Pathways SSIEM Academy

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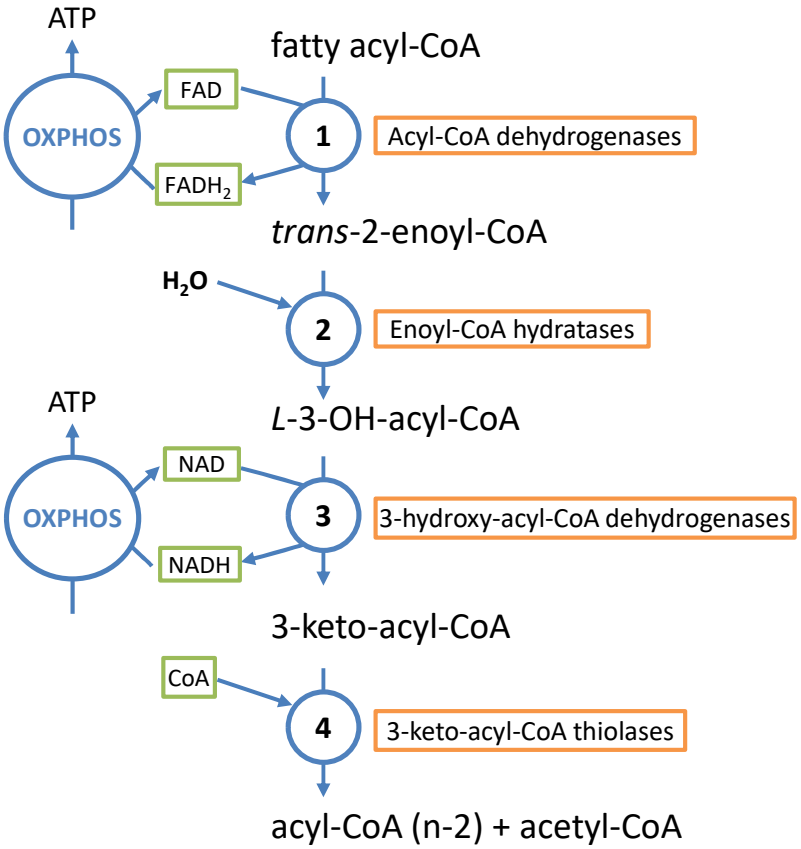
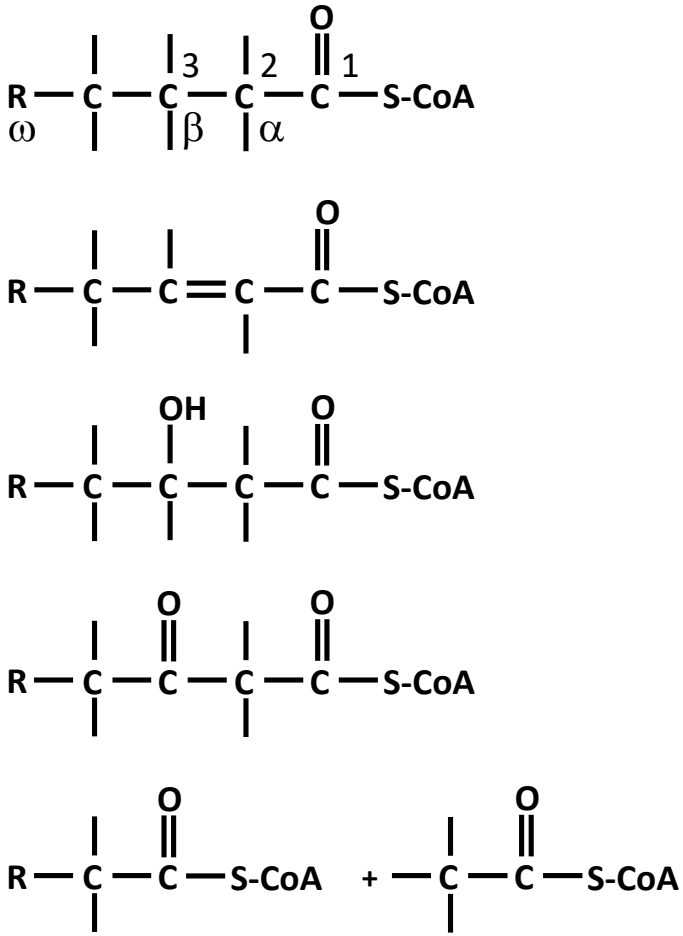
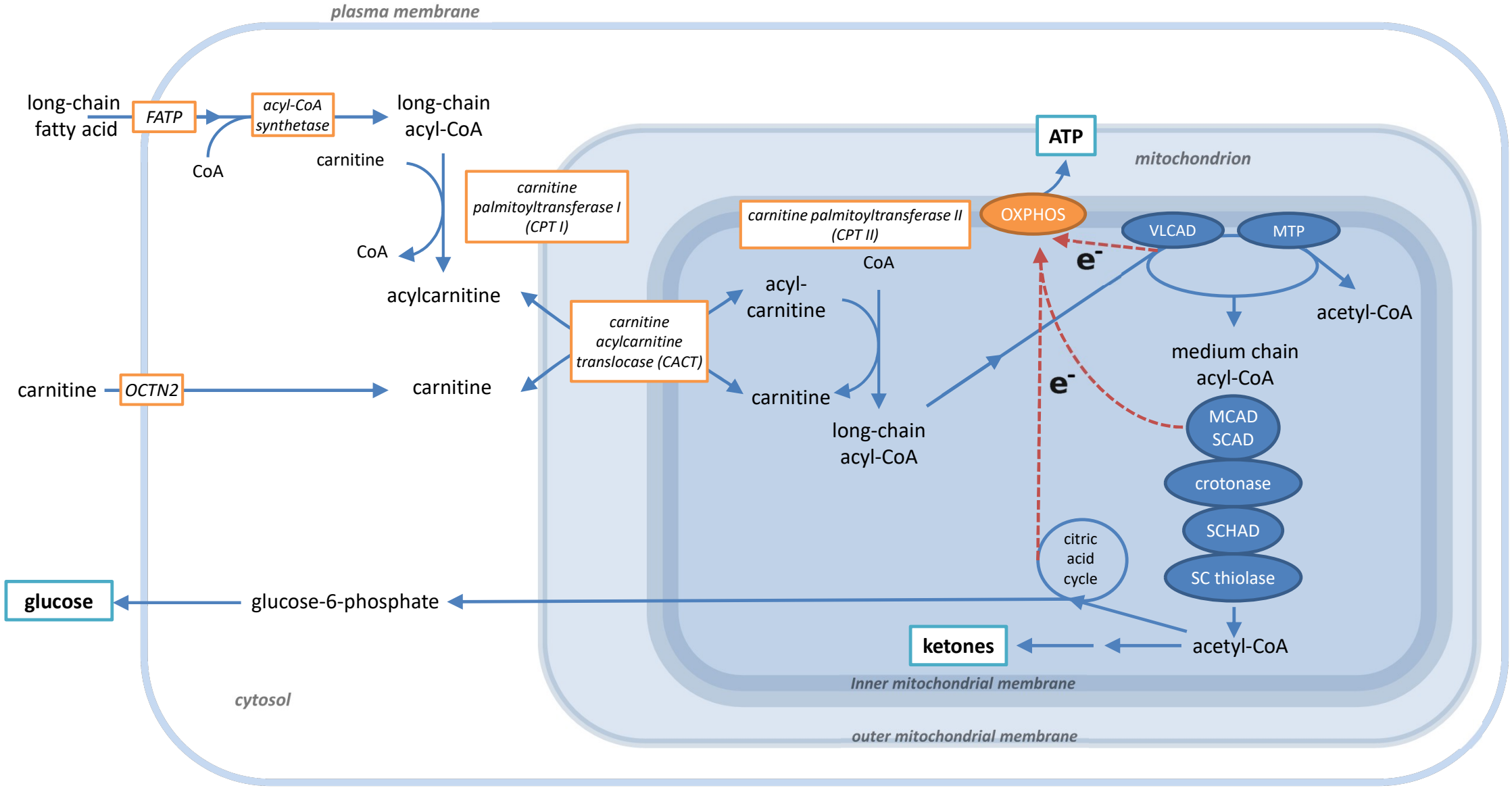
Mitochondrial β-oxidation

