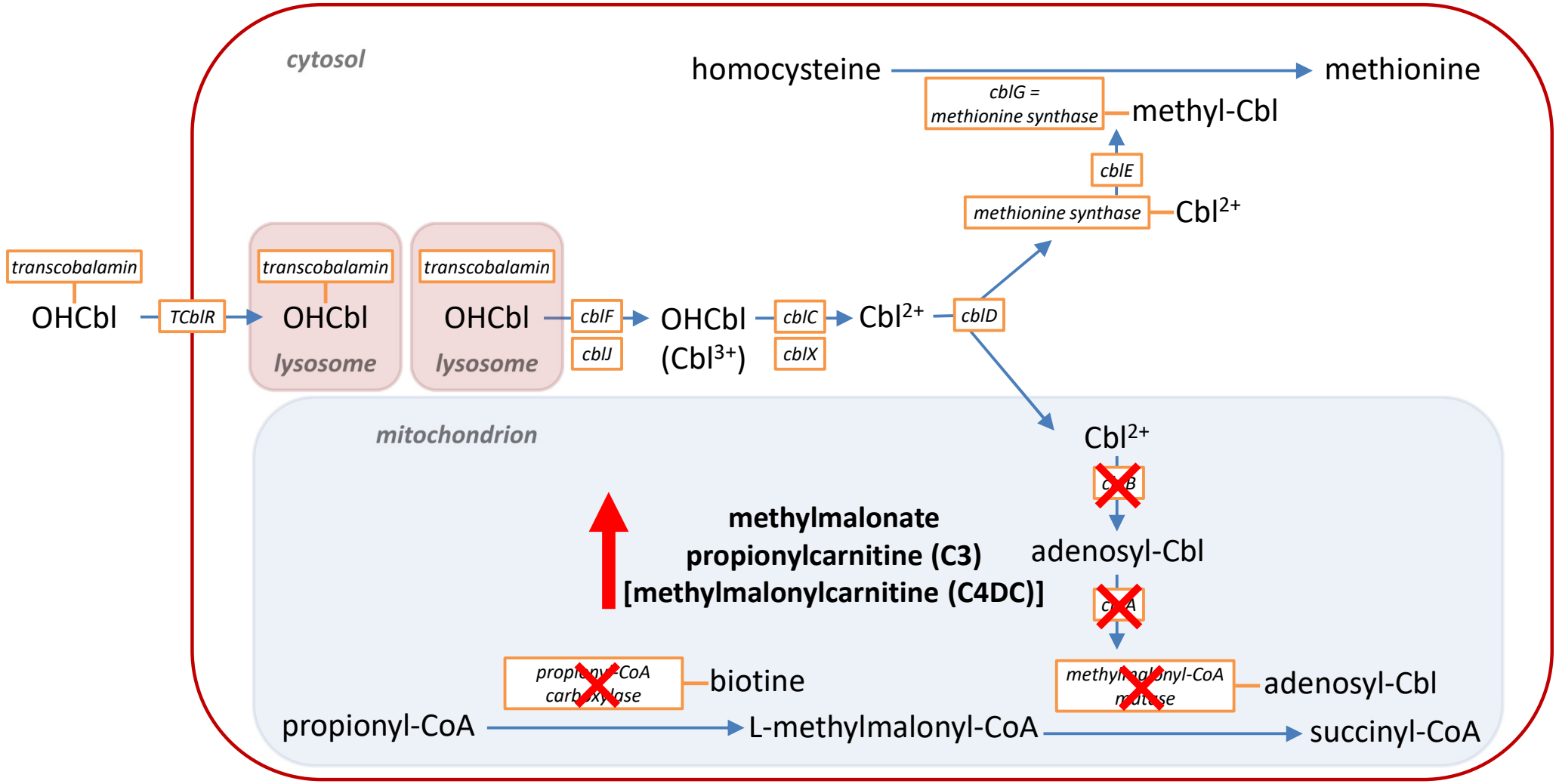
cobalamin transport and metabolism



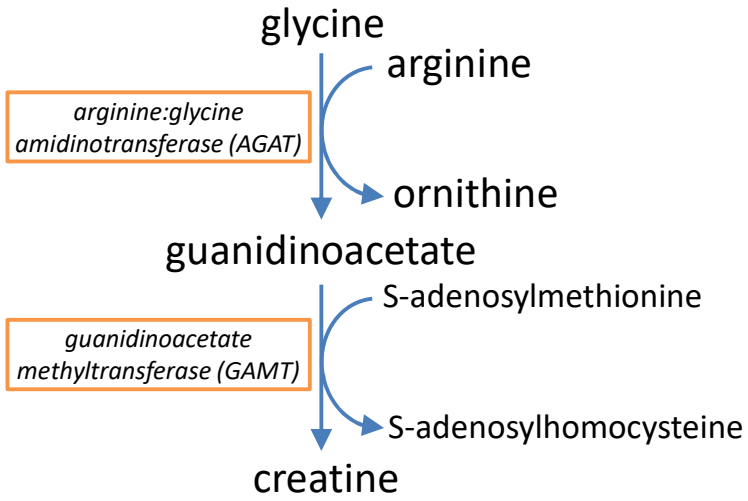
cobalamin transport and metabolism – CblC deficiency



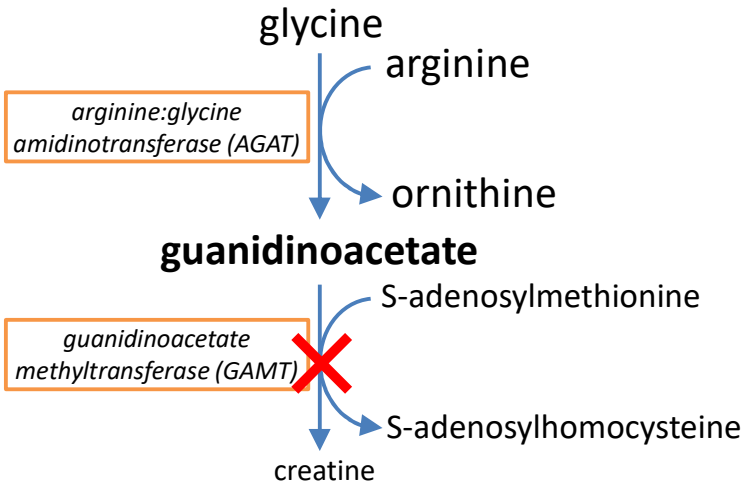
DD MMAuria without hyperhomocysteinemia



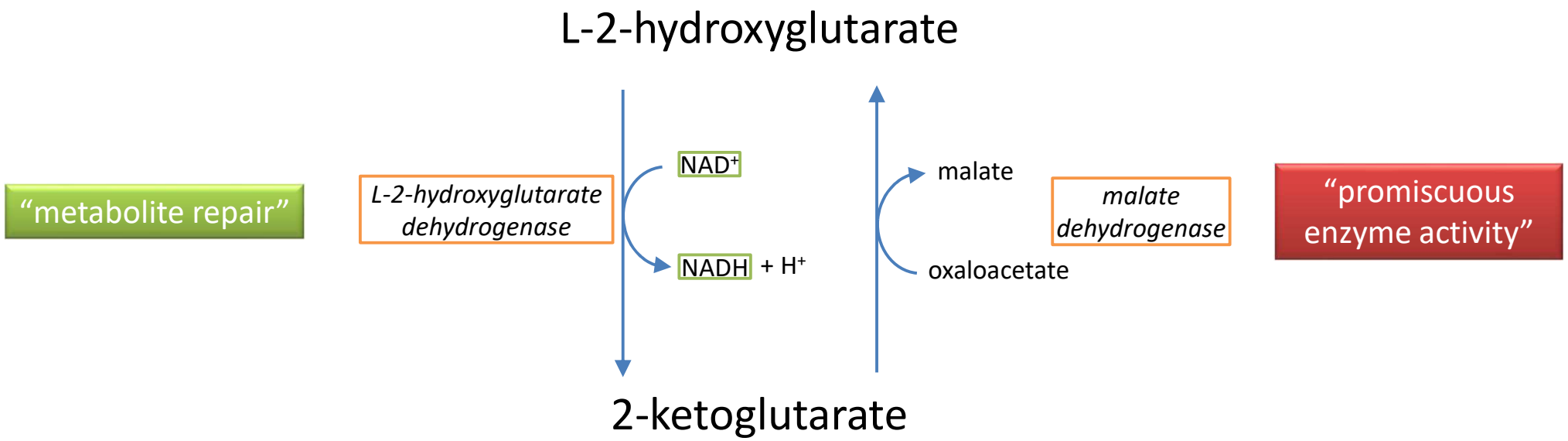
creatine synthesis



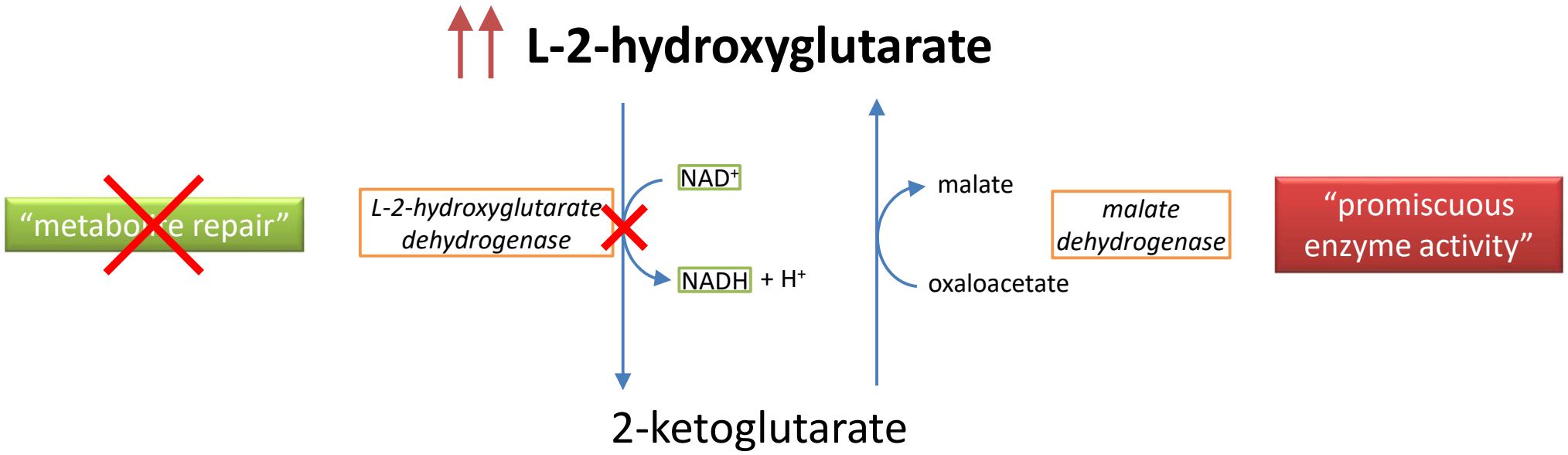
creatine synthesis – GAMT deficiency



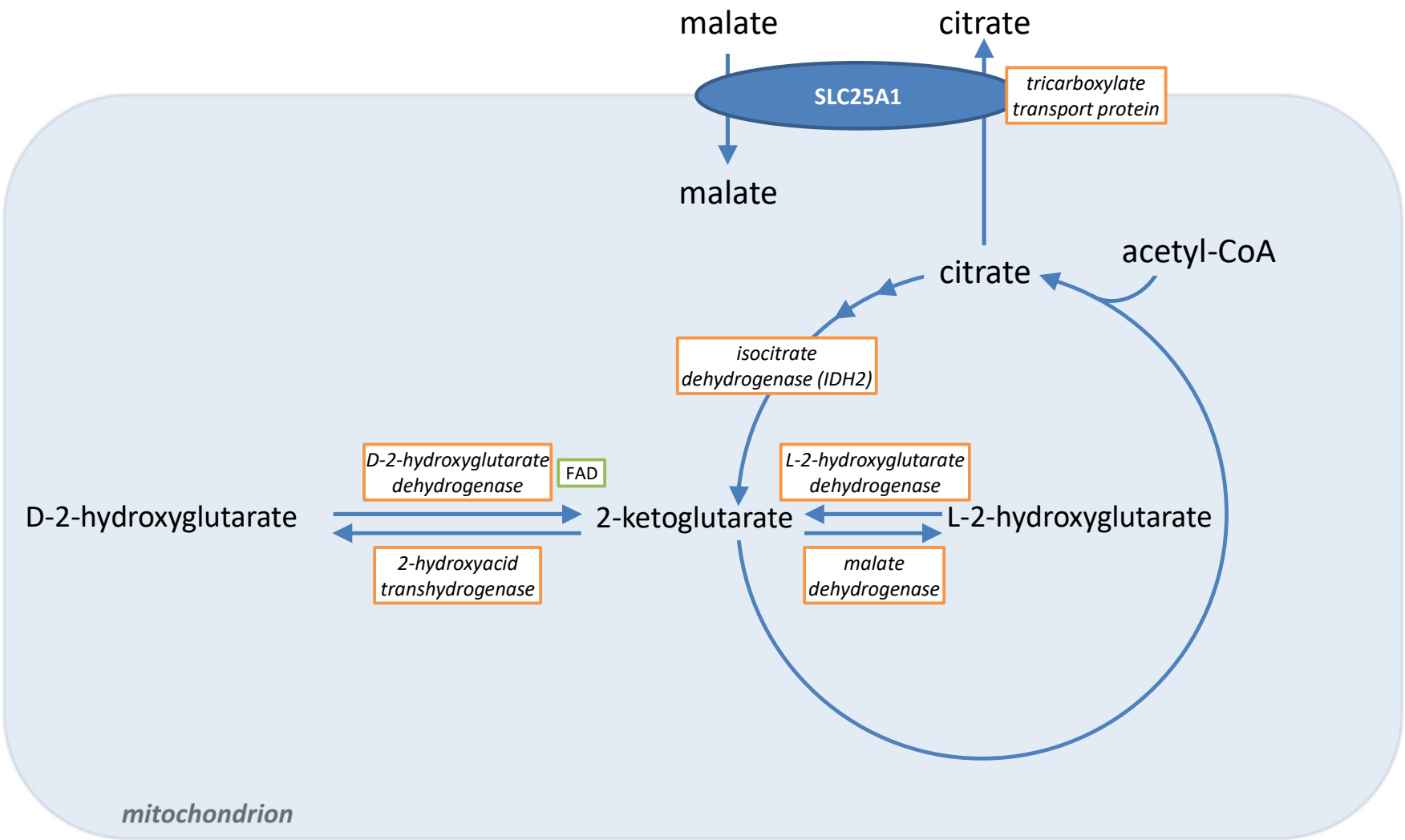
L-2-hydroxyglutarate dehydrogenase

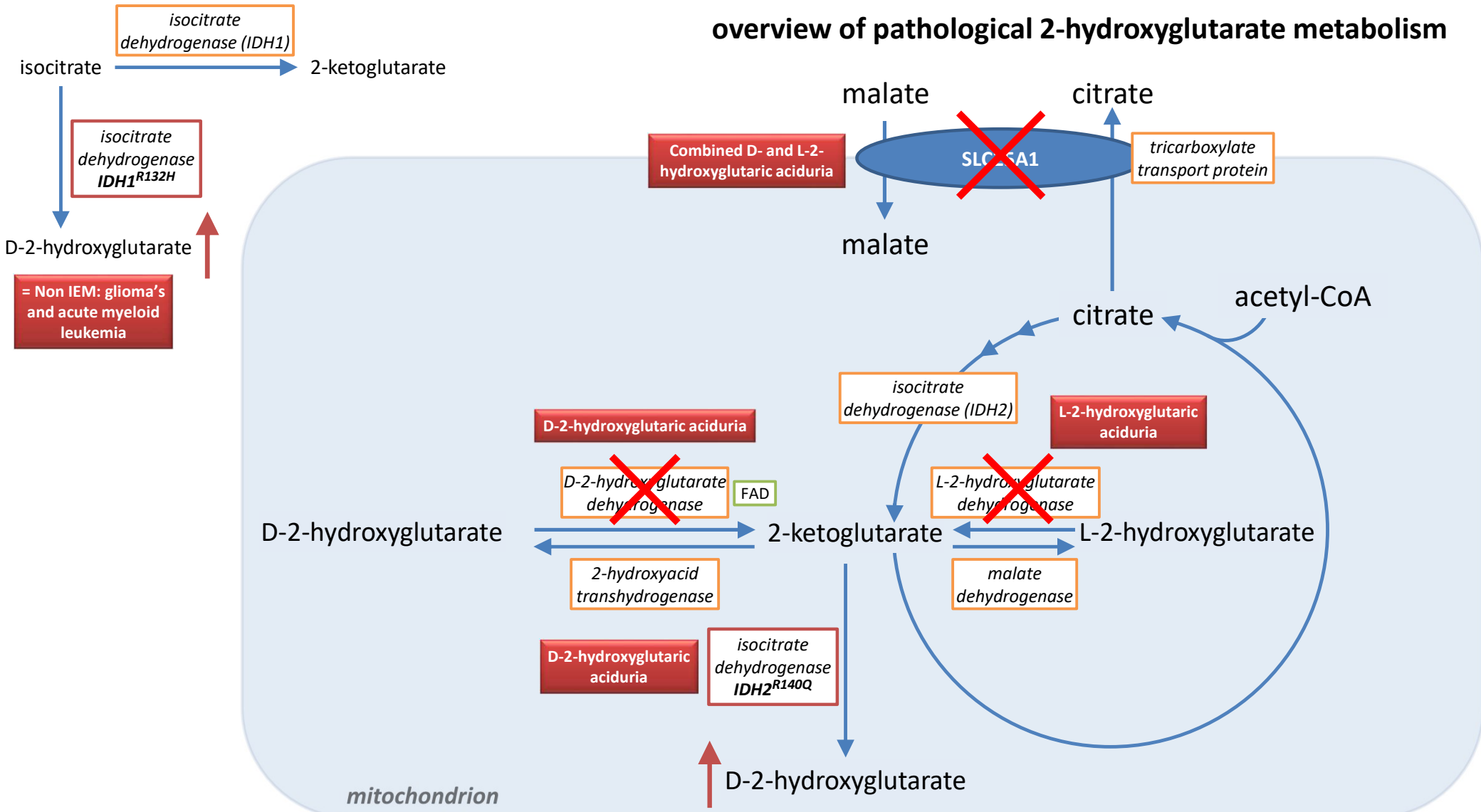


L-2-hydroxyglutarate dehydrogenase deficiency

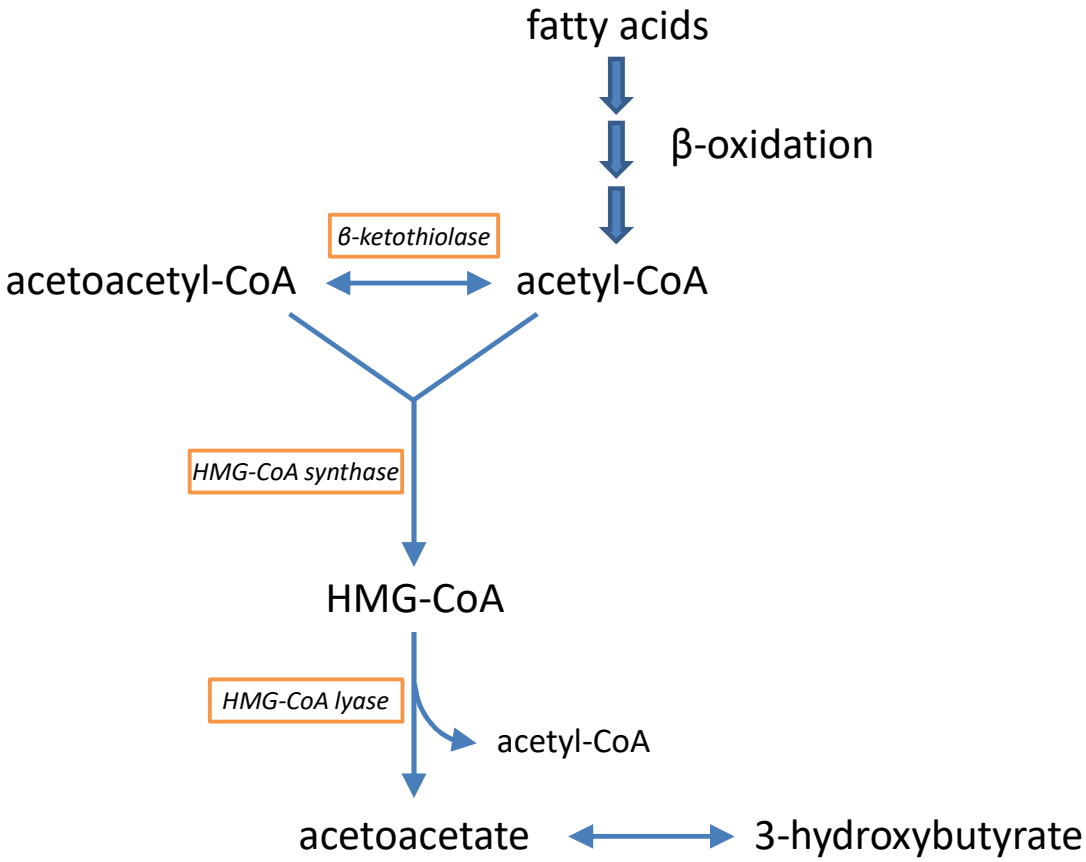


2-hydroxyglutarate metabolism

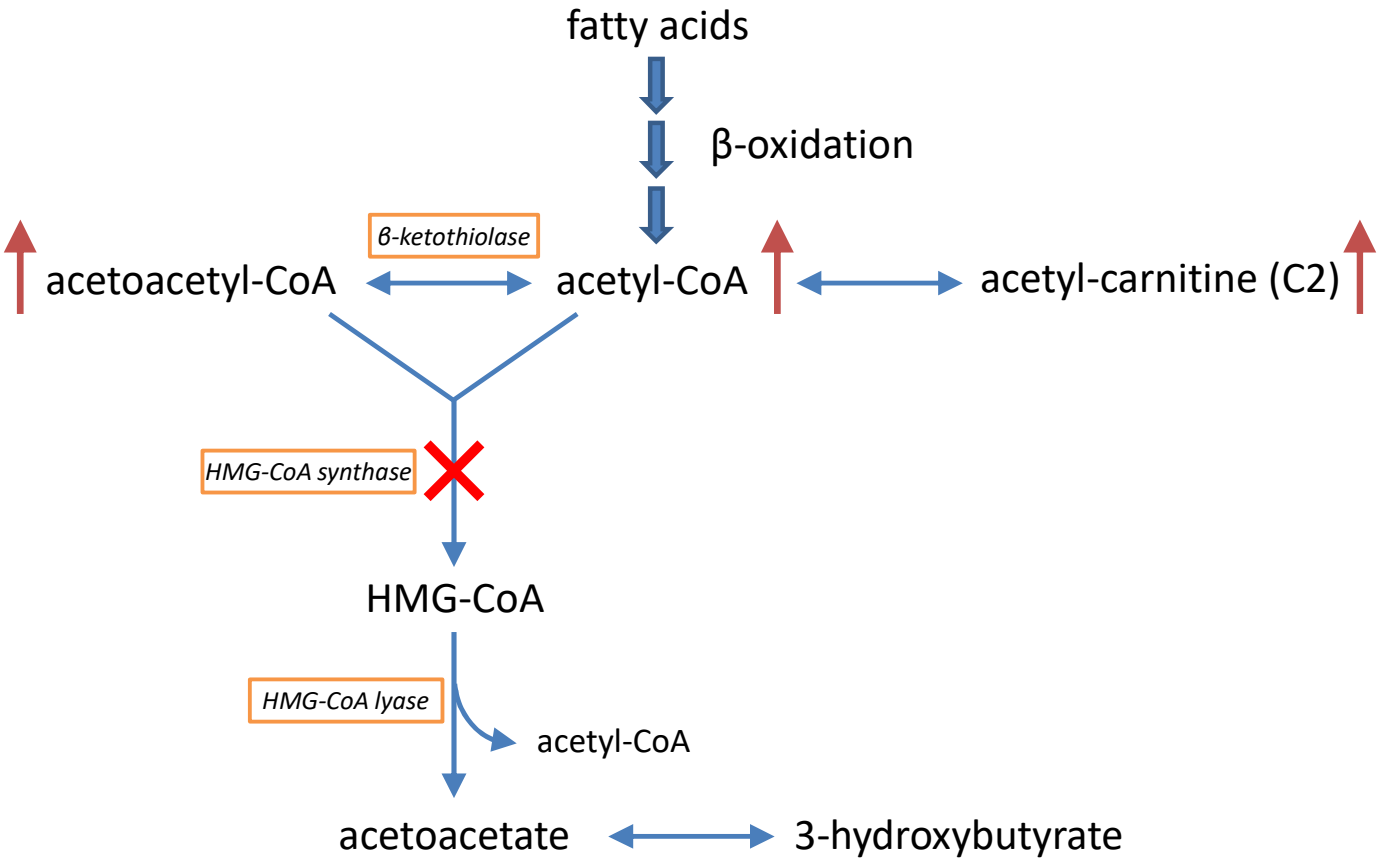



isocitrate dehydrogenase (IDH1)
isocitrate
2-ketoglutarate
isocitrate dehydrogenase IDH1R132H
D-2-hydroxyglutarate
= Non IEM: glioma's and acute myeloid leukemia
overview of pathological 2-hydroxyglutarate metabolism
malate
citrate
Combined D- and L-2-hydroxyglutaric aciduria
SLC25A1
tricarboxylate transport protein
malate
citrate
acetyl-CoA
isocitrate dehydrogenase (IDH2)
D-2-hydroxyglutaric aciduria
L-2-hydroxyglutaric aciduria
D-2-hydroxyglutarate dehydrogenase
FAD
L-2-hydroxyglutarate dehydrogenase
D-2-hydroxyglutarate
2-ketoglutarate
L-2-hydroxyglutarate
2-hydroxyacid transhydrogenase
malate dehydrogenase
D-2-hydroxyglutaric aciduria
isocitrate dehydrogenase IDH2R140Q
D-2-hydroxyglutarate
mitochondrion

ketogenesis

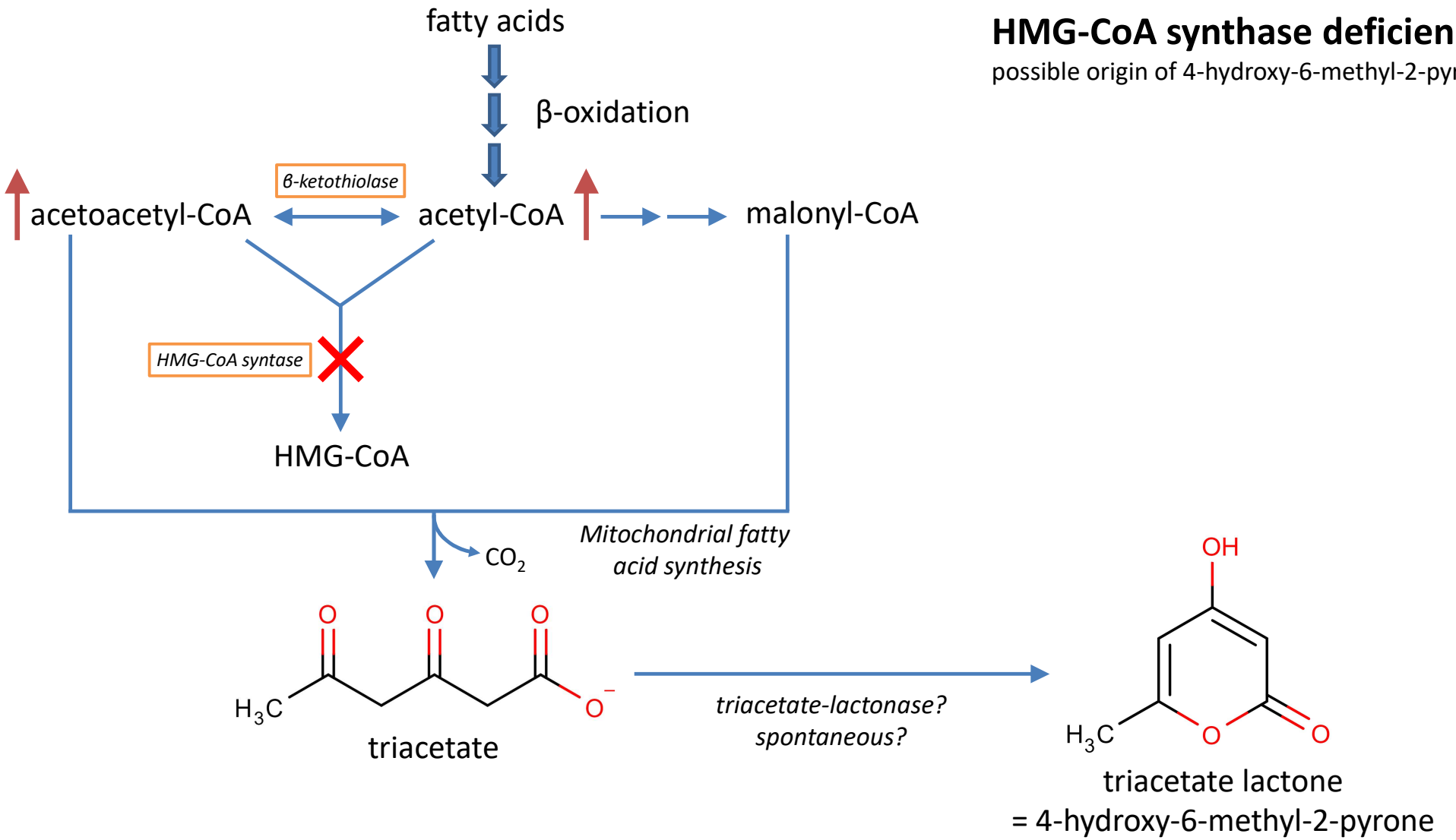


HMG-CoA synthase deficiency

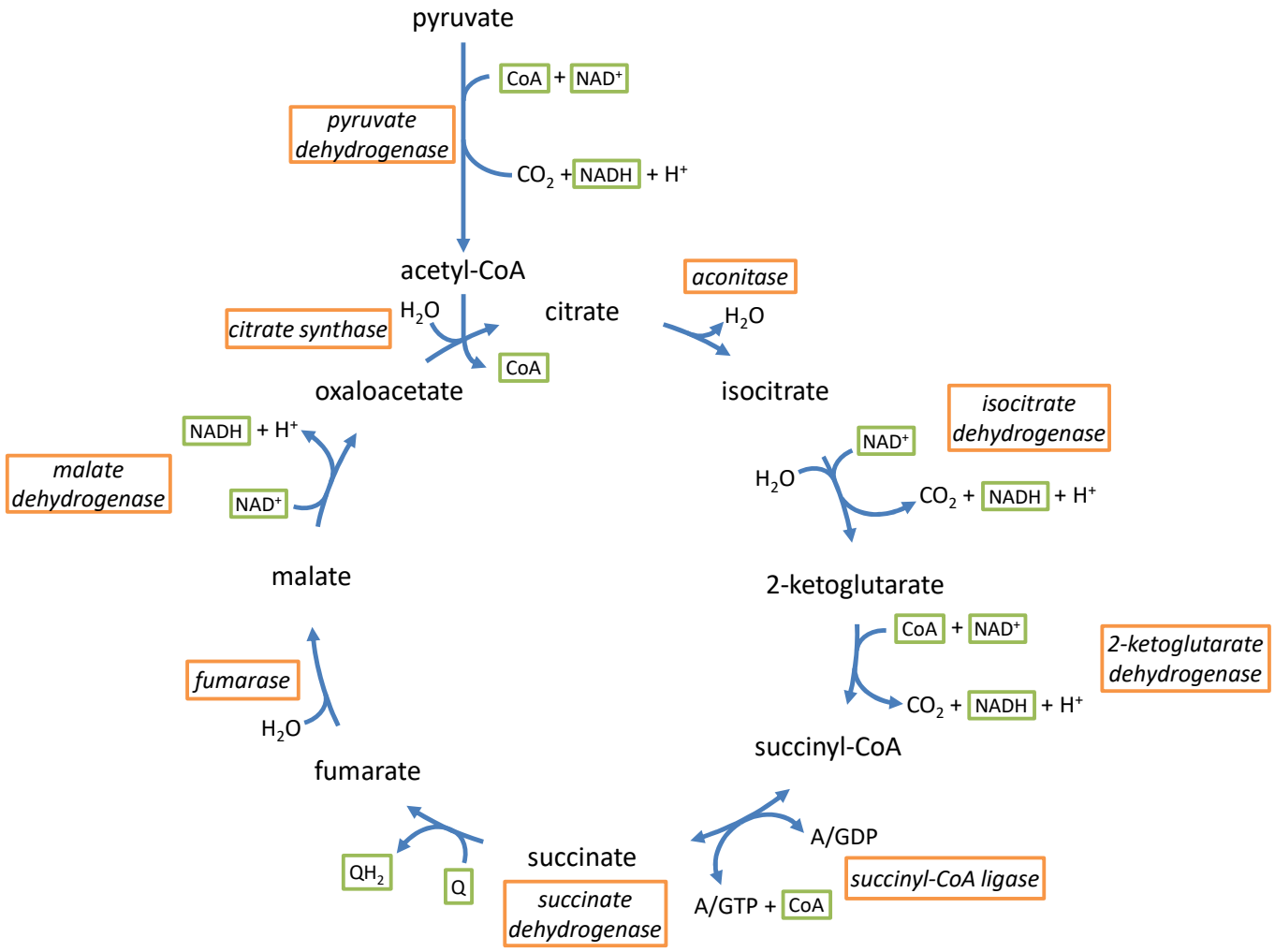


HMG-CoA synthase deficiency

possible origin of 4-hydroxy-6-methyl-2-pyrone



the citric acid cycle



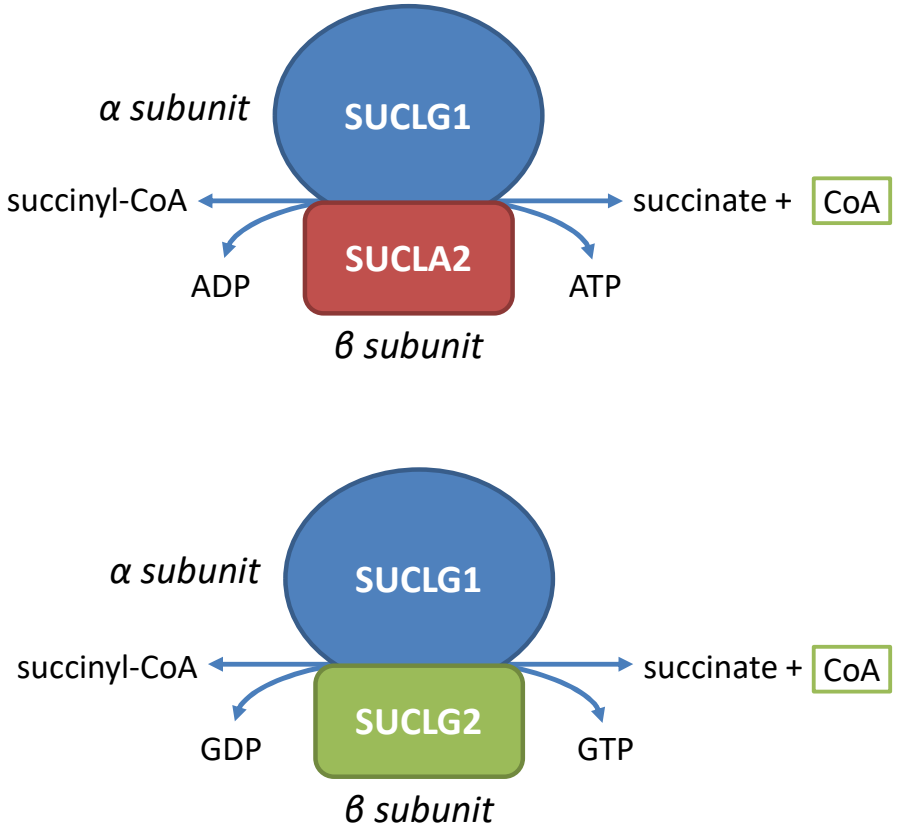
metabolite

enzyme

cofactor

- Succinyl-CoA ligase / synthetase
  - **SUCLG1**
    - **α subunit** of complex
  - **SUCLA2**
    - **β subunit** gives specificity for ADP
  - **SUCLG2**
    - **β subunit** gives specificity for GDP

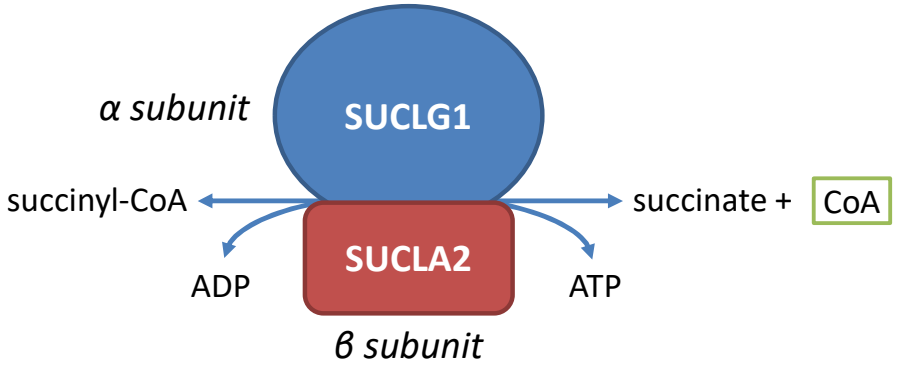
Succinyl-CoA ligase (SUCL) complex

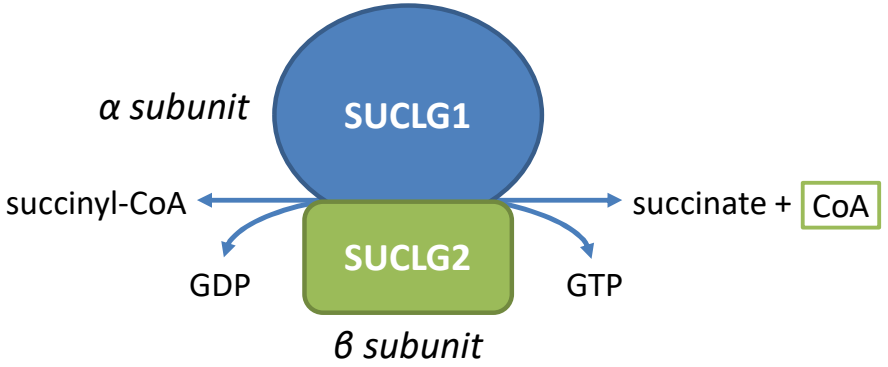


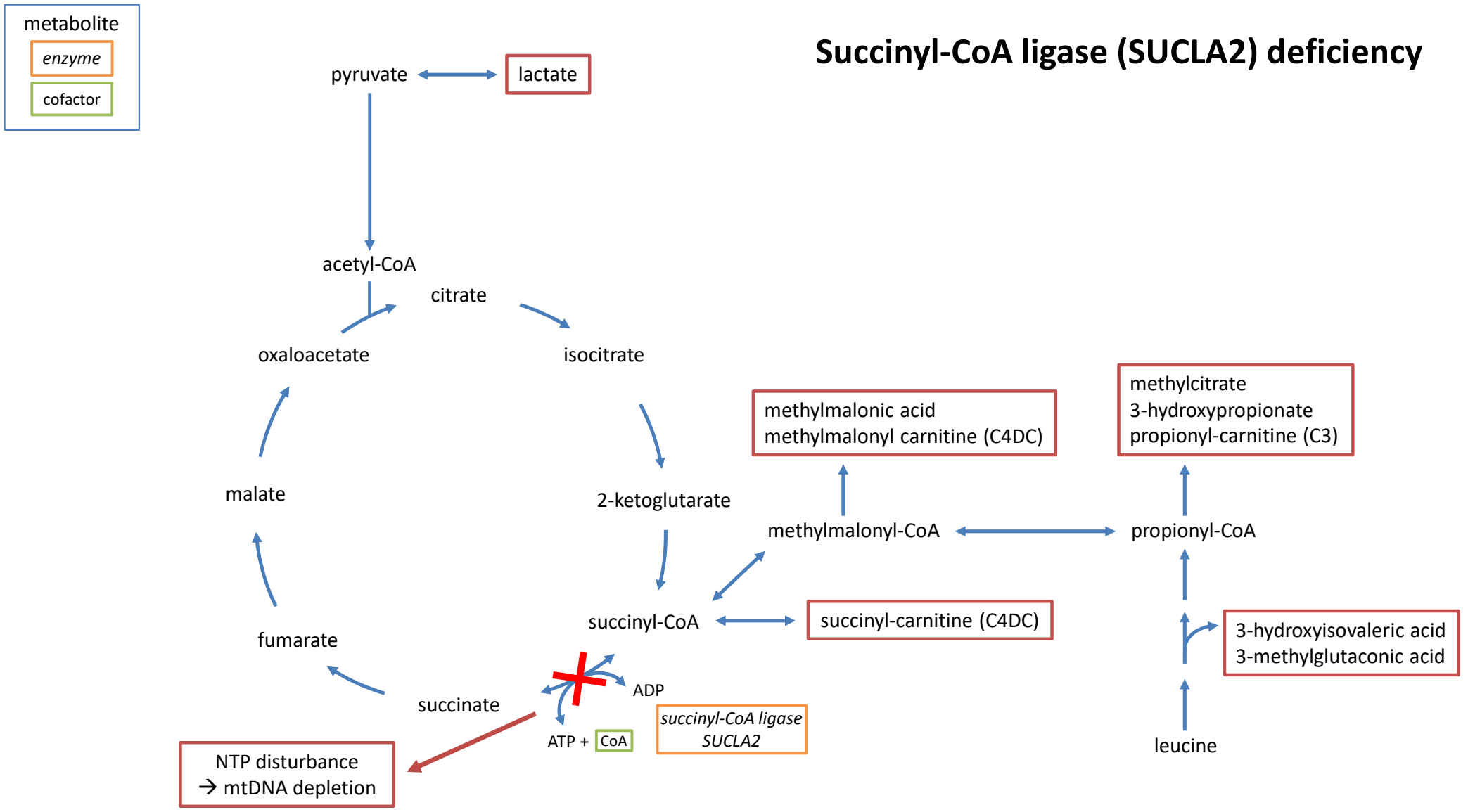
- Succinyl-CoA ligase / synthetase
  - **SUCLG1**
    - **α subunit** of complex
  - **SUCLA2**
    - **β subunit** gives specificity for ADP
  - **SUCLG2**
    - **β subunit** gives specificity for GDP

