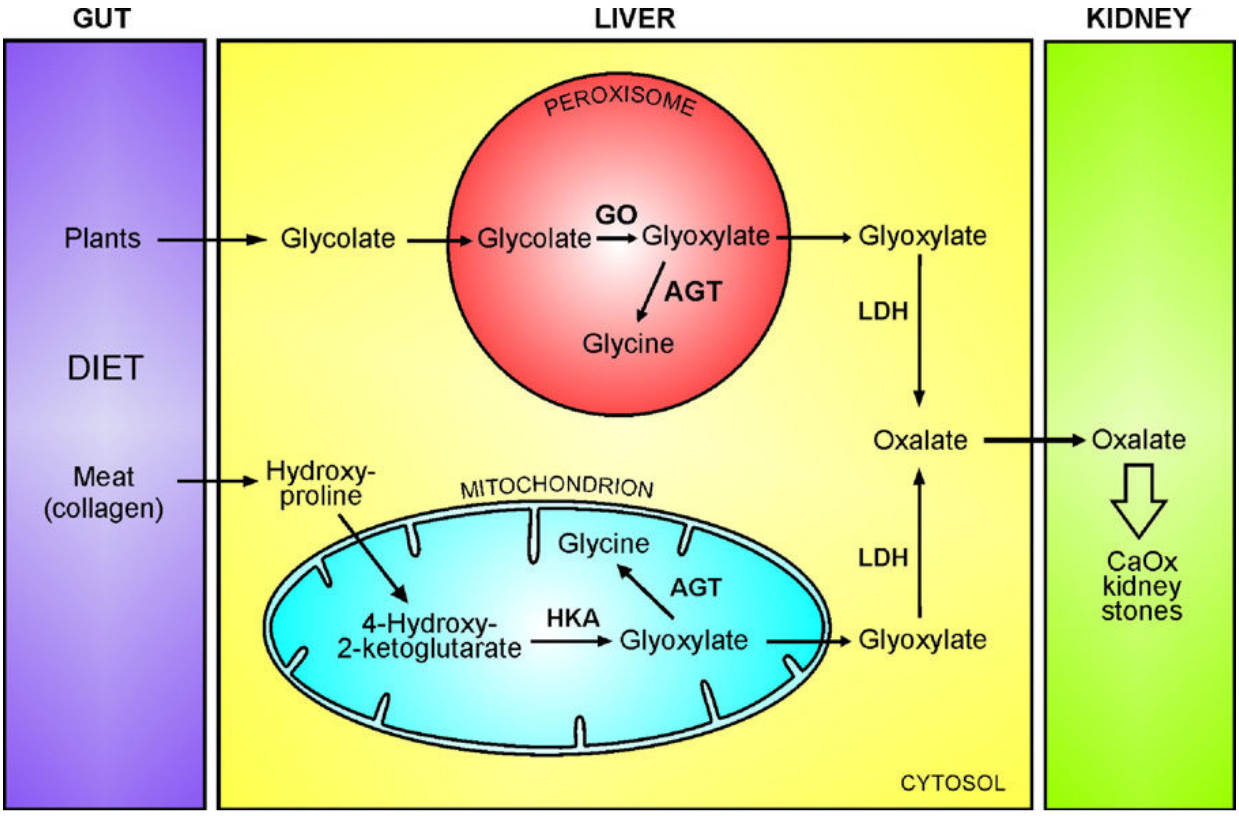
ALANINE:GLYOXYLATE AMINOTRANSFERASE

AGT is unusual insofar as it can be targeted to different parts of the cell (i.e. peroxisomes and/or mitochondria) under different circumstances. Under the influence of dietary selection pressure, its subcellular distribution has changed on at least twenty occasions during the evolution of mammals. In extant species, AGT tends to be peroxisomal in herbivores, mitochondrial in carnivores, and both peroxisomal and mitochondrial in omnivores. AGT deficiency in humans leads to the autosomal recessive disorder primary hyperoxaluria type 1 (PH1), which is characterised by excessive synthesis and excretion of oxalate and the deposition of insoluble calcium oxalate in the kidney and urinary tract. In the largest single subset of patients, AGT is mistargeted from the peroxisomes to the mitochondria due to the synergistic interaction between a common polymorphism and a disease-specific mutation. Although still catalytically active, AGT is metabolically inefficient when mislocalized to human mitochondria.



Diet and the intracellular compartmentalization of AGT in mammals. The major precursor of glyoxylate in herbivores is glycolate which is converted to glyoxylate in the peroxisomes, catalysed by glycolate oxidase (GO). In carnivores, the major precursor is hydroxyproline, which is converted to glyoxylate by a number of steps, the last of which catalysed by 4-hydroxy-2-ketoglutarate aldolase (HKA) occurs in the mitochondria. Efficient detoxification of glyoxylate must occur at its site of synthesis. Therefore, alanine:glyoxylate aminotransferase (AGT) is best located in the peroxisomes in herbivores and the mitochondria in carnivores. LDH, lactate dehydrogenase