metabolite
enzyme
cofactor

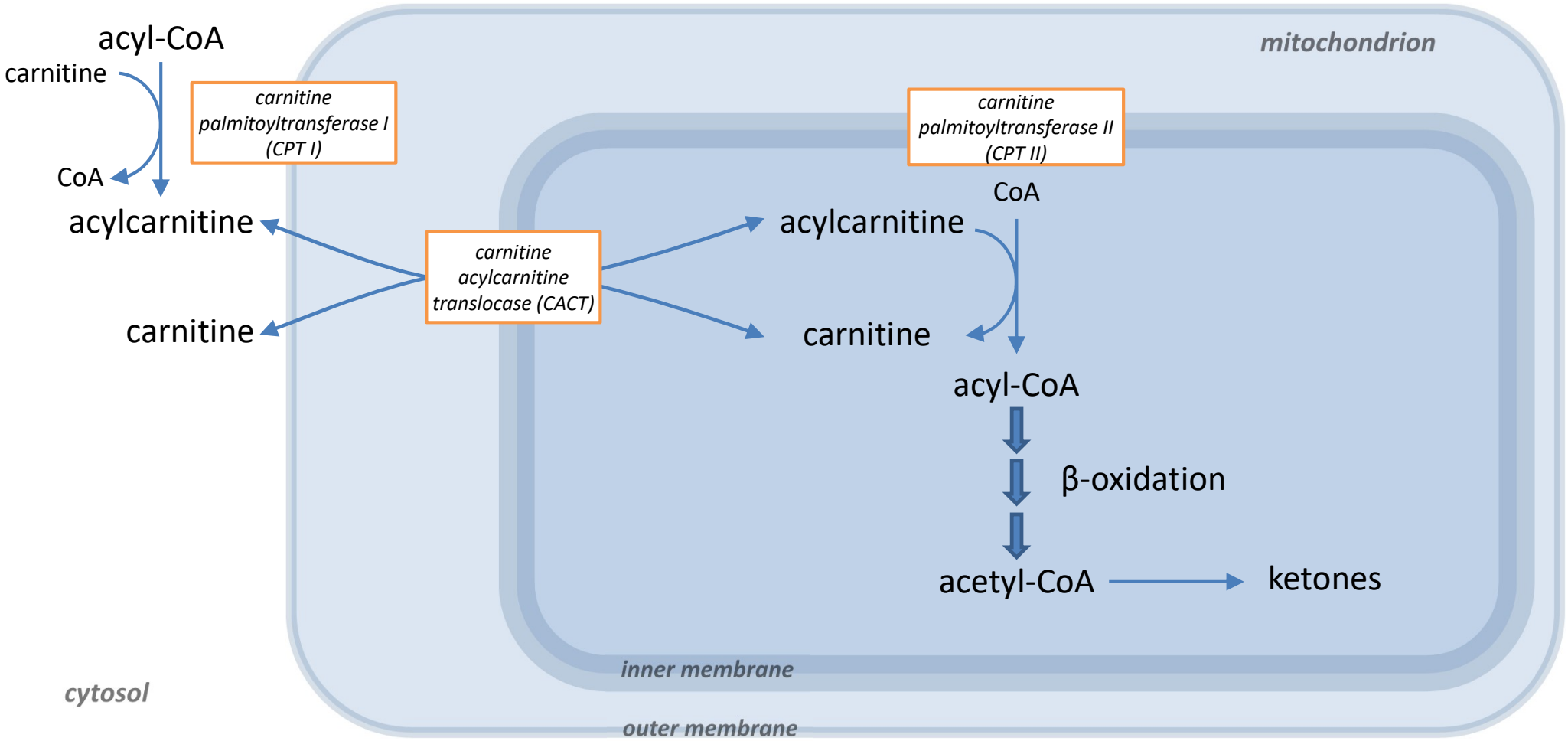


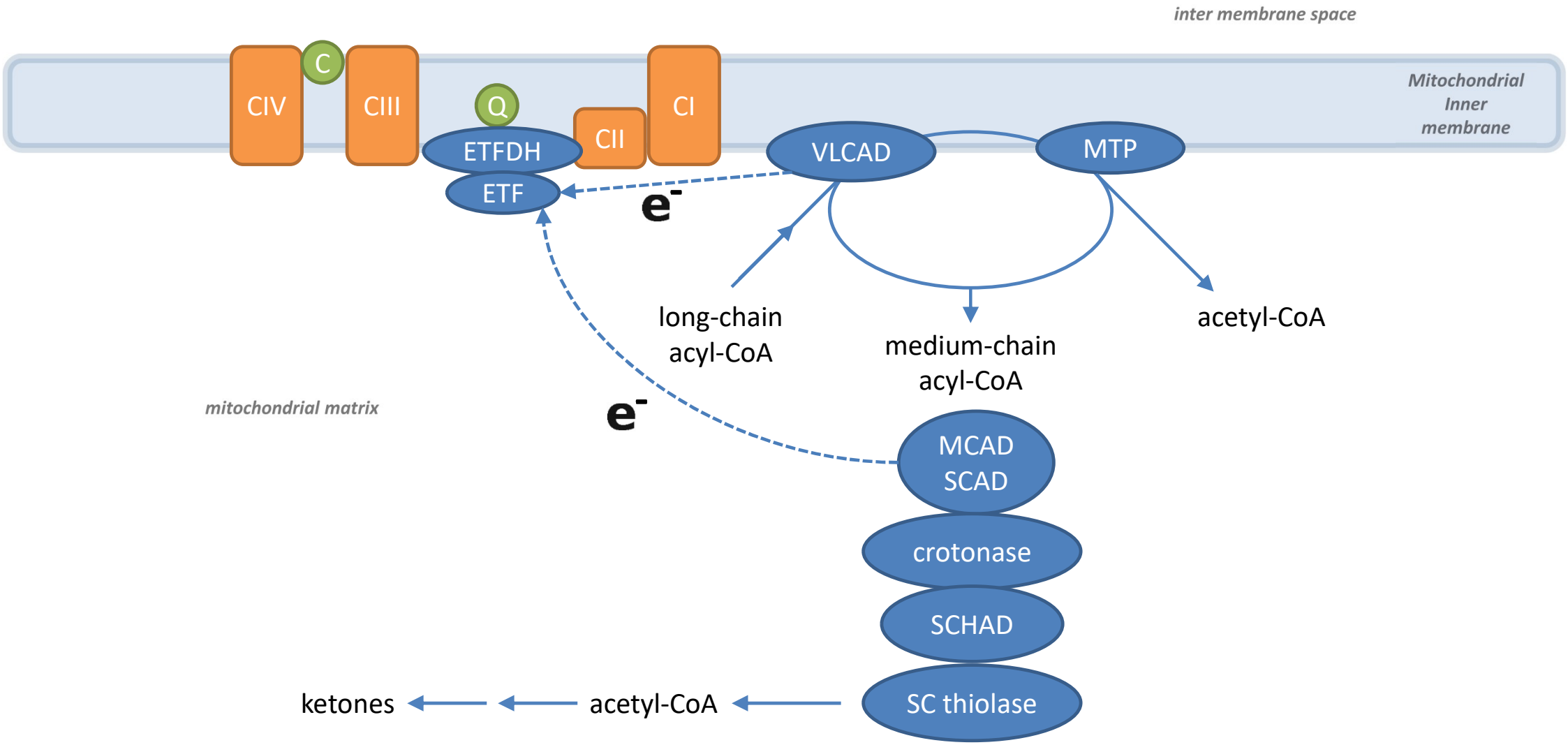


Mitochondrial fatty acid β-oxidation

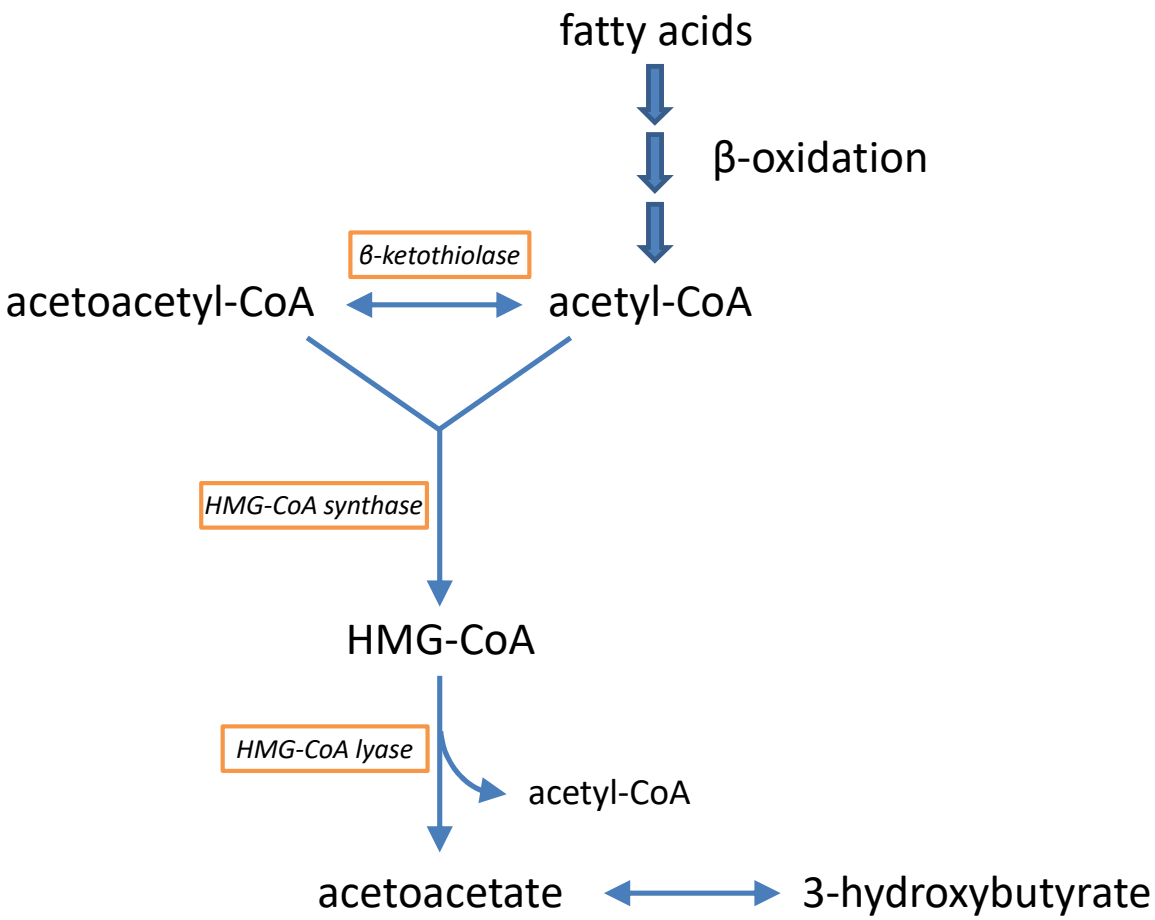


The carnitine shuttle / cycle

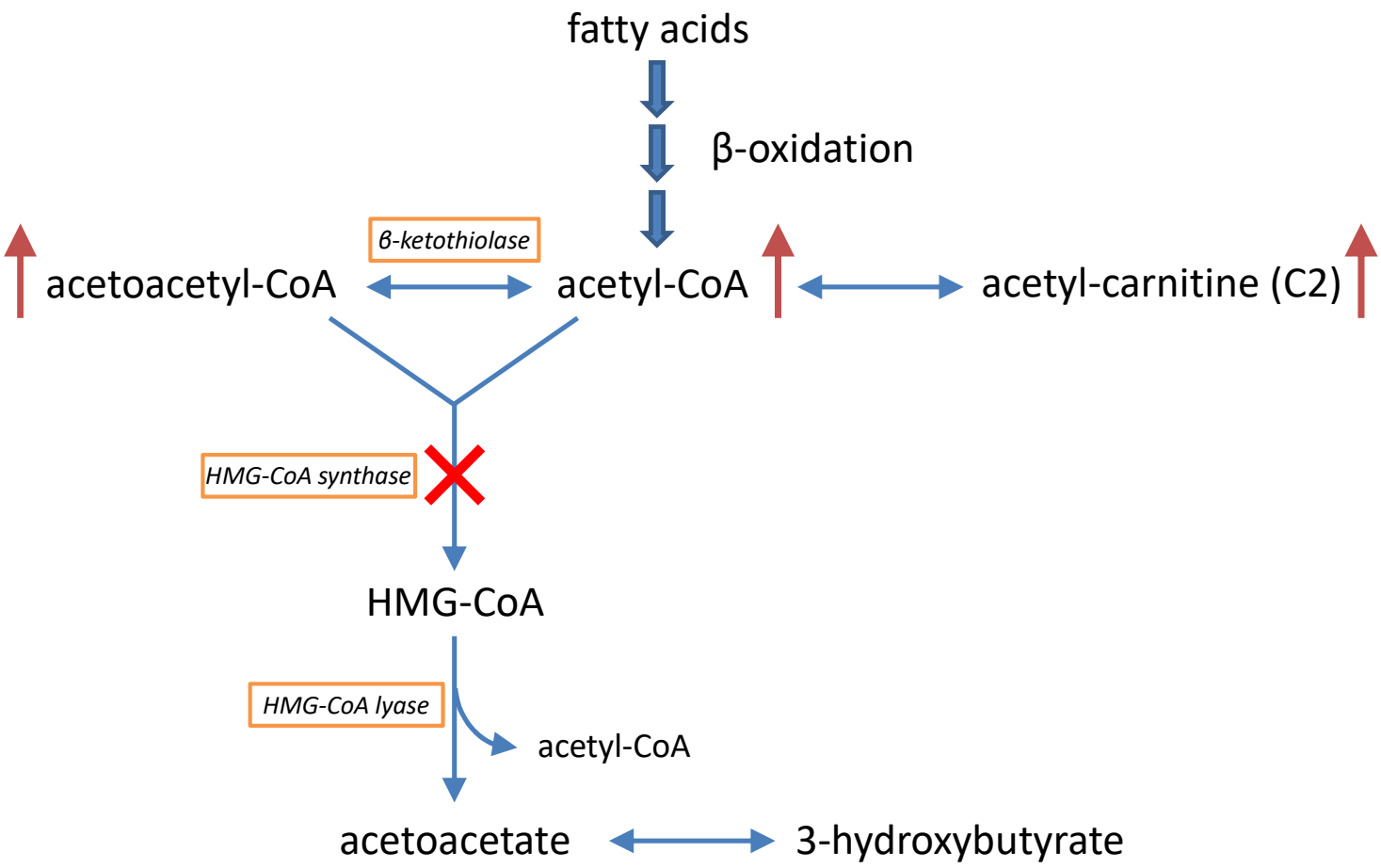


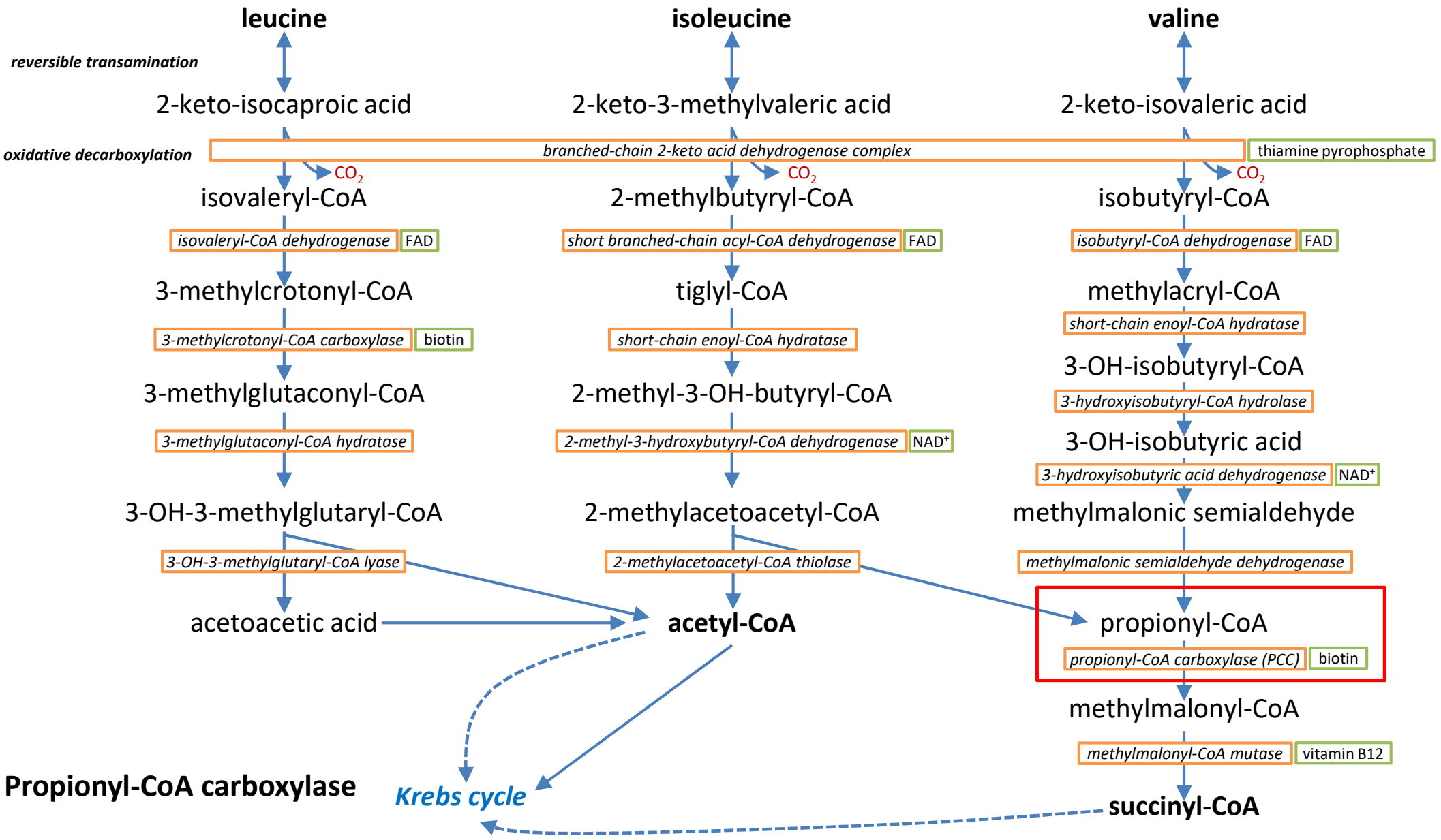

inter membrane space
Mitochondrial Inner membrane
CIV
C
CIII
Q
ETFDH
CII
CI
ETF
e-
VLCAD
MTP
long-chain acyl-CoA
medium-chain acyl-CoA
acetyl-CoA
mitochondrial matrix
e-
MCAD
SCAD
crotonase
SCHAD
SC thiolase
ketones