- SUCL forms a complex with nucleoside diphosphate kinase (NDK)
- NDK is needed for mitochondrial NTP homeostasis and thus mtDNA replication
- Deficiency of the SUCL complex leads to disturbance of NTP homeostasis and mtDNA depletion
- SUCL deficiencies also are categorized as mtDNA depletion syndromes

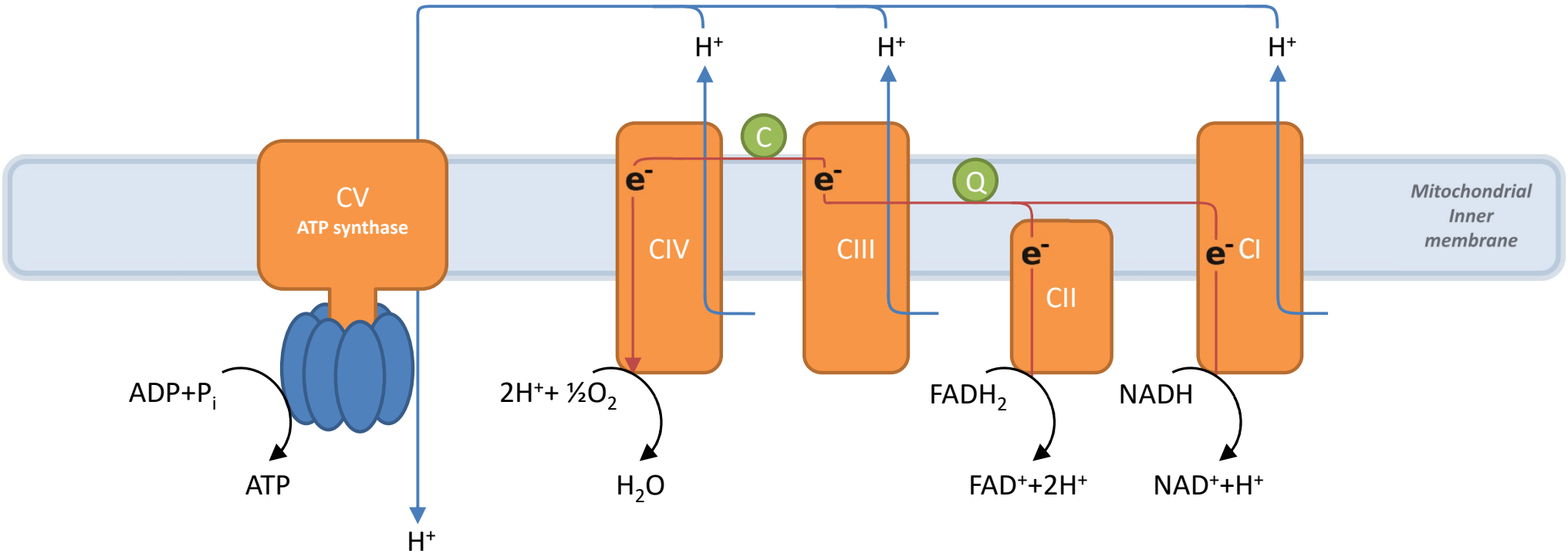
Succinyl-CoA ligase (SUCL) complex



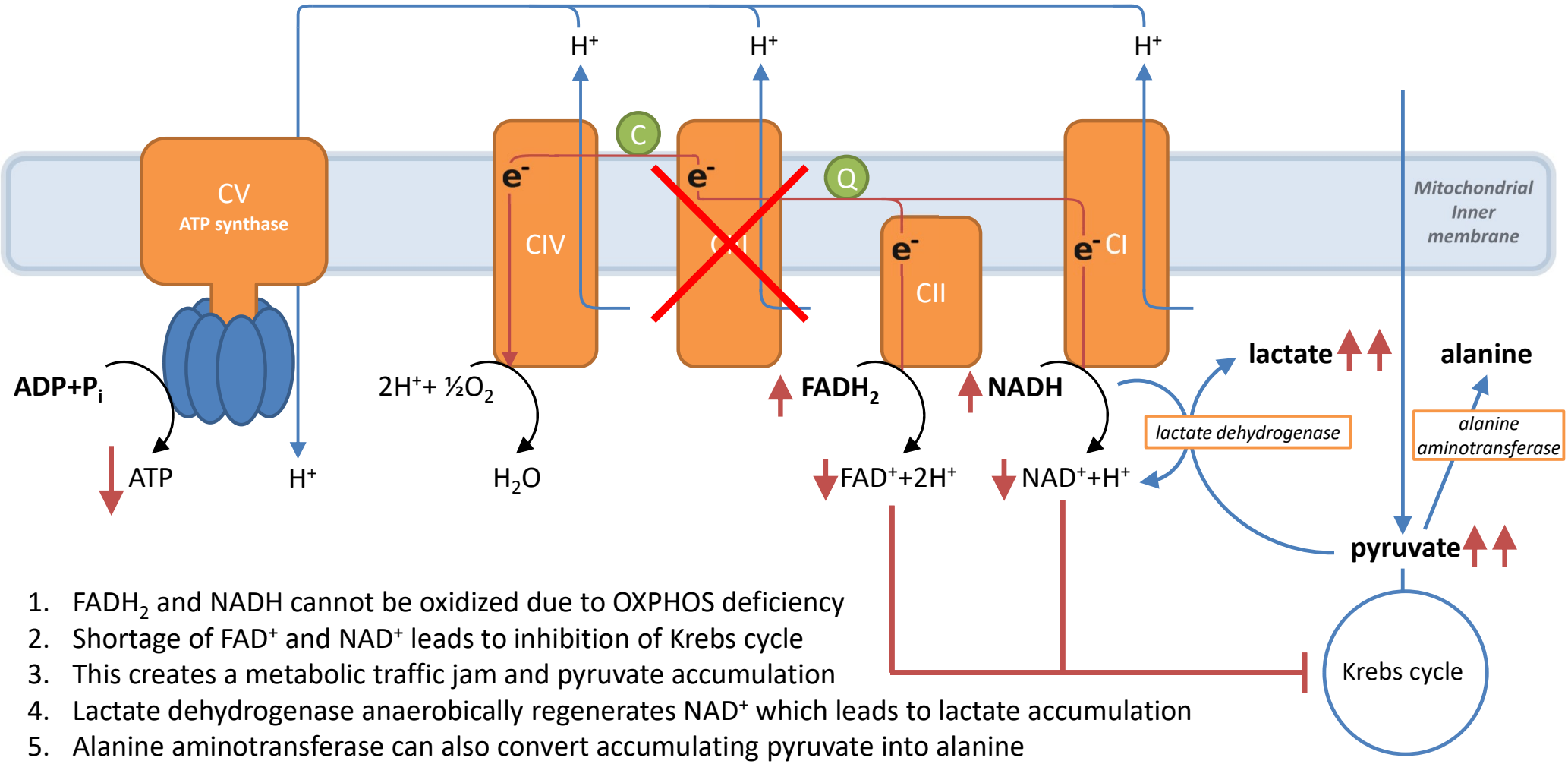



metabolite
enzyme
cofactor
Succinyl-CoA ligase (SUCLA2) deficiency
pyruvate
lactate
acetyl-CoA
citrate
oxaloacetate
isocitrate
malate
2-ketoglutarate
methylmalonic acid
methylmalonyl carnitine (C4DC)
methylcitrate
3-hydroxypropionate
propionyl-carnitine (C3)
methylmalonyl-CoA
propionyl-CoA
succinyl-CoA
succinyl-carnitine (C4DC)
fumarate
succinate
ADP
ATP + CoA
succinyl-CoA ligase
SUCLA2
3-hydroxyisovaleric acid
3-methylglutaconic acid
leucine
NTP disturbance
→ mtDNA depletion

the mitochondrial oxidative phosphorylation system (OXPHOS)

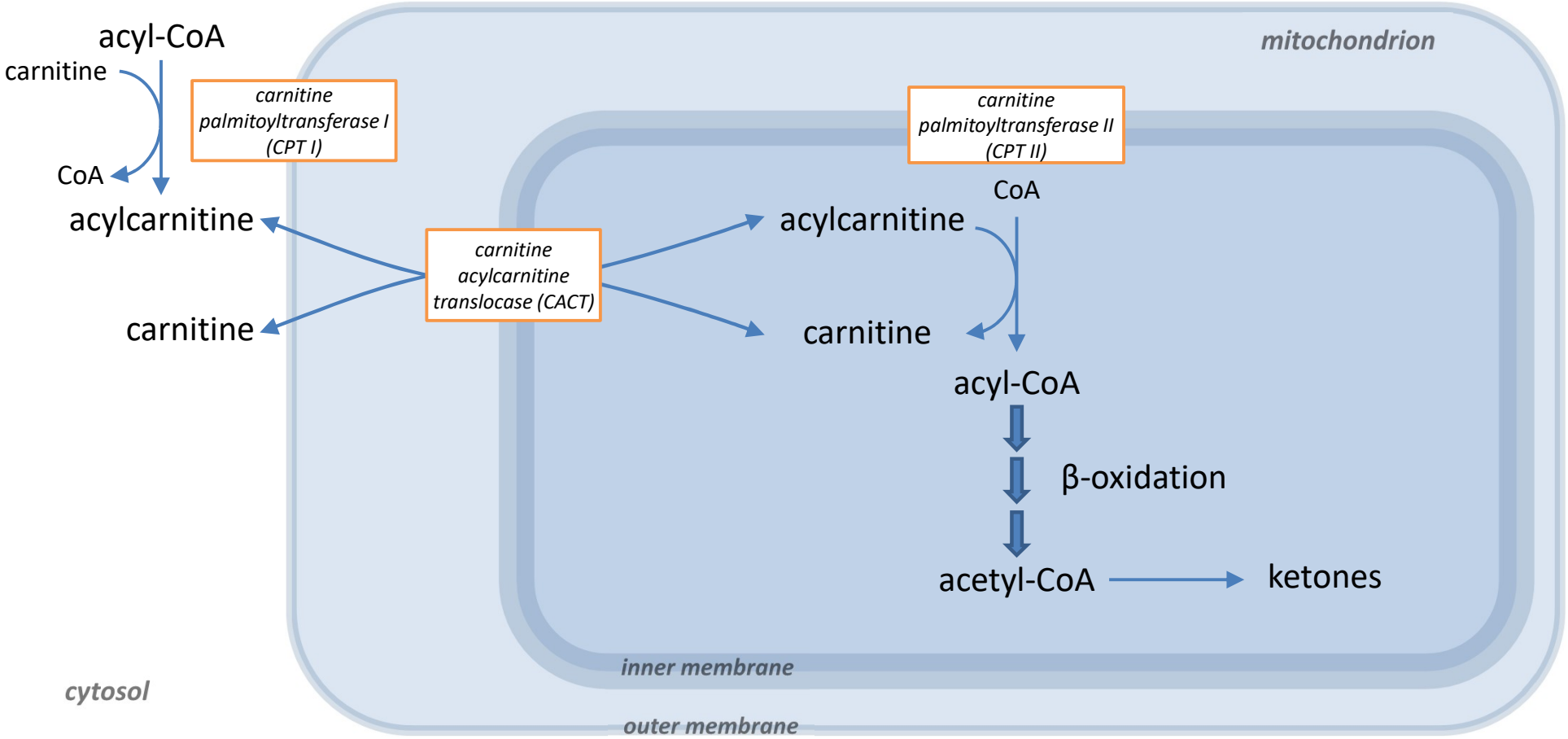


Mitochondriopathy with OXPHOS deficiency

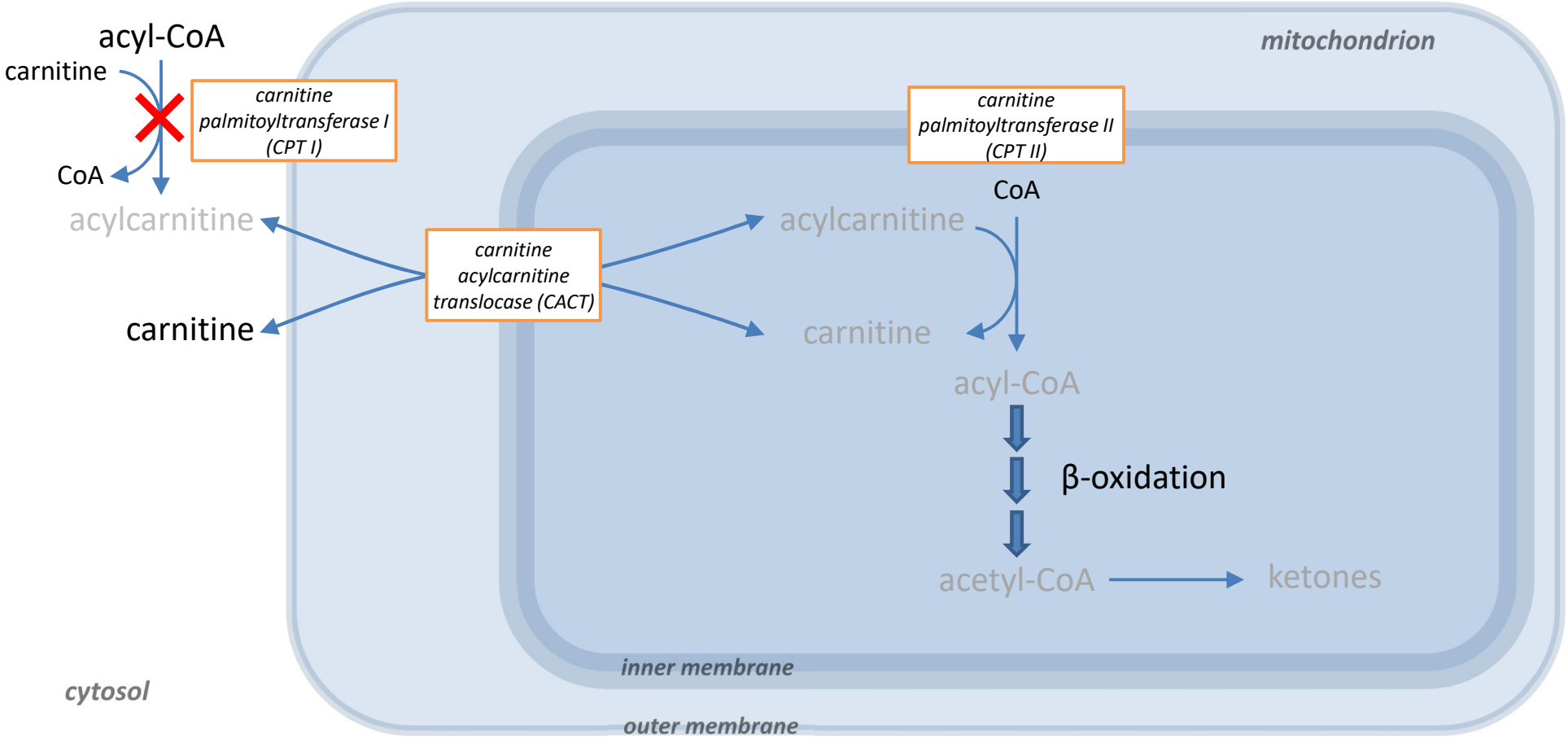


1. $FADH_2$ and NADH cannot be oxidized due to OXPHOS deficiency
2. Shortage of FAD^+ and NAD^+ leads to inhibition of Krebs cycle
3. This creates a metabolic traffic jam and pyruvate accumulation
4. Lactate dehydrogenase anaerobically regenerates NAD^+ which leads to lactate accumulation
5. Alanine aminotransferase can also convert accumulating pyruvate into alanine

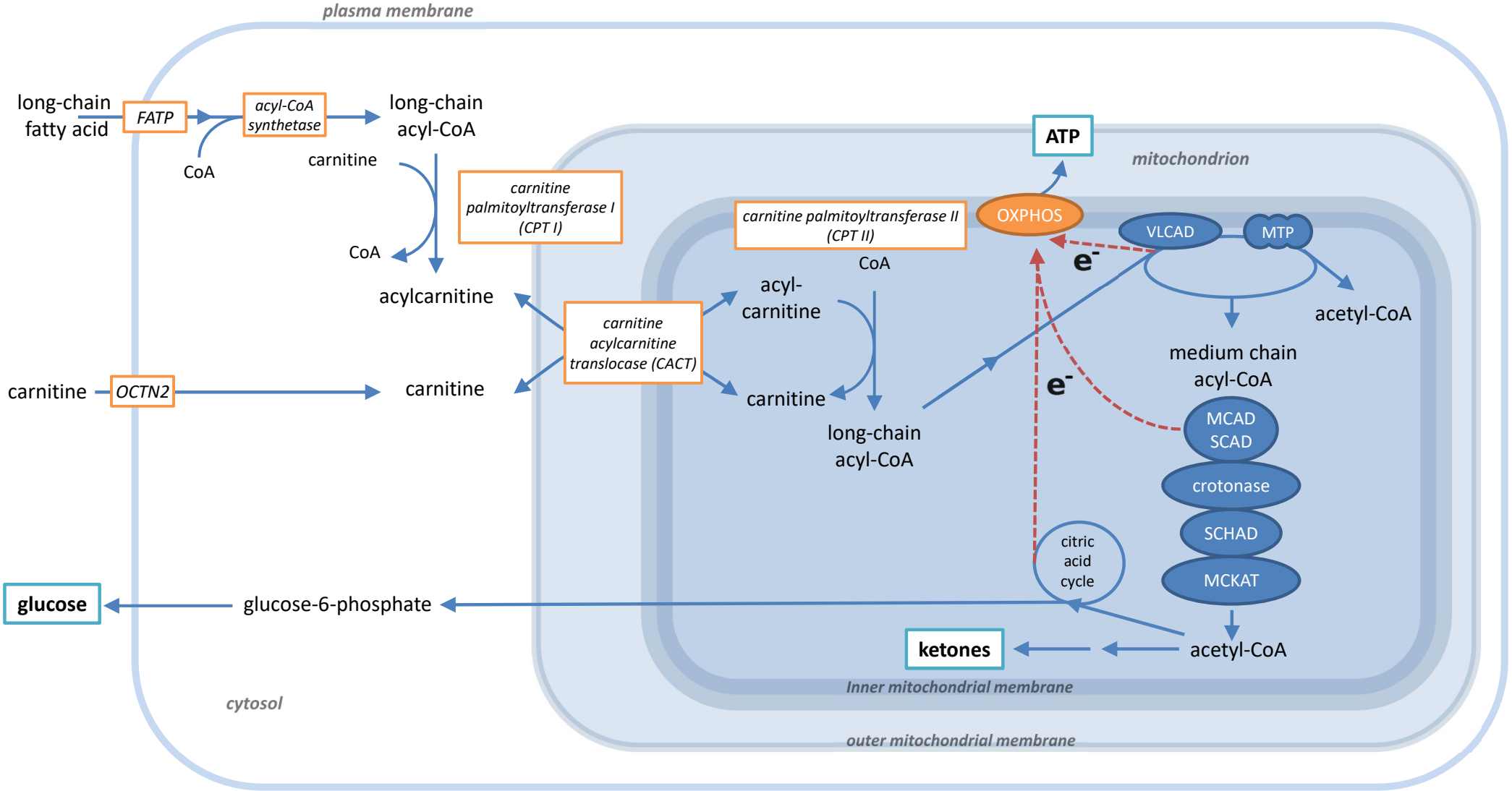
the carnitine shuttle / cycle

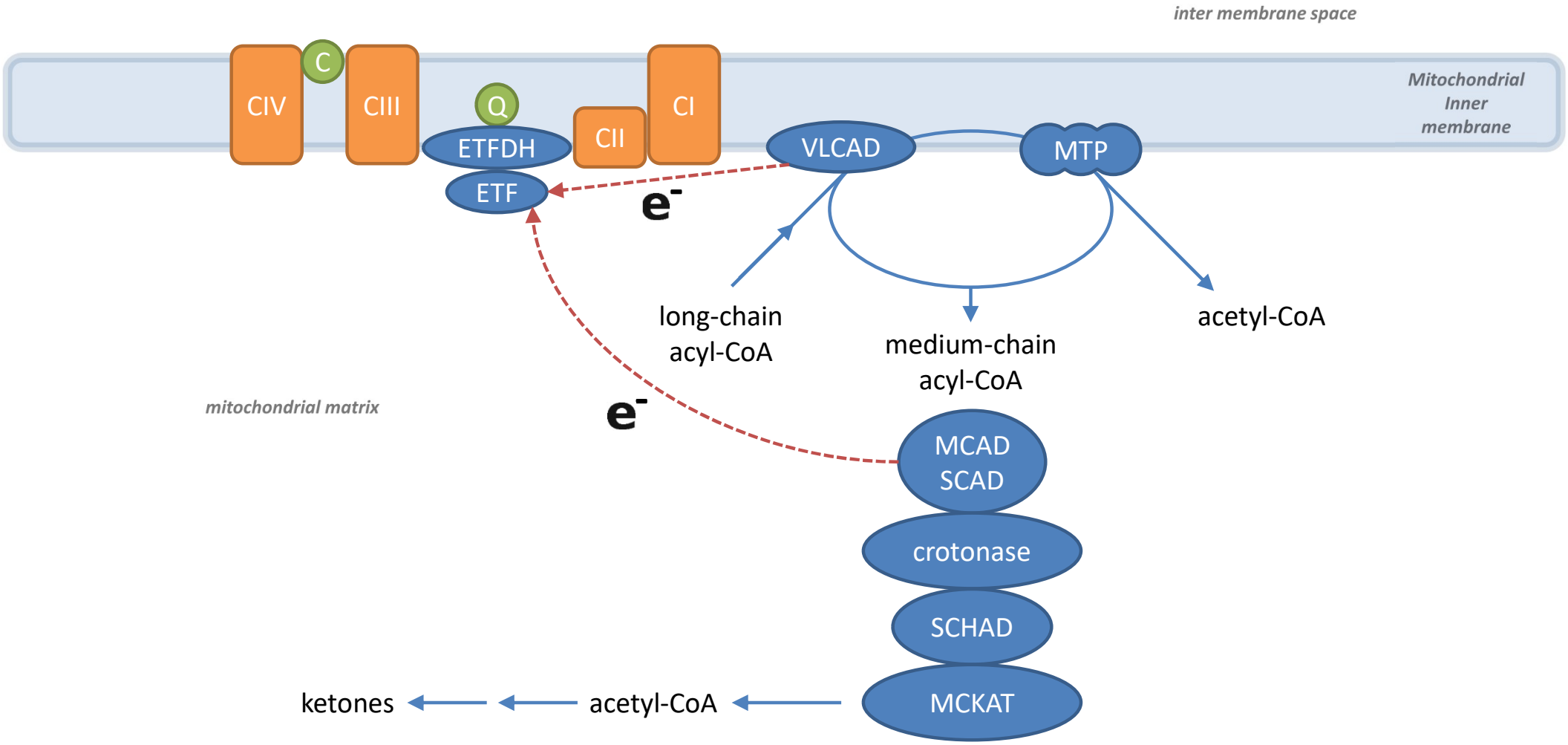


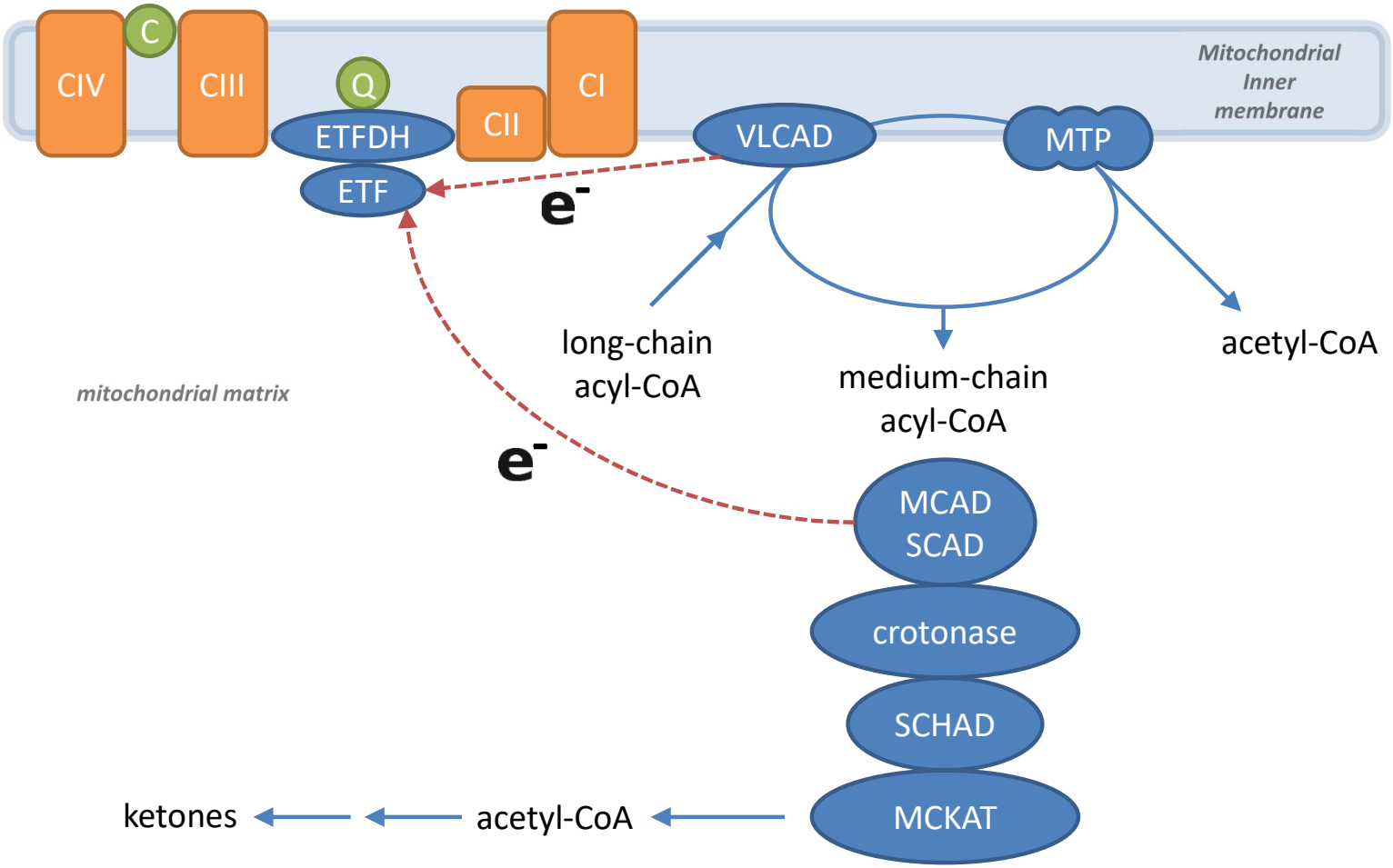
CPT I deficiency

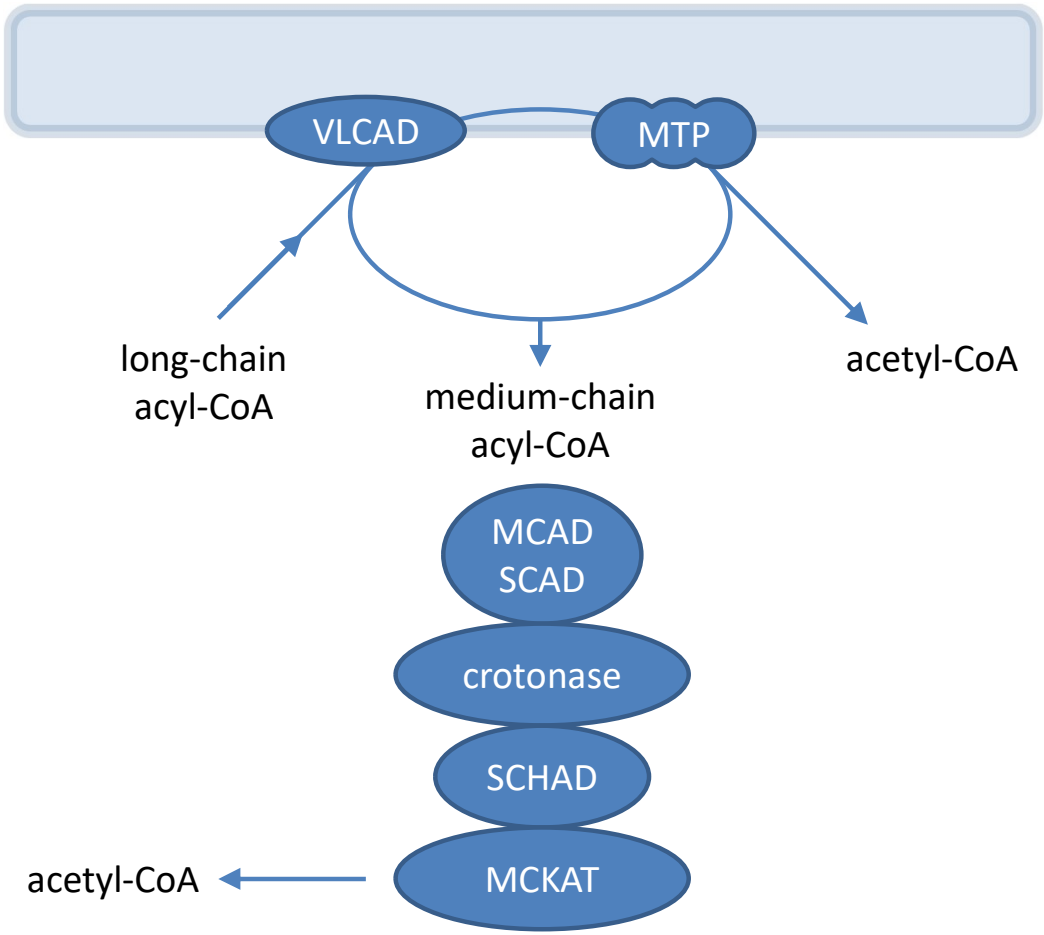


Mitochondrial fatty acid β-oxidation

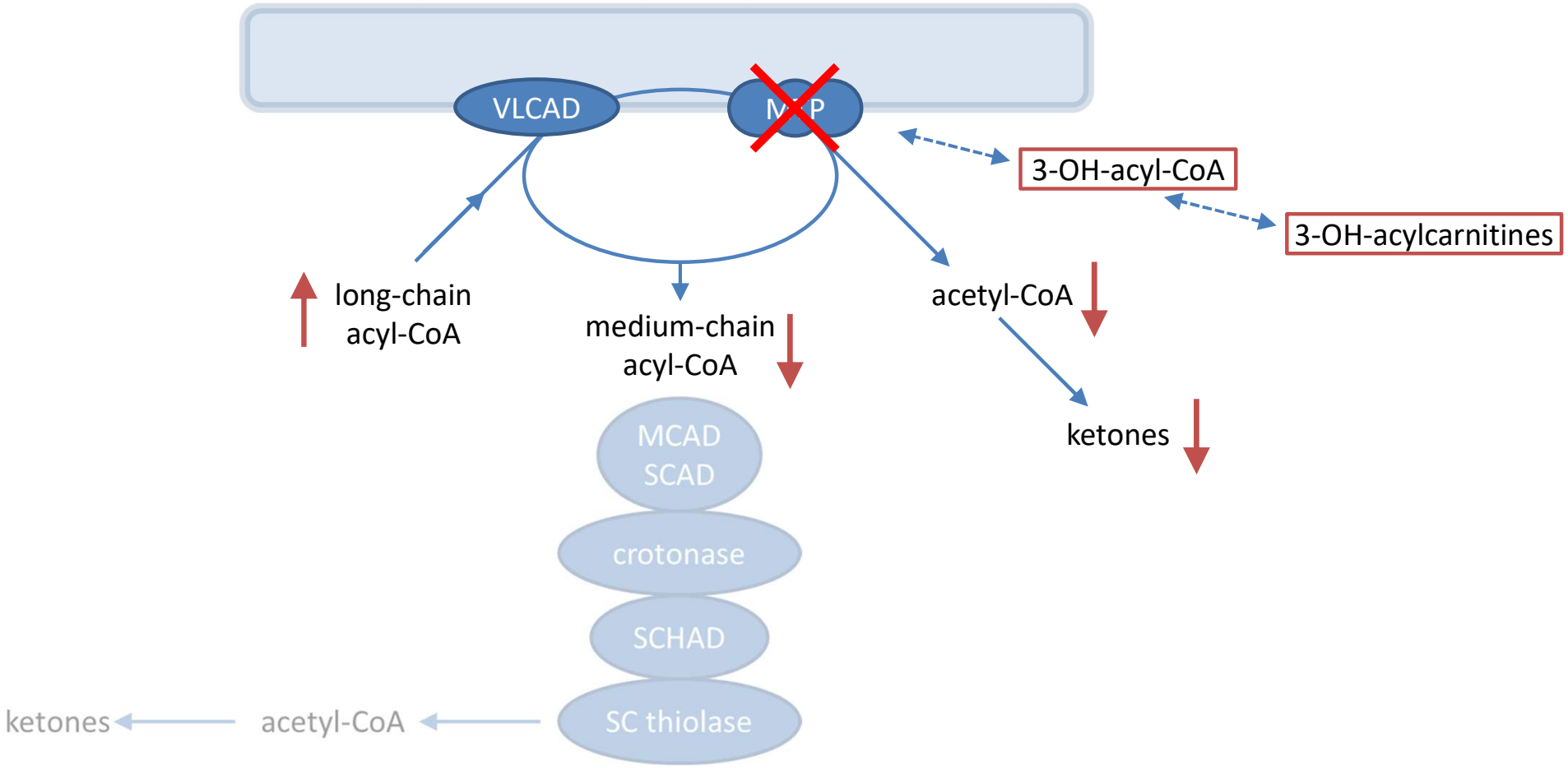



inter membrane space
Mitochondrial Inner membrane
CIV
C
CIII
Q
ETFDH
ETF
CII
CI
VLCAD
MTP
e-
long-chain acyl-CoA
medium-chain acyl-CoA
acetyl-CoA
mitochondrial matrix
e-
MCAD
SCAD
crotonase
SCHAD
MCKAT
ketones
acetyl-CoA

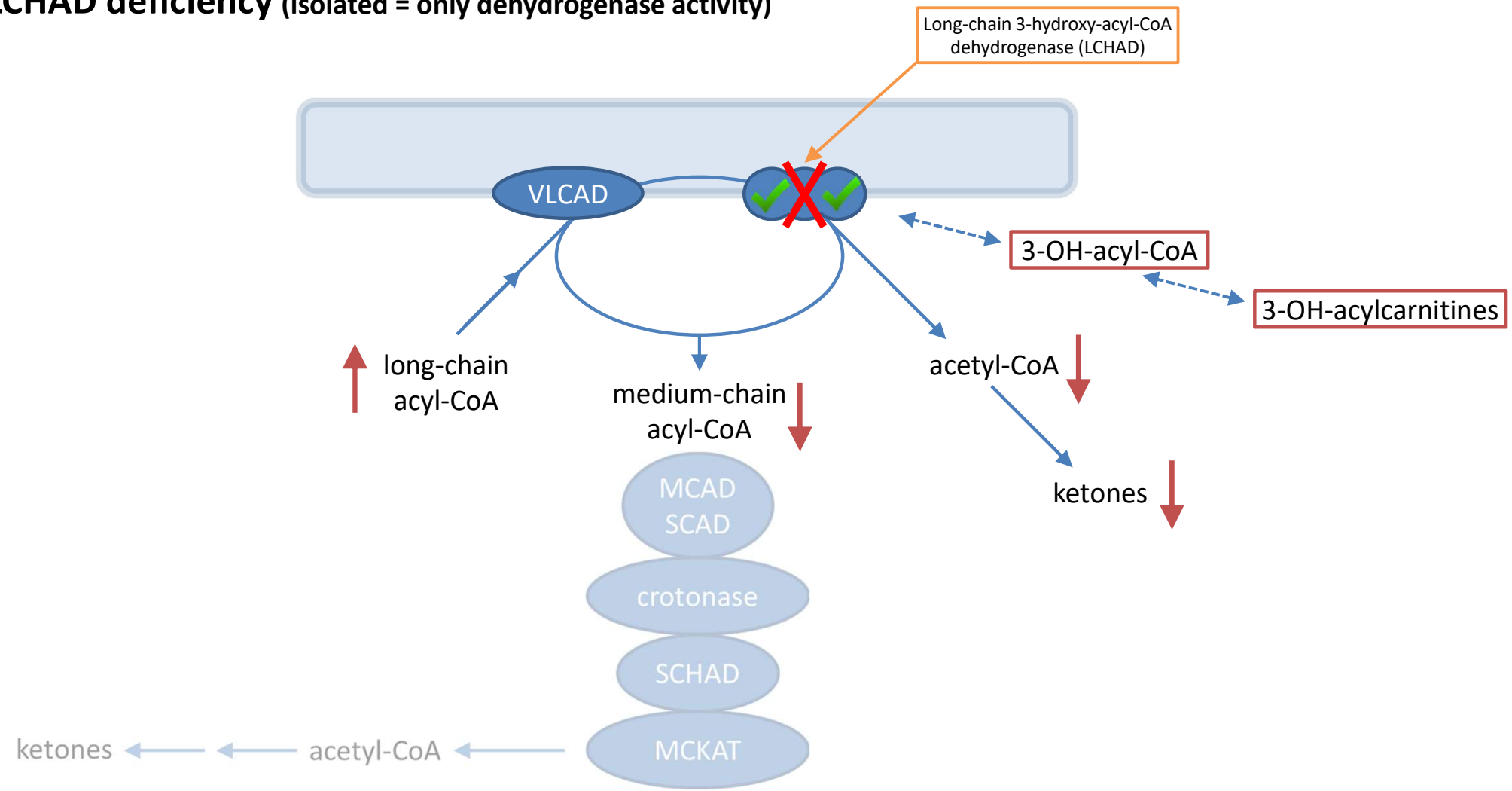

CIV
C
CIII
Q
ETFDH
ETF
CII
CI
Mitochondrial
Inner
membrane
VLCAD
MTP
e-
long-chain
acyl-CoA
medium-chain
acyl-CoA
acetyl-CoA
mitochondrial matrix
e-
MCAD
SCAD
crotonase
SCHAD
MCKAT
ketones
acetyl-CoA


VLCAD
MTP
long-chain
acyl-CoA
medium-chain
acyl-CoA
acetyl-CoA
MCAD
SCAD
crotonase
SCHAD
MCKAT
acetyl-CoA

MTP deficiency (compete = all activities)

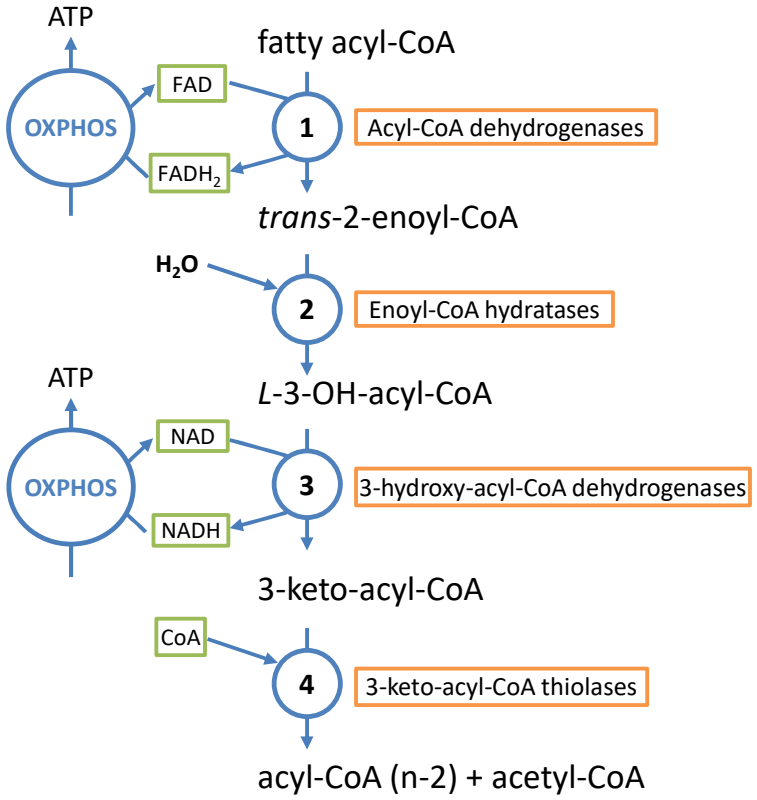


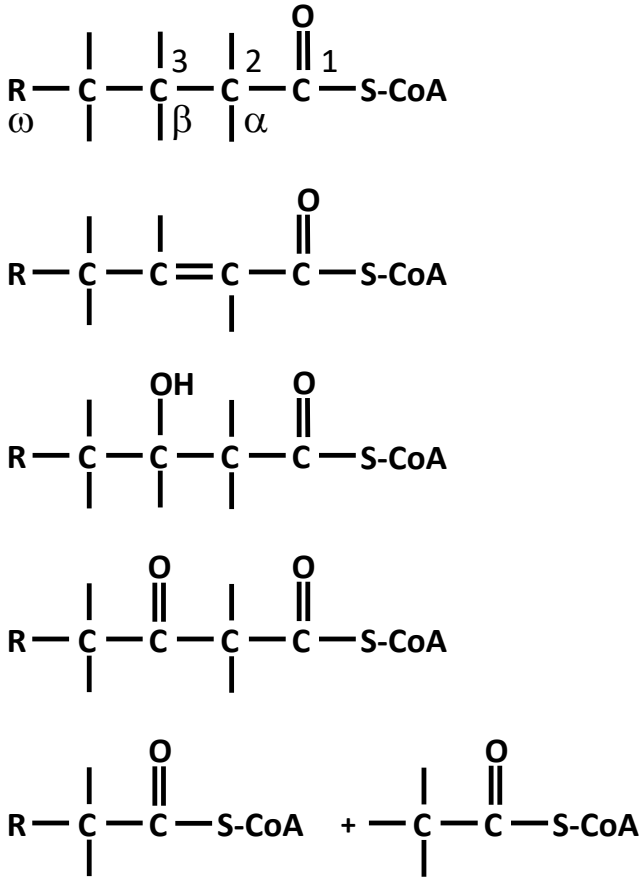
LCHAD deficiency (isolated = only dehydrogenase activity)



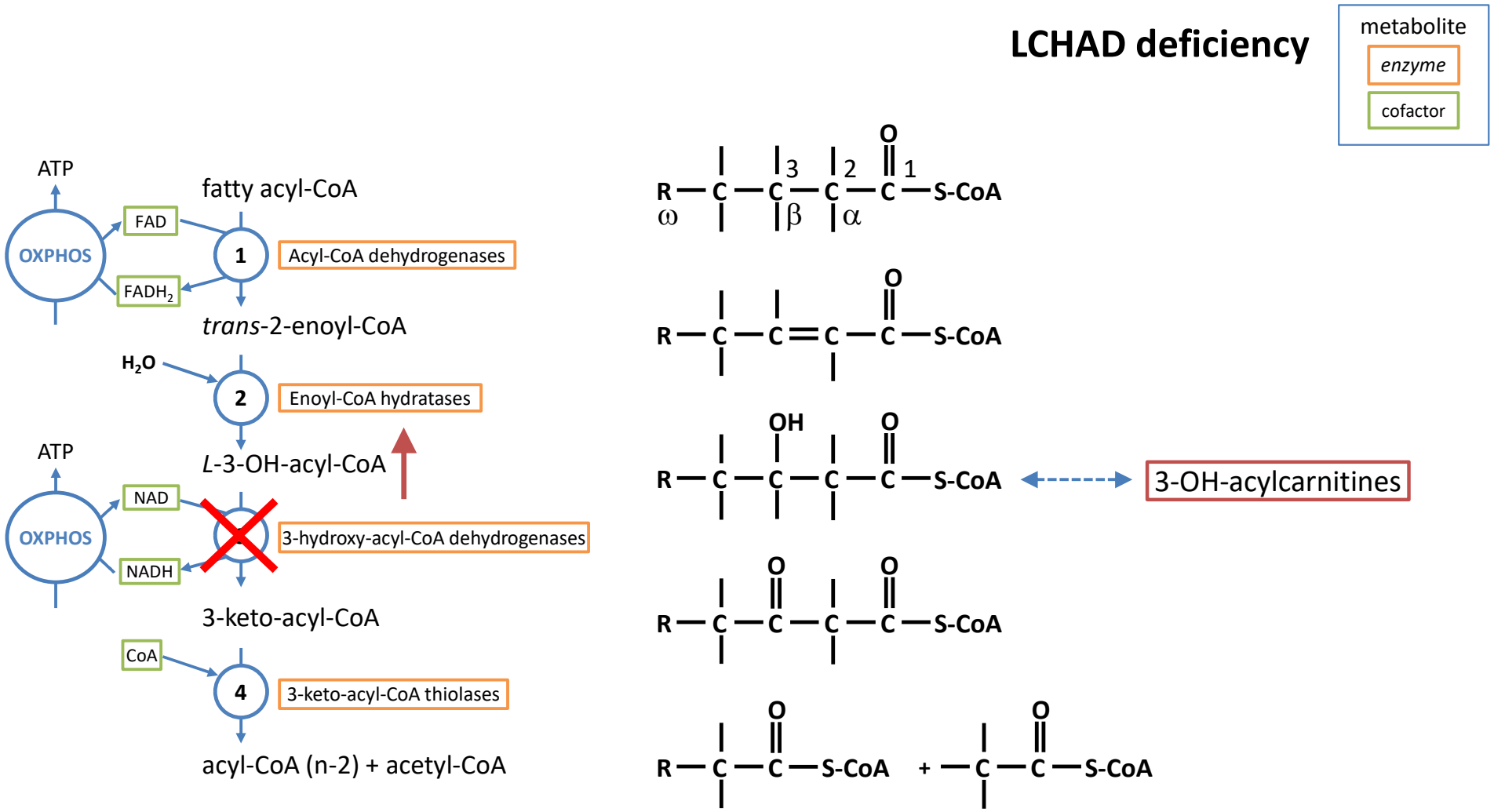
Mitochondrial β-oxidation

metabolite
enzyme
cofactor

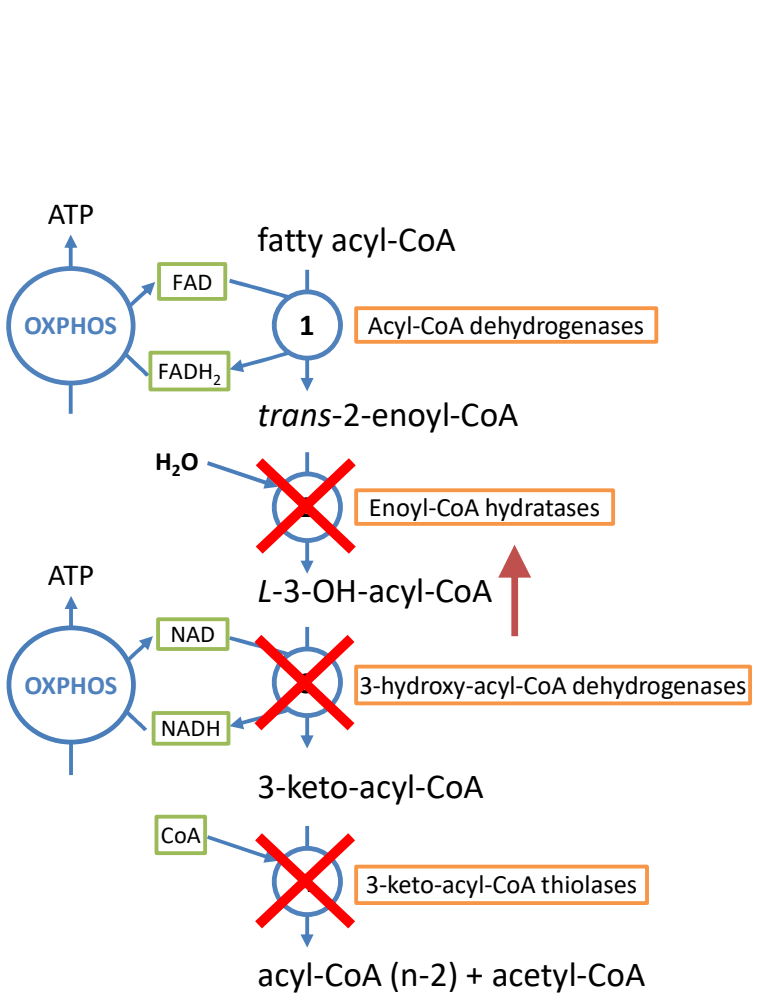


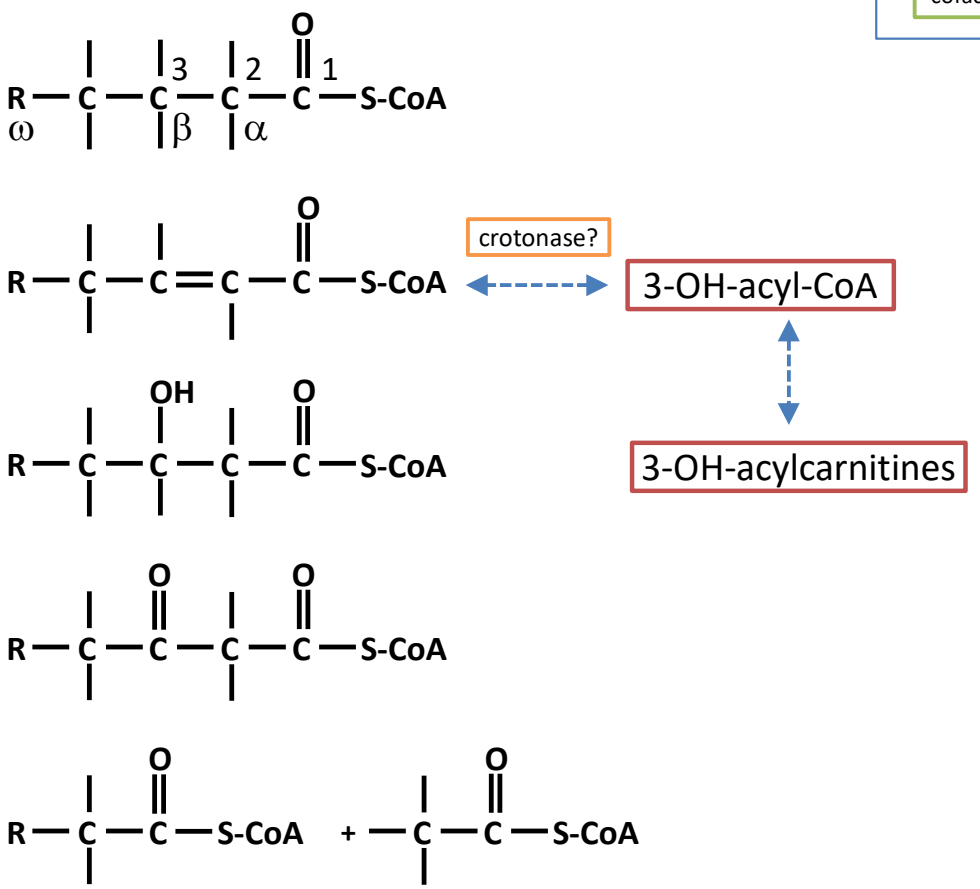


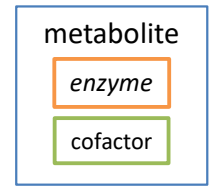
LCHAD deficiency



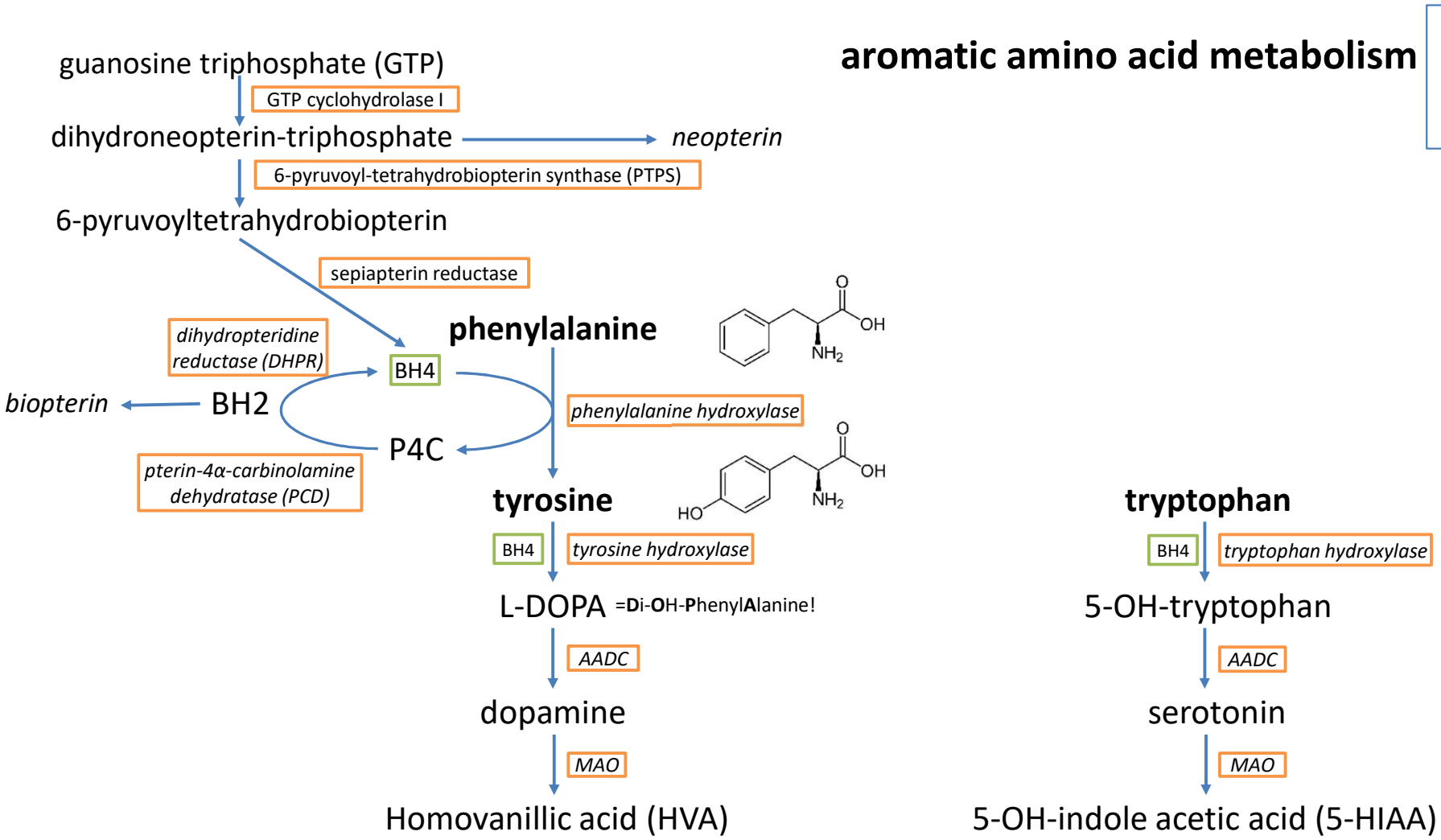
MTP deficiency





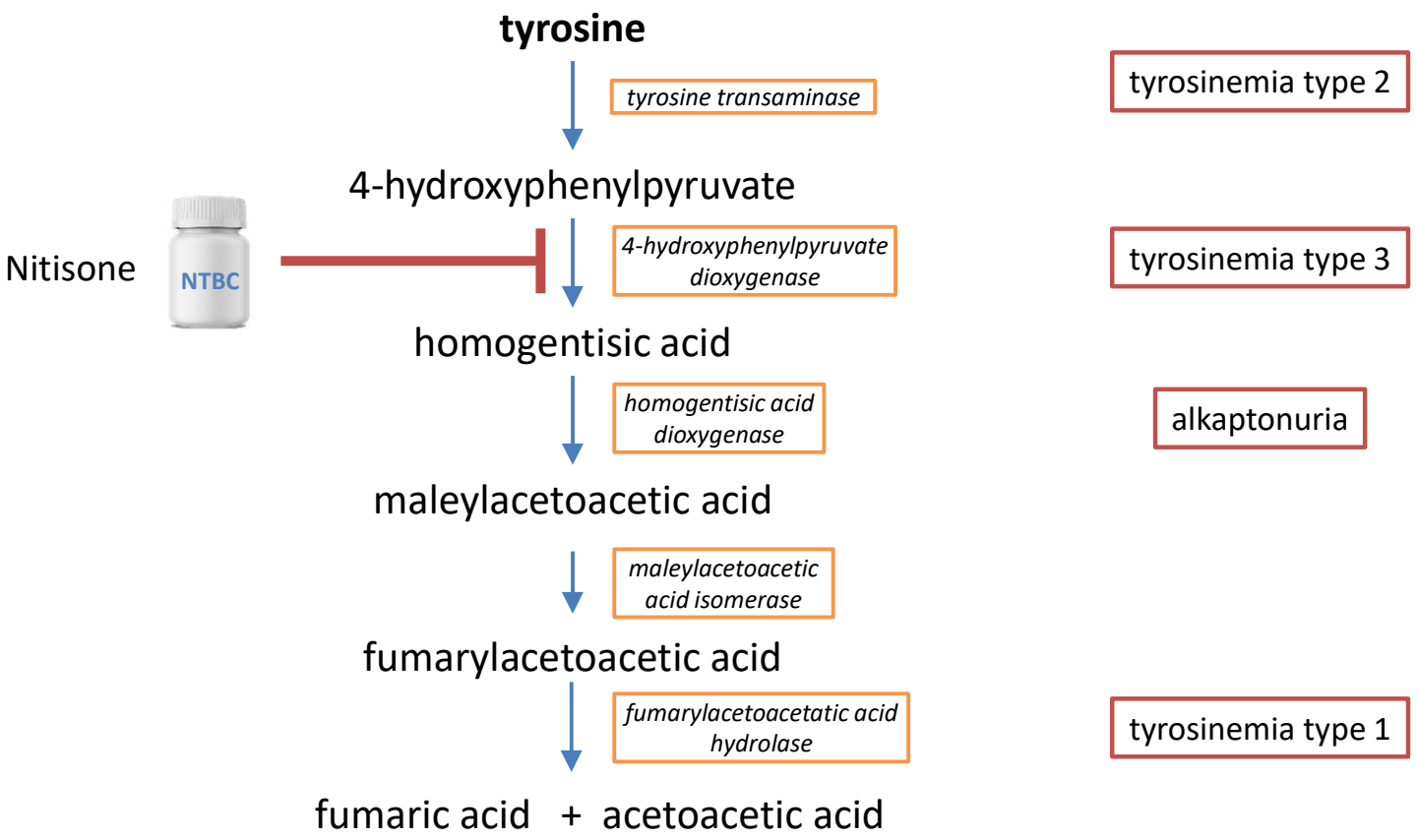


aromatic amino acid metabolism

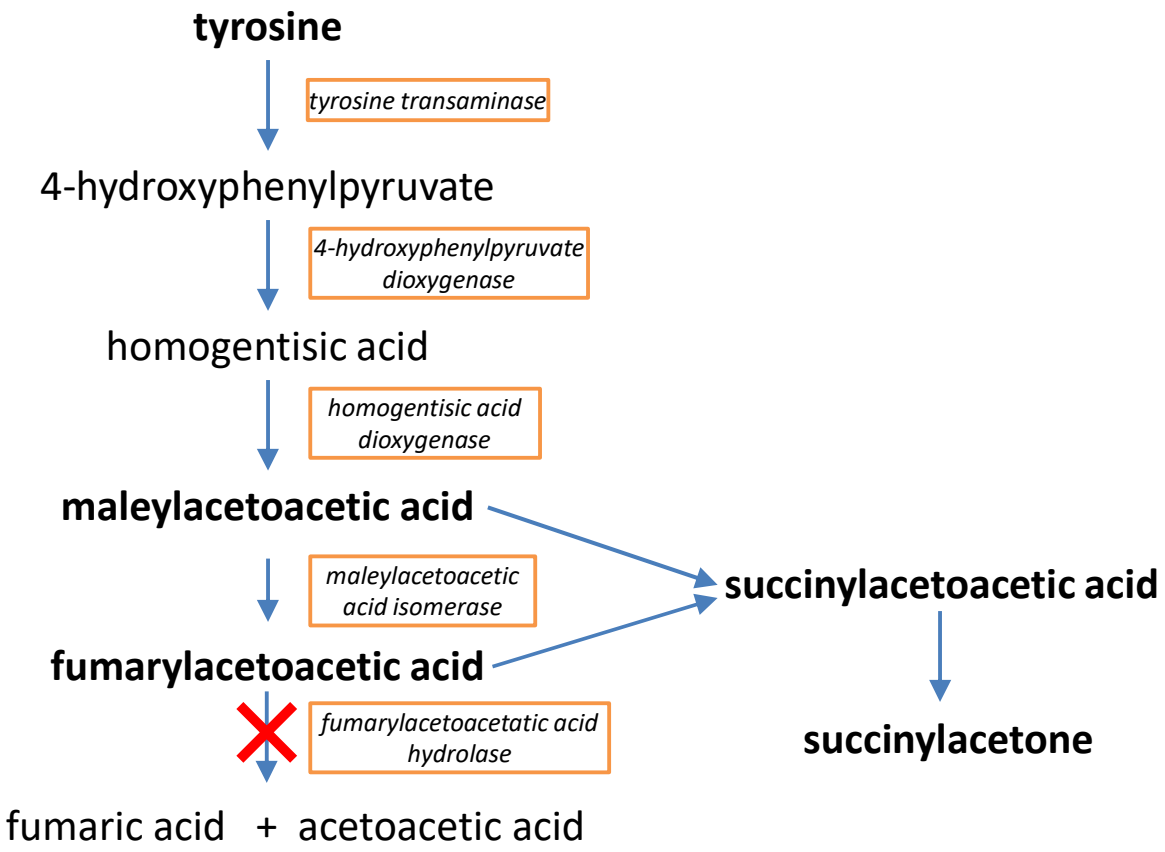


BH4: tetrahydrobioperin
BH2: dihydrobiopterin
P4C: pterin-4α-carbinolamine

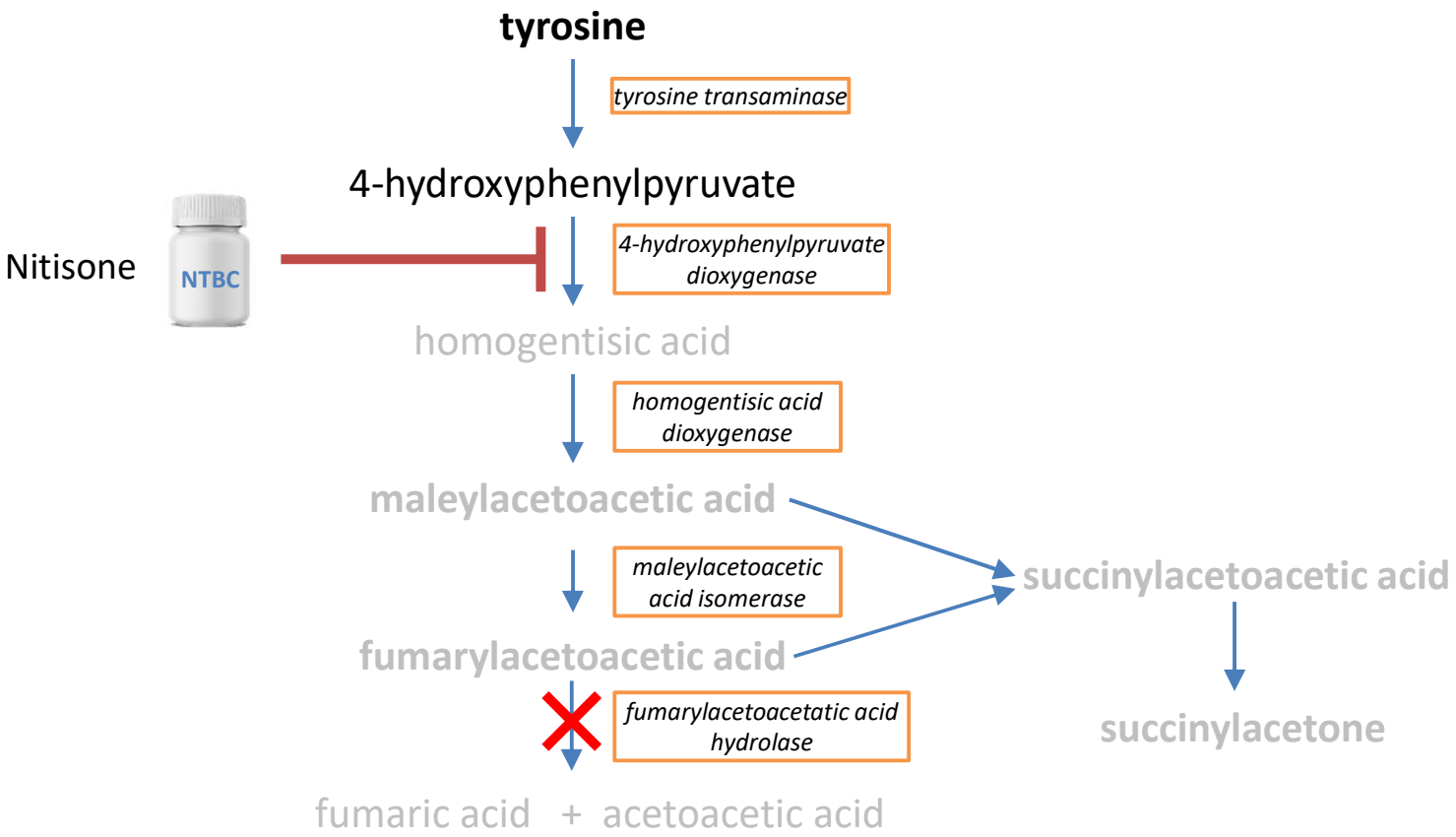
tyrosine metabolism



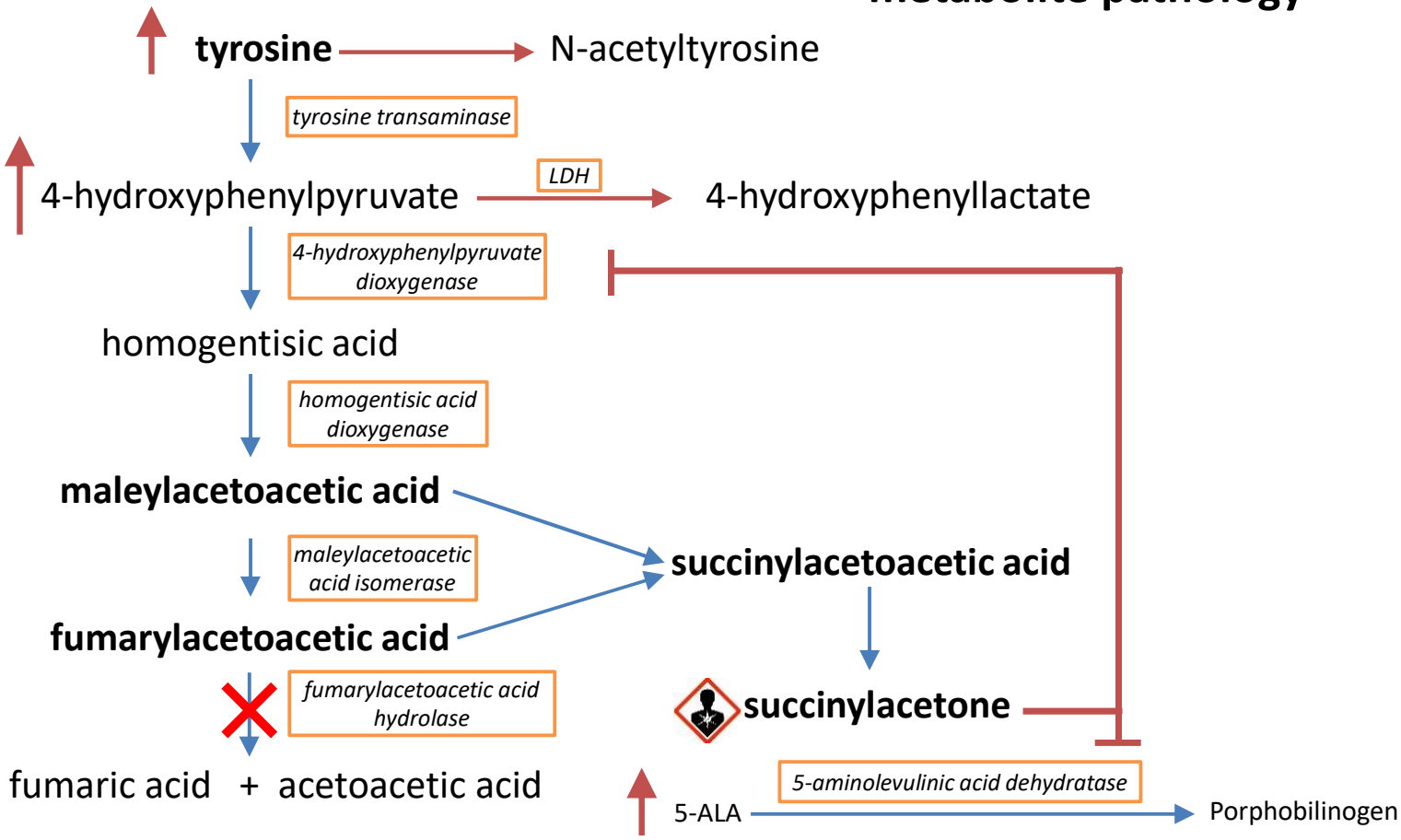
tyrosinemia type 1



tyrosinemia type 1 with NTBC



tyrosinemia type 1 metabolite pathology



tyrosinemia type 1

tyrosine

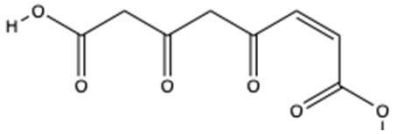
↓ *tyrosine transaminase*

4-hydroxyphenylpyruvate

↓ *4-hydroxyphenylpyruvate dioxygenase*

homogentisic acid

↓ *homogentisic acid dioxygenase*



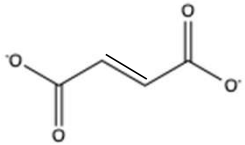
maleylacetoacetic acid

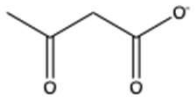
↓ *maleylacetoacetic acid isomerase*

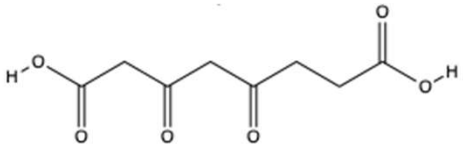
fumarylacetoacetic acid

✕ *fumarylacetoacetic acid hydrolase*

fumaric acid + acetoacetic acid



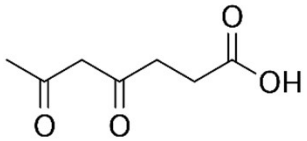


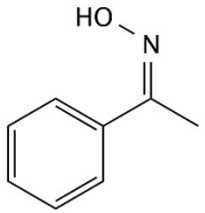


succinylacetoacetic acid

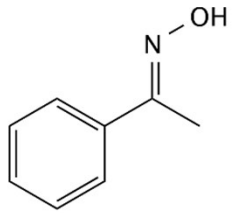
↓

succinylacetone





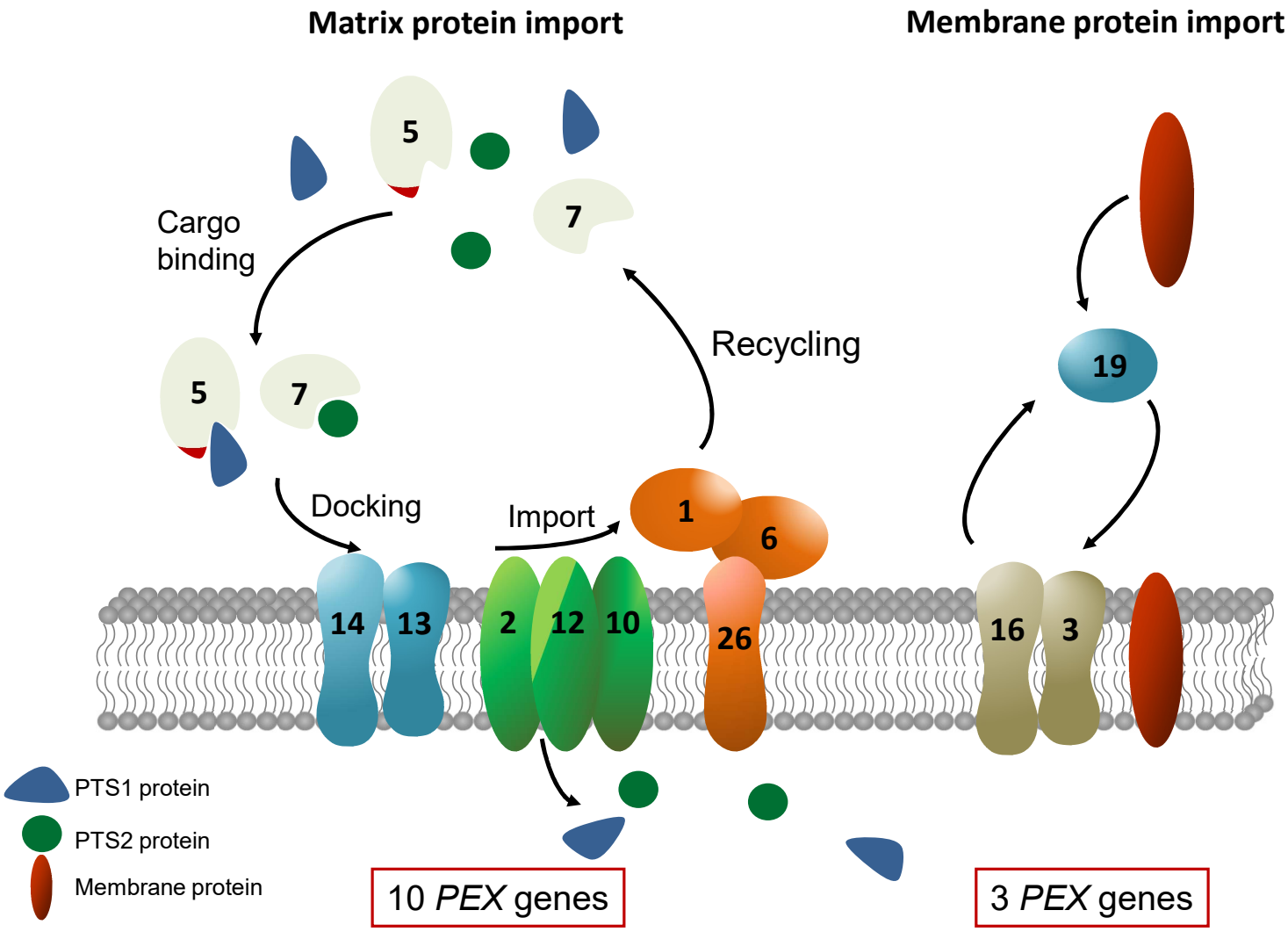
syn (Z)



anti (E)

2 keto groups: 4 possible oximes:
syn/syn --- syn/anti --- anti/syn --- anti/anti
+partial methoxime formation! → multiple peaks