acetyl-CoA

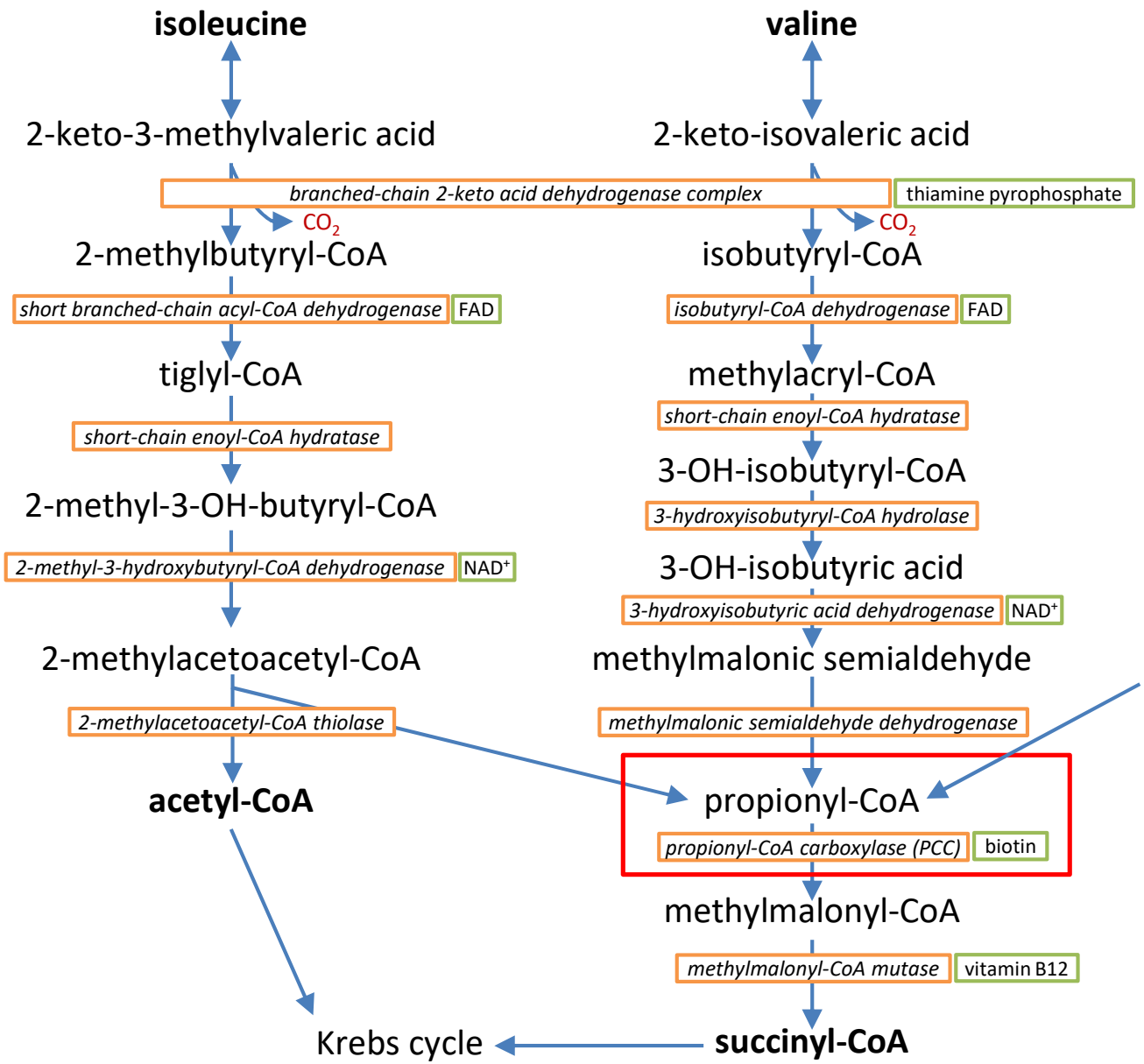
ketogenesis



HMG-CoA synthase deficiency



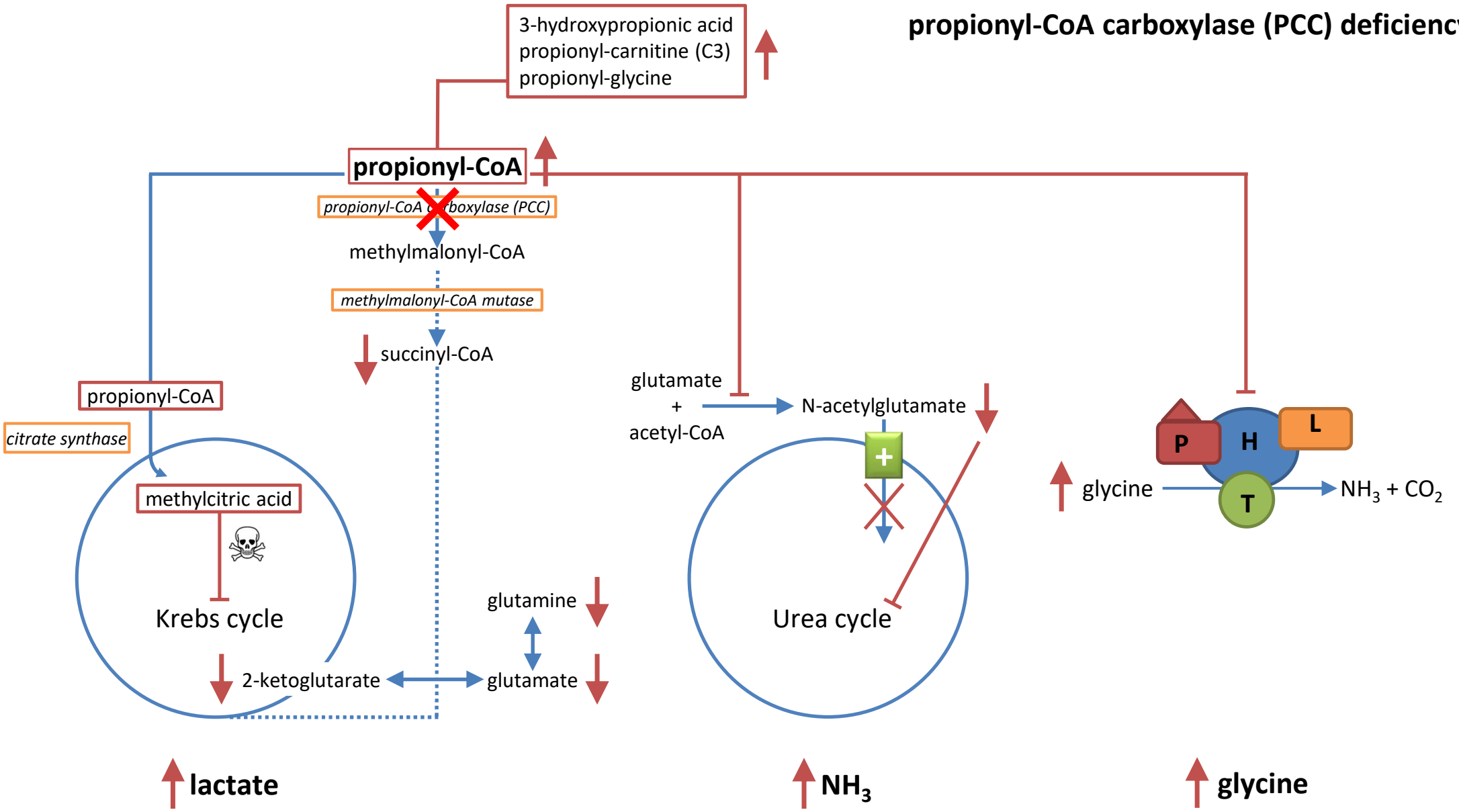

leucine
isoleucine
valine
reversible transamination
2-keto-isocaproic acid
2-keto-3-methylvaleric acid
2-keto-isovaleric acid
oxidative decarboxylation
branched-chain 2-keto acid dehydrogenase complex
thiamine pyrophosphate
CO2
CO2
CO2
isovaleryl-CoA
2-methylbutyryl-CoA
isobutyryl-CoA
isovaleryl-CoA 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
Propionyl-CoA carboxylase