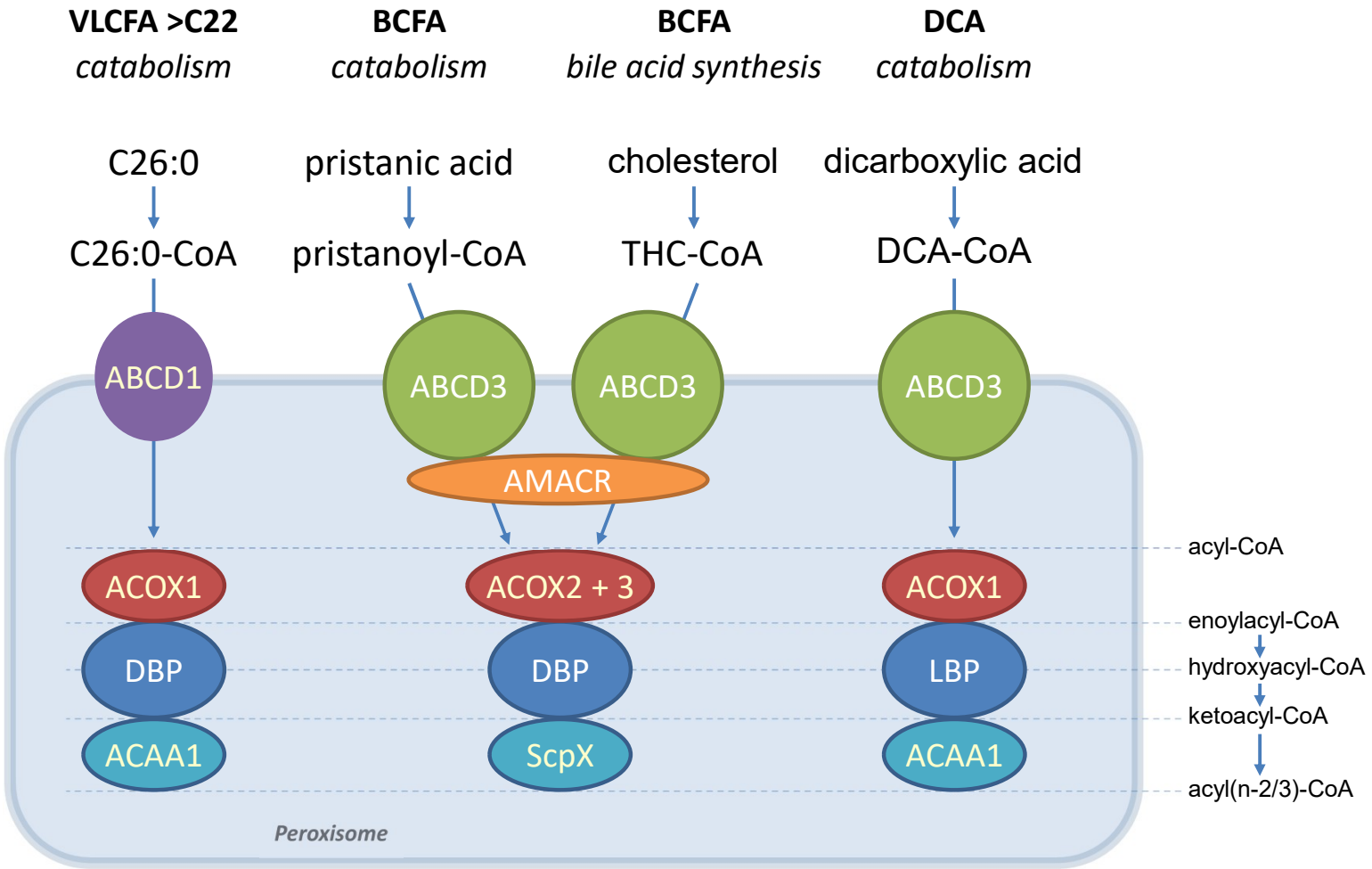
peroxisomal protein import



ABCD1 = ALDP = adrenoleukodystrophy protein
ABCD3 = PMP70 = peroxisomal membrane protein 70
ACOX = acyl-CoA oxidase
AMACR = α-methylacyl-CoA reductase
DBP = D-bifunctional protein
LBP = L-bifunctional protein
ACAA1 = 3-Ketoacyl-CoA thiolase
ScpX = sterol carrier protein X

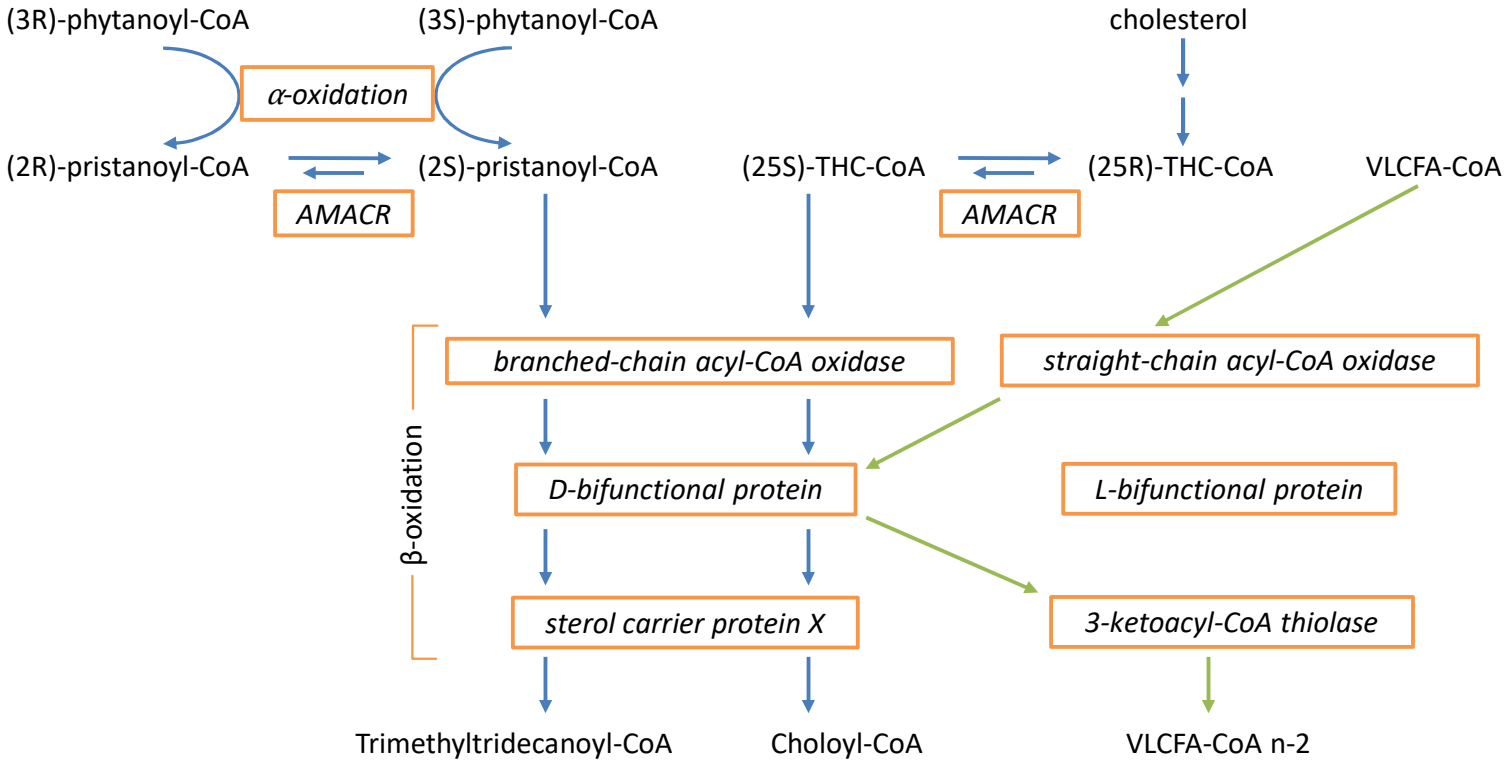
peroxisomal β-oxidation

import and degradation



ALTERNATIVE
(no DCA)

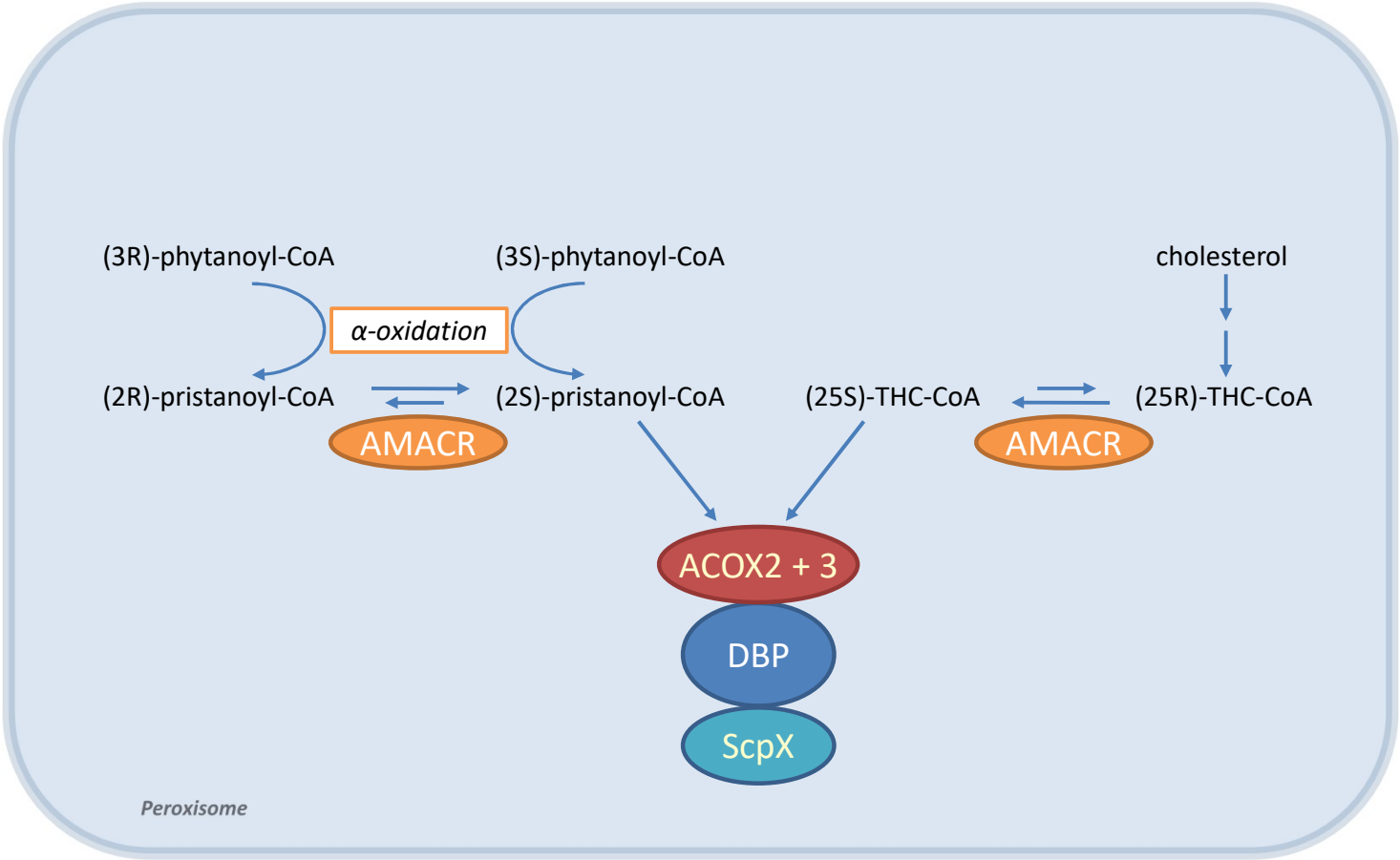
peroxisomal fatty acid metabolism
VLCFA and BCFA



THC(A) = di/trihydroxycholestanoic (acid)

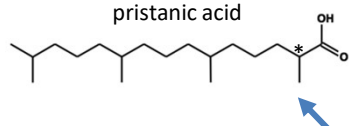
peroxisomal fatty acid metabolism

chirality matters

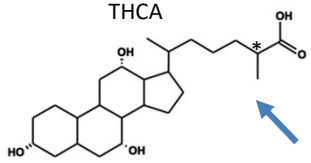


2-methyl branched-chain

pristanic acid



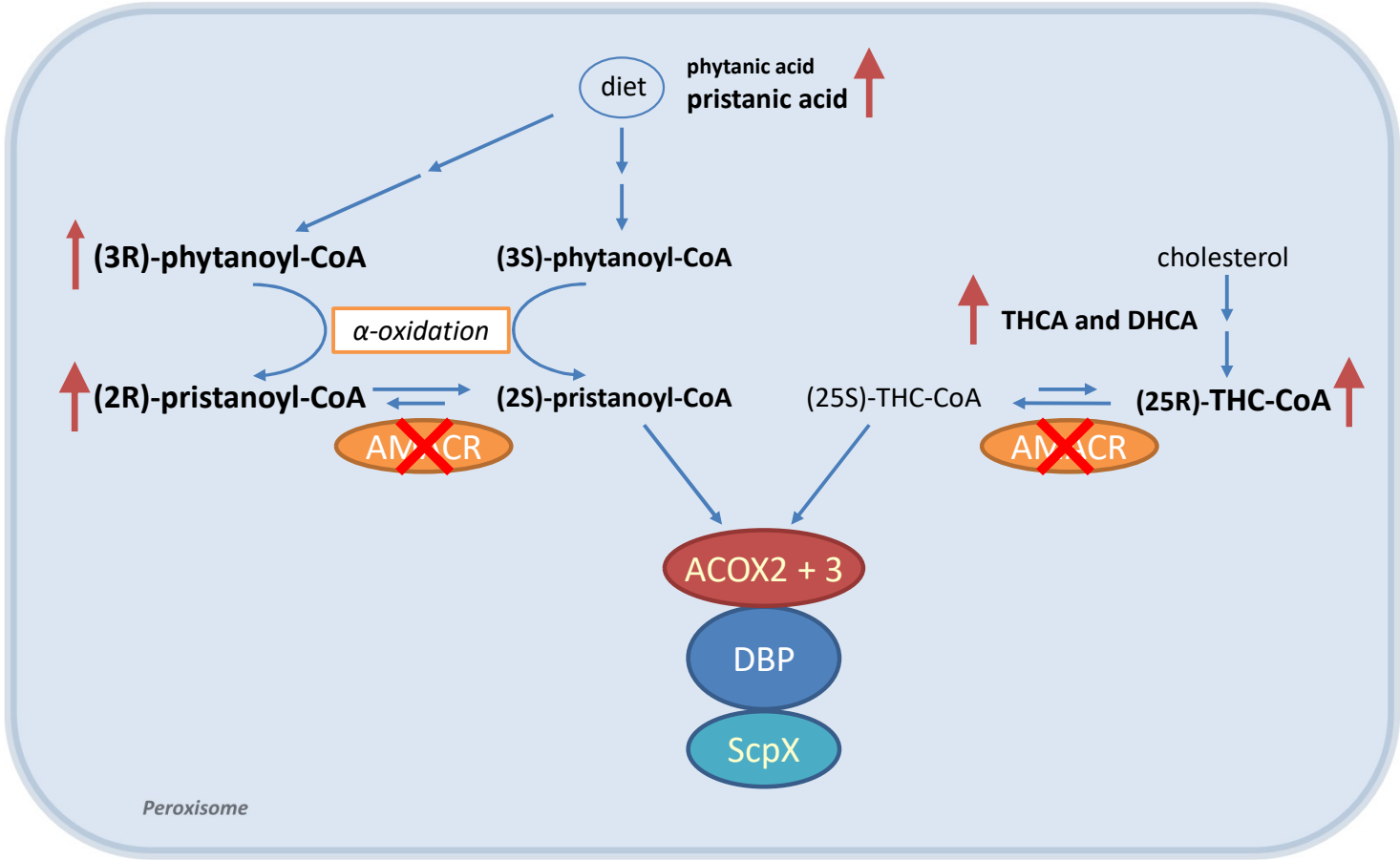
THCA



*asymmetric carbon atom

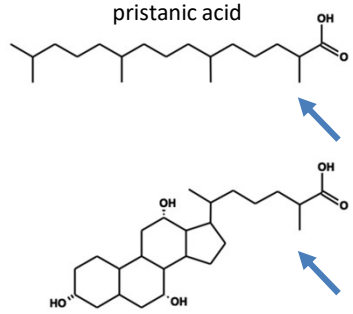
α-methylacyl-CoA racemase deficiency

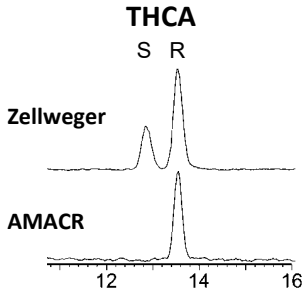
chirality matters



2-methyl branched-chain

pristanic acid

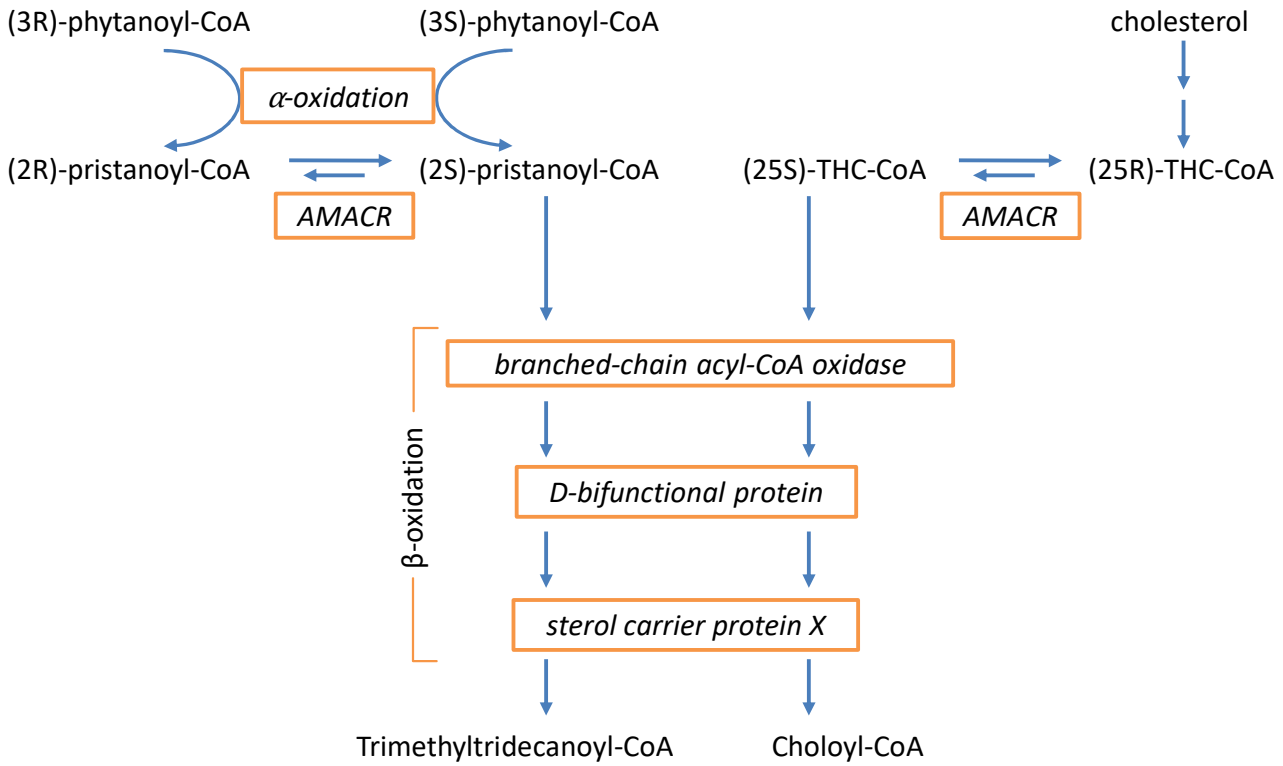




ALTERNATIVE

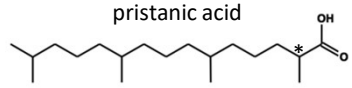
peroxisomal fatty acid metabolism

chirality matters

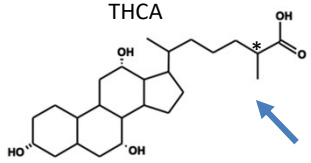


2-methyl branched-chain

pristanic acid



THCA



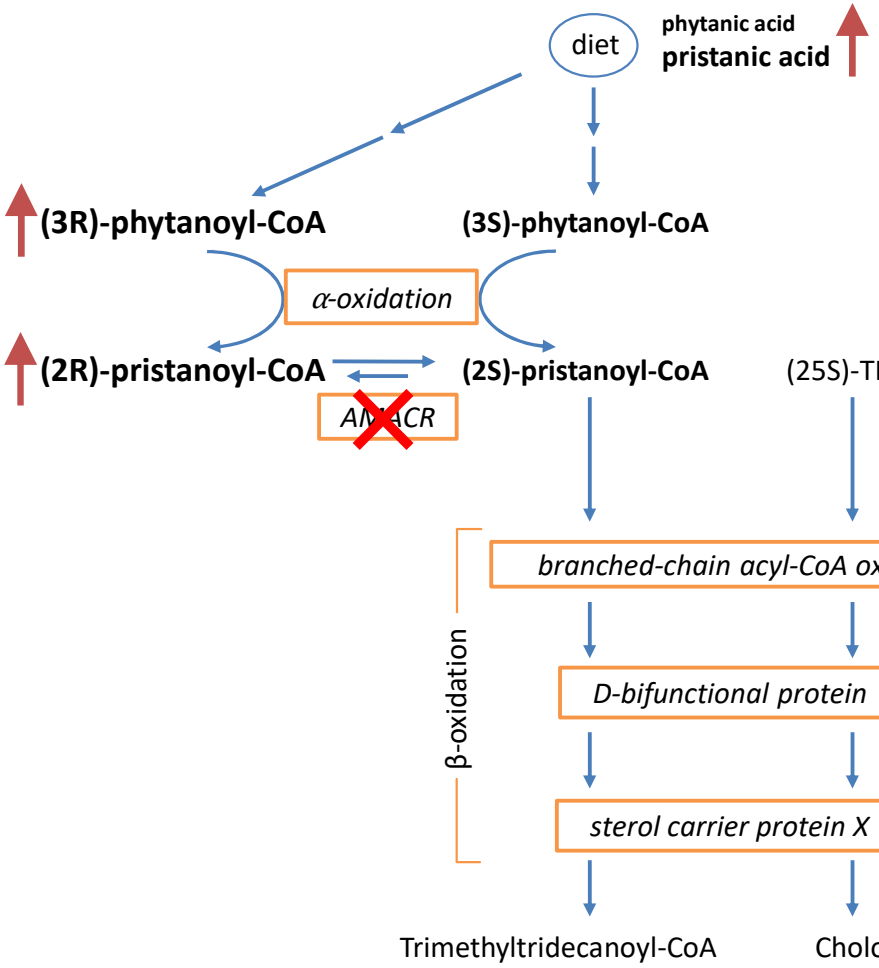
*asymmetric carbon atom

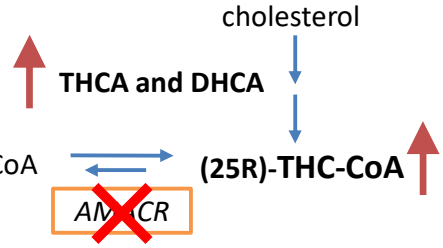
THC(A) = di/trihydroxycholestanoic (acid)

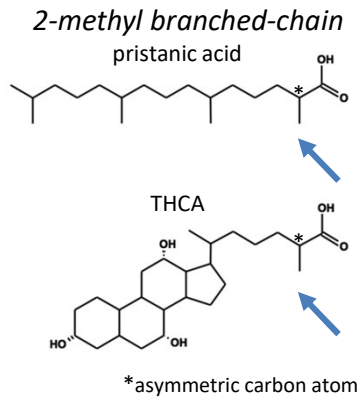
ALTERNATIVE

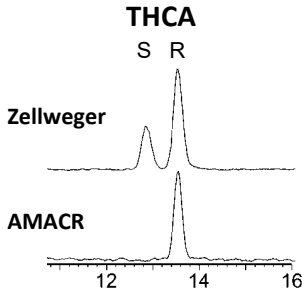
α-methylacyl-CoA racemase deficiency

chirality matters



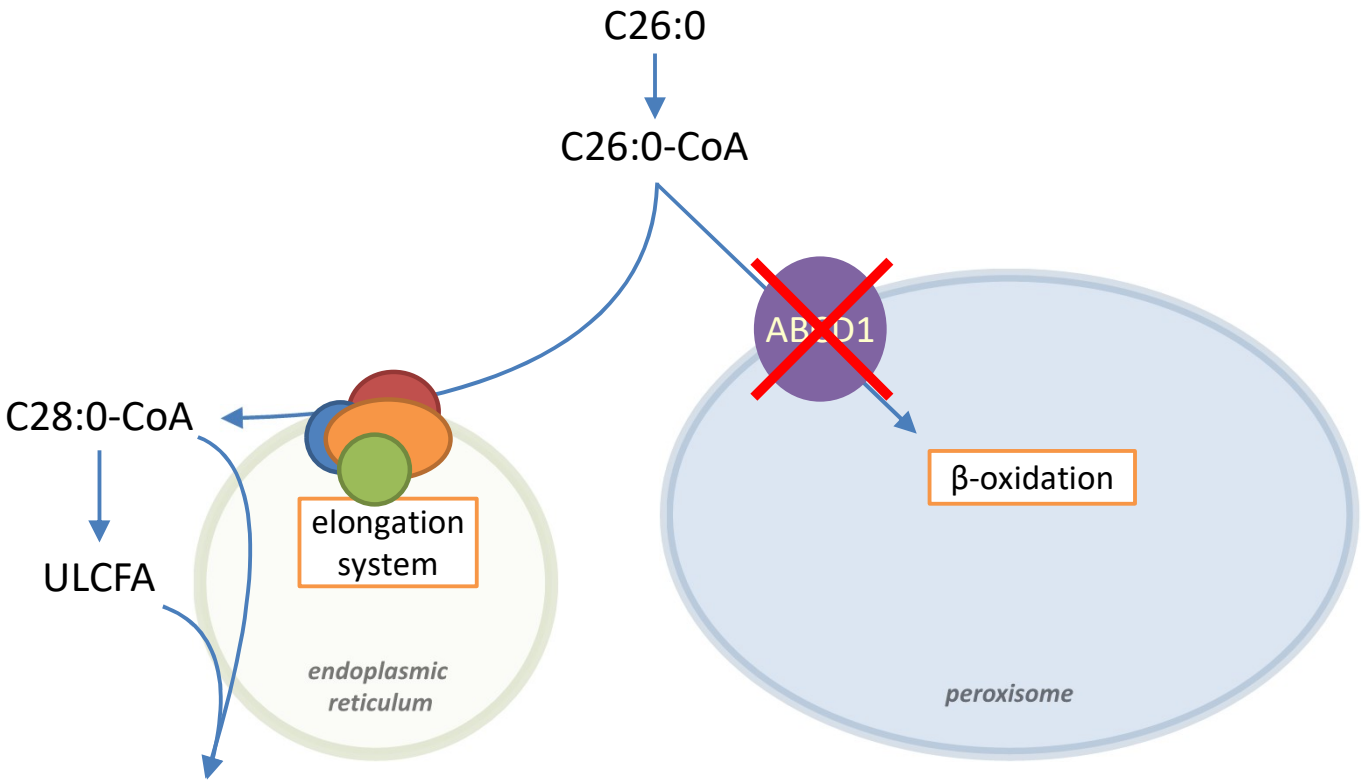






THCA = trihydroxycholestanoic acid

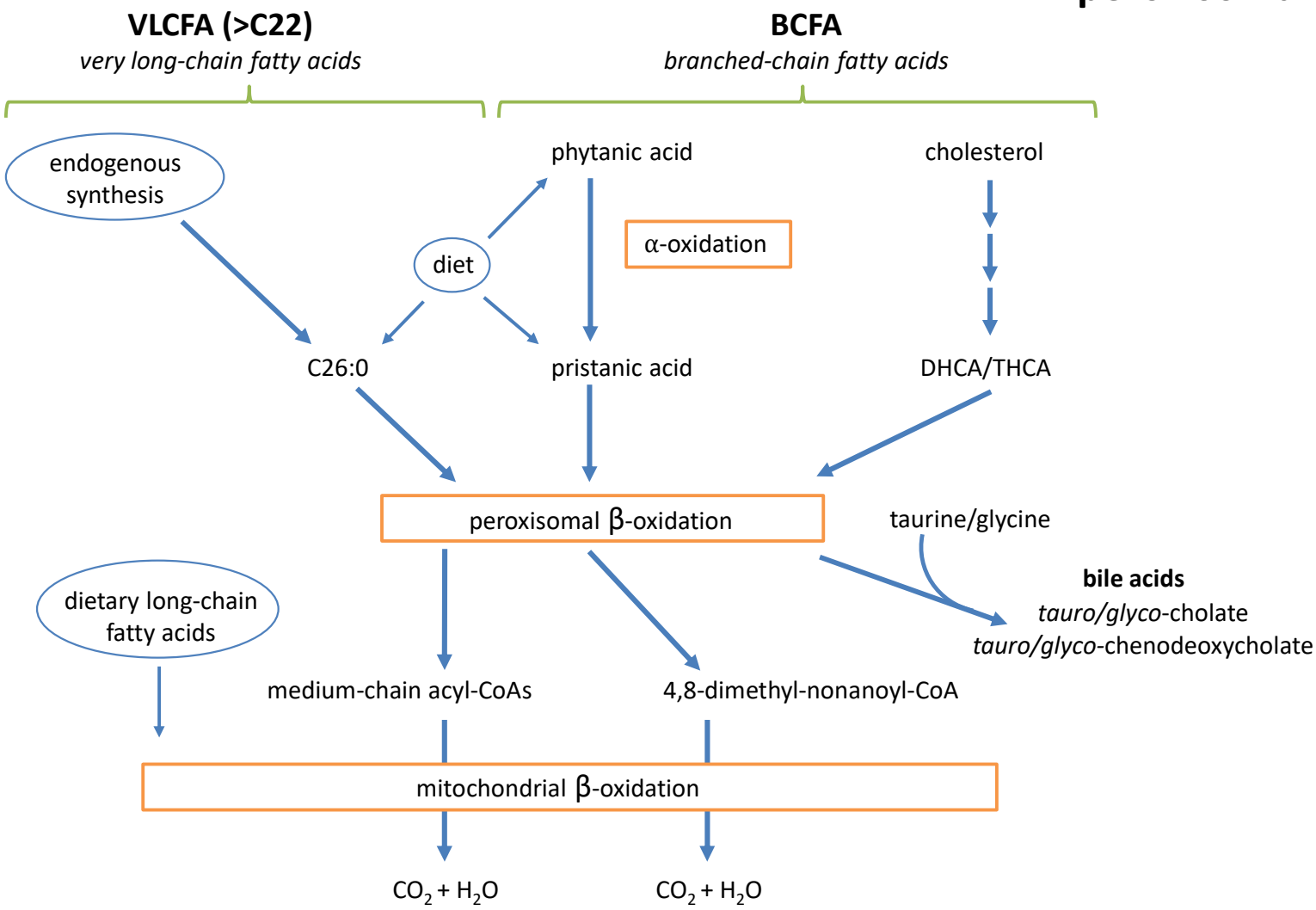
adrenoleukodystrophy



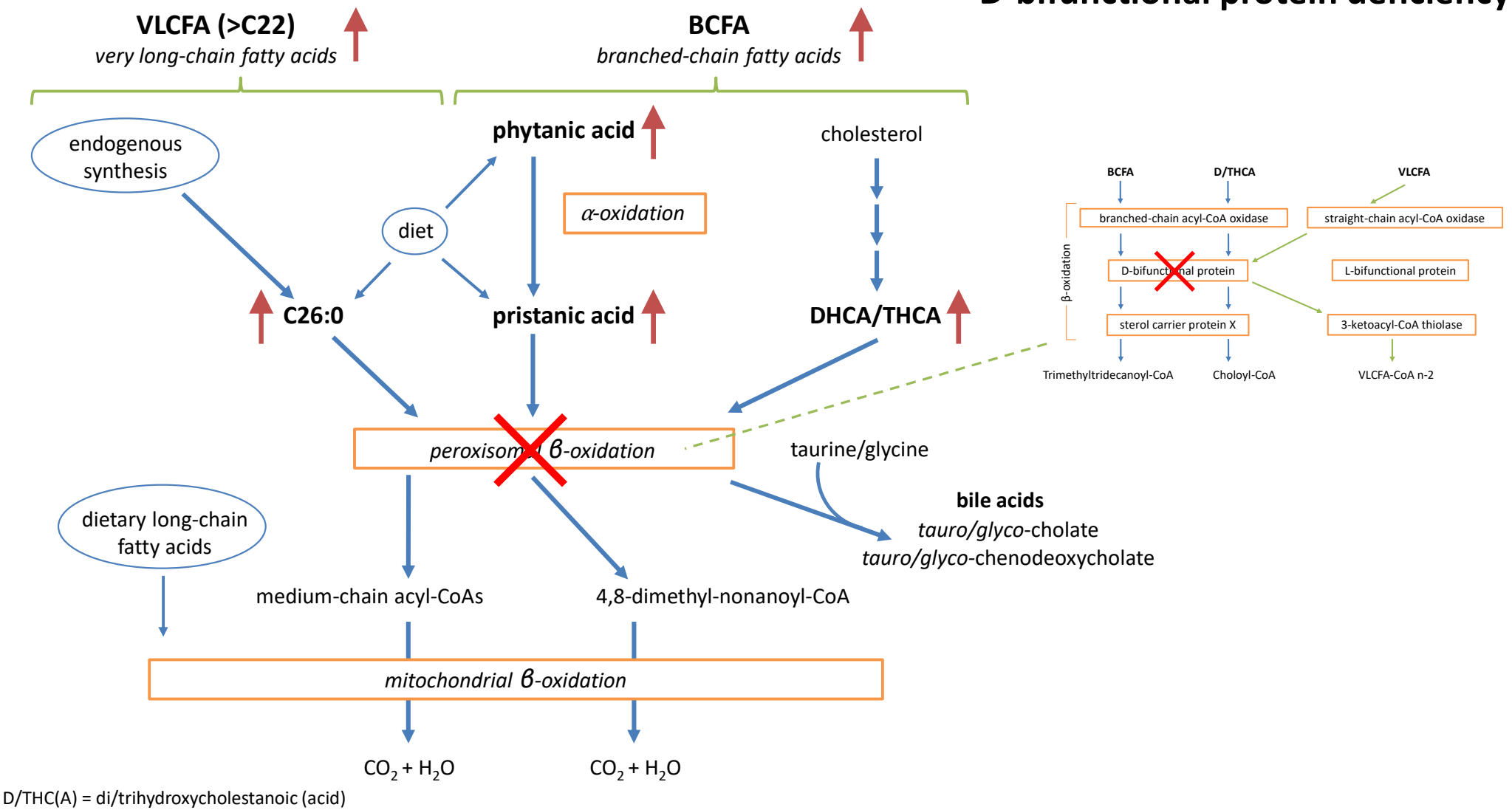
VLCFA and ULCFA incorporation in membrane lipids

Biomarkers: C26:0-lysoPC and total VLCFA

peroxisomal fatty acid metabolism
overview

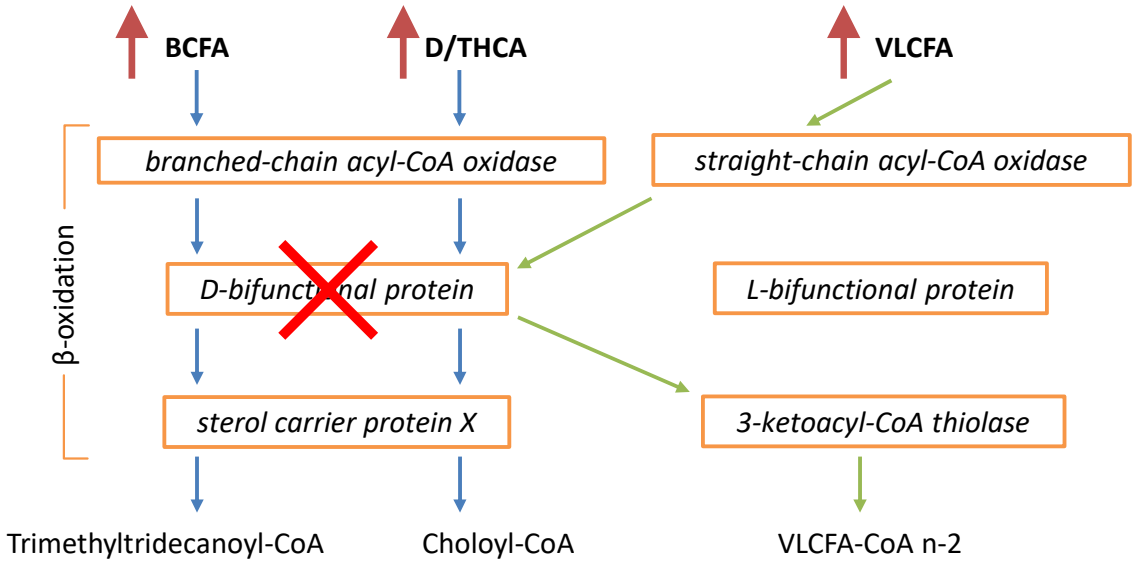


D-bifunctional protein deficiency

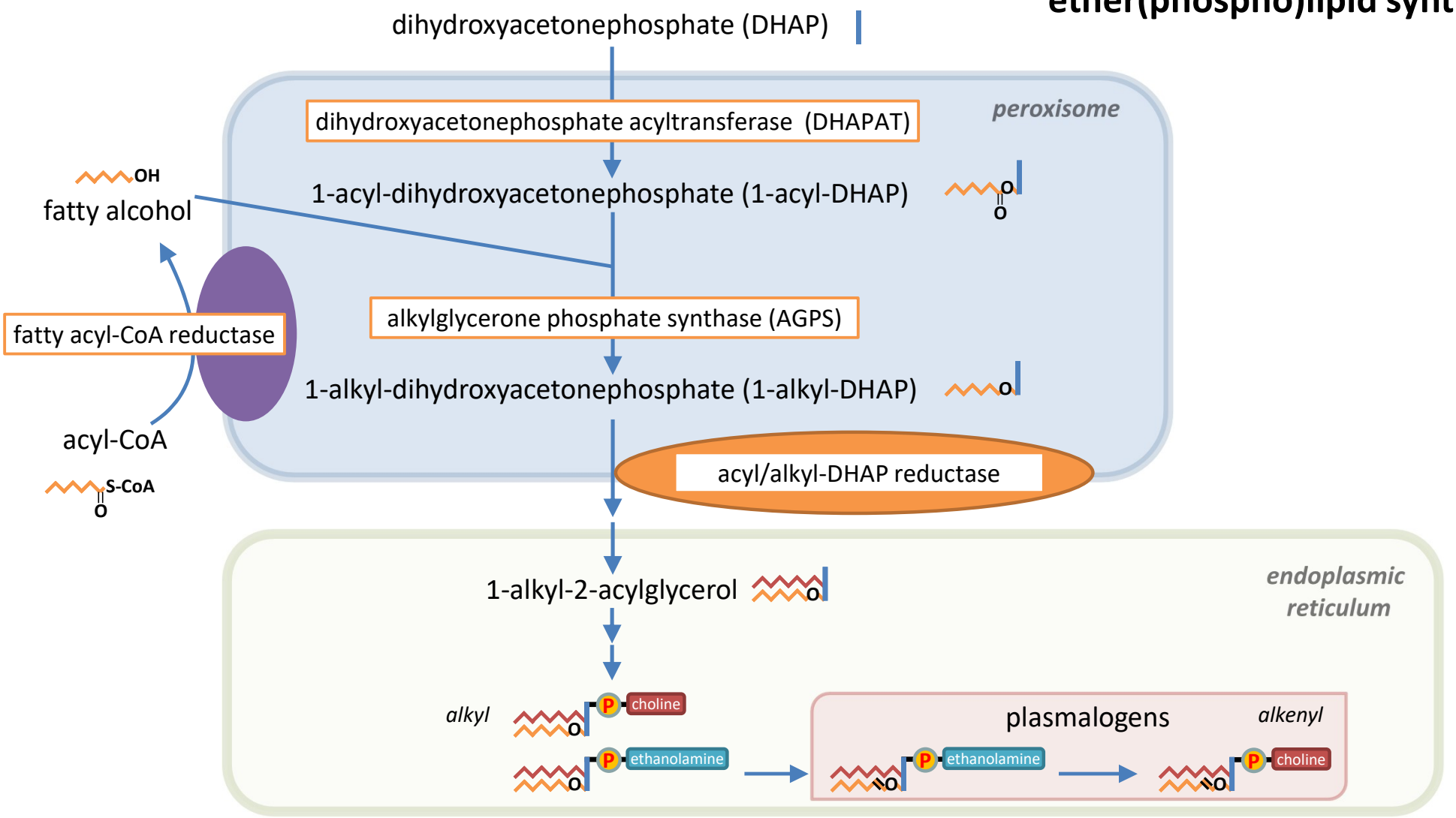


D/THC(A) = di/trihydroxycholestanoic (acid)