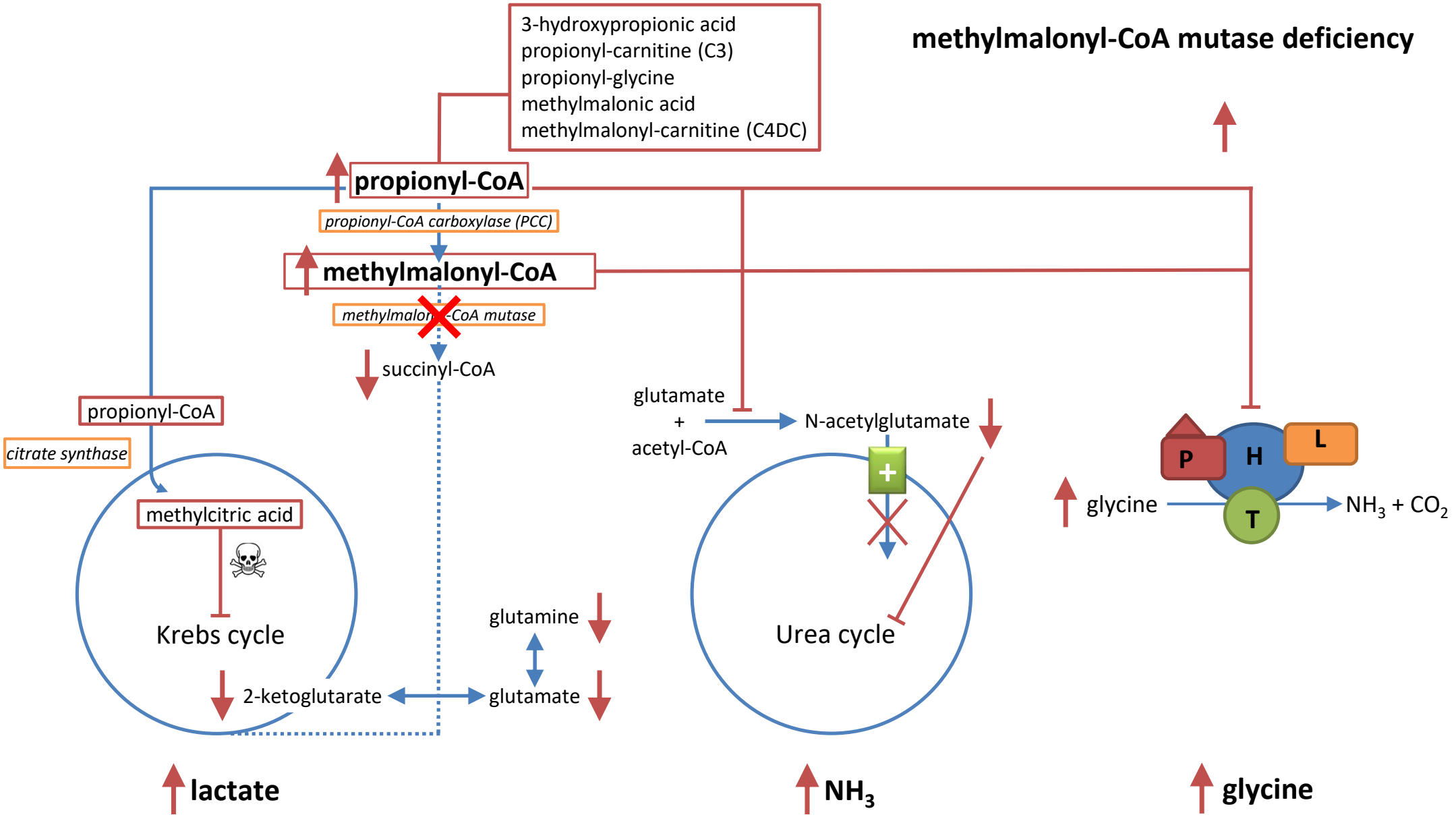


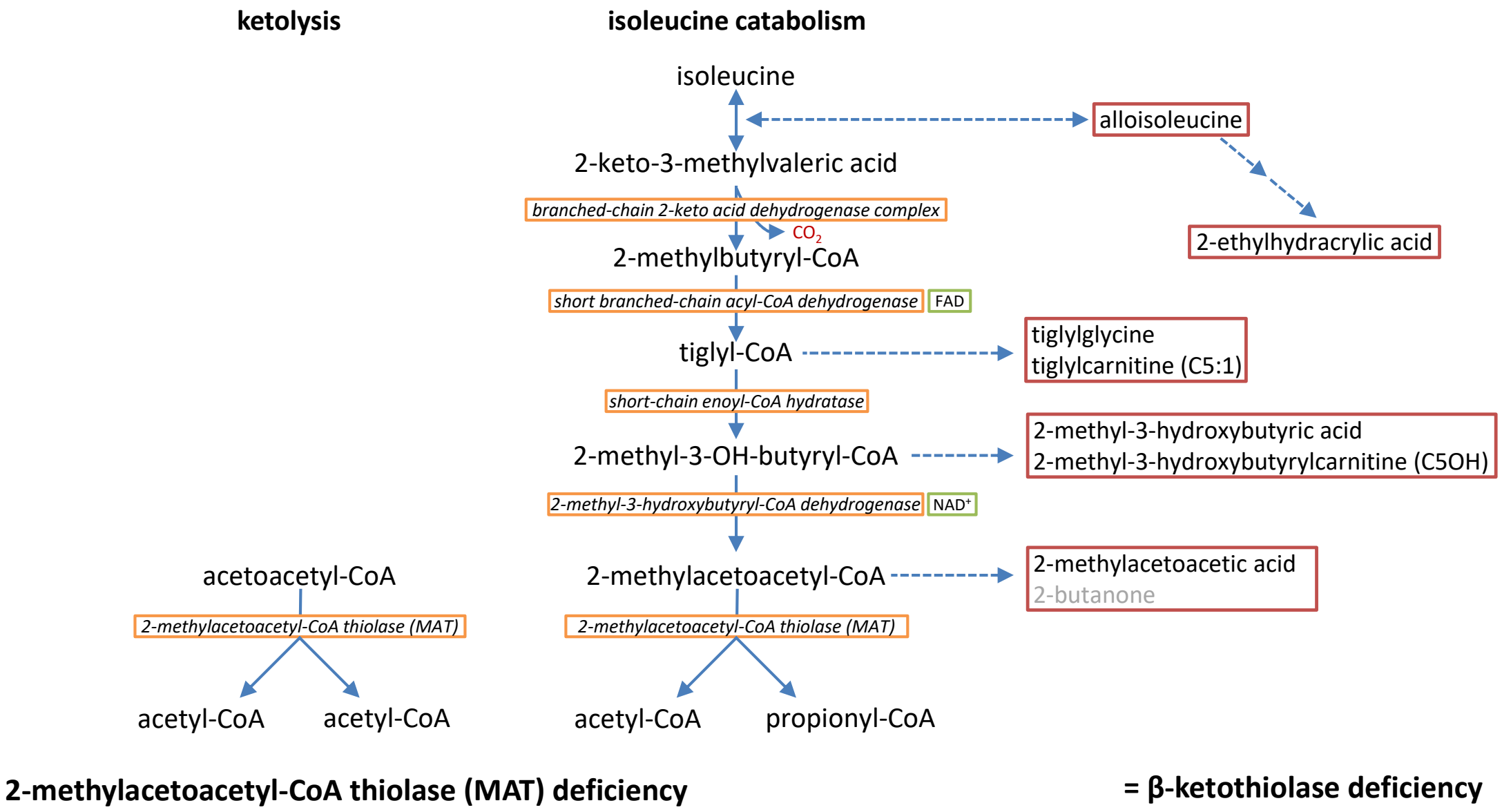
propionyl-CoA carboxylase (PCC)

(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

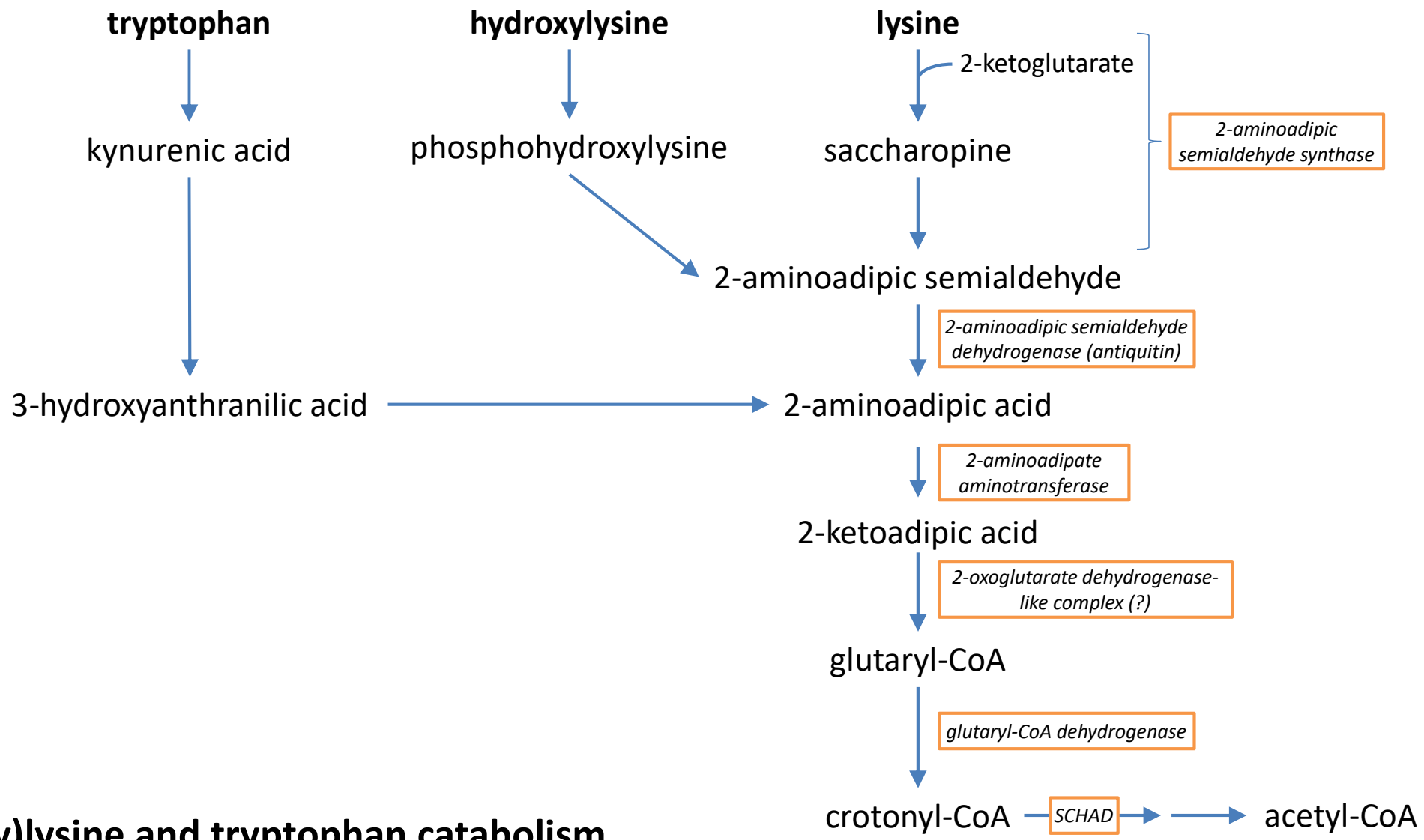

propionyl-CoA carboxylase (PCC) deficiency
3-hydroxypropionic acid
propionyl-carnitine (C3)
propionyl-glycine
propionyl-CoA
propionyl-CoA carboxylase (PCC)
methylmalonyl-CoA
methylmalonyl-CoA mutase
succinyl-CoA
propionyl-CoA
citrate synthase
methylcitric acid
Krebs cycle
2-ketoglutarate
glutamine
glutamate
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