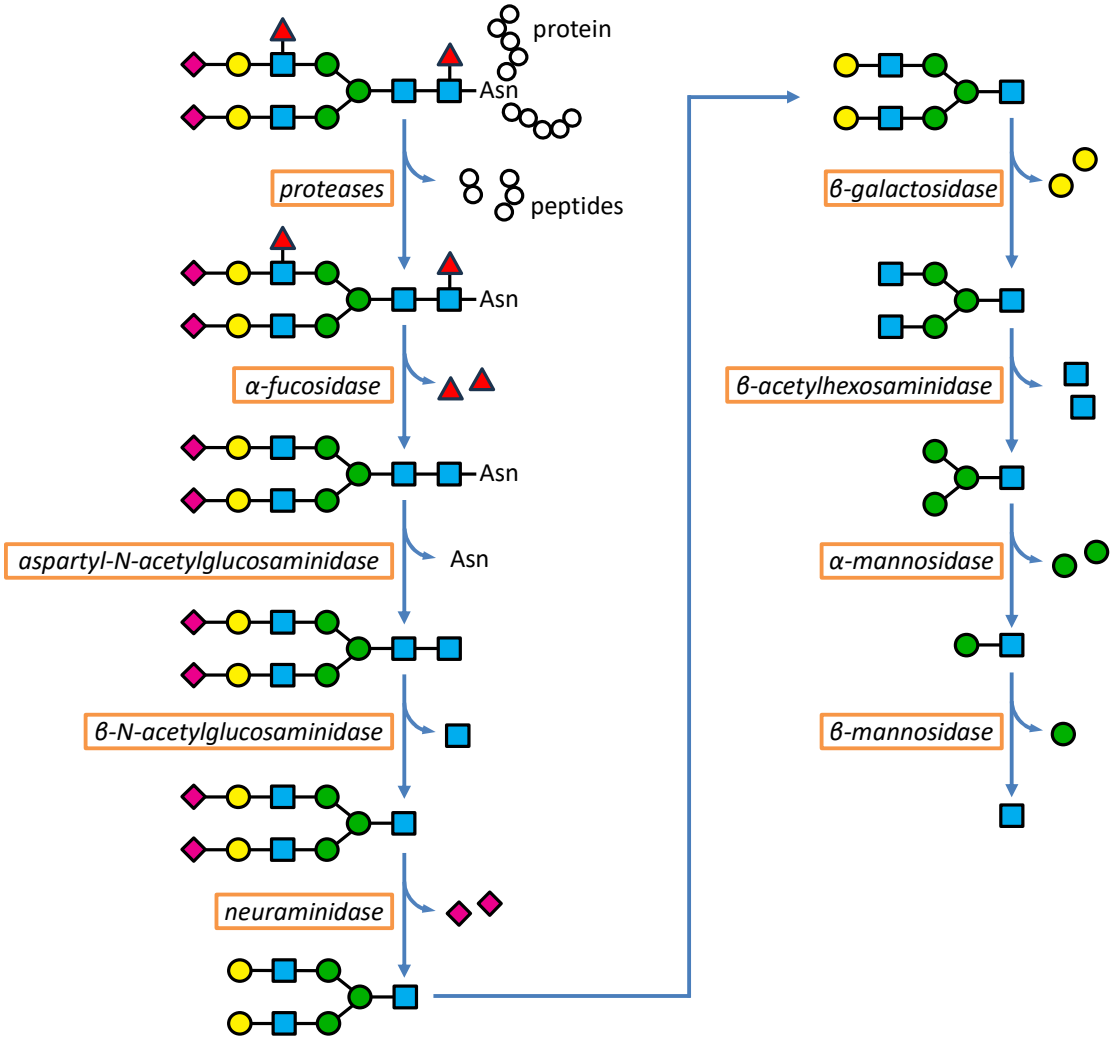
D-bifunctional protein deficiency

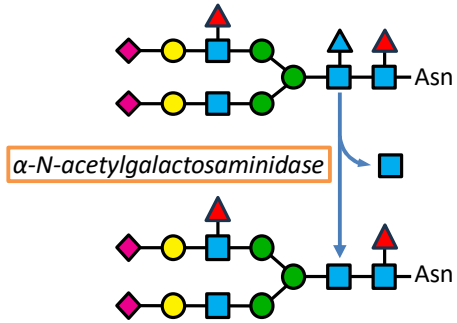


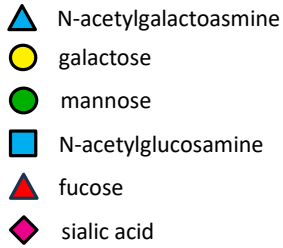
ether(phospho)lipid synthesis



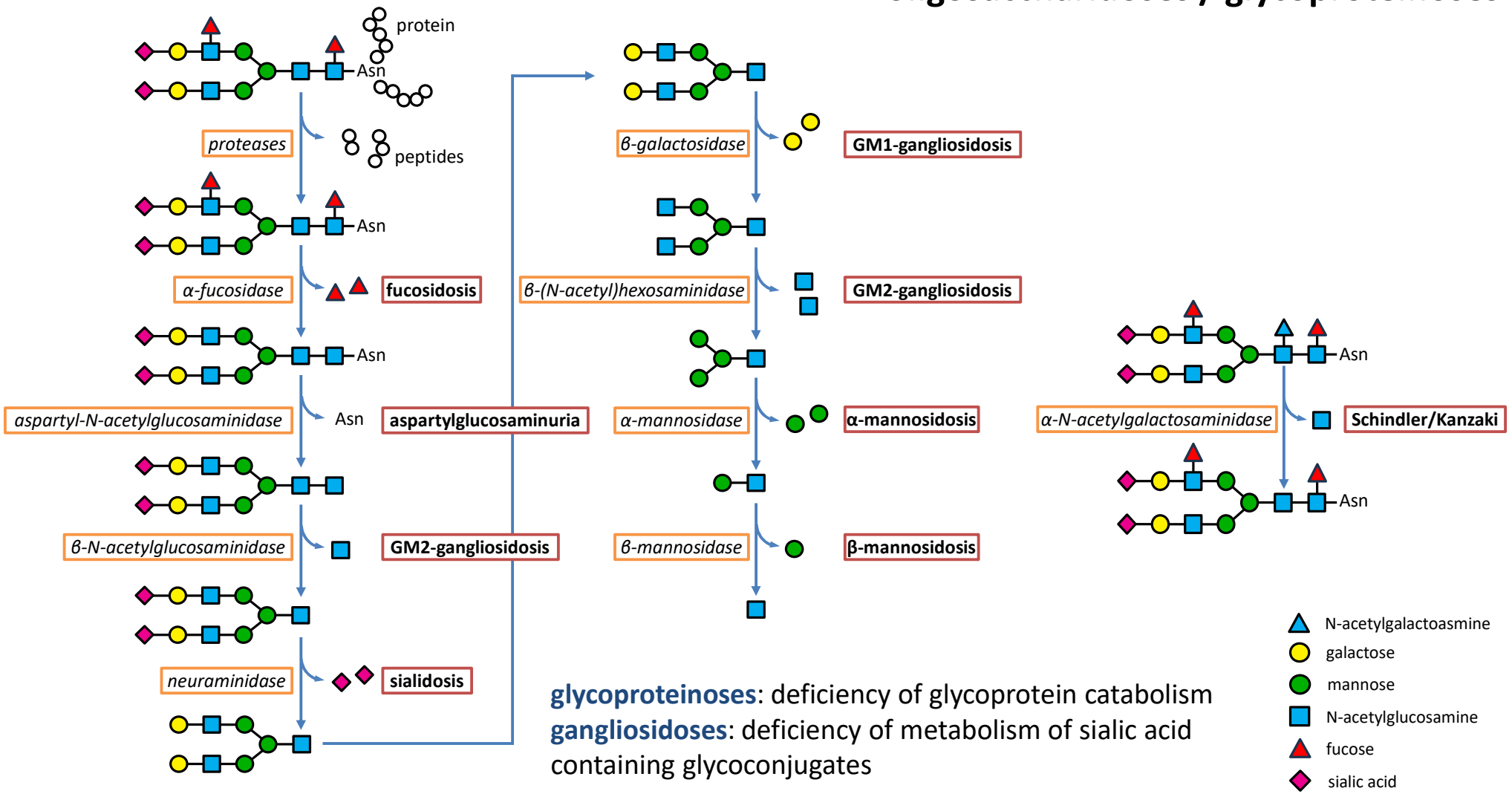
oligosaccharide catabolism







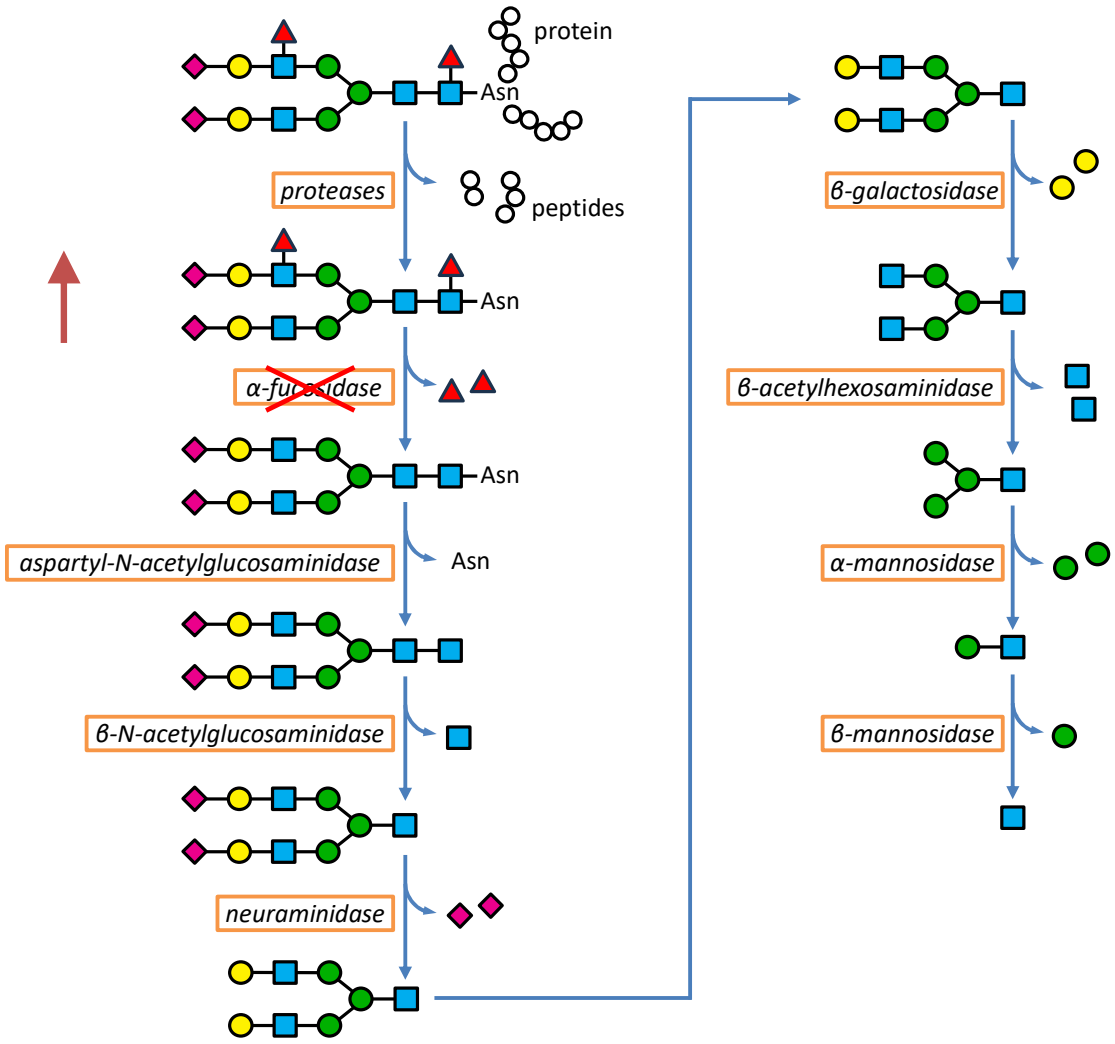
oligosaccharidoses / glycoproteinoses

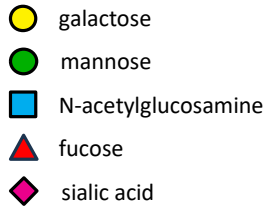


glycoproteinoses: deficiency of glycoprotein catabolism
gangliosidoses: deficiency of metabolism of sialic acid containing glycoconjugates

fucosidosis

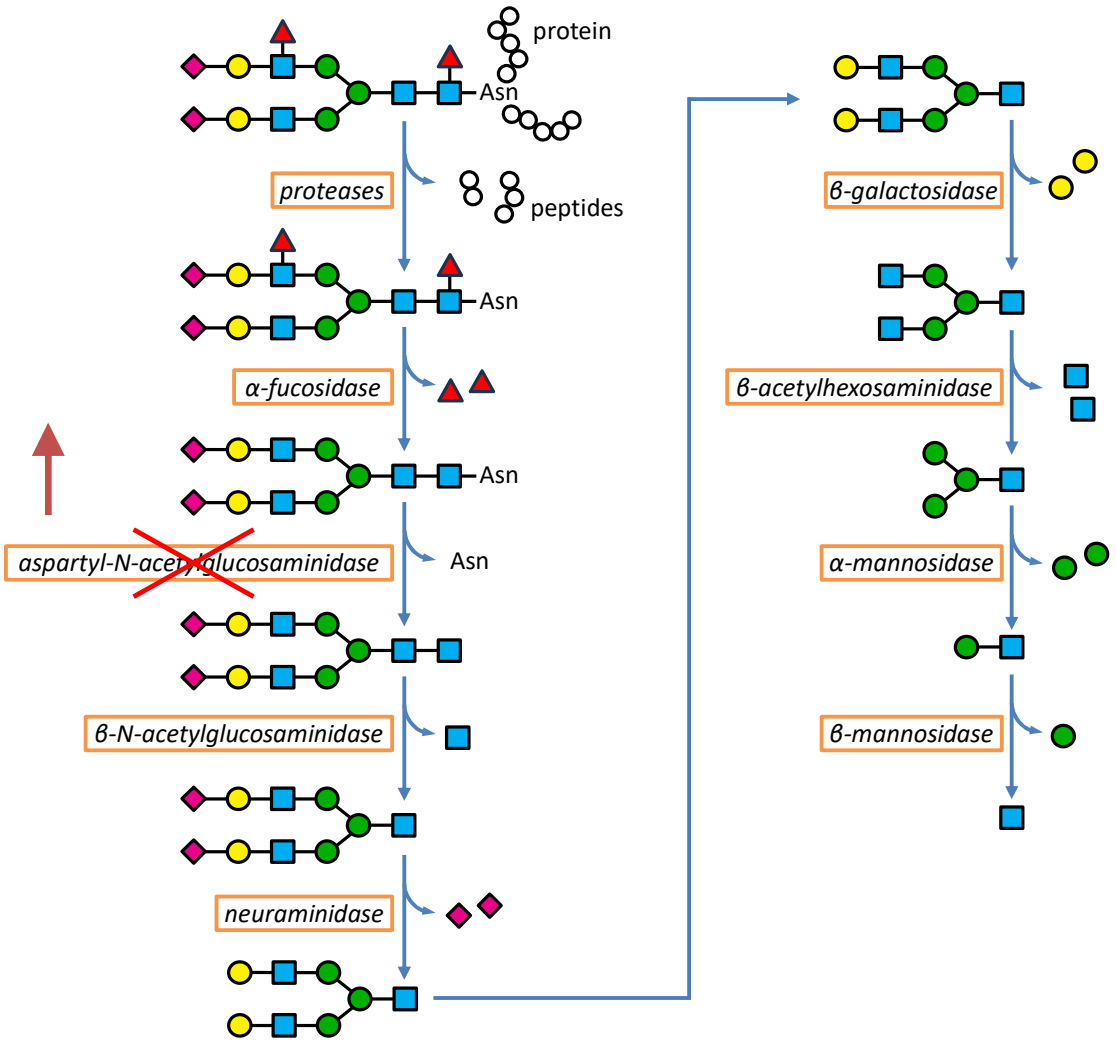
α-fucosidase deficiency

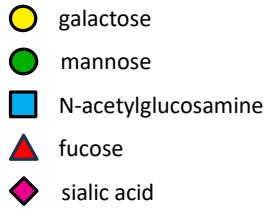




N-aspartylglucosaminuria

aspartyl-N-acetylglucosaminidase deficiency

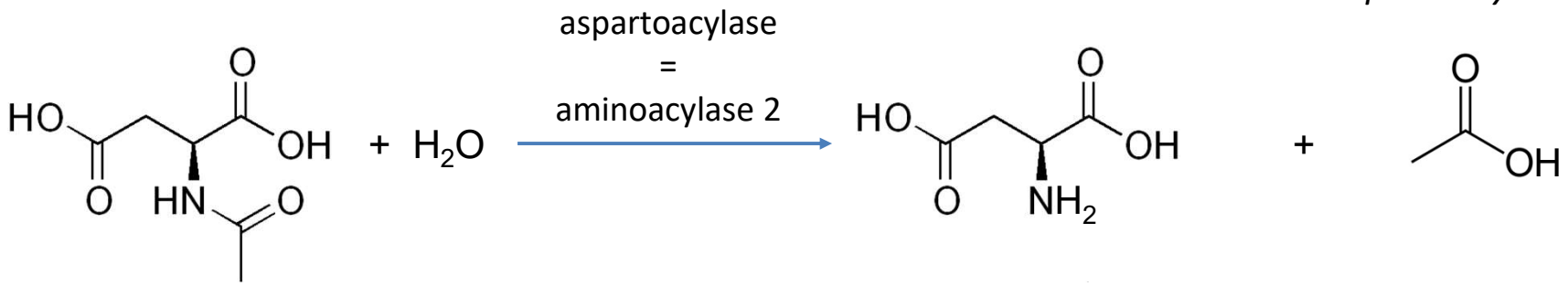




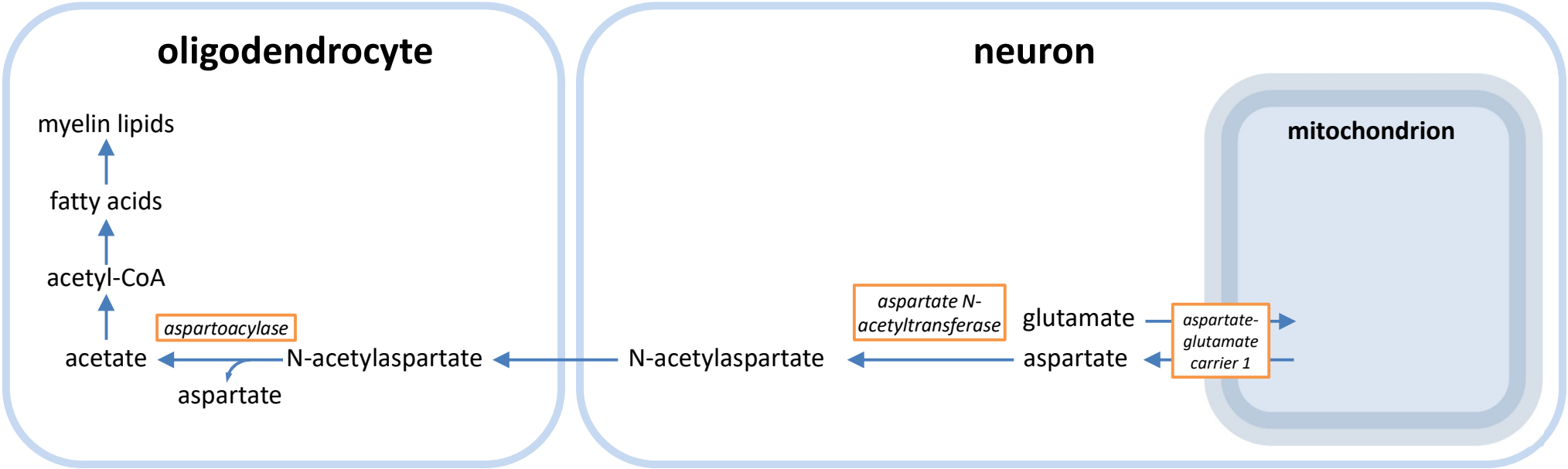
ASPA

Canavan

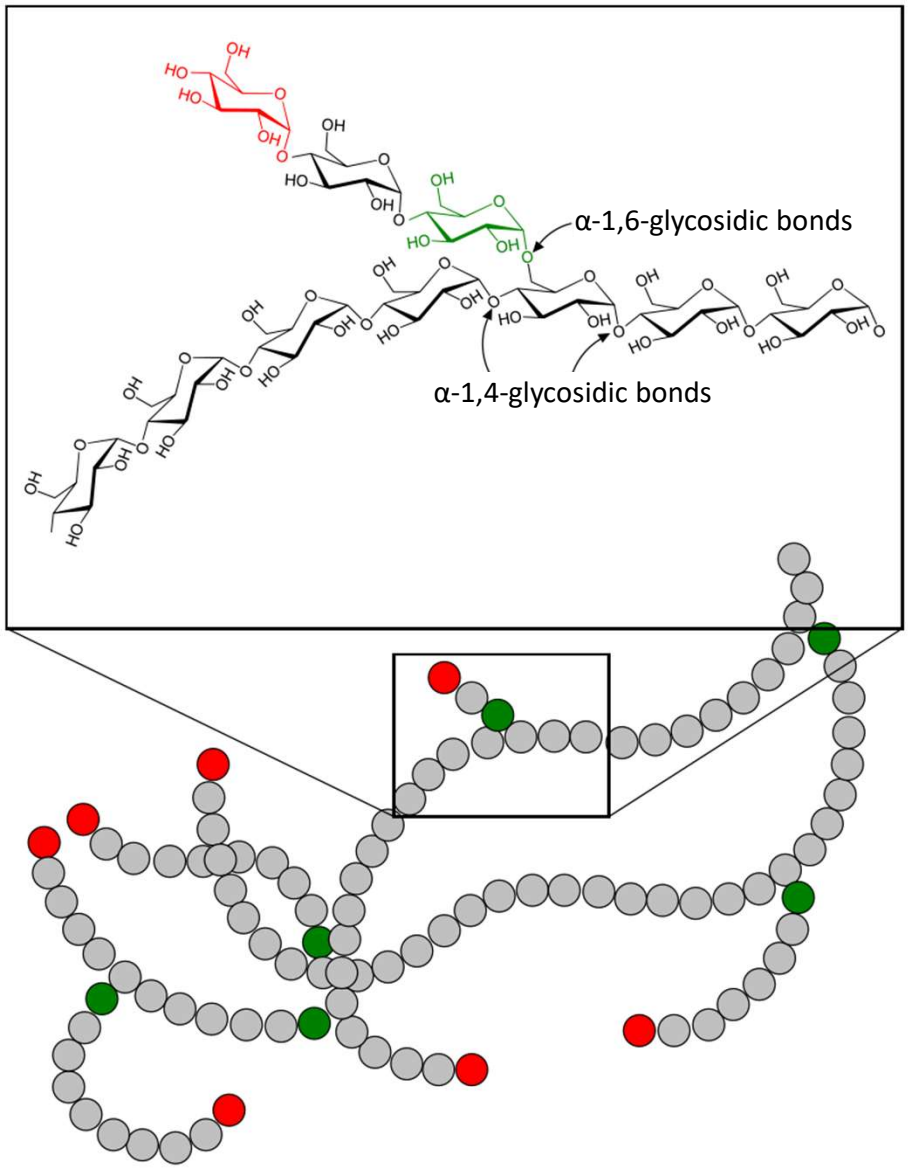
aspartoacylalse deficiency



N-acetylaspartate | aspartate | acetate



Wibom R et al. N Engl J Med. 2009 361(5):489-95. PMID: 19641205



Pompe disease / glycogen storage disease

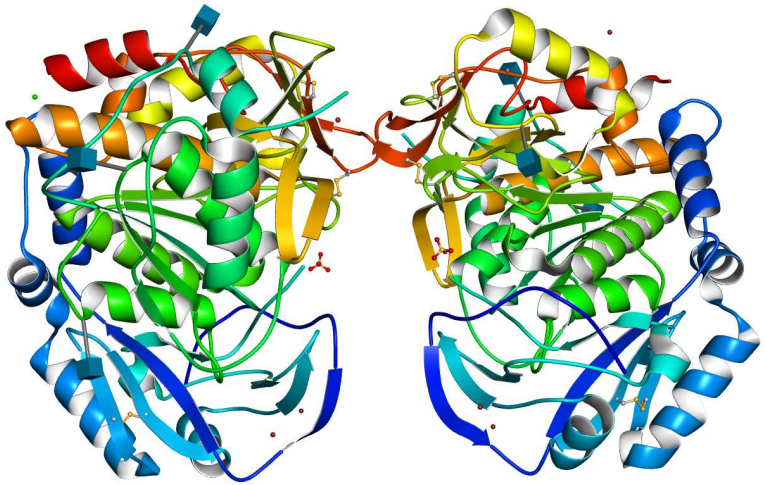
acid α-glucosidase deficiency

- acid α-glucosidase hydrolyses α-1,4 and α-1,6 glycosidic linkages in glycogen

Glycogen - Glycogen storage disease - Wikipedia

Ceroid lipofuscinosis neuronal 2, CLN2, Jansky-Bielschowsky disease

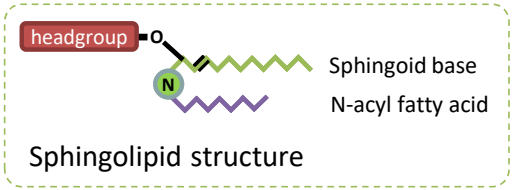
Lysosomal tripeptidyl-peptidase 1 deficiency

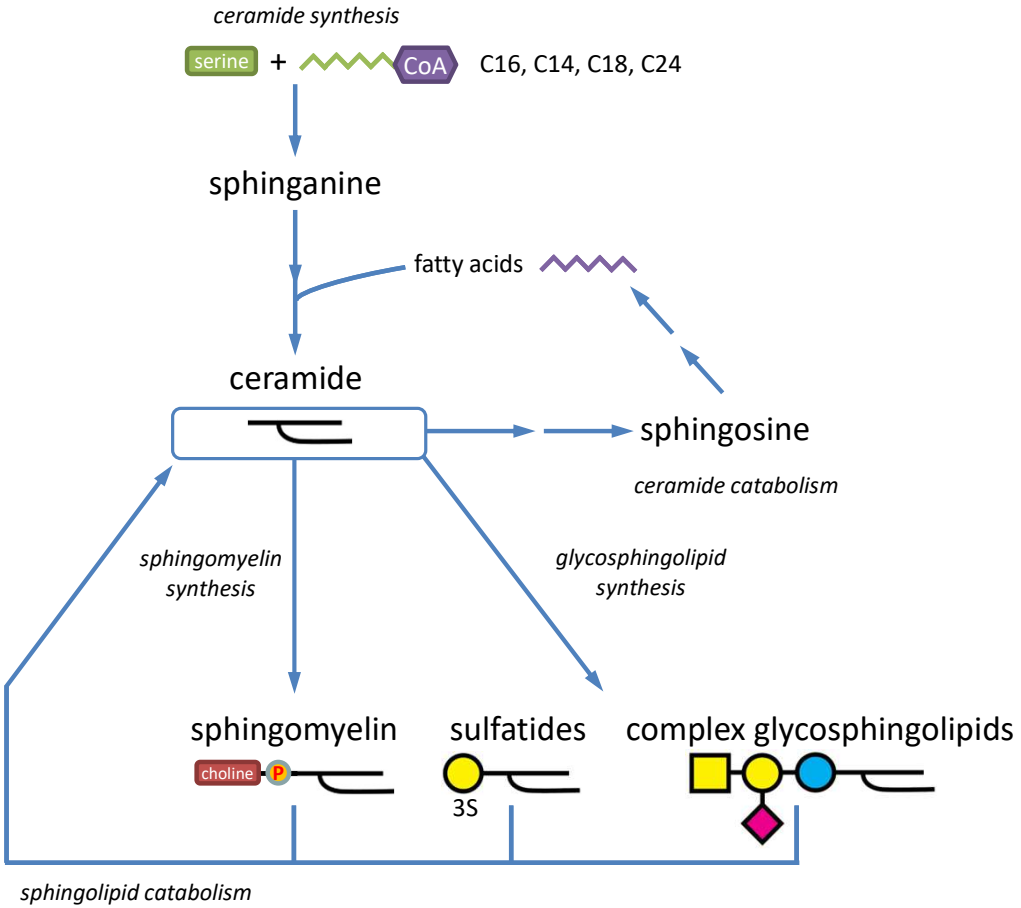


- TTP1 removes tripeptides from the N-terminus of polypeptides
- When deficient mitochondrial ATP synthase subunit c is known to accumulate

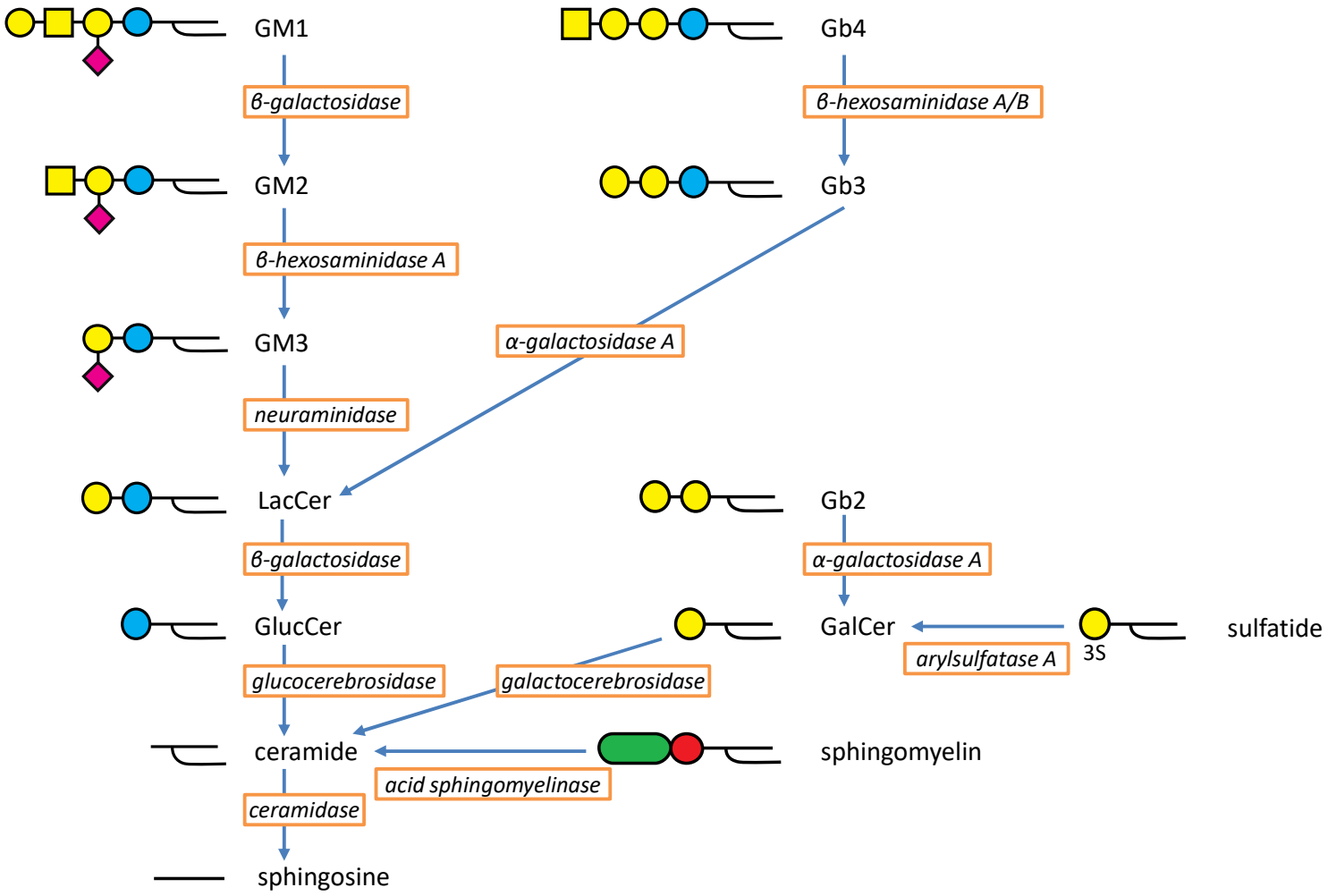
3ee6 - Crystal Structure Analysis of Tripeptidyl peptidase -I - Summary - Protein Data Bank Japan (pdbj.org)

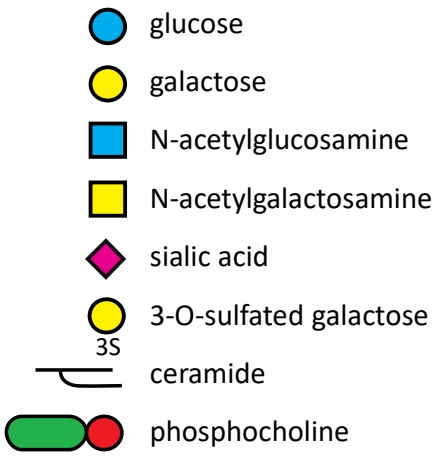
sphingolipid metabolism





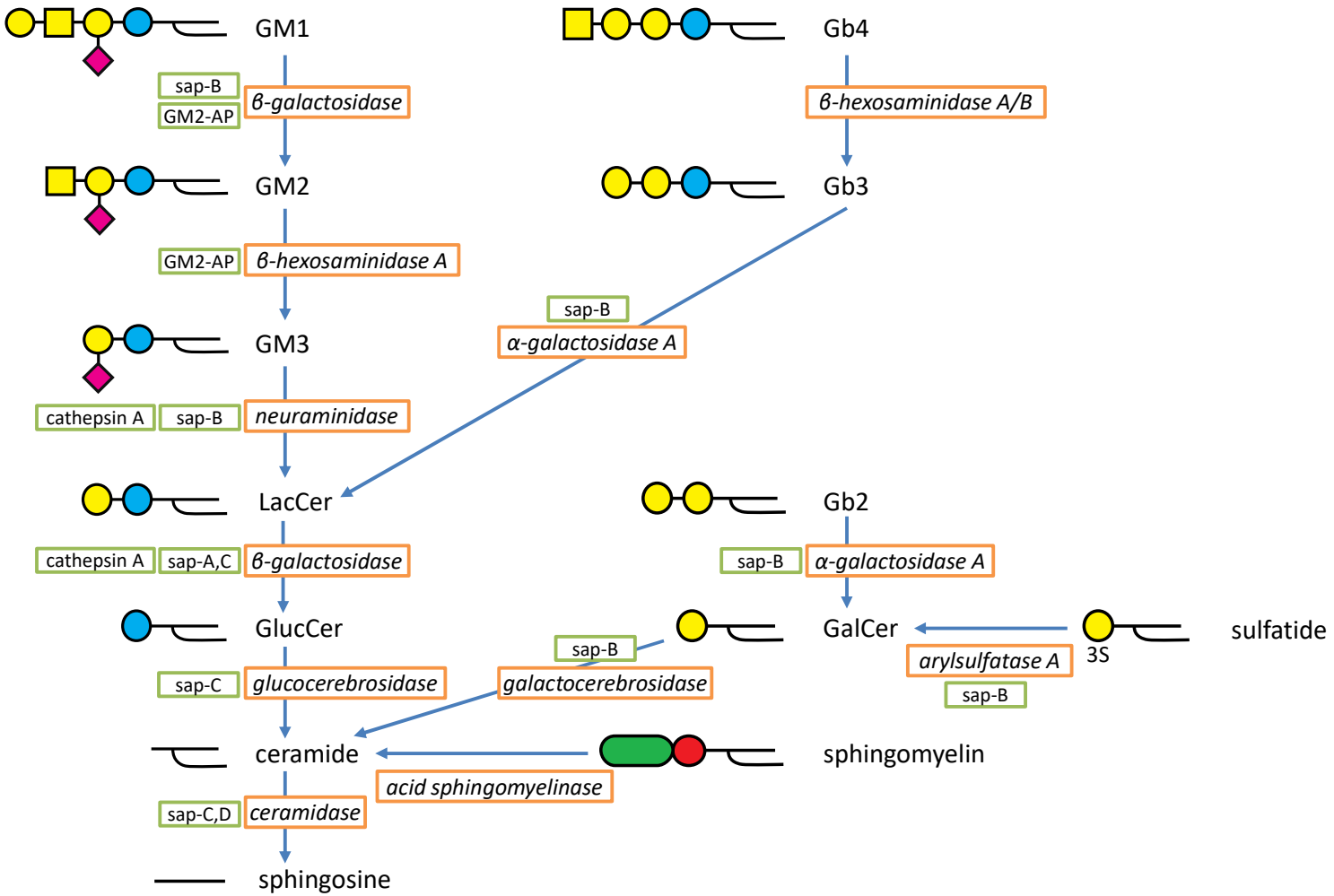
sphingolipid catabolism





sphingolipid catabolism

with cofactors



glucose

galactose

N-acetylglucosamine

N-acetylgalactosamine

sialic acid

3-O-sulfated galactose

3S

ceramide

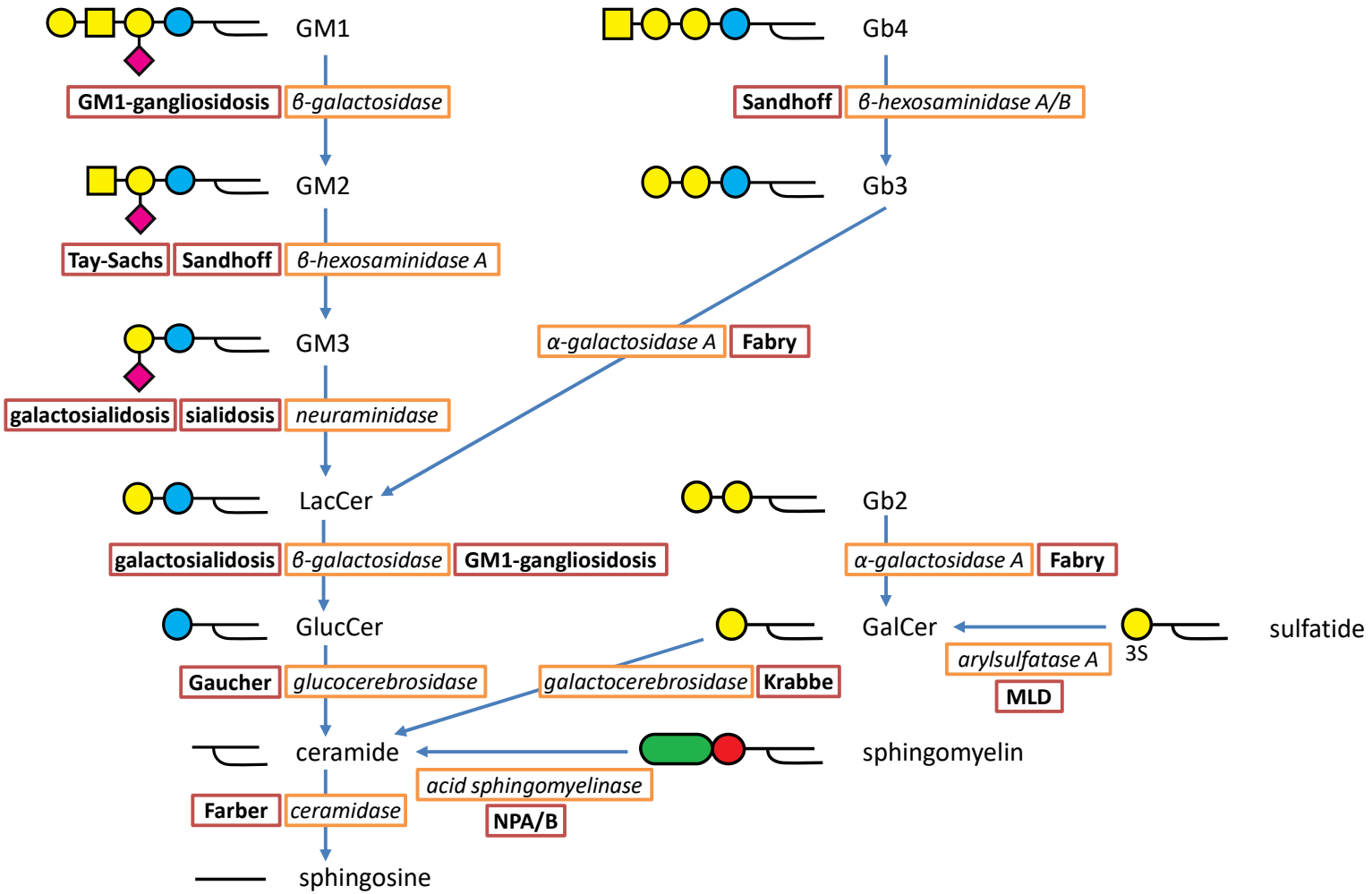
phosphocholine

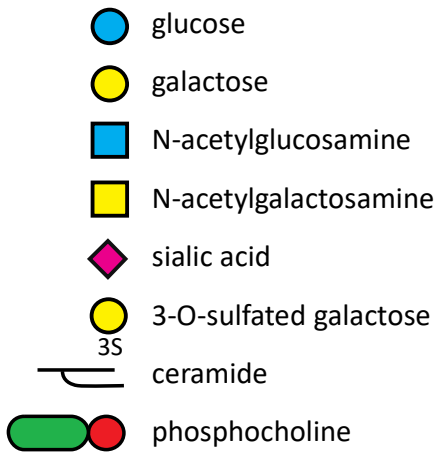
saposin deficiencies lead to various sphingolipidoses

cathepsin A deficiency leads to galactosialidosis

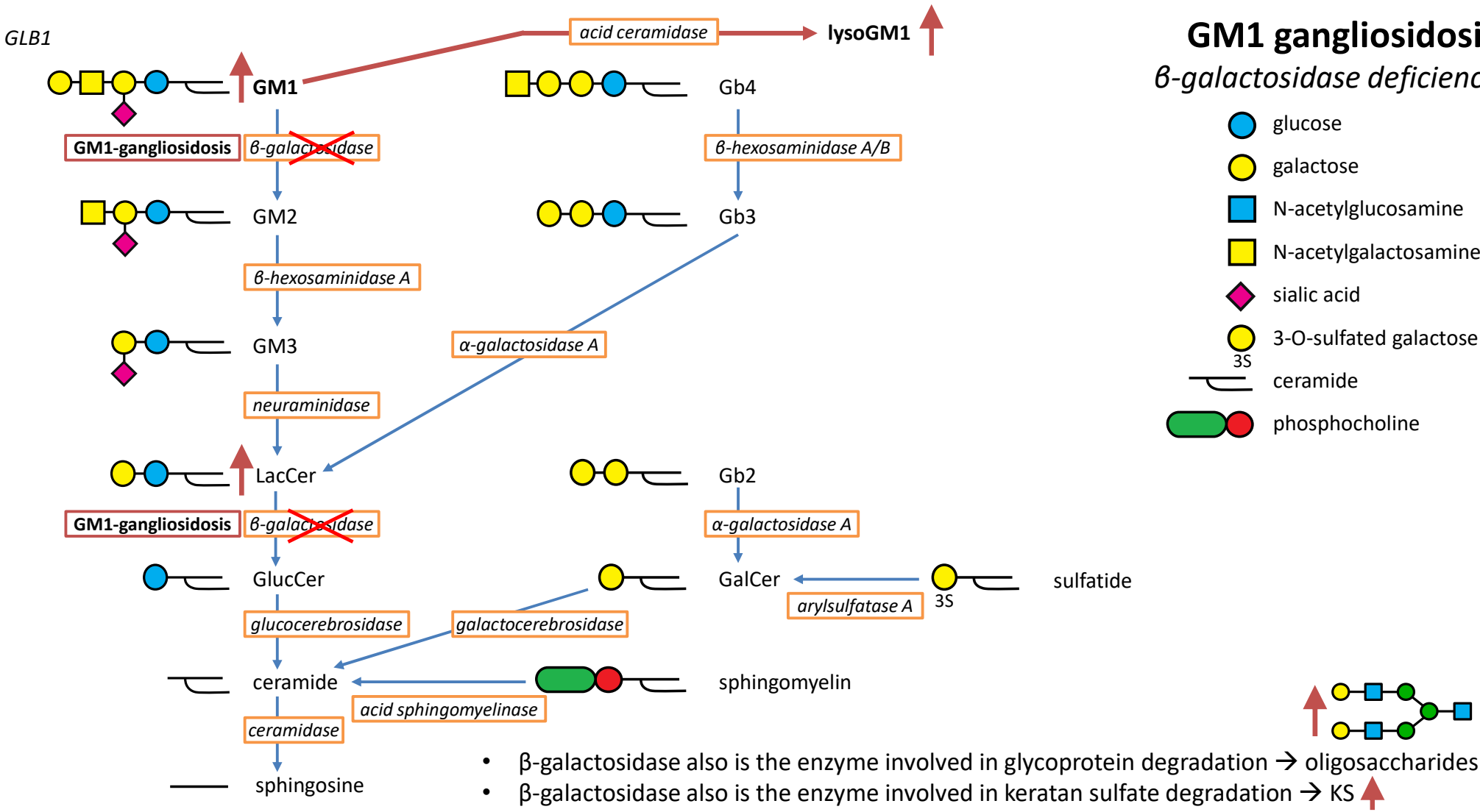
sphingolipid catabolism

disorders

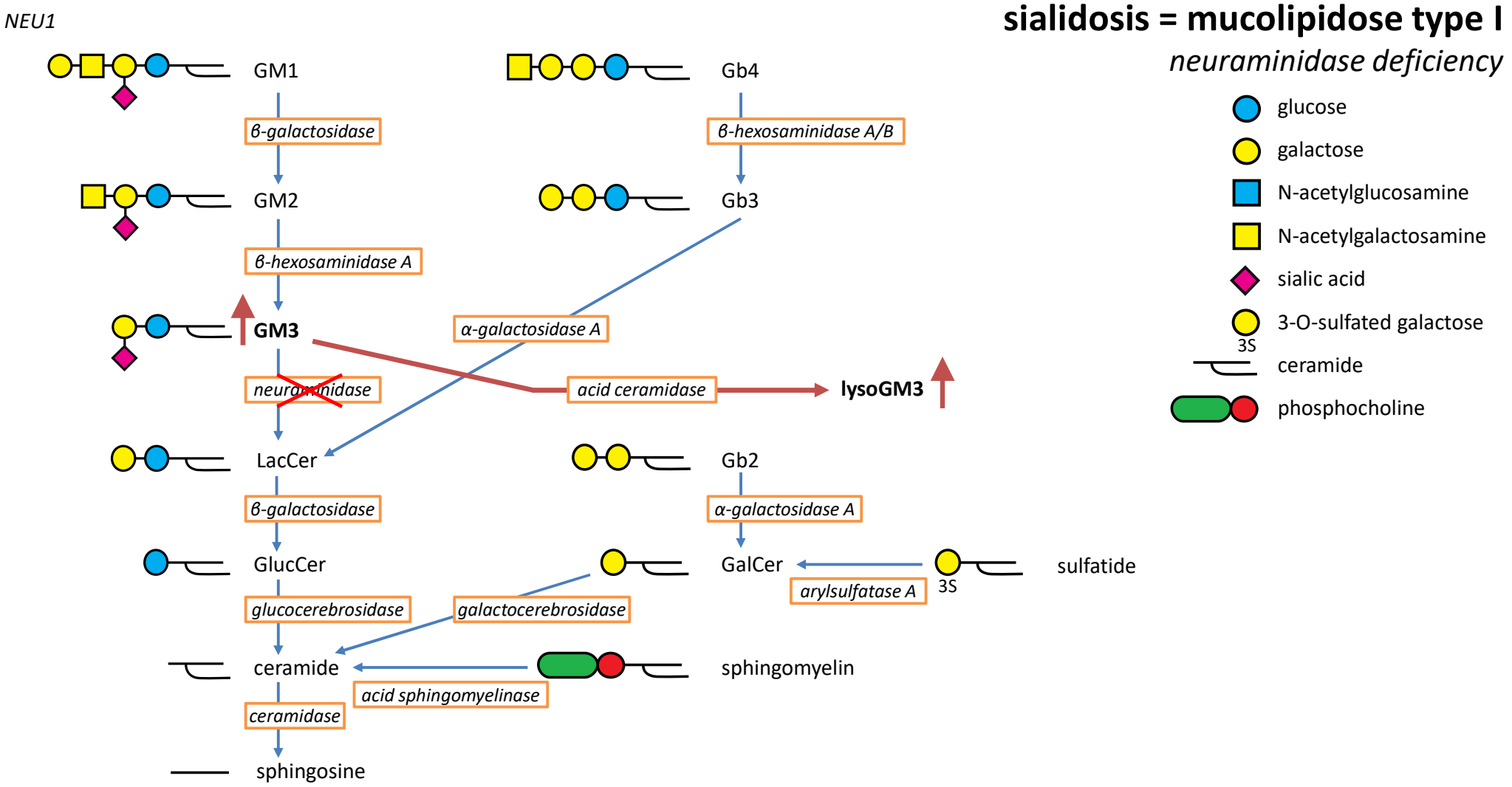


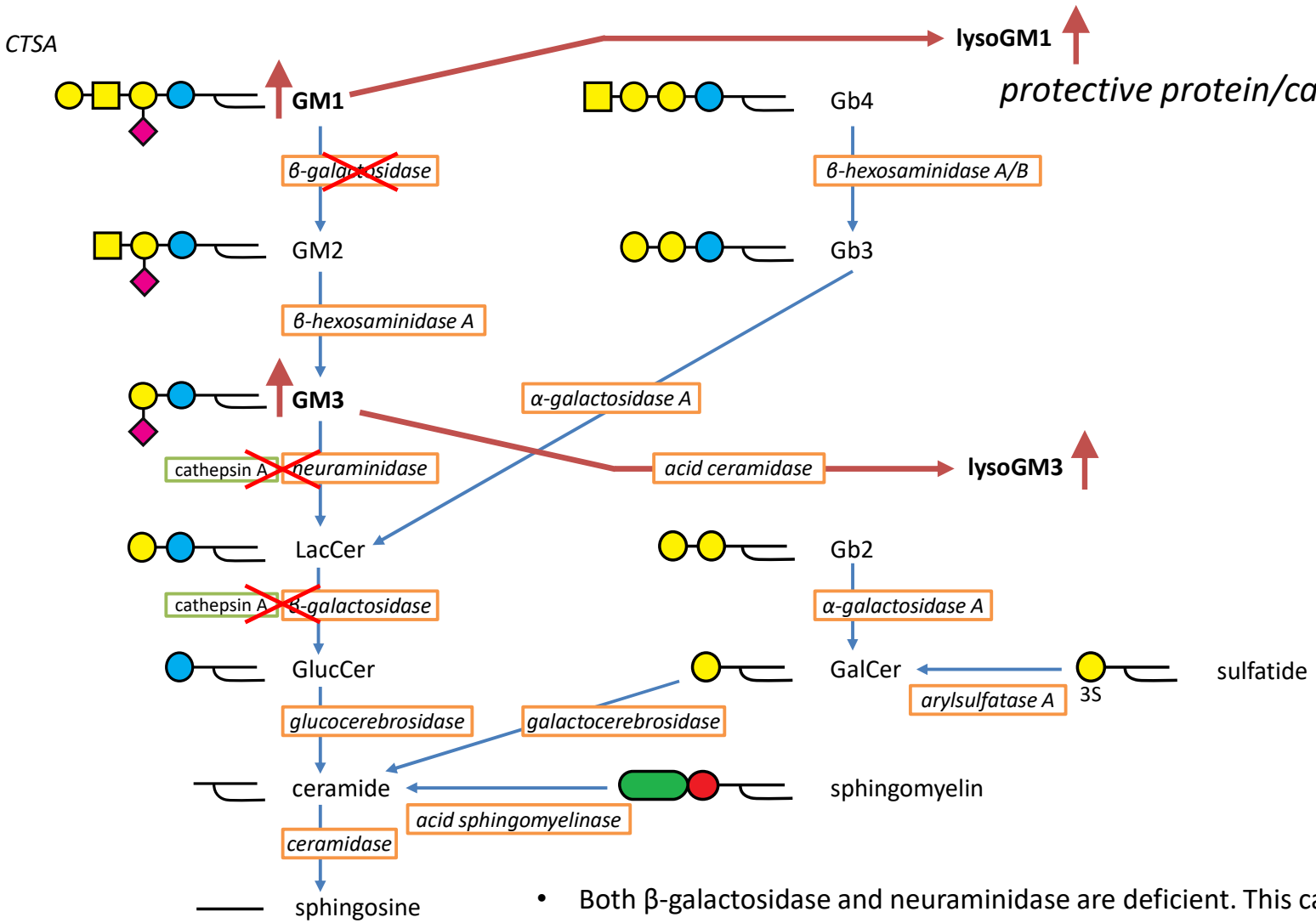


cathepsin A deficiency causes **galactosialidosis**



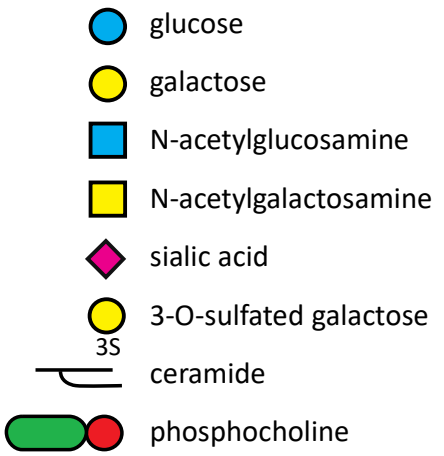
- β-galactosidase also is the enzyme involved in glycoprotein degradation → oligosaccharides
- β-galactosidase also is the enzyme involved in keratan sulfate degradation → KS
- Deficiency of β-galactosidase can either cause GM1 gangliosidosis or MPS IV B = Morquio B


NEU1
sialidosis = mucolipidose type I
neuraminidase deficiency
glucose
galactose
N-acetylglucosamine
N-acetylgalactosamine
sialic acid
3-O-sulfated galactose
3S
ceramide
phosphocholine
GM1
ß-galactosidase
GM2
ß-hexosaminidase A
GM3
neuraminidase
LacCer
ß-galactosidase
GlucCer
glucocerebrosidase
ceramide
ceramidase
sphingosine
Gb4
ß-hexosaminidase A/B
Gb3
α-galactosidase A
acid ceramidase
lysoGM3
Gb2
α-galactosidase A
GalCer
arylsulfatase A
3S
sulfatide
galactocerebrosidase
sphingomyelin
acid sphingomyelinase



galactosialidosis

protective protein/cathepsin A (PPCA) deficiency

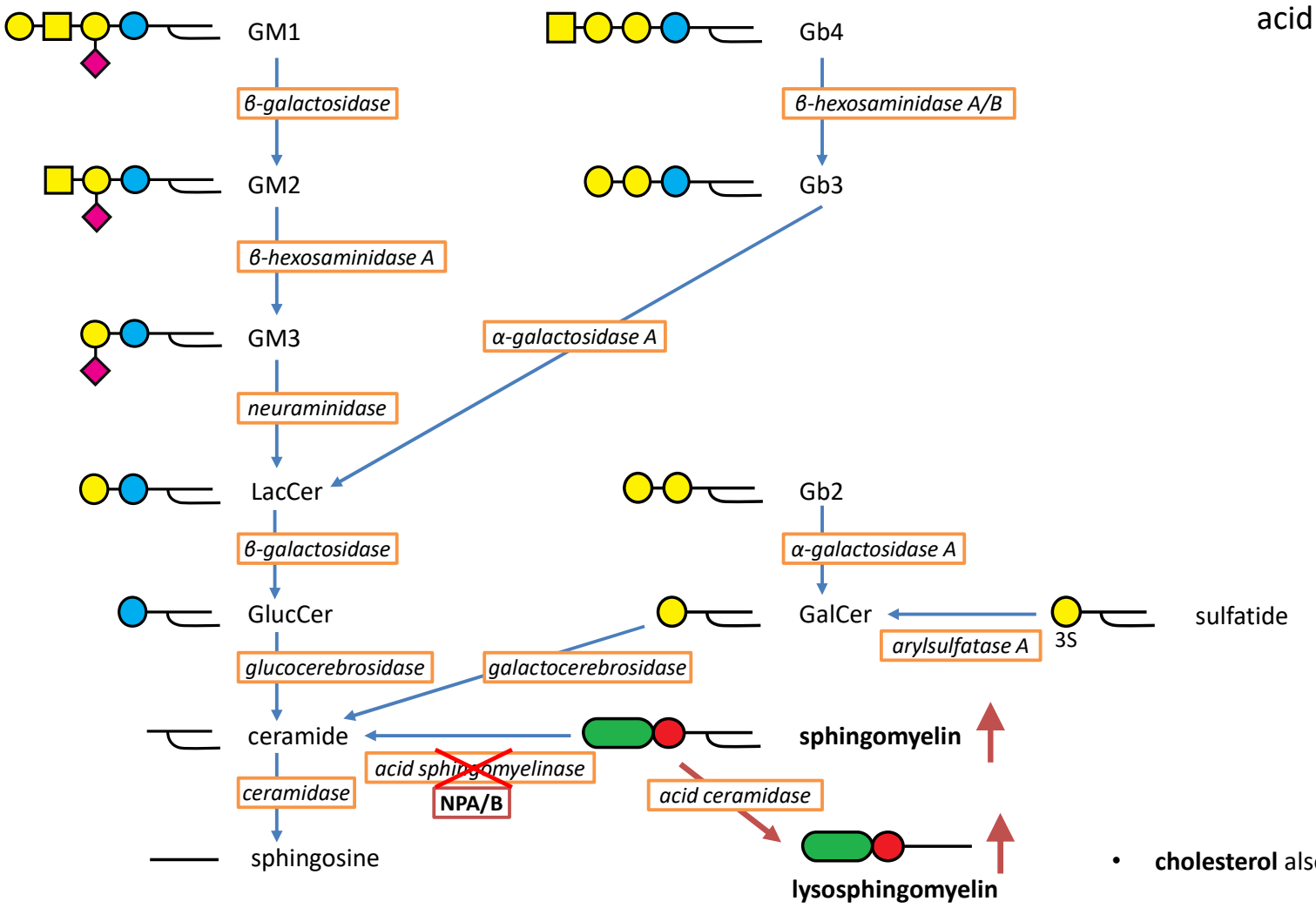


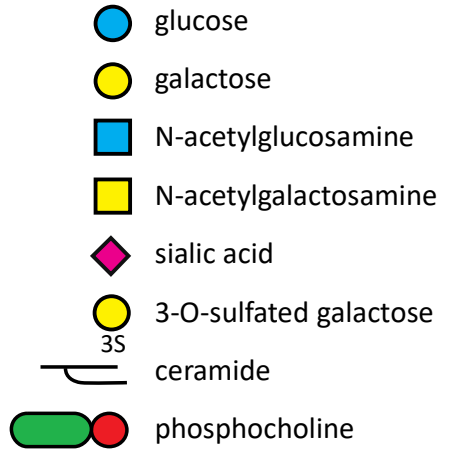
- Both β-galactosidase and neuraminidase are deficient. This causes ganglioside accumulation (GM1/GM3) but also oligosaccharide (N-glycosylation) and keratan sulfate (GAGs) accumulation

SMPD1

Niemann-Pick A/B

acid sphingomyelinase deficiency



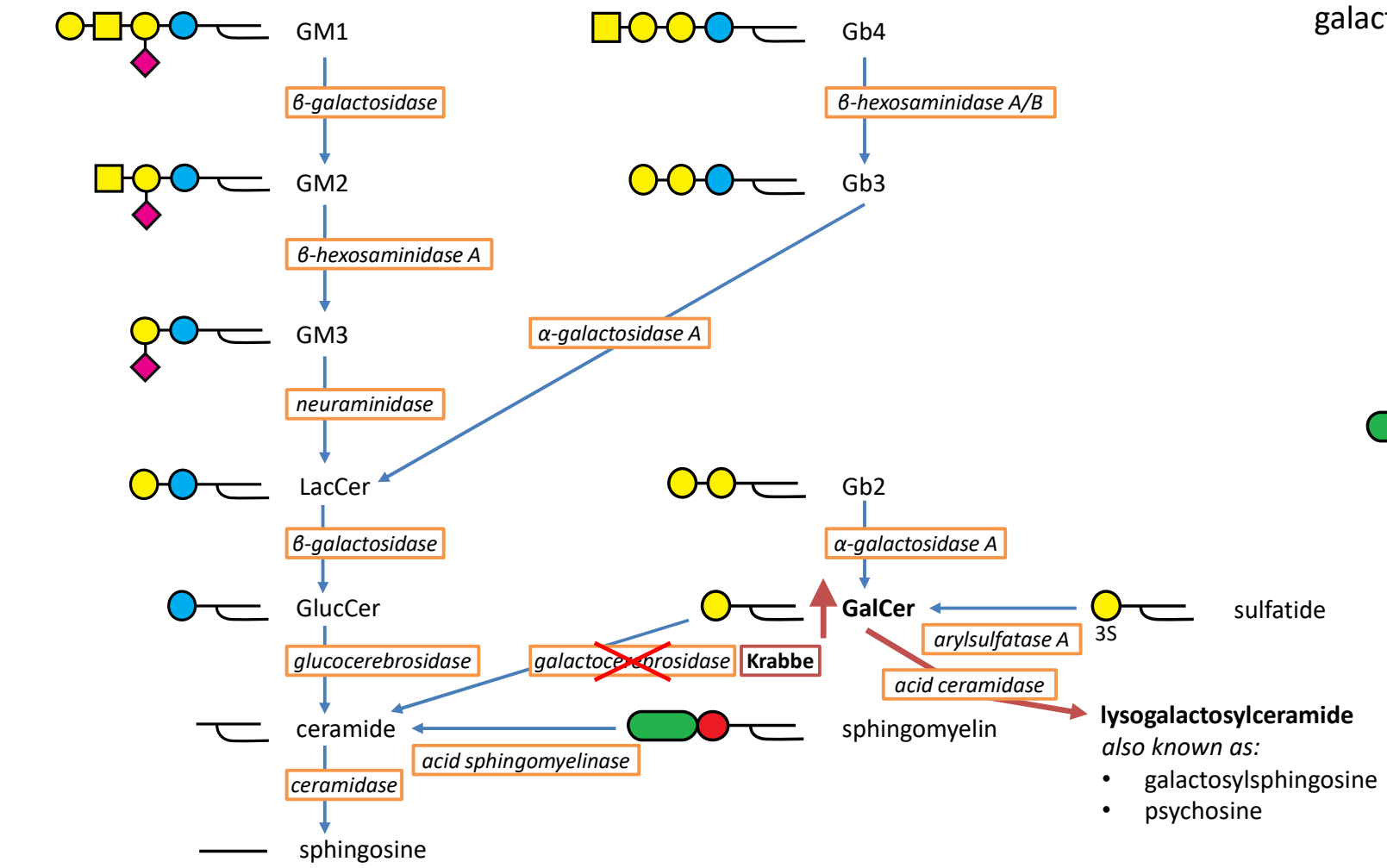


- **cholesterol** also accumulates in the lysosome

GALC

Krabbe disease

galactocerebrosidase deficiency



glucose

galactose

N-acetylglucosamine

N-acetylgalactosamine

sialic acid

3-O-sulfated galactose

3S

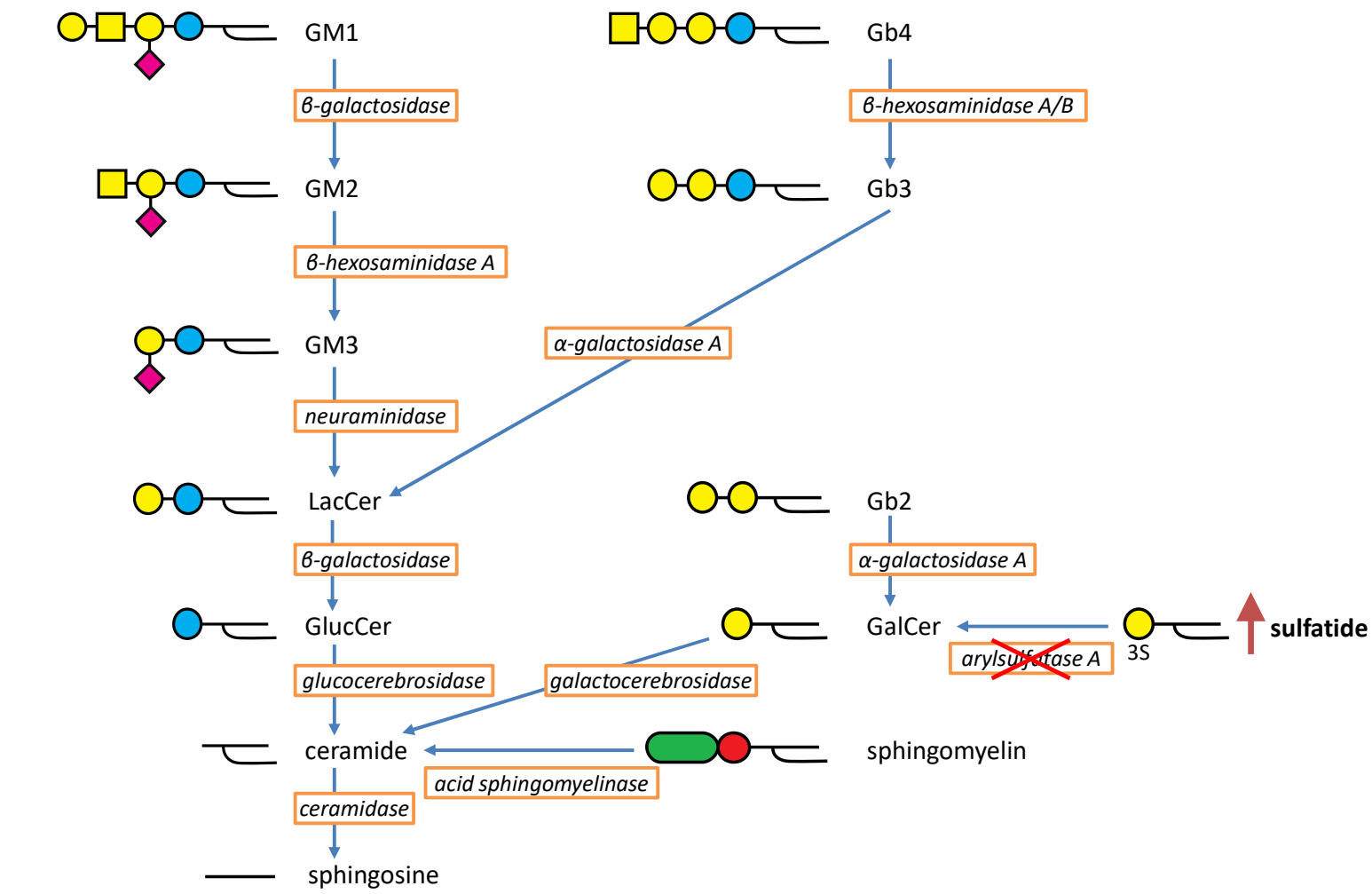
ceramide

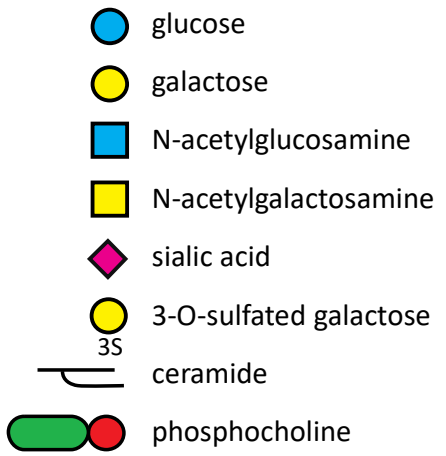
phosphocholine

ARSA

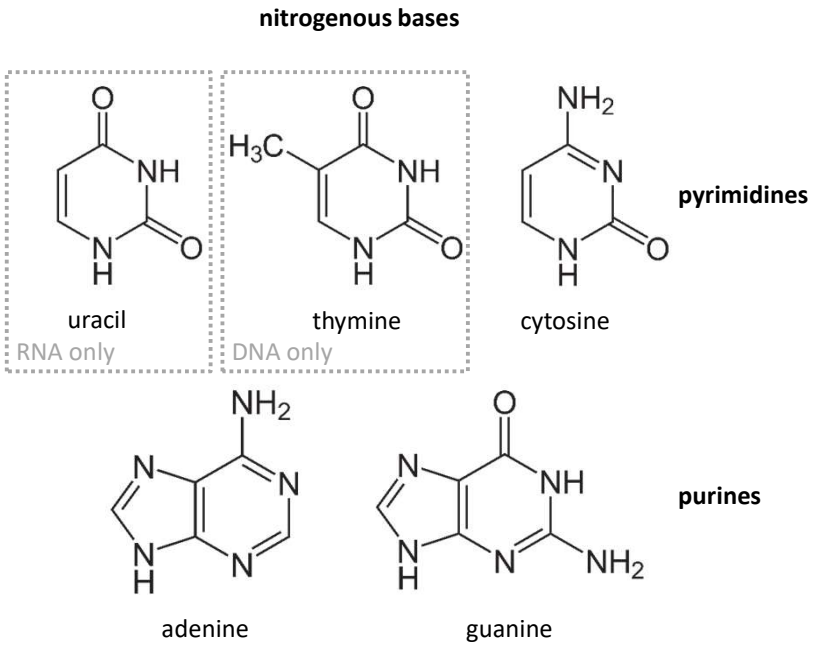
metachromatic leukodystrophy

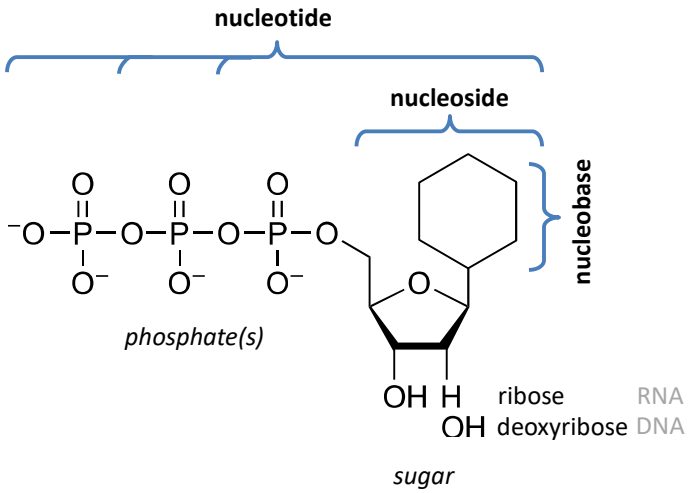
arylsulfatase A deficiency





purines and pyrimidines





What's in the name?

Purines and pyrimidines
–ine are nitrogenous bases*
*[except uracil/uridine]

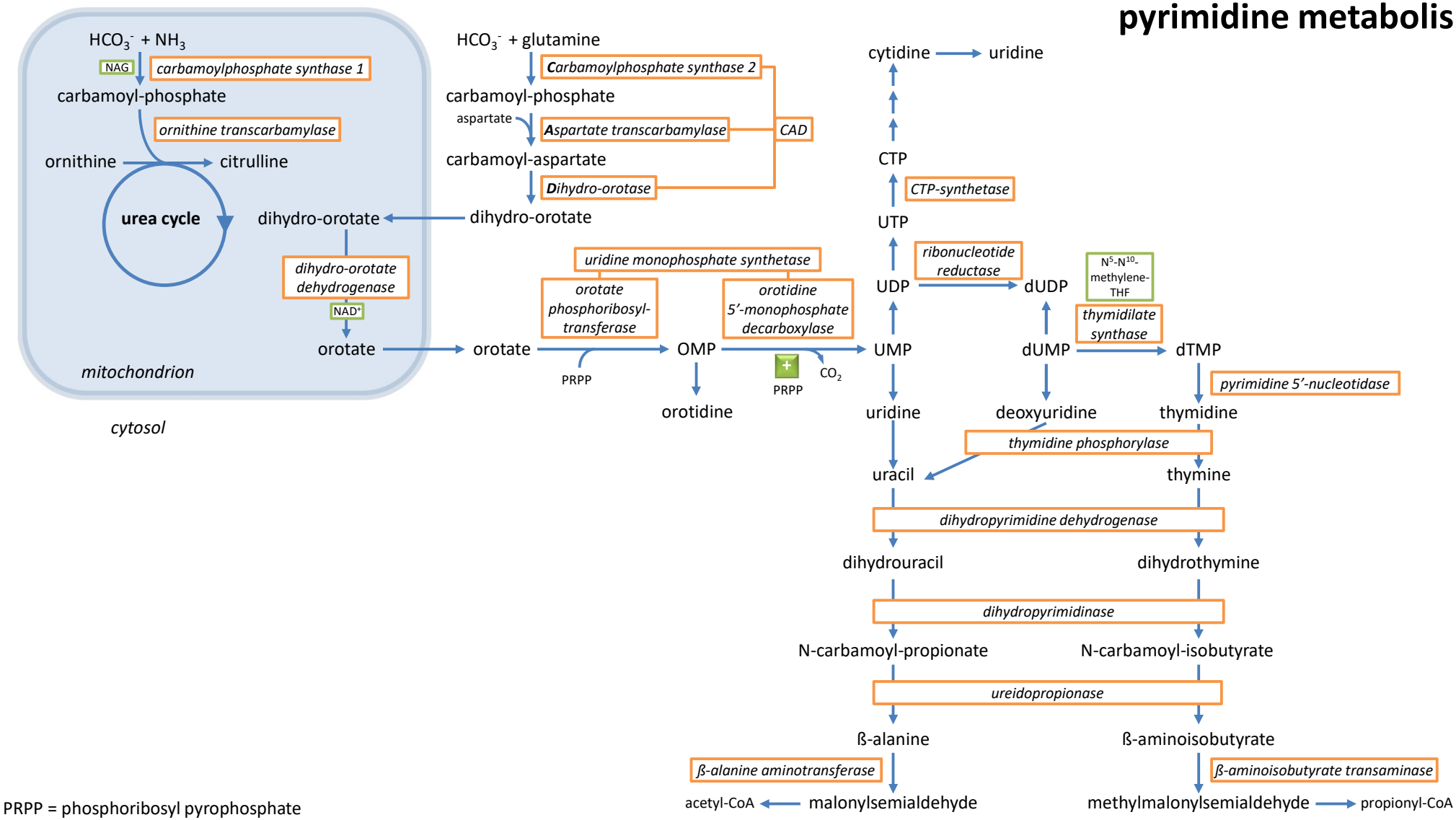
Purines:
–osine are nucleosides/tides
*[except cytosine]