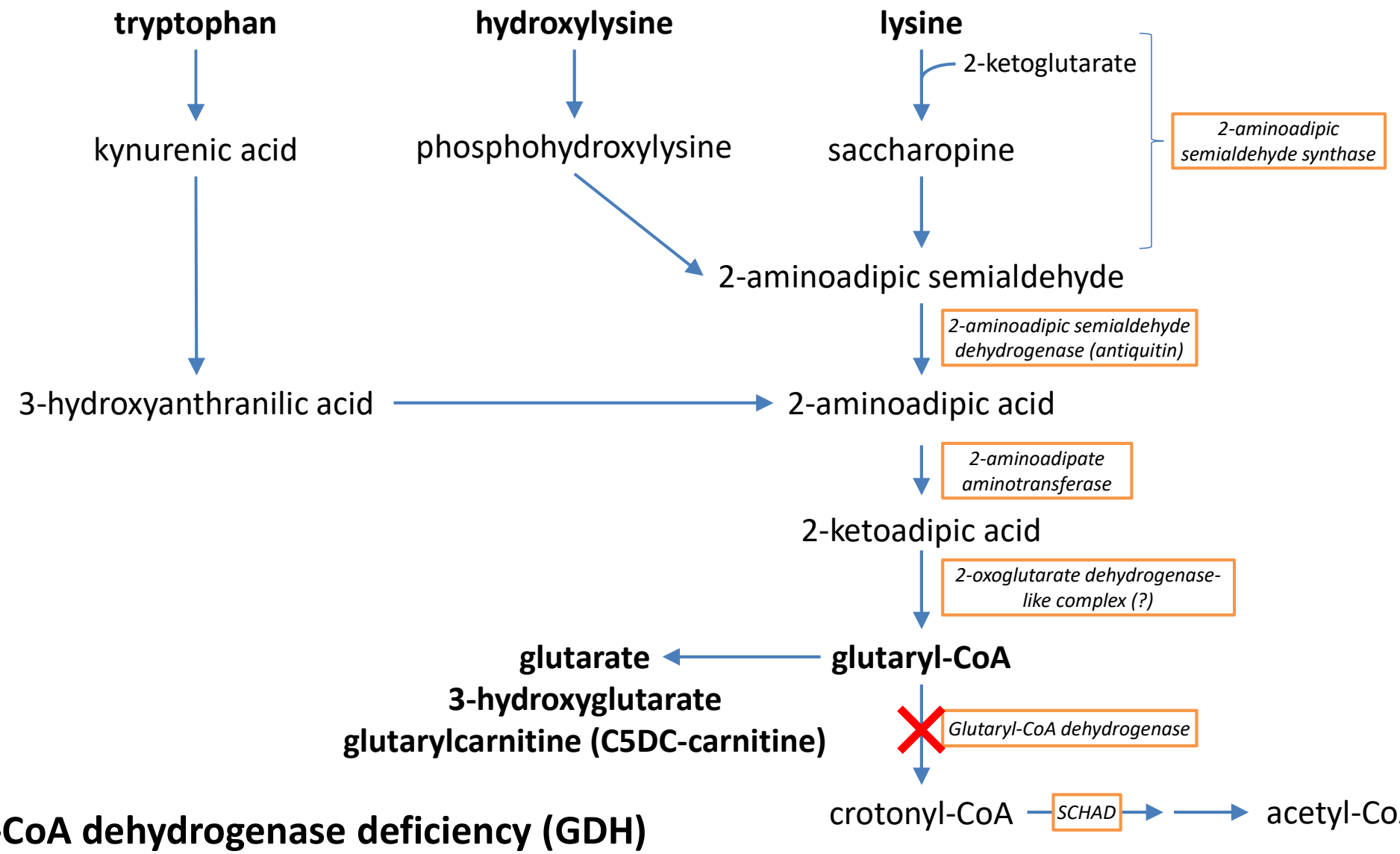


2-methylacetoacetyl-CoA thiolase (MAT) deficiency

= β-ketothiolase deficiency

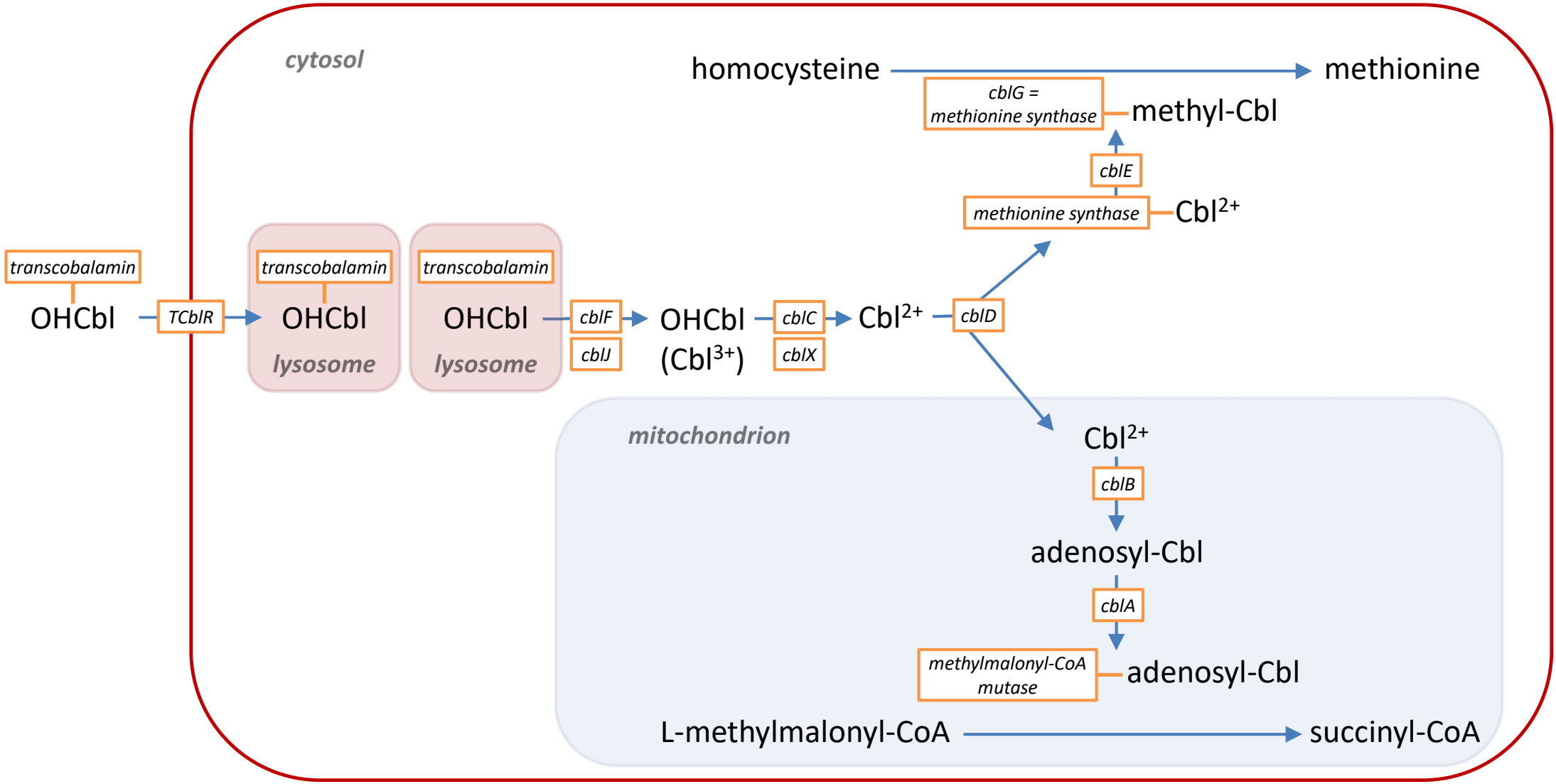


(hydroxy)lysine and tryptophan catabolism

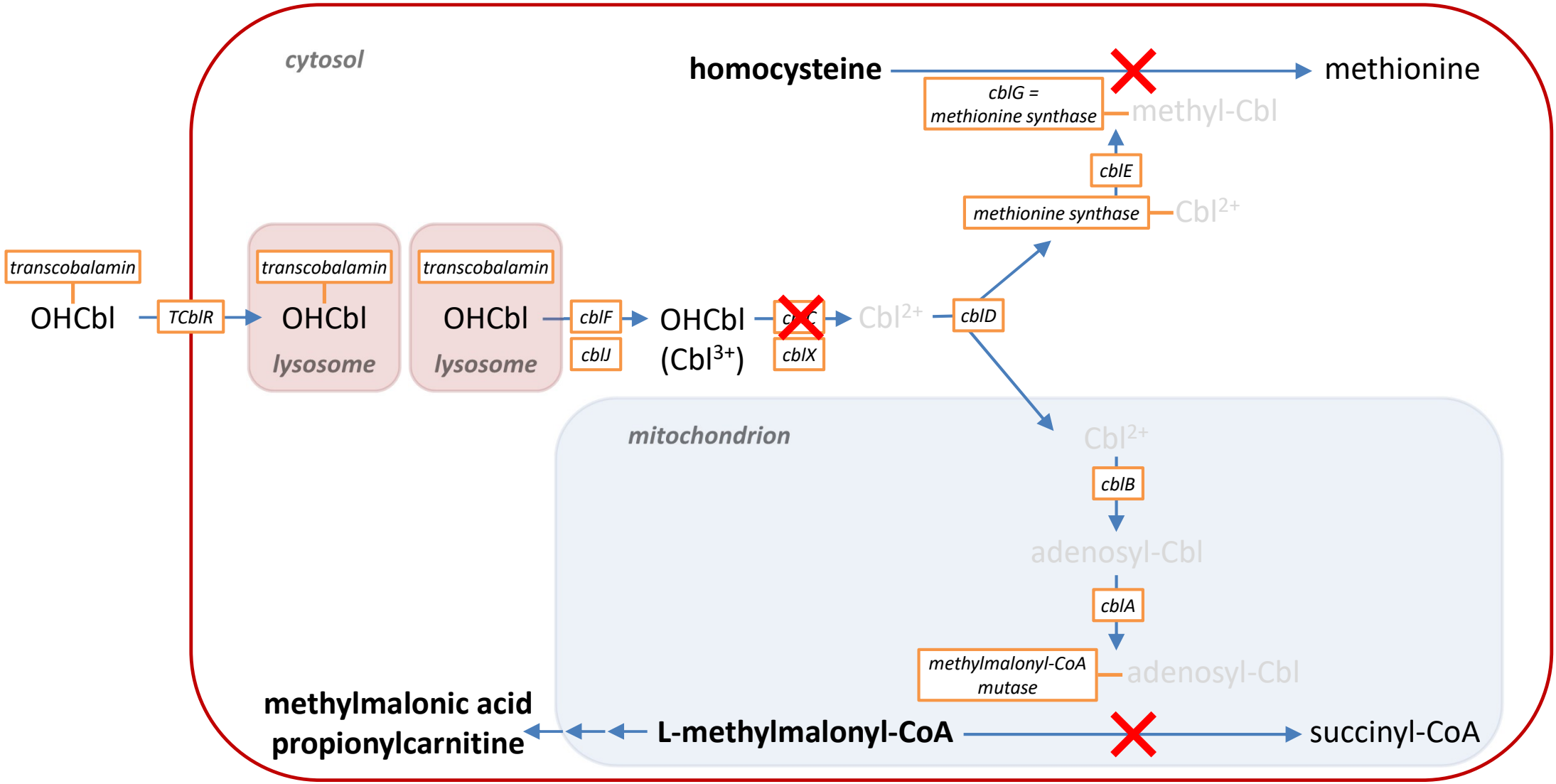


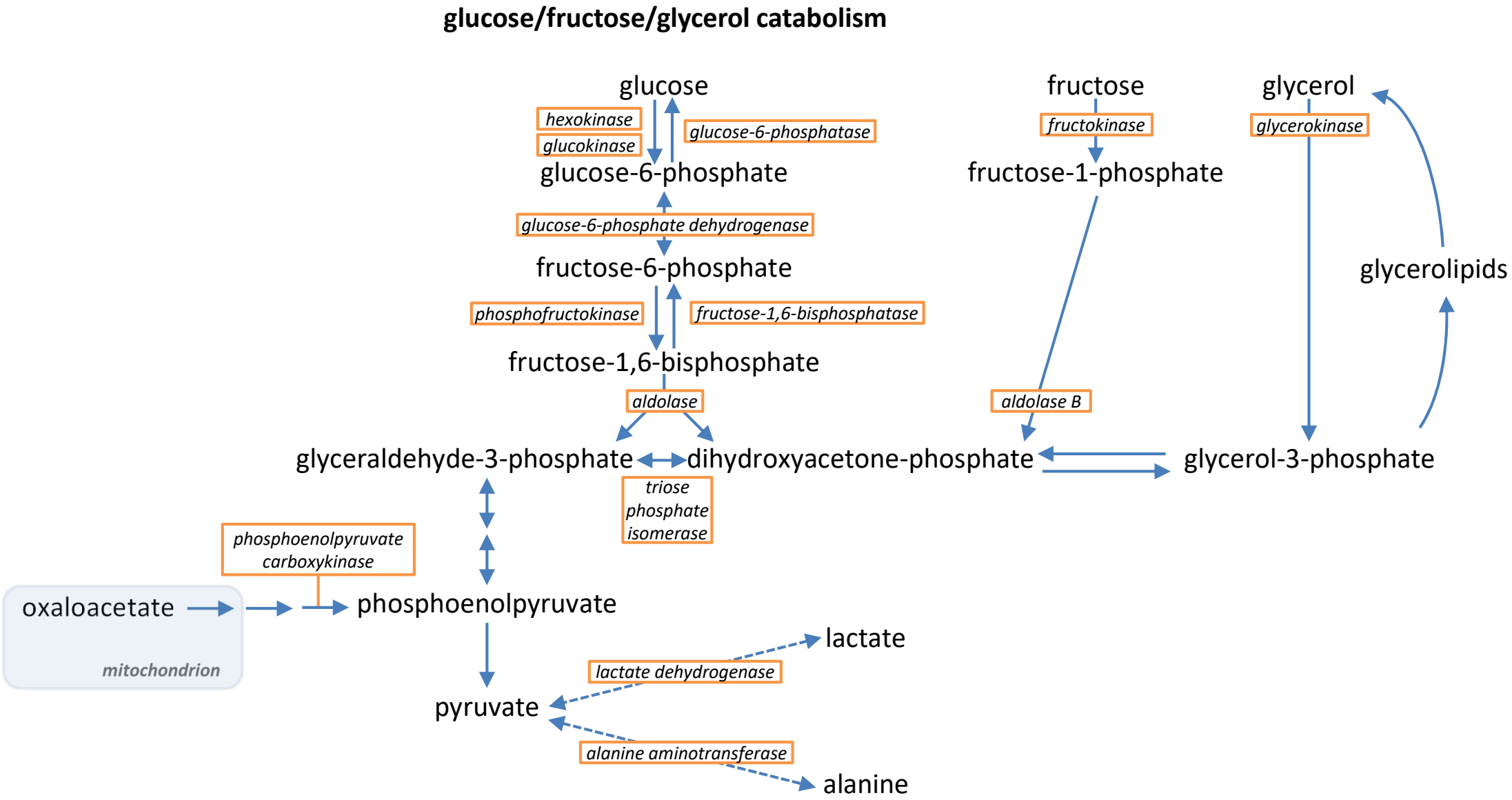
glutaryl-CoA dehydrogenase deficiency (GDH)

cobalamin transport and metabolism

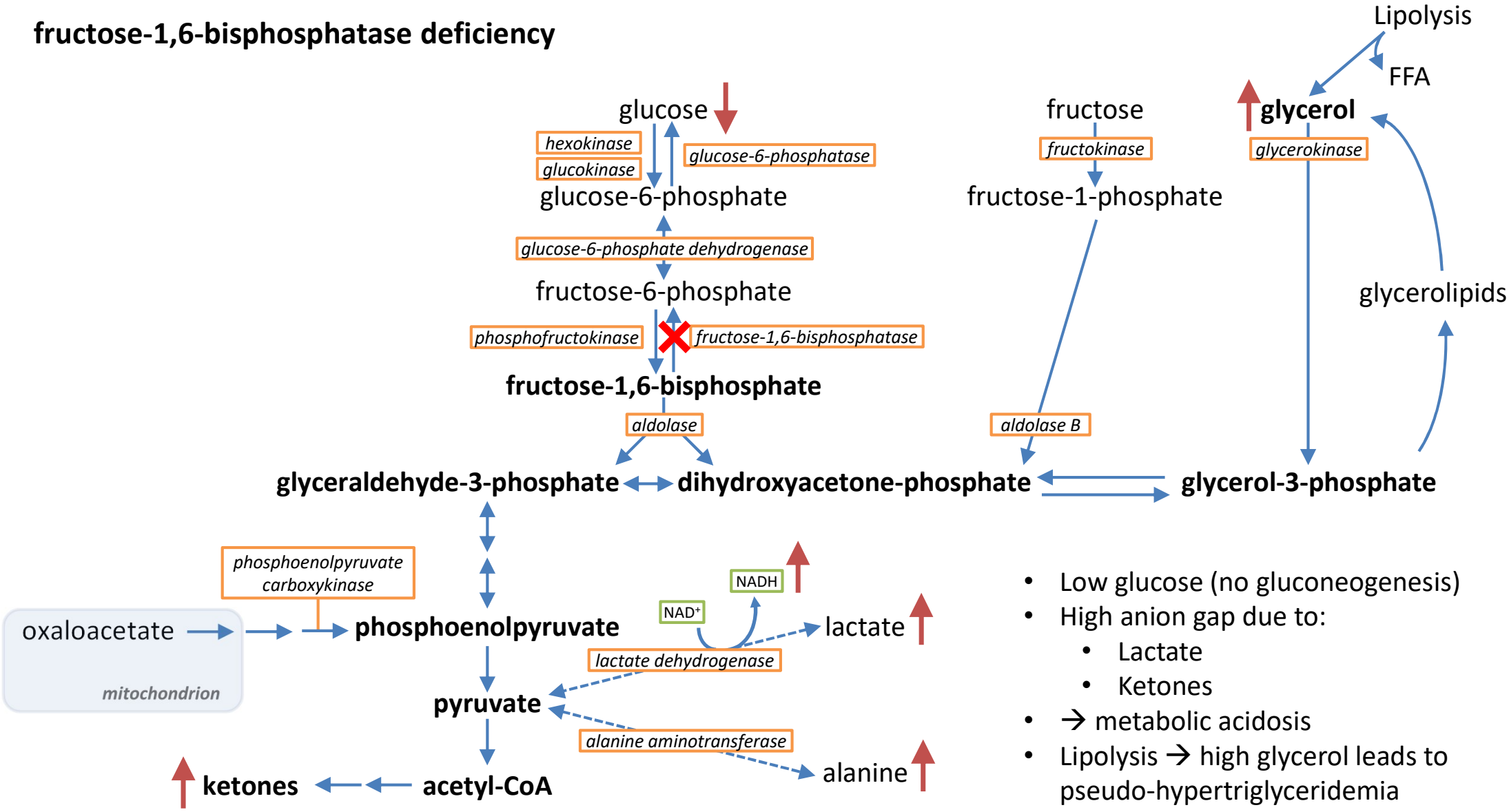


cobalamin transport and metabolism – CblC deficiency



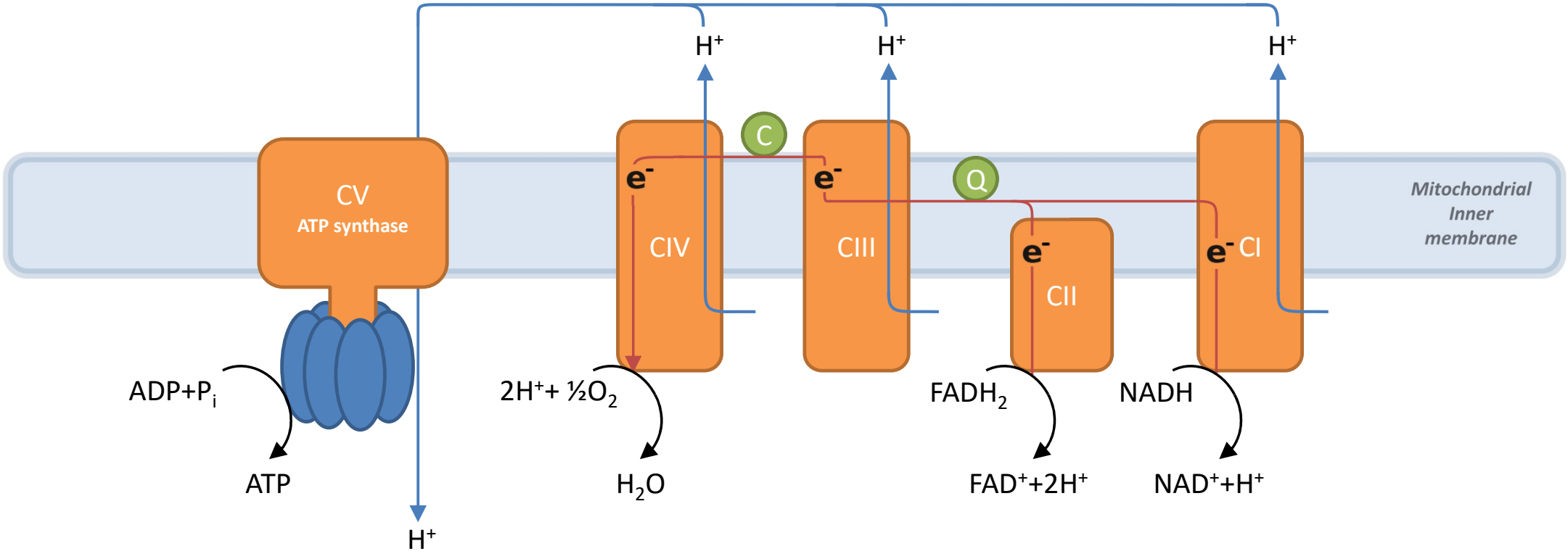

glucose/fructose/glycerol catabolism
glucose
hexokinase
glucokinase
glucose-6-phosphatase
glucose-6-phosphate
glucose-6-phosphate dehydrogenase
fructose-6-phosphate
phosphofructokinase
fructose-1,6-bisphosphatase
fructose-1,6-bisphosphate
aldolase
glyceraldehyde-3-phosphate
dihydroxyacetone-phosphate
triose phosphate isomerase
fructose
fructokinase
fructose-1-phosphate
aldolase B
glycerol
glycerokinase
glycerolipids
glycerol-3-phosphate
phosphoenolpyruvate carboxykinase
oxaloacetate
mitochondrion
phosphoenolpyruvate
lactate
lactate dehydrogenase
pyruvate
alanine aminotransferase
alanine

fructose-1,6-bisphosphatase deficiency

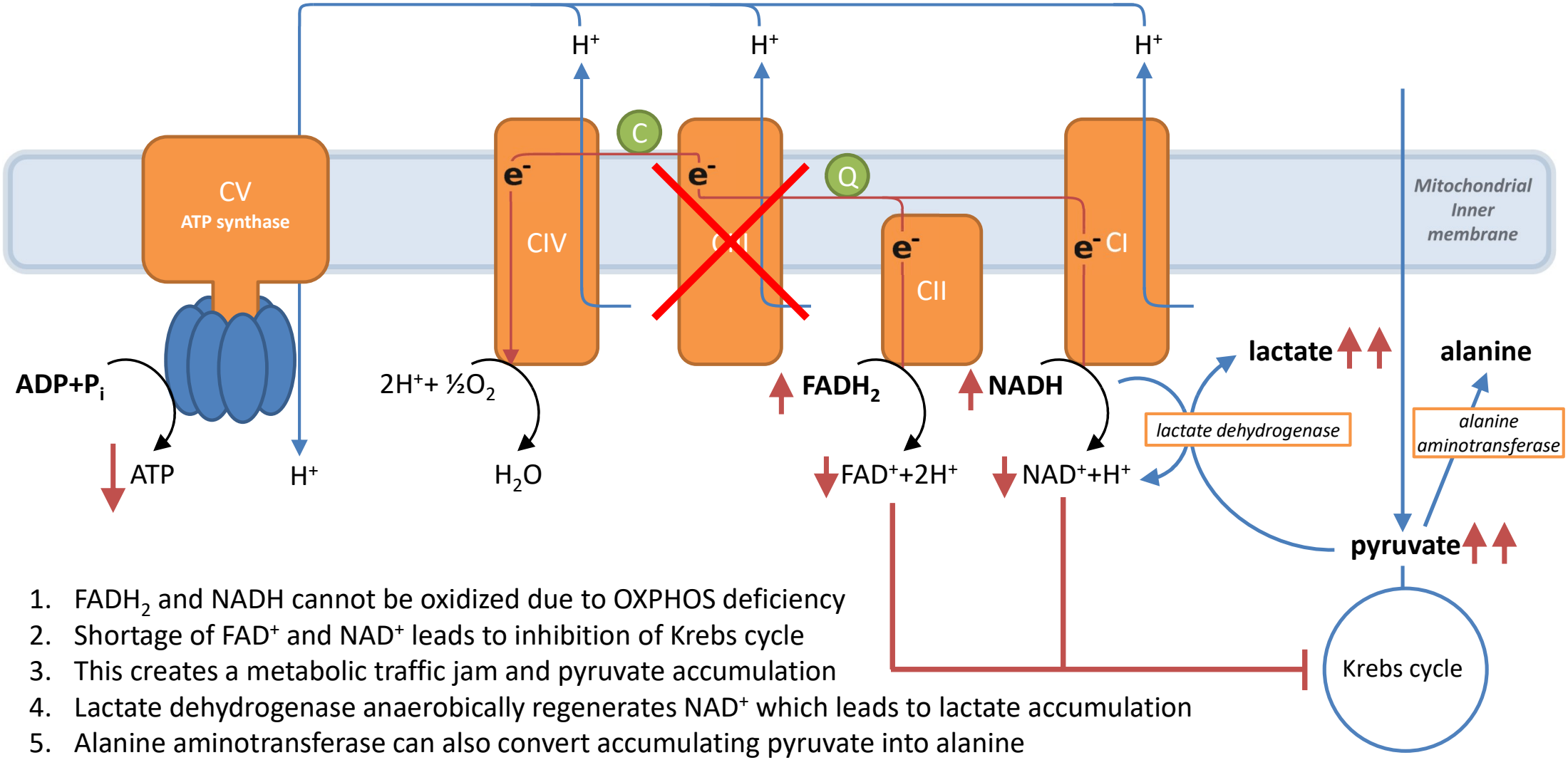


- Low glucose (no gluconeogenesis)
- High anion gap due to:
  - Lactate
  - Ketones
- → metabolic acidosis
- Lipolysis → high glycerol leads to pseudo-hypertriglyceridemia

the mitochondrial oxidative phosphorylation system (OXPHOS)

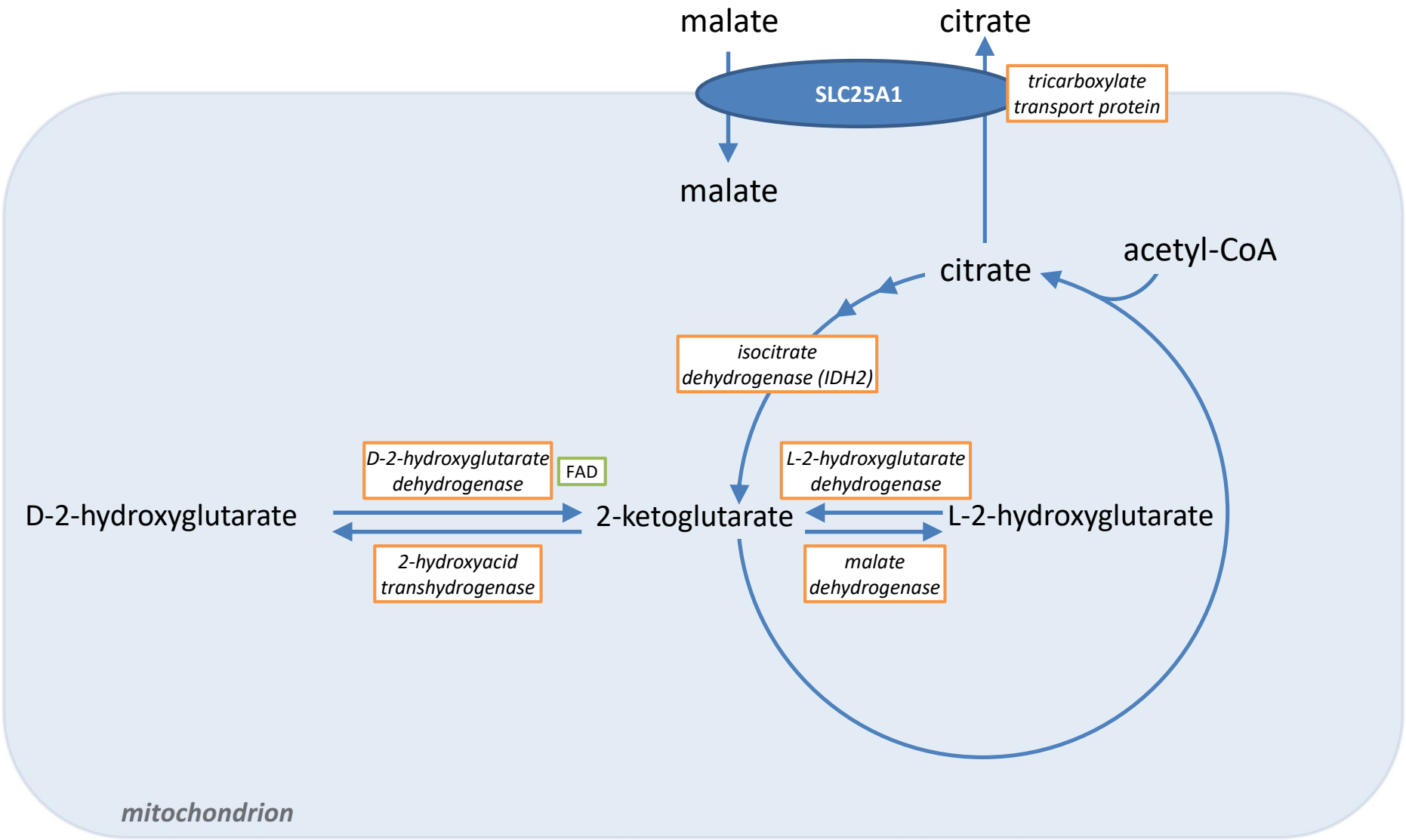


Mitochondriopathy with OXPHOS deficiency

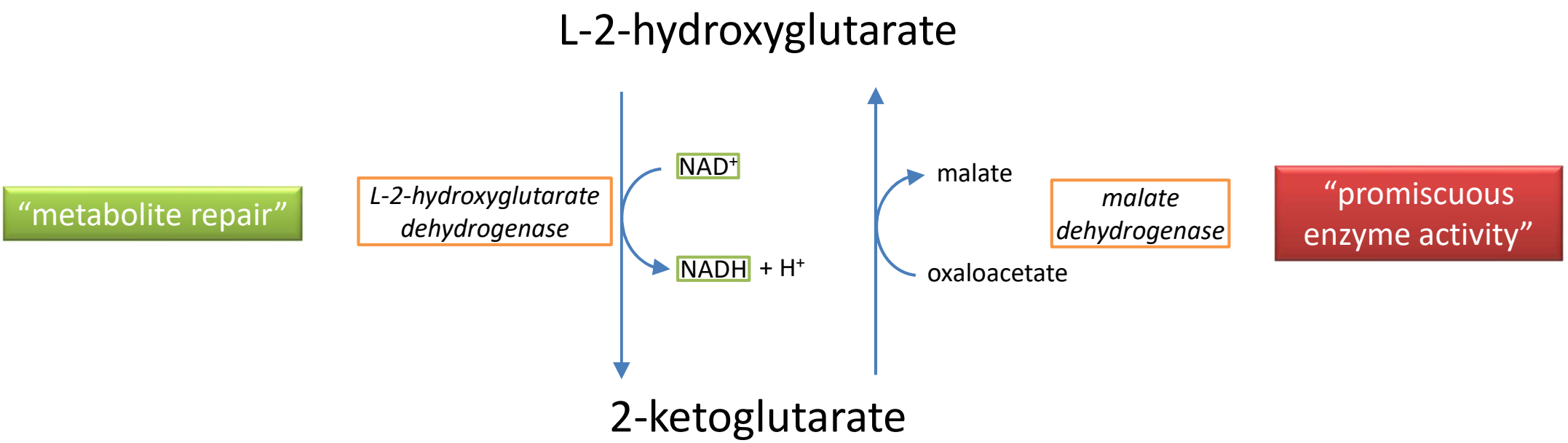


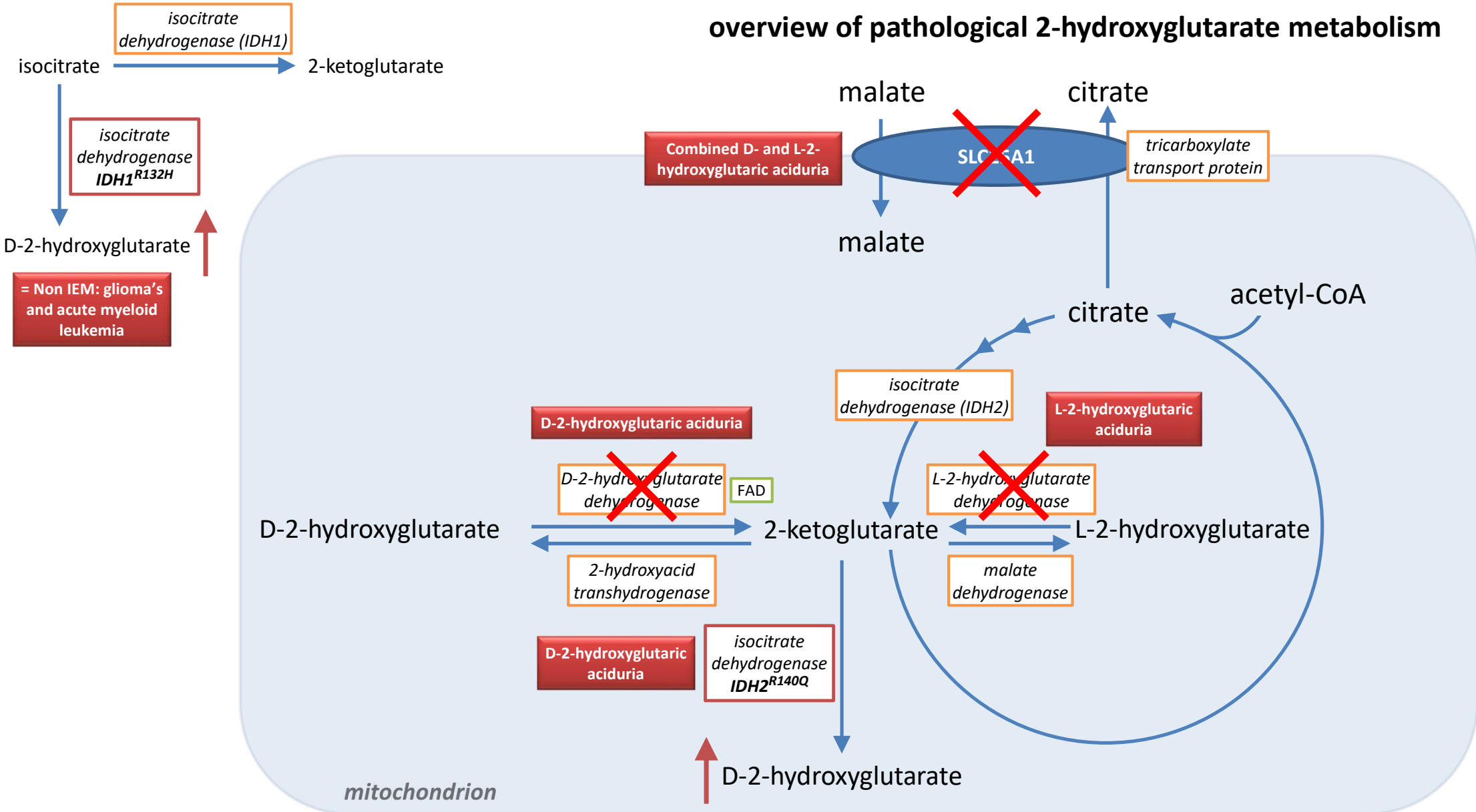
1. $FADH_2$ and NADH cannot be oxidized due to OXPHOS deficiency
2. Shortage of FAD^+ and NAD^+ leads to inhibition of Krebs cycle
3. This creates a metabolic traffic jam and pyruvate accumulation
4. Lactate dehydrogenase anaerobically regenerates NAD^+ which leads to lactate accumulation
5. Alanine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