Pyrimidines:
–idine are nucleosides/tides

Naming of bases, nucleosides and nucleotides

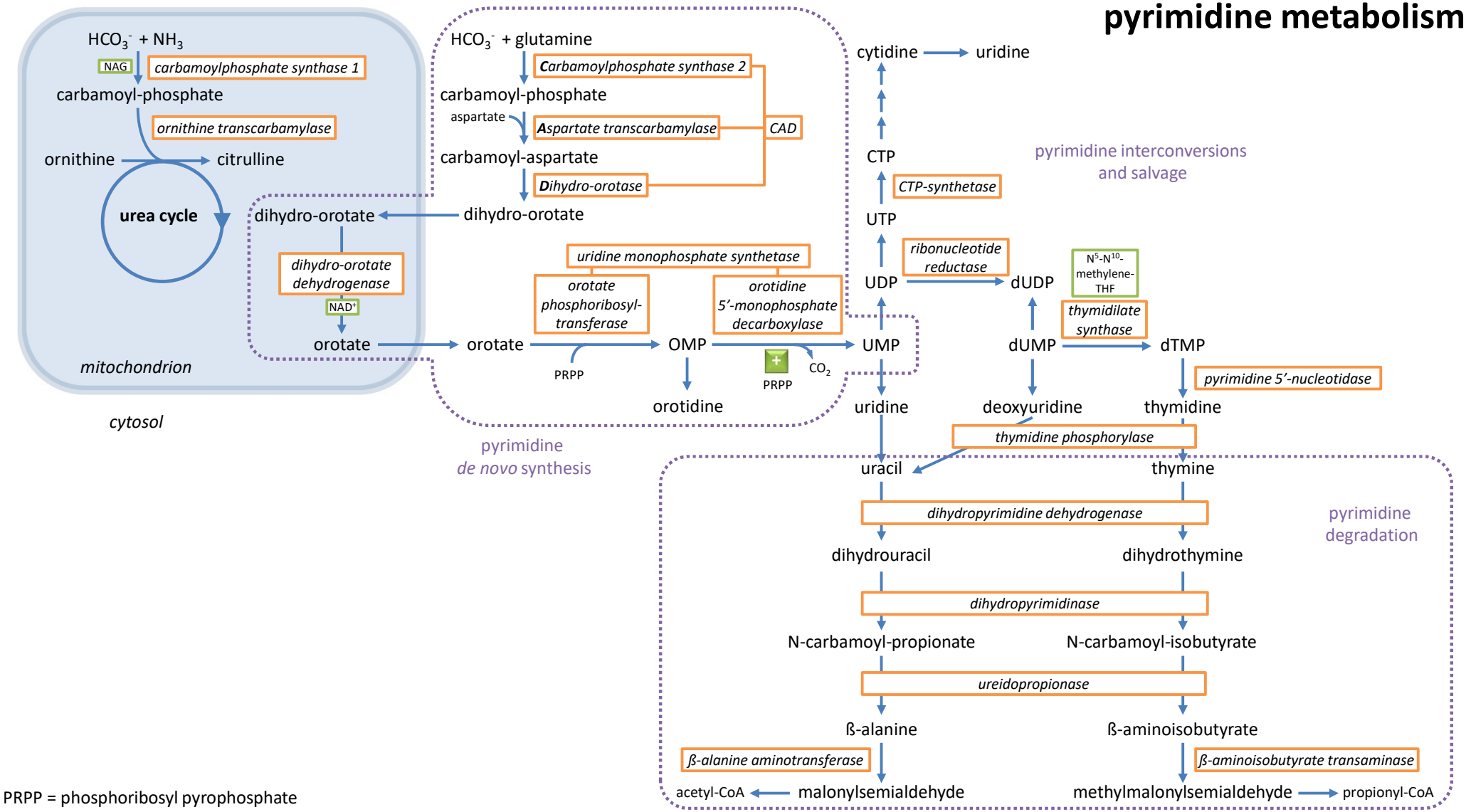
Category	**Nitrogeous Base (Nucleobase)**	**Nucleoside (Ribose)**	**Deoxynucleoside (Deoxyribose)**	**Nucleotide (Ribose)**	**Deoxynucleotide (Deoxyribose)** *[only monophosphate]*
Purines	Adenine	Adenosine	Deoxyadenosine	Adenosine Monophosphate (AMP)	Deoxyadenosine Monophosphate (dAMP)
	Guanine	Guanosine	Deoxyguanosine	Guanosine Monophosphate (GMP)	Deoxyguanosine Monophosphate (dGMP)
	Hypoxanthine	Inosine	Deoxyinosine	Inosine Monophosphate (IMP)	-
Pyrimidines	Cytosine	Cytidine	Deoxycytidine	Cytidine Monophosphate (CMP)	Deoxycytidine Monophosphate (dCMP)
	Thymine	-	Thymidine (Deoxythymidine)	-	Thymidine Monophosphate (dTMP)
	Uracil	Uridine	Deoxyuridine	Uridine Monophosphate (UMP)	-

pyrimidine metabolism

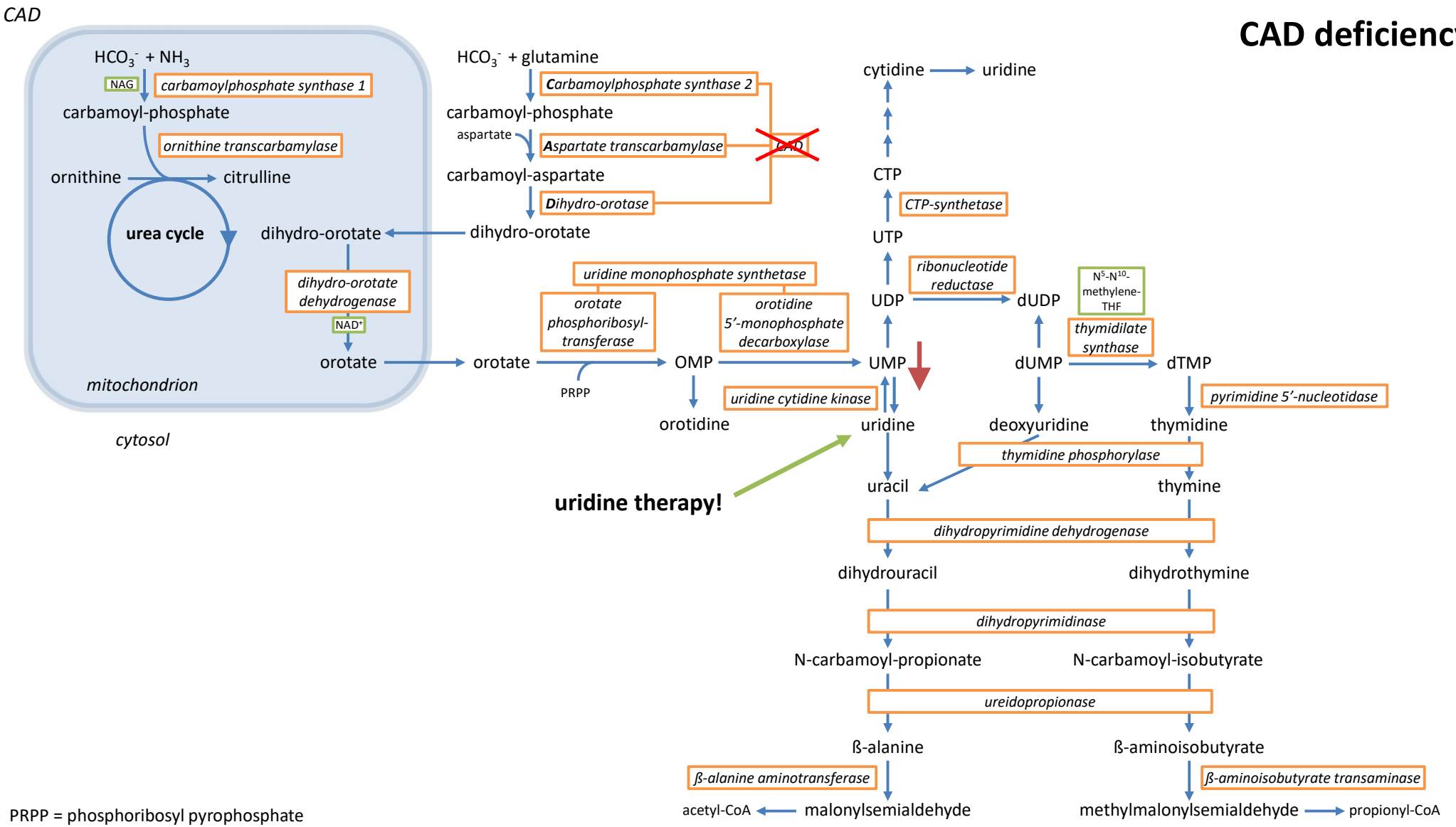


PRPP = phosphoribosyl pyrophosphate

pyrimidine metabolism



PRPP = phosphoribosyl pyrophosphate

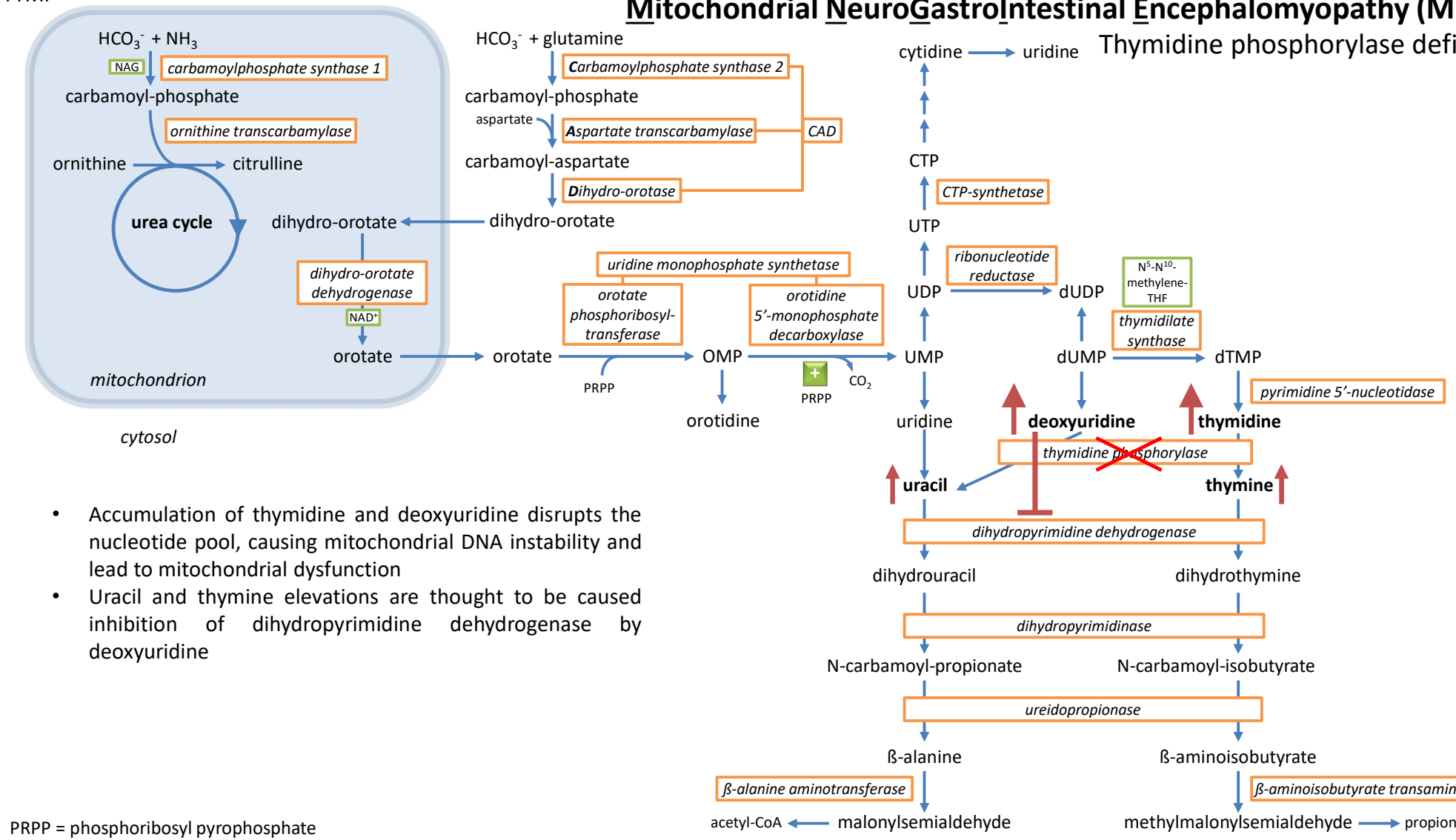


PRPP = phosphoribosyl pyrophosphate

TYMP

Mitochondrial NeuroGastroIntestinal Encephalomyopathy (MNGIE)

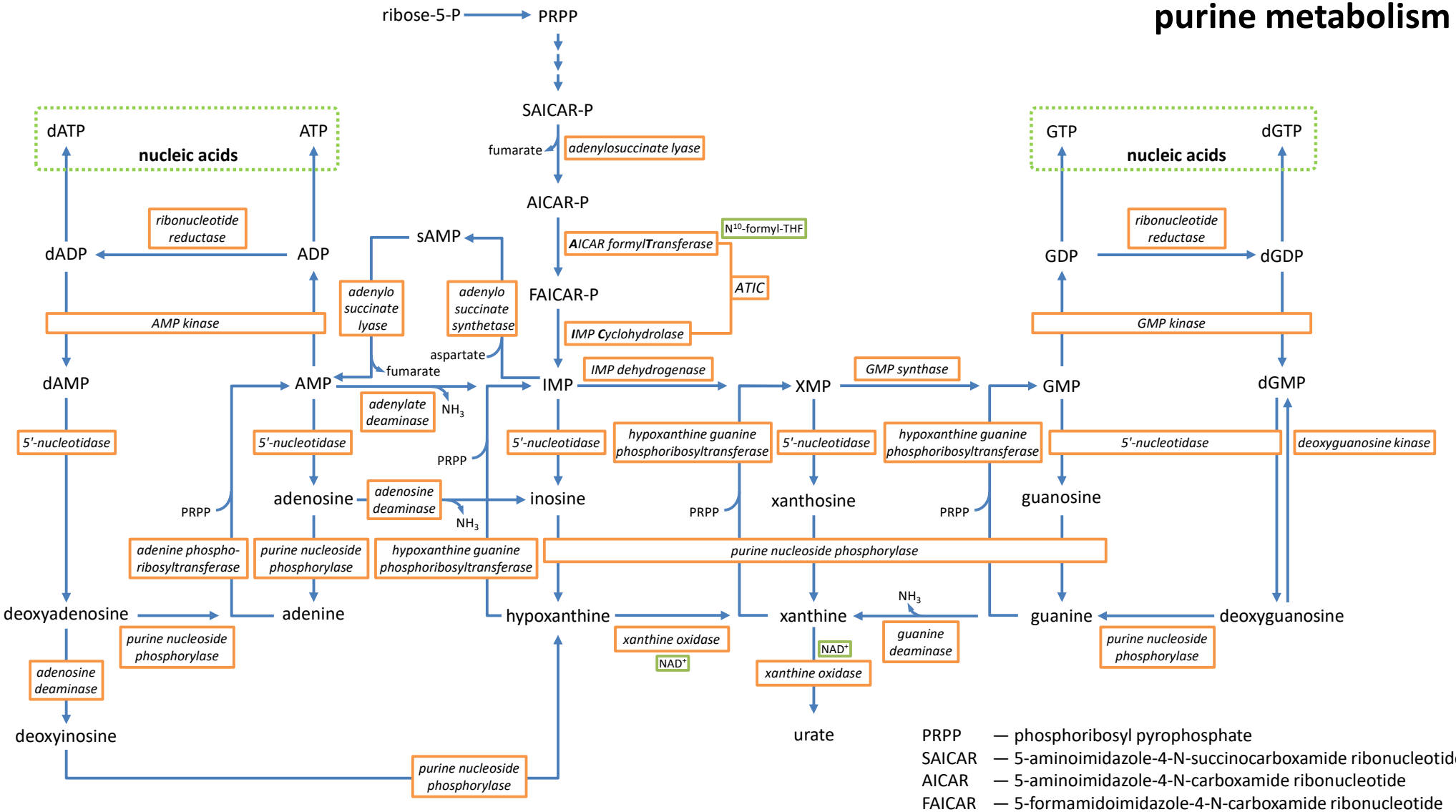
Thymidine phosphorylase deficiency



- Accumulation of thymidine and deoxyuridine disrupts the nucleotide pool, causing mitochondrial DNA instability and lead to mitochondrial dysfunction
- Uracil and thymine elevations are thought to be caused inhibition of dihydropyrimidine dehydrogenase by deoxyuridine

PRPP = phosphoribosyl pyrophosphate

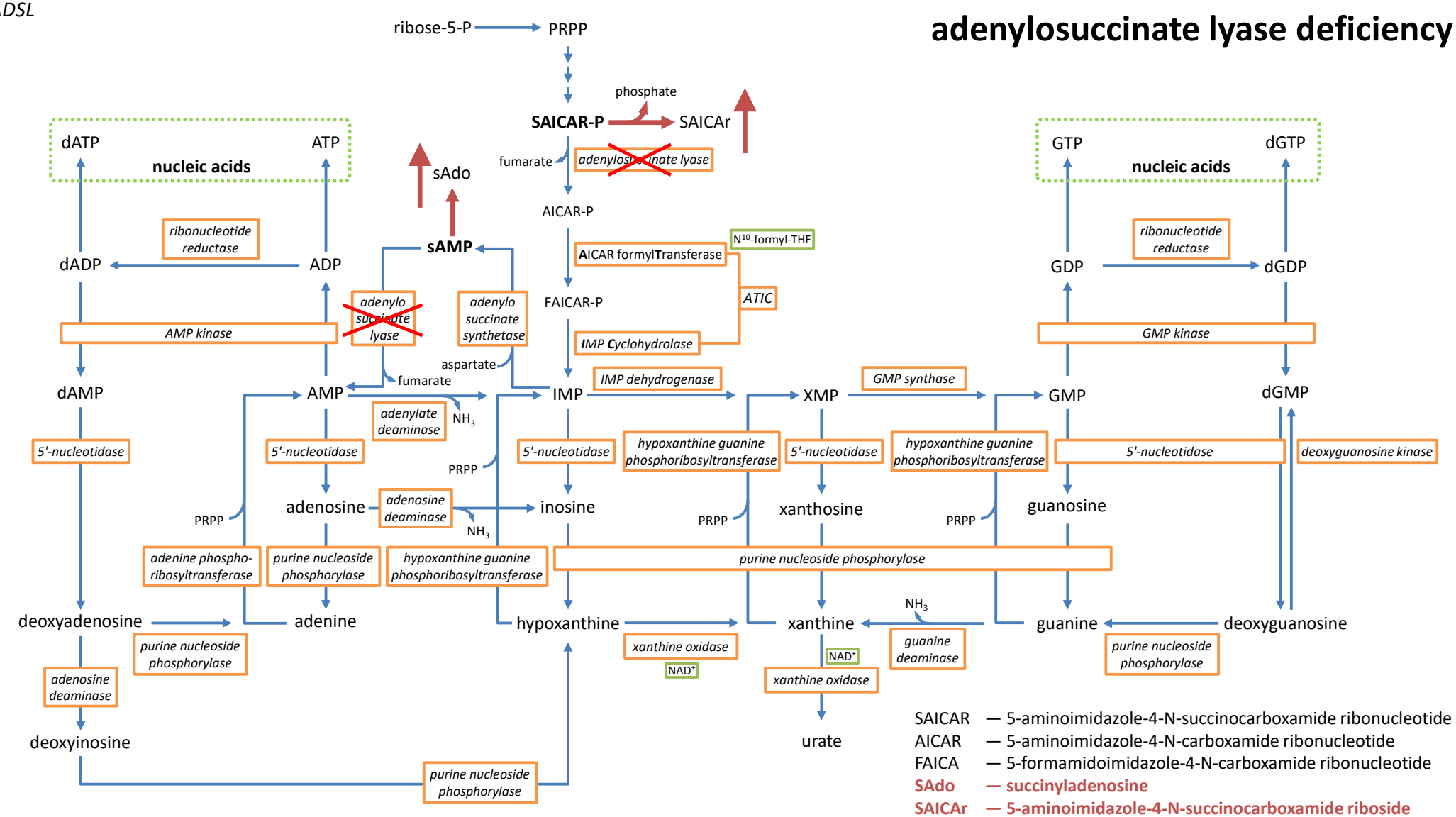
purine metabolism



PRPP — phosphoribosyl pyrophosphate
SAICAR — 5-aminoimidazole-4-N-succinocarboxamide ribonucleotide
AICAR — 5-aminoimidazole-4-N-carboxamide ribonucleotide
FAICAR — 5-formamidoimidazole-4-N-carboxamide ribonucleotide

ADSL

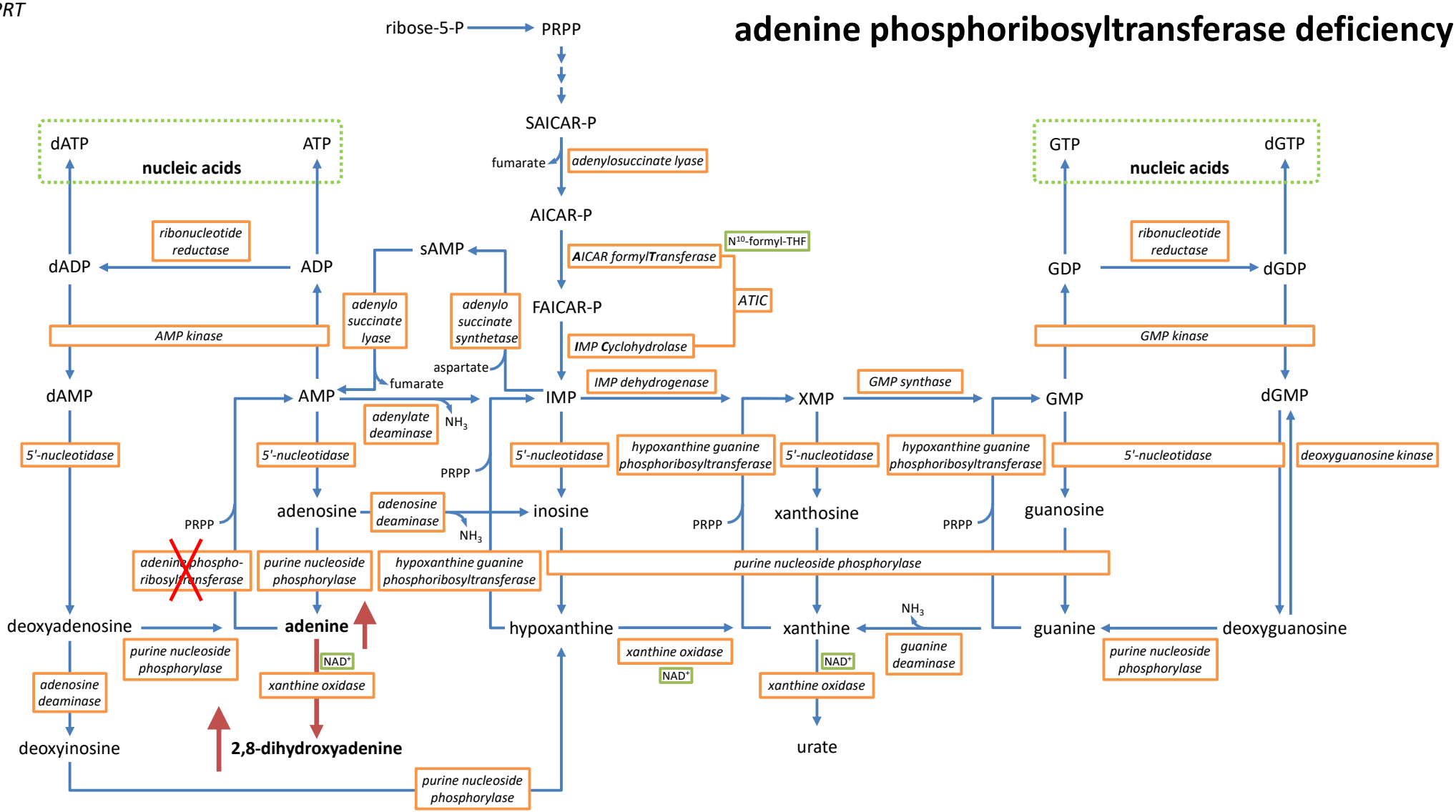
adenylosuccinate lyase deficiency



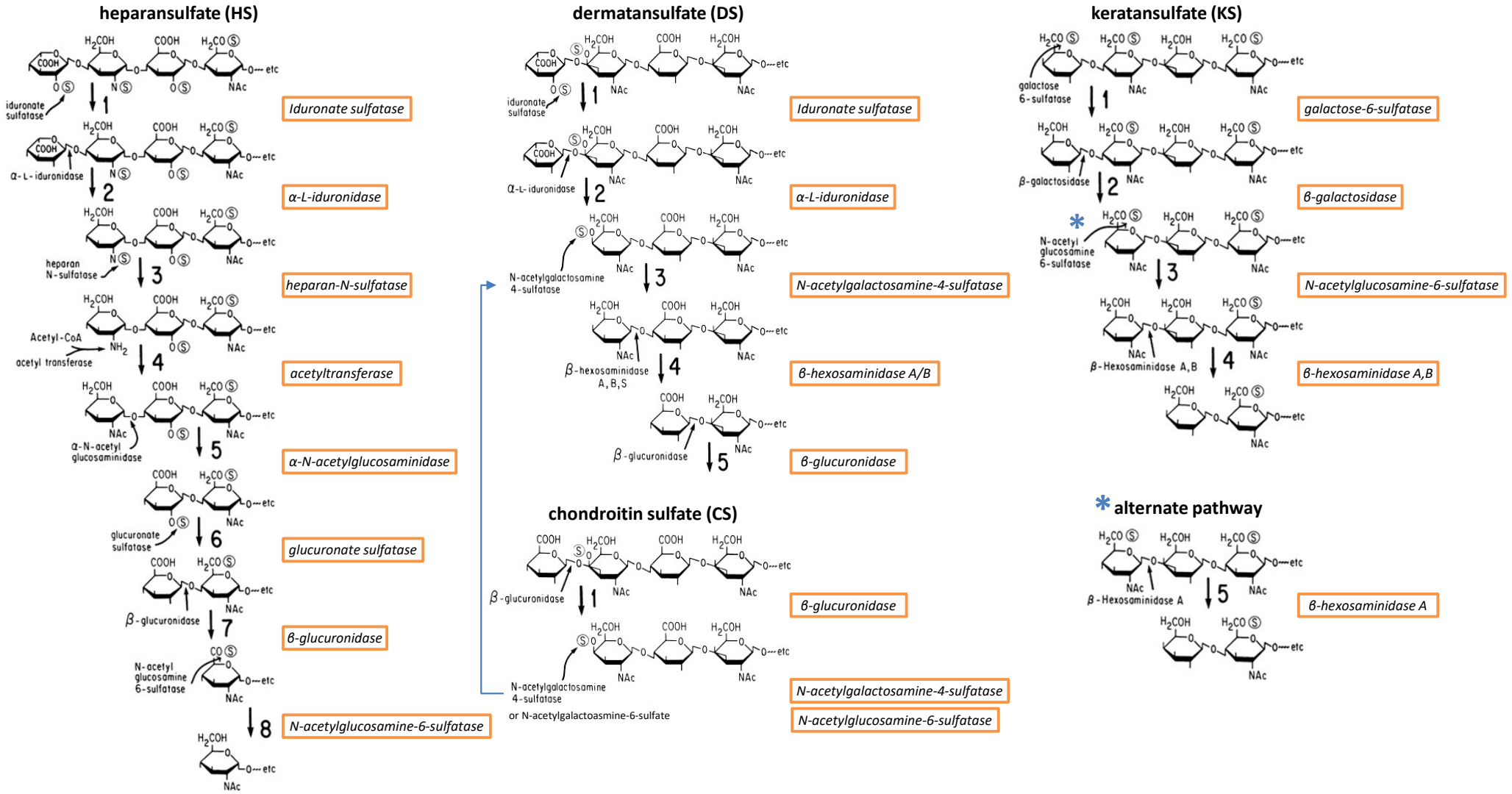
SAICAR — 5-aminoimidazole-4-N-succinocarboxamide ribonucleotide
AICAR — 5-aminoimidazole-4-N-carboxamide ribonucleotide
FAICA — 5-formamidoimidazole-4-N-carboxamide ribonucleotide
SAdo — succinyladenosine
SAICAr — 5-aminoimidazole-4-N-succinocarboxamide riboside

APRT

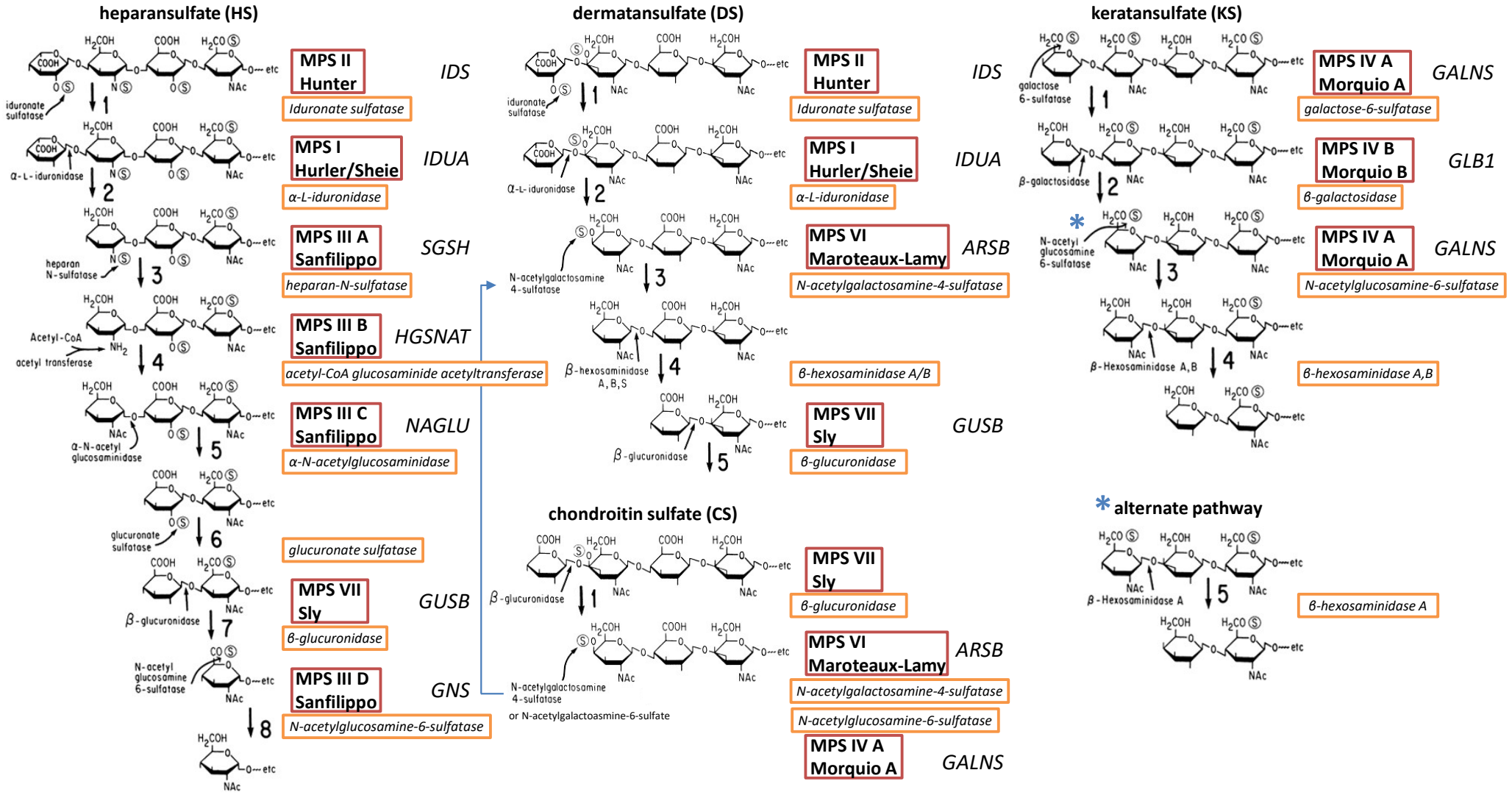
adenine phosphoribosyltransferase deficiency