2-hydroxyglutarate metabolism

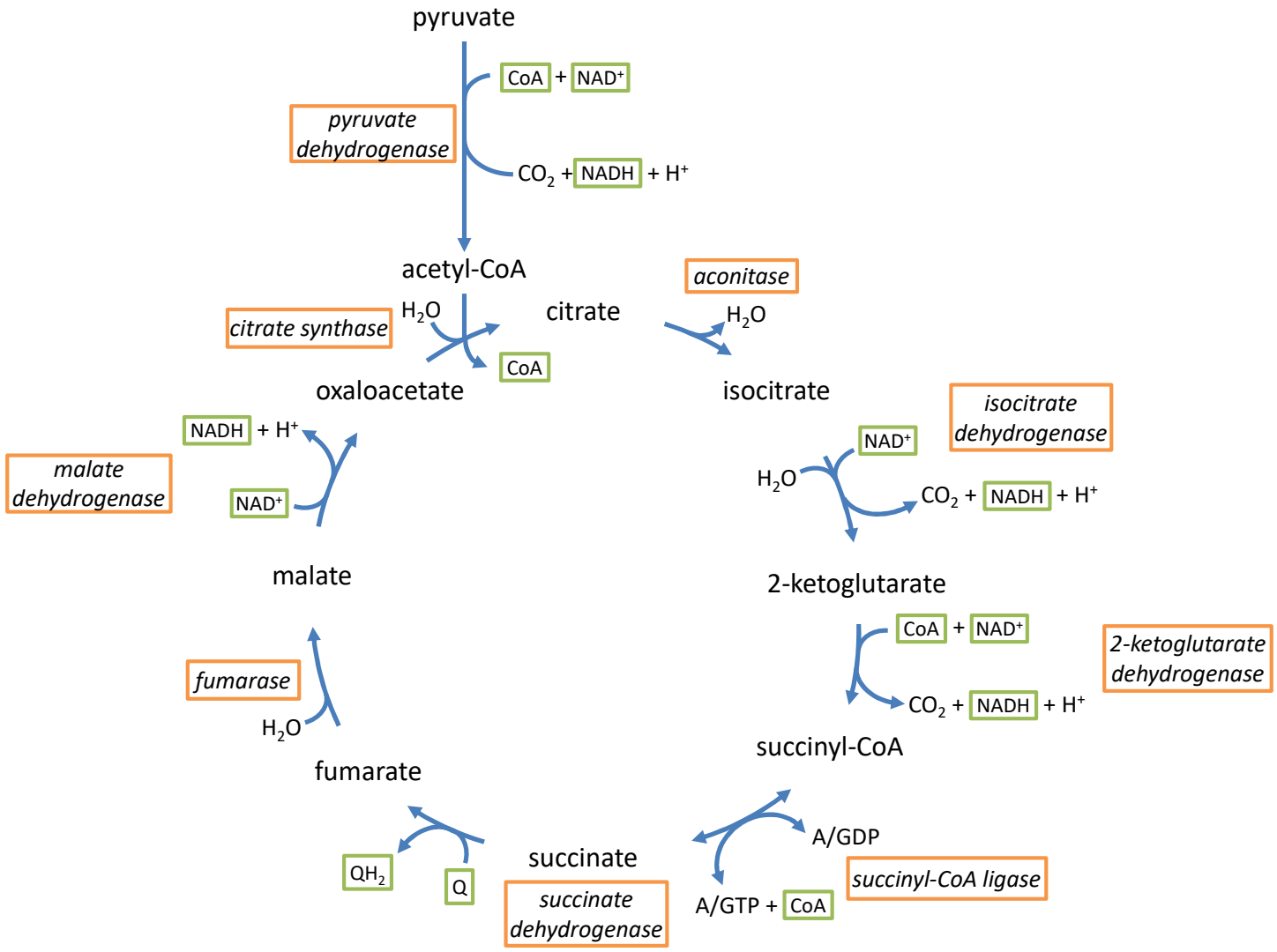


L-2-hydroxyglutarate dehydrogenase




isocitrate
isocitrate dehydrogenase (IDH1)
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)
L-2-hydroxyglutaric aciduria
D-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

the citric acid cycle



metabolite

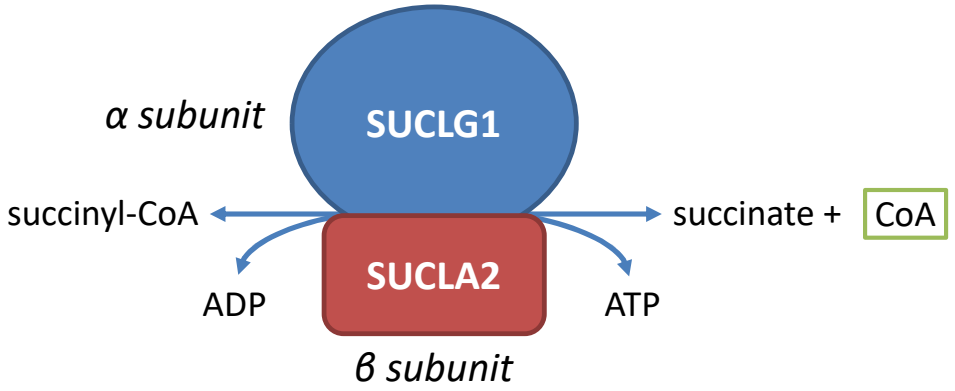
enzyme

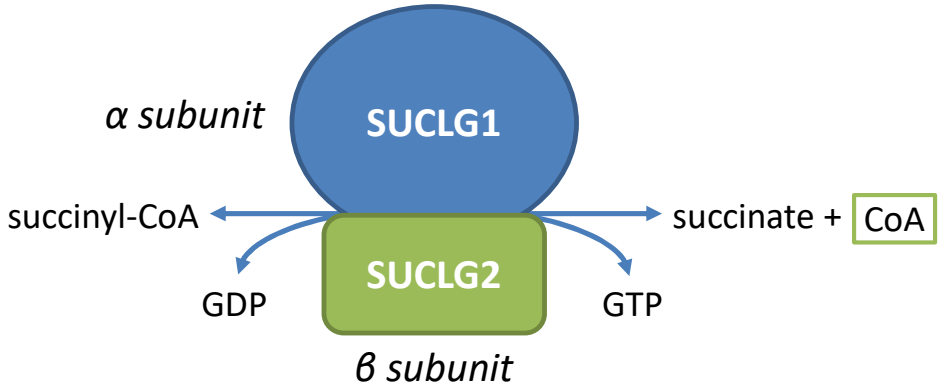
cofactor

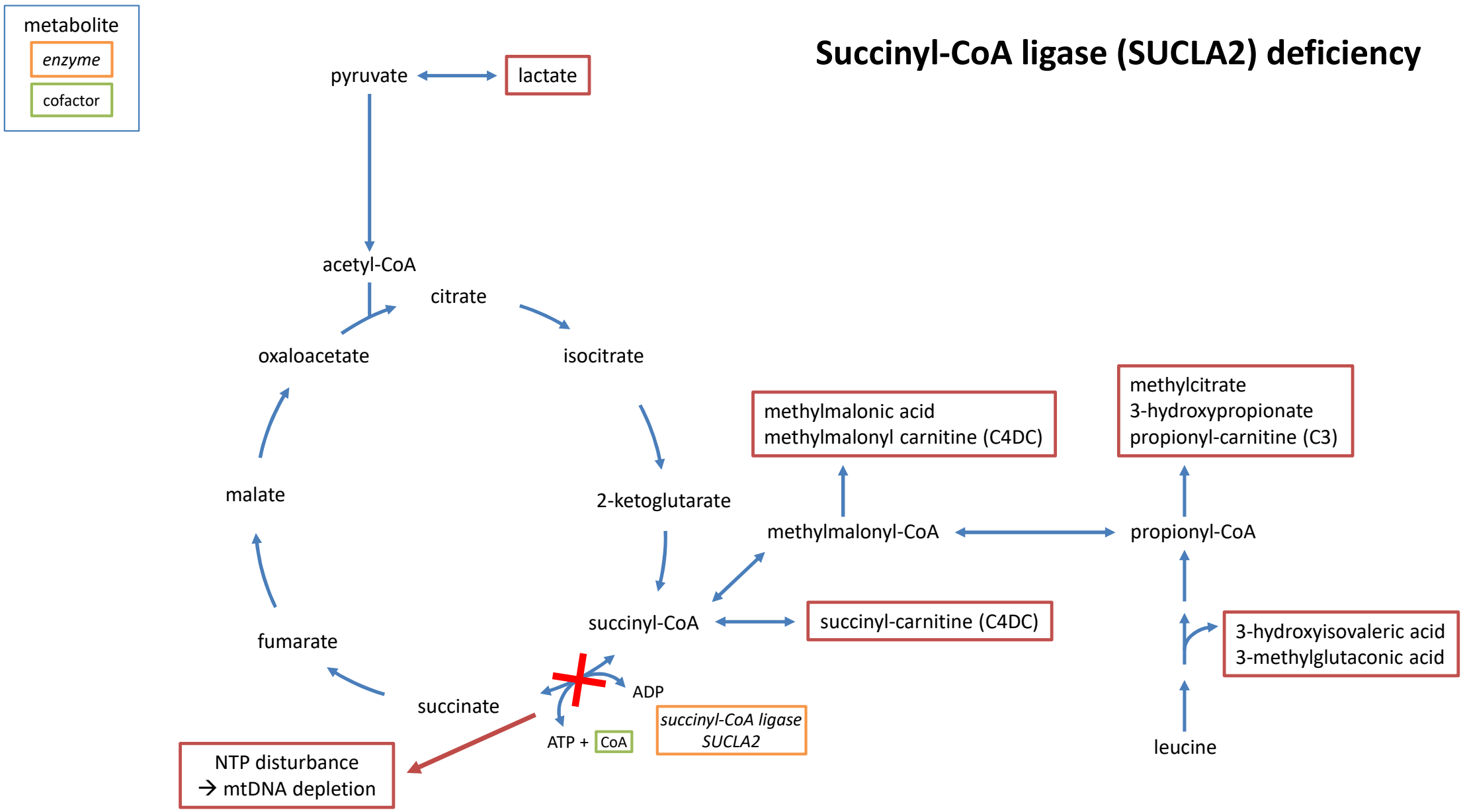
- Succinyl-CoA ligase / synthetase
  - **SUCLG1**
    - **α subunit** of complex
  - **SUCLA2**
    - **β subunit** gives specificity for ADP
  - **SUCLG2**
    - **β subunit** gives specificity for GDP

- 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
2-ketoglutarate
malate
fumarate
succinate
succinyl-CoA
methylmalonic acid
methylmalonyl carnitine (C4DC)
methylmalonyl-CoA
propionyl-CoA
methylcitrate
3-hydroxypropionate
propionyl-carnitine (C3)
succinyl-carnitine (C4DC)
3-hydroxyisovaleric acid
3-methylglutaconic acid
leucine
ADP
ATP + CoA
succinyl-CoA ligase
SUCLA2
NTP disturbance
→ mtDNA depletion