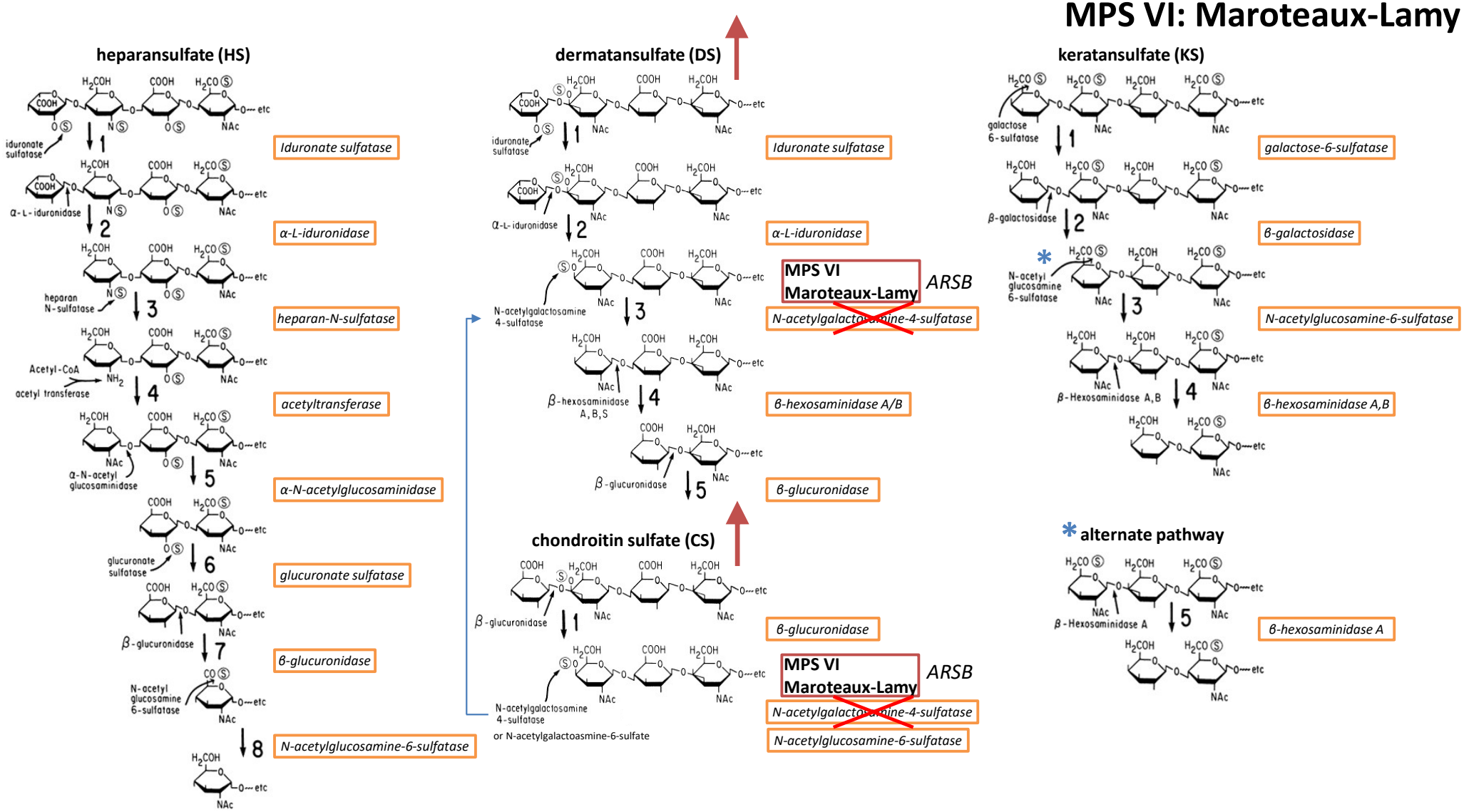
Glycosaminoglycan (GAGs) degradation



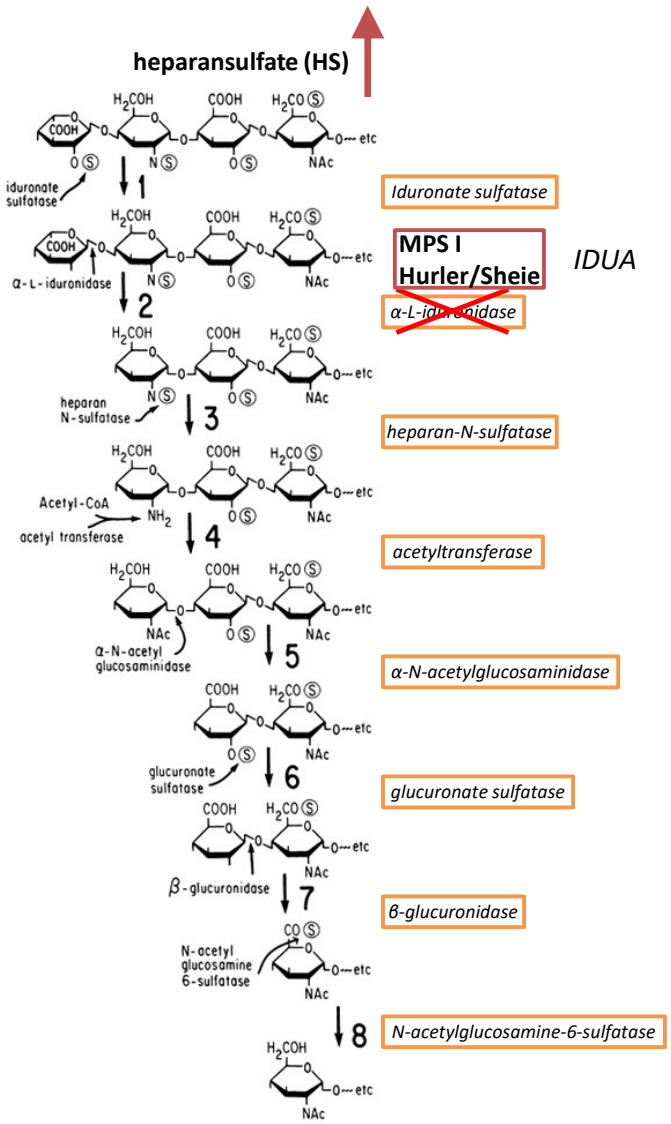
Mucopolysaccharidoses



MPS VI: Maroteaux-Lamy



MPS I: Hurler, Hurler-Scheie, Sheie



Iduronate sulfatase

MPS I Hurler/Sheie

IDUA

~~*α-L-iduronidase*~~

heparan-N-sulfatase

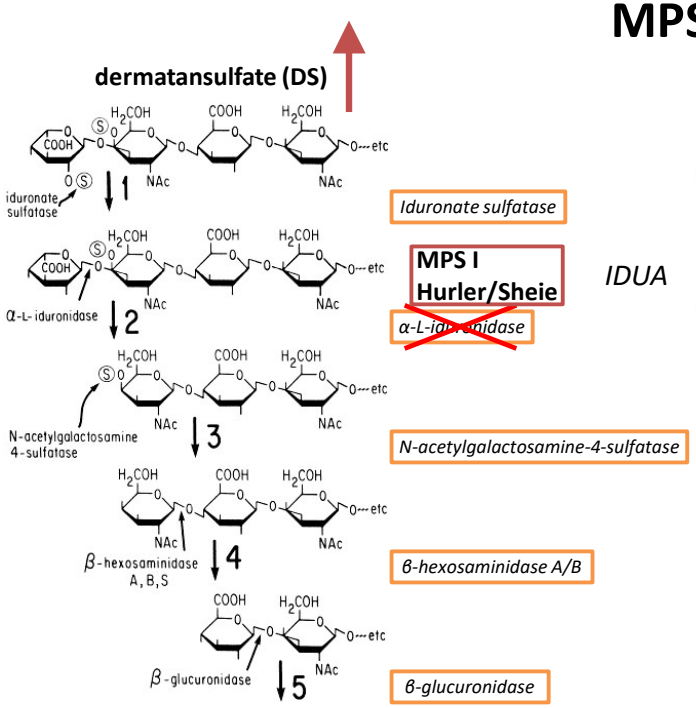
acetyltransferase

α-N-acetylglucosaminidase

glucuronate sulfatase

β-glucuronidase

N-acetylglucosamine-6-sulfatase



Iduronate sulfatase

MPS I Hurler/Sheie

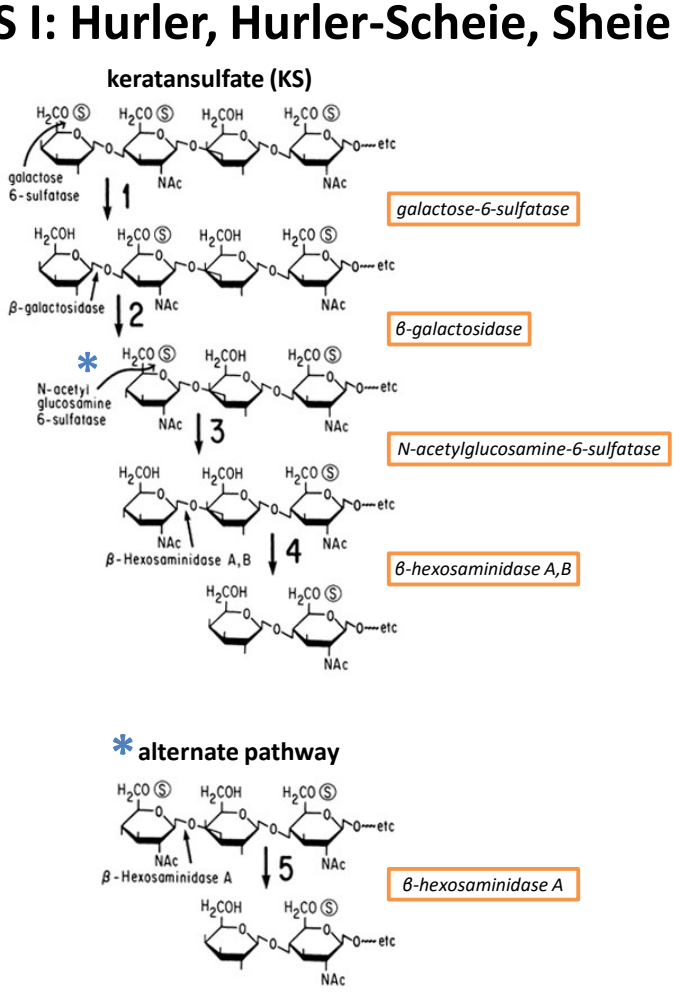
IDUA

~~*α-L-iduronidase*~~

N-acetylgalactosamine-4-sulfatase

β-hexosaminidase A/B

β-glucuronidase



galactose-6-sulfatase

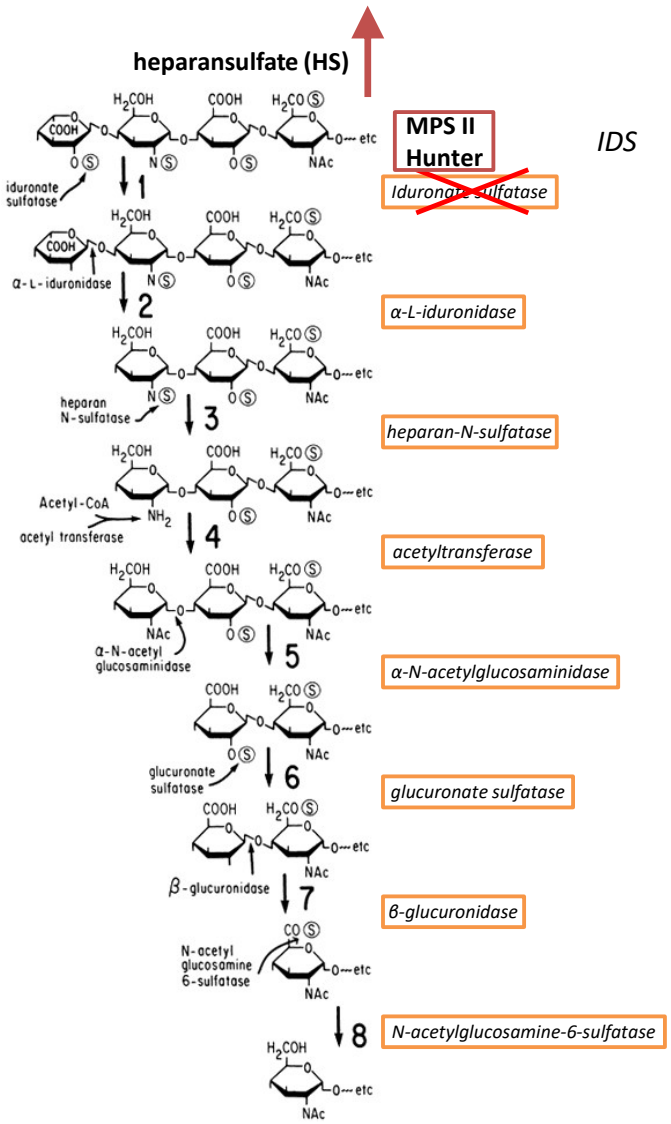
β-galactosidase

N-acetylglucosamine-6-sulfatase

β-hexosaminidase A,B

β-hexosaminidase A

MPS II: Hunter



Iduronate sulfatase

α-L-iduronidase

heparan-N-sulfatase

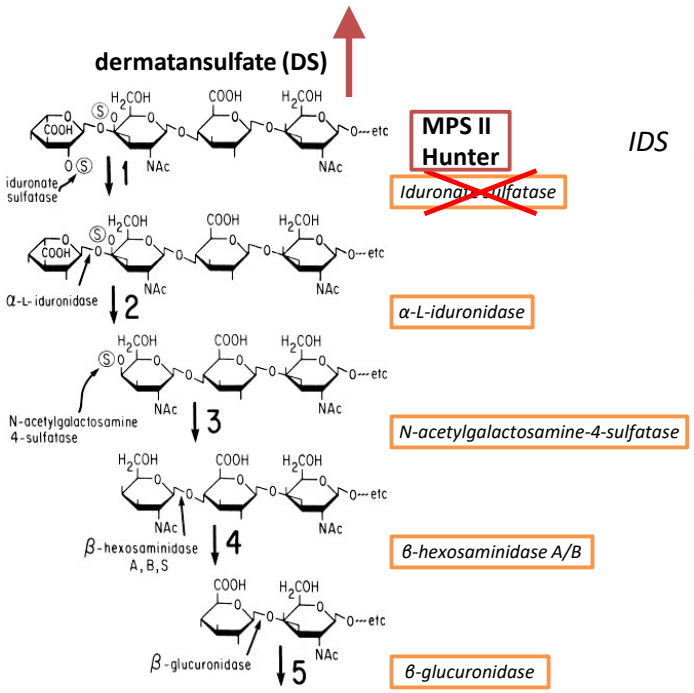
acetyltransferase

α-N-acetylglucosaminidase

glucuronate sulfatase

β-glucuronidase

N-acetylglucosamine-6-sulfatase



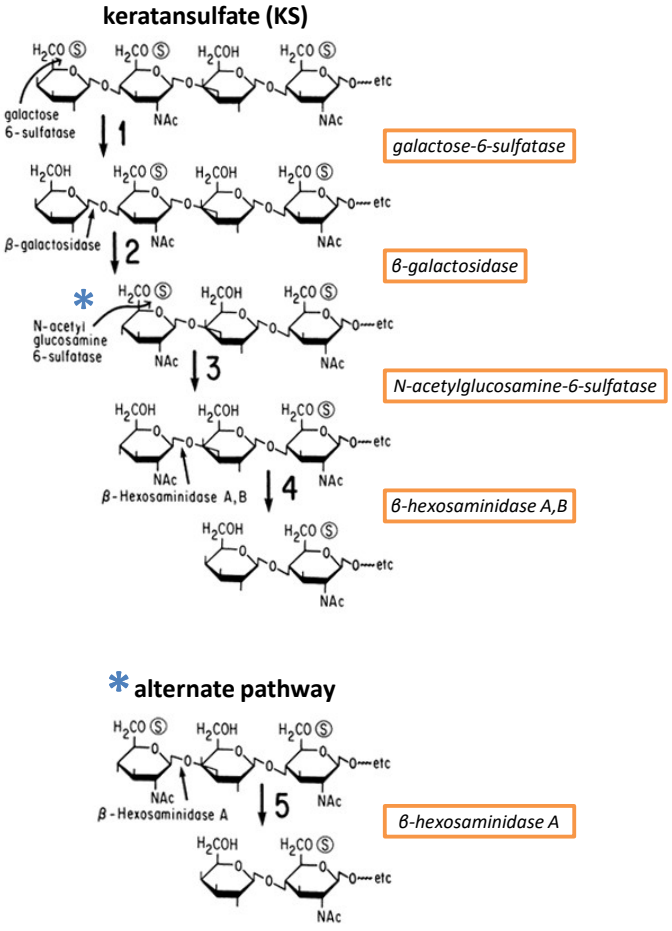
Iduronate sulfatase

α-L-iduronidase

N-acetylgalactosamine-4-sulfatase

β-hexosaminidase A/B

β-glucuronidase



galactose-6-sulfatase

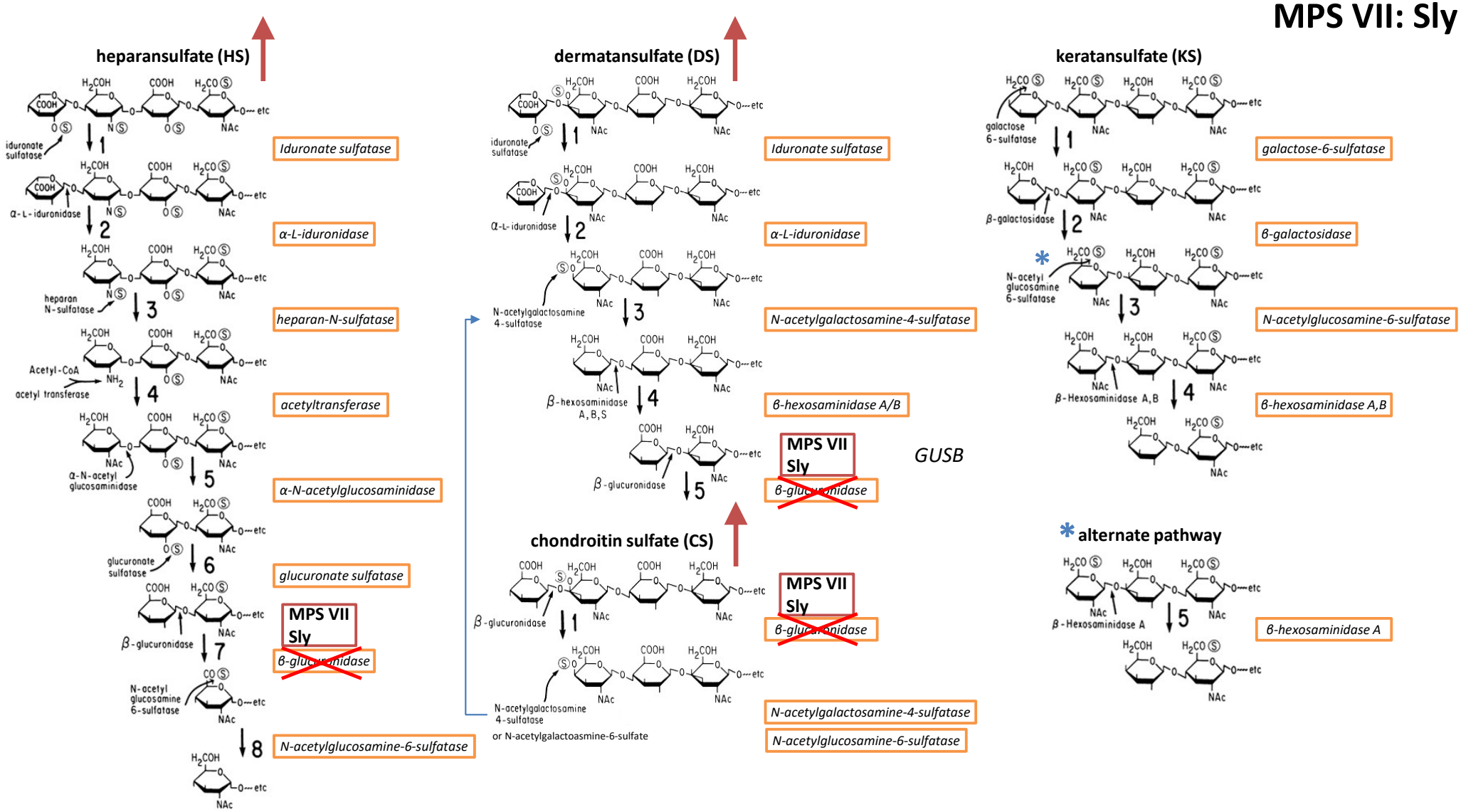
β-galactosidase

N-acetylglucosamine-6-sulfatase

β-hexosaminidase A,B

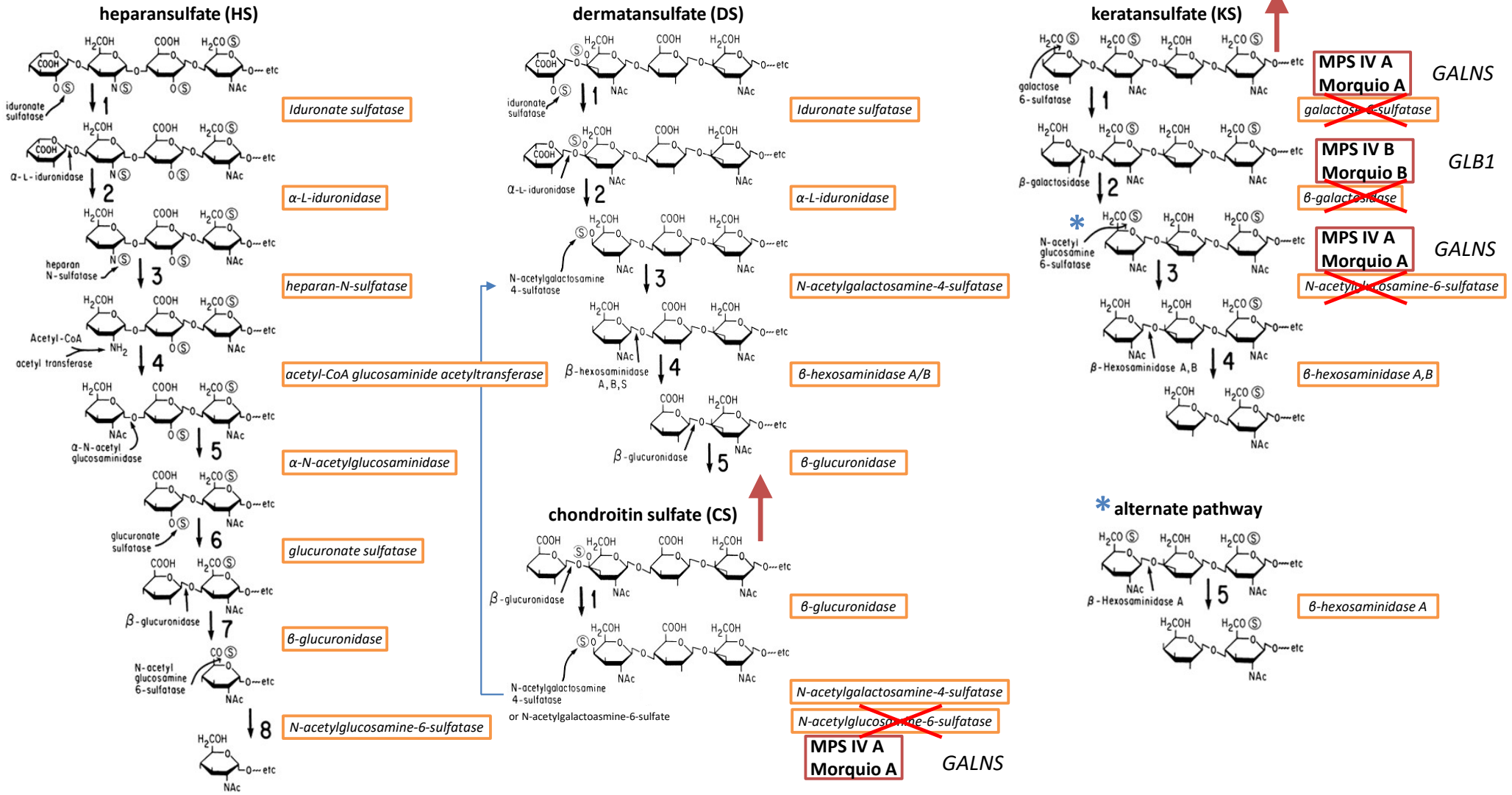
β-hexosaminidase A

MPS VII: Sly


heparansulfate (HS)
Iduronate sulfatase
α-L-iduronidase
heparan N-sulfatase
Acetyl-CoA
acetyl transferase
α-N-acetylglucosaminidase
glucuronate sulfatase
β-glucuronidase
N-acetyl glucosamine 6-sulfatase
dermatansulfate (DS)
Iduronate sulfatase
α-L-iduronidase
N-acetylgalactosamine 4-sulfatase
β-hexosaminidase A, B, S
β-glucuronidase
chondroitin sulfate (CS)
β-glucuronidase
N-acetylgalactosamine 4-sulfatase
or N-acetylgalactoasmine-6-sulfate
keratansulfate (KS)
galactose 6-sulfatase
β-galactosidase
N-acetyl glucosamine 6-sulfatase
β-Hexosaminidase A, B
β-Hexosaminidase A
1
2
3
4
5
6
7
8
Iduronate sulfatase
α-L-iduronidase
heparan-N-sulfatase
acetyltransferase
α-N-acetylglucosaminidase
glucuronate sulfatase
β-glucuronidase
N-acetylglucosamine-6-sulfatase
MPS VII Sly
N-acetylgalactosamine-4-sulfatase
β-hexosaminidase A/B
β-glucuronidase
MPS VII Sly
GUSB
β-glucuronidase
MPS VII Sly
N-acetylgalactosamine-4-sulfatase
N-acetylglucosamine-6-sulfatase
galactose-6-sulfatase
β-galactosidase
N-acetylglucosamine-6-sulfatase
β-hexosaminidase A,B
alternate pathway
β-hexosaminidase A

JD0

MPS IV: Morquio

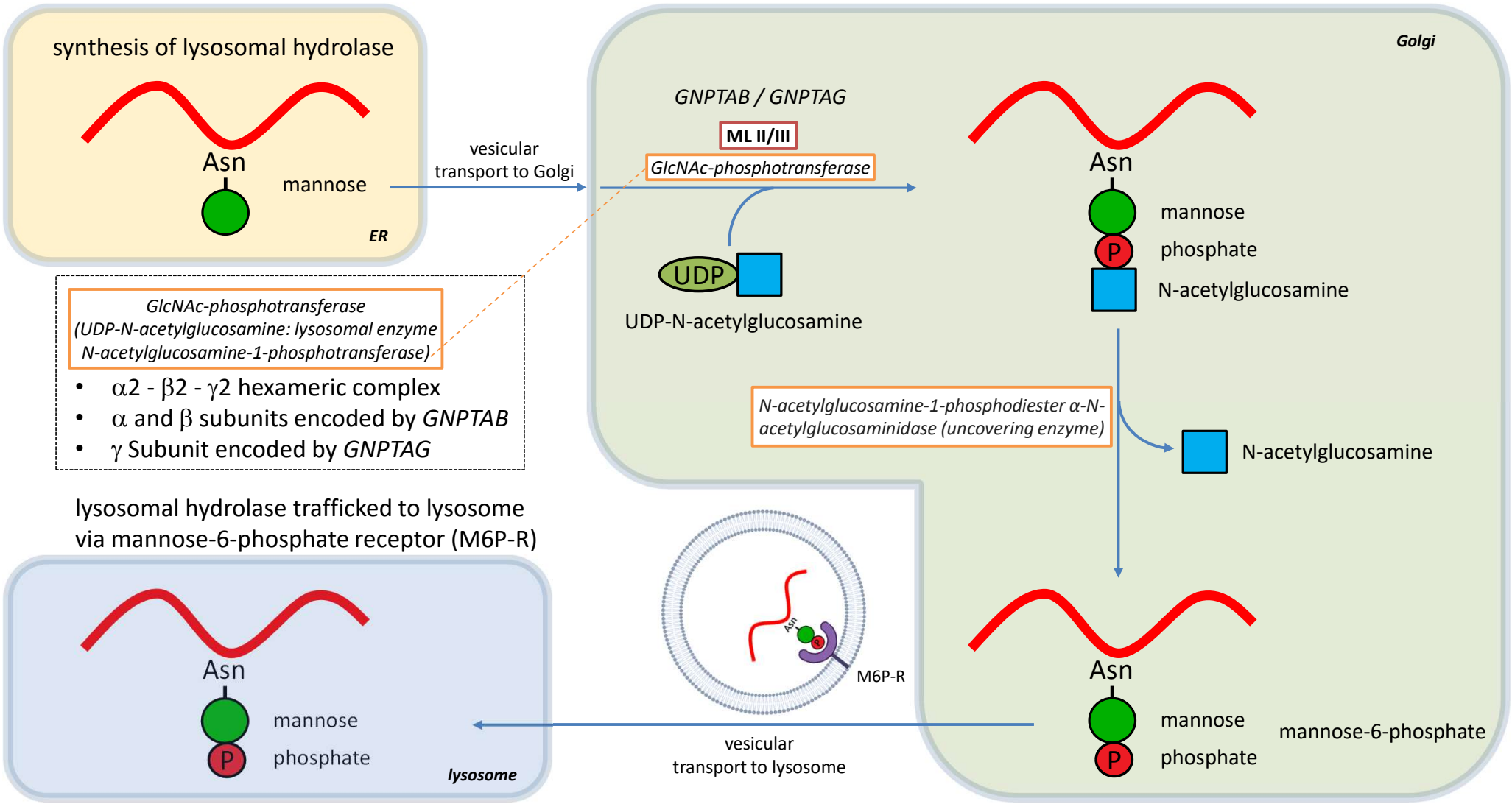


Slide 111

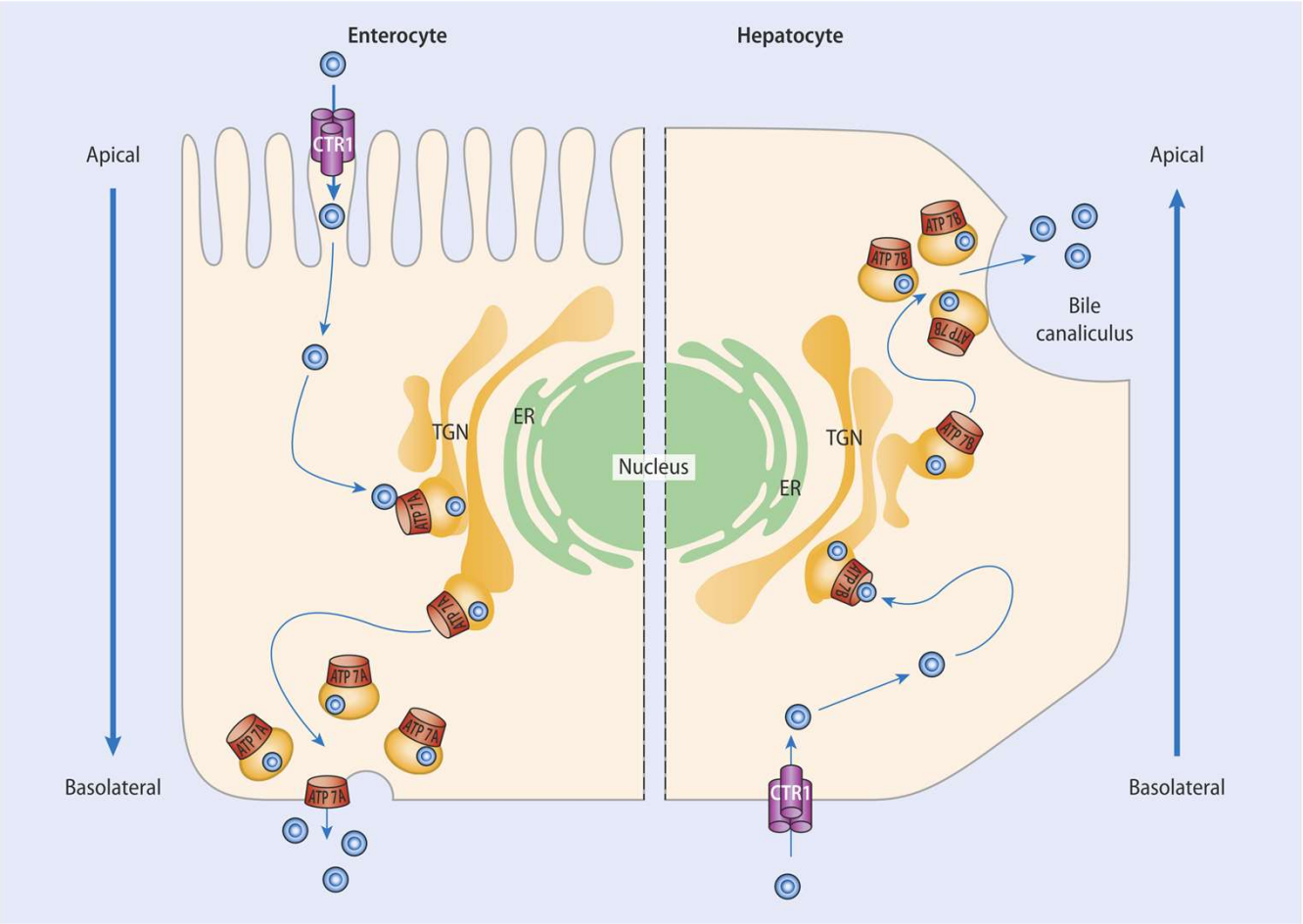
JD0 N-acetylglucosamine-6-sulfatase is encoded by GNS (gene for MPS IIID) not GALNS, which encodes N-acetylgalactosamine-sulfate sulfatase

James Davison, 2024-04-16T13:11:10.413

Mucolipidosis II/III



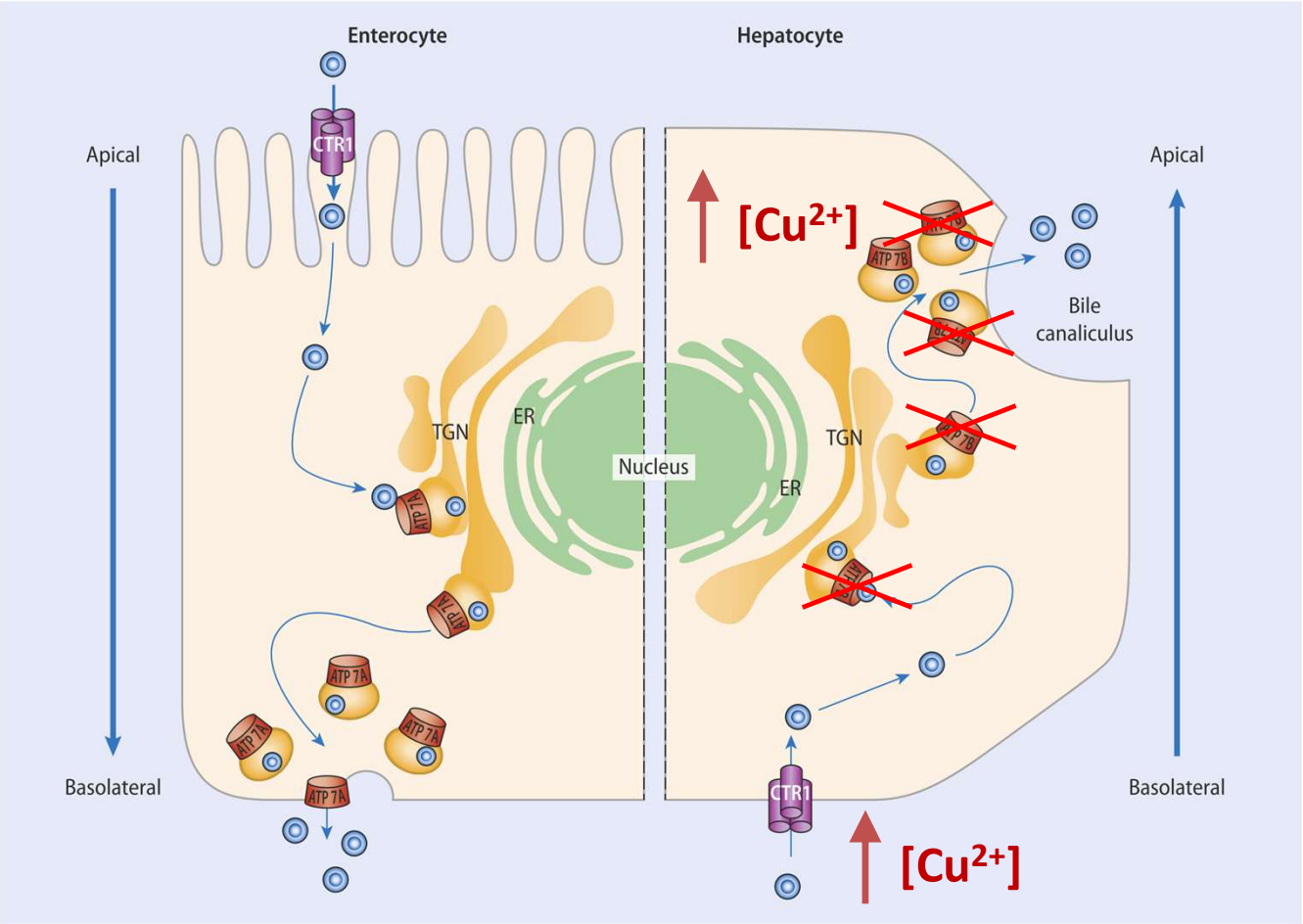
Cellular copper metabolism



- copper enters the cell through CTR1
- ATP7A is the enterocyte basolateral exporter *towards the blood*
- ATP7B is the hepatocyte exporter *towards the bile*
- both ATP7A/7B reside in the Golgi. Upon rise in [copper] they migrate to cell periphery and/or plasma membrane for excretion of copper

Inborn Metabolic Diseases, Diagnosis and Treatment
2022 Editors: Jean-Marie Saudubray, Matthias R. Baumgartner, Ángeles García-Cazorla, John Walter

Wilson disease



- Autosomal recessive disorder due to mutations in *ATP7B*
- Leads to gradual accumulation of copper in liver, brain, kidney and cornea etc.

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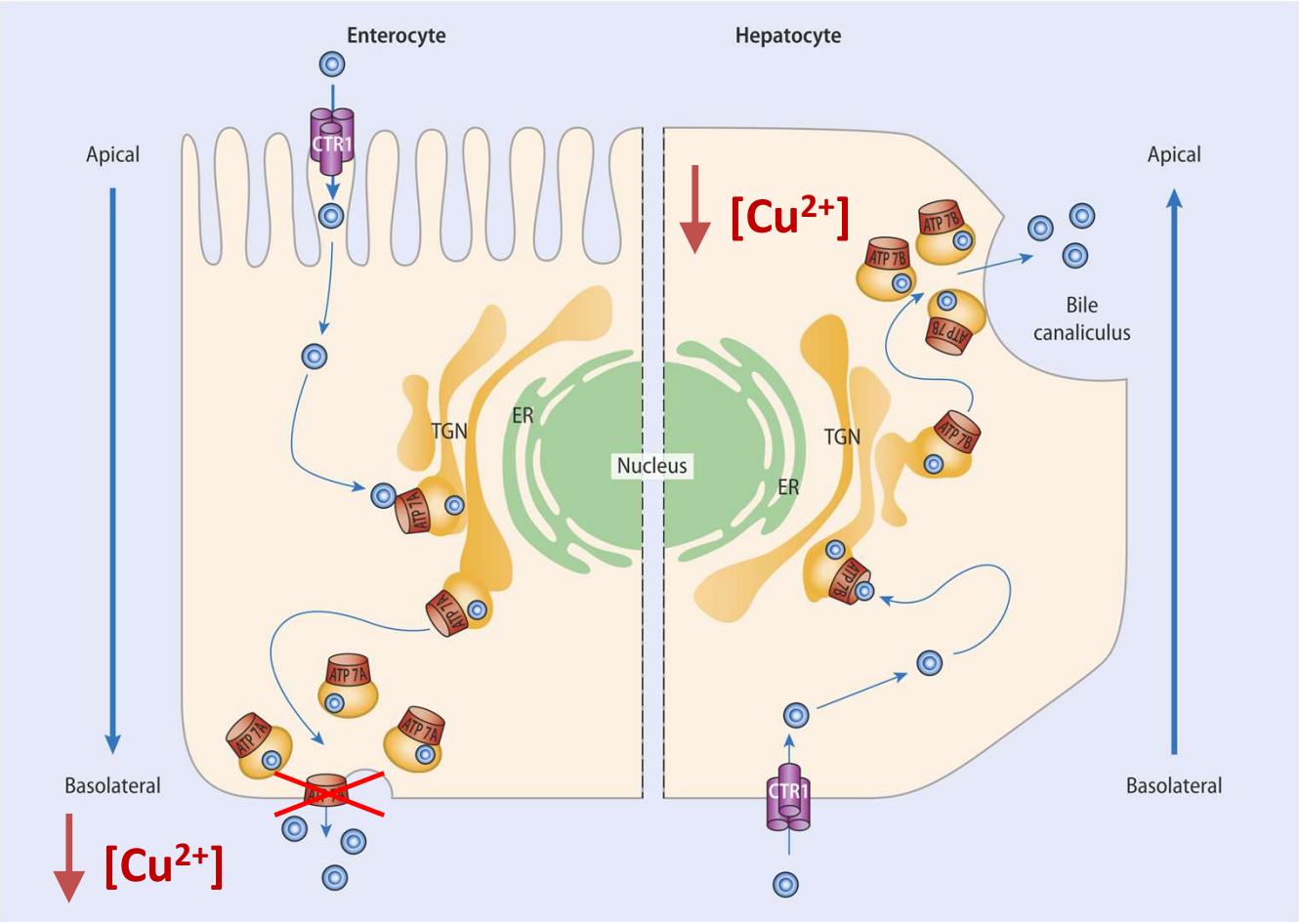
Menkes syndrome



- X-linked disorder due to mutations in *ATP7A*
- This leads to general copper deficiency
- This leads to deficiency of copper-requiring enzymes including those for:
  - Catecholamine synthesis
  - Neuropeptide precursor processing
  - Respiratory chain

Inborn Metabolic Diseases, Diagnosis and Treatment
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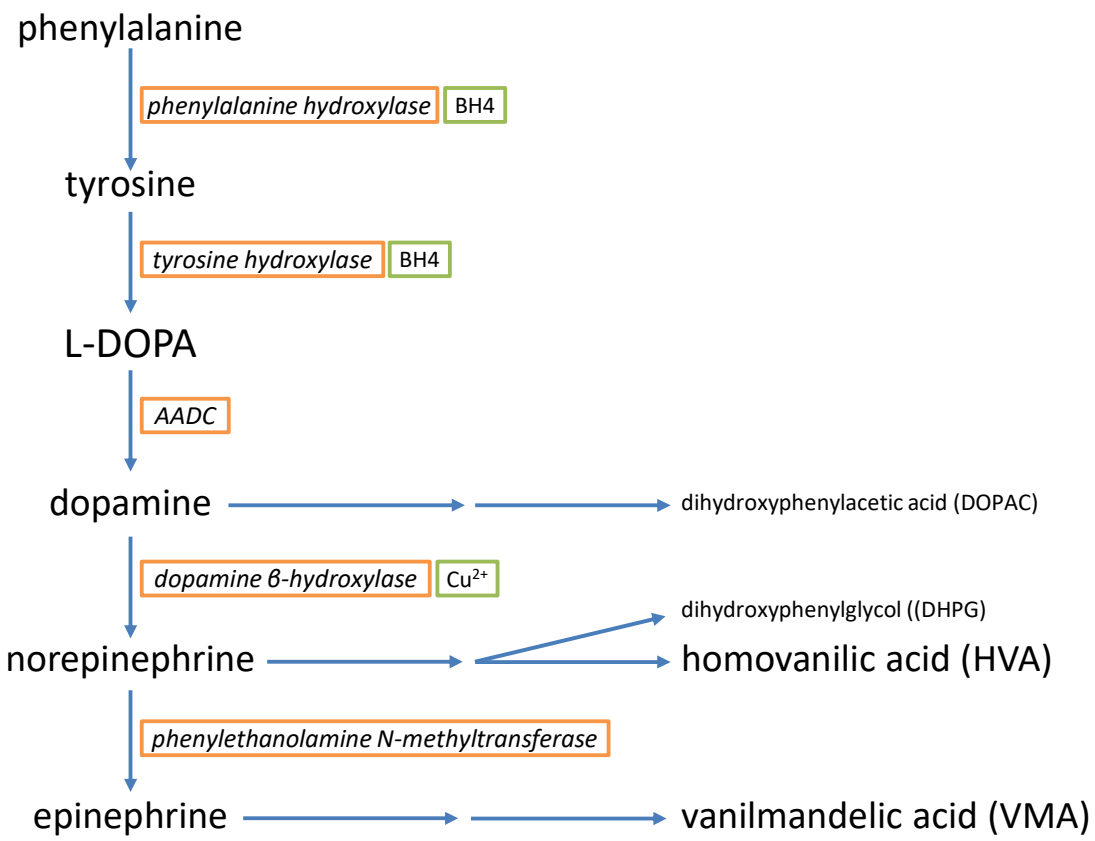
Menkes syndrome

neurotransmitter consequences

Normal catecholamine synthesis and degradation

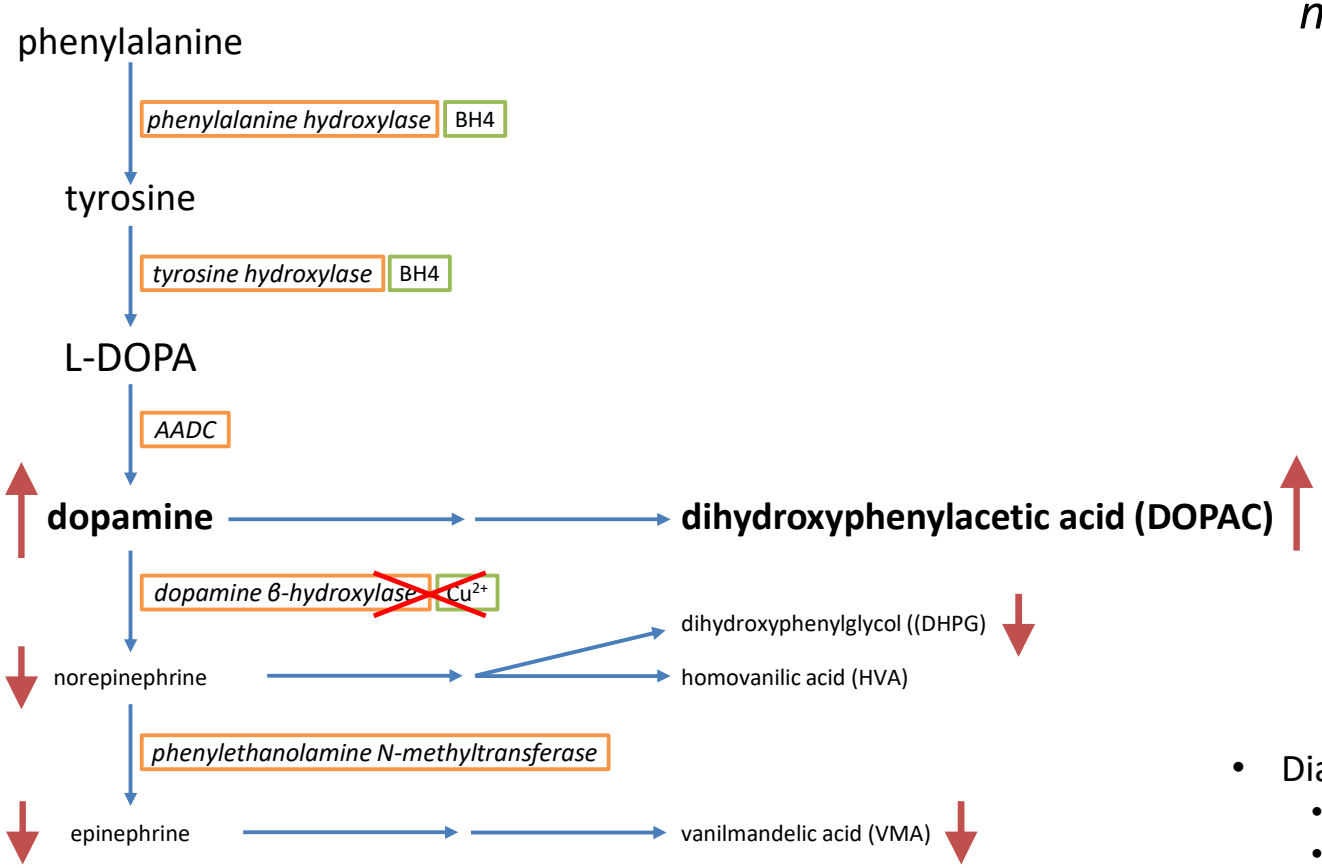


BH4: tetrahydrobioperin

Menkes syndrome

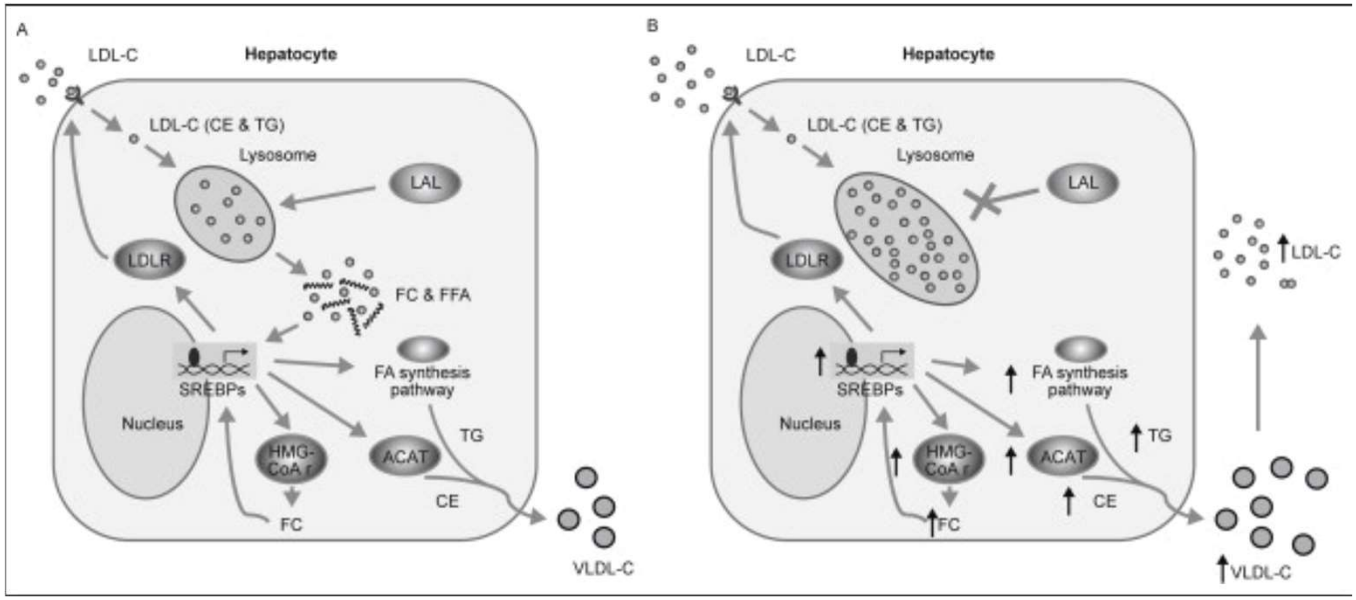
neurotransmitter consequences

catecholamine synthesis and degradation in Menkes



- Diagnostic ratio's
  - Dopamine/norepinephrine
  - DOPAC/DHPG

BH4: tetrahydrobioperin



Schematic view of cellular cholesterol homoeostasis in (A) healthy individuals and (B) patients with LAL-D. ACAT, acyl-cholesterol acyltransferase; CE, cholesteryl esters; FA, fatty acid; FC, free cholesterol; FFA, free fatty acid; HMG-CoA r, hydroxymethylglutaryl-coenzyme A reductase; LAL, lysosomal acid lipase; LAL-D, LAL deficiency; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; SREBPs, sterol regulatory element binding proteins; TG, triglyceride; VLDL-C, very-low-density lipoprotein cholesterol.

https://doi.org/10.1016/j.atherosclerosis.2014.04.003