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Aminolevulinic acid synthase

Connected to:
GlycineD-Aminolevulinic acidALAS2

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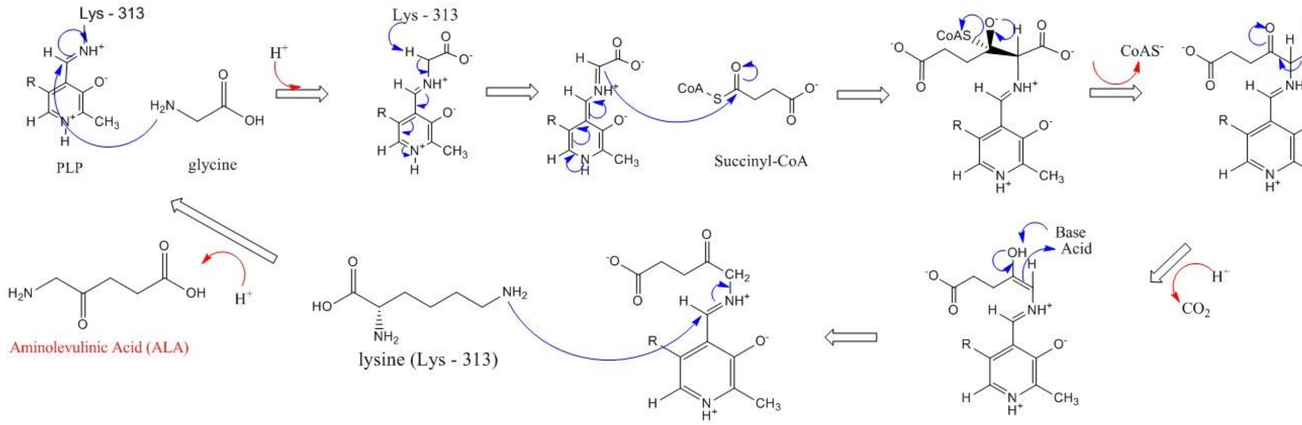
ALA synthase (EC 2.3.1.37), or ALAS, catalyzes the synthesis of D-Aminolevulinic acid (ALA) the first common precursor in the biosynthesis of all tetrapyrroles such as hemes, cobalamins and chlorophylls.[1] The enzyme is expressed in all non-plant eukaryotes and the α-class of proteobacteria. Other organisms produce ALA through a three enzyme pathway known as the Shemin pathway. ALA is synthesized through the condensation of glycine and succinyl-CoA. In humans, transcription of ALA synthase is tightly controlled by the presence ofFe^{2+}-binding elements, to prevent accumulation of porphyrin intermediates in the absence of iron. There are two forms of ALA synthase in the body. One form is expressed in red blood cell precursor cells (ALAS2), whereas the other (ALAS1) is ubiquitously expressed throughout the body. The red blood cell form is coded by a gene on chromosome x, whereas the other form is coded by a gene on chromosome 3. The disease X-linked sideroblastic anemia is caused by mutations in the ALA synthase gene on chromosome X, whereas no diseases are known to be caused by mutations in the other gene. Gain of function mutations in the erythroid specific ALA synthase gene have been shown recently to cause a previously unknown form of porphyria known as X-linked-dominant protoporphyria.

Enzyme Structure and Properties

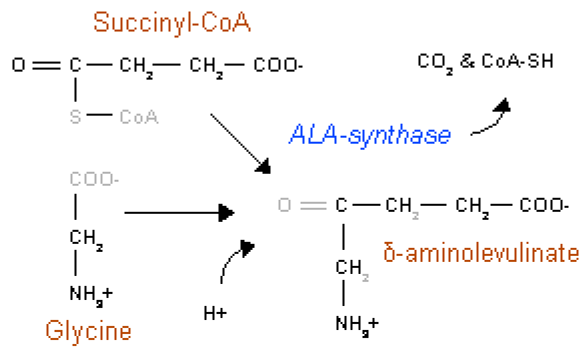
PLP-dependent enzymes are prevalent because they are needed to transform amino acids into other resources.[2] ALAS is a homodimer with similarly sized sub units and the active sites consisting of amino acid side chains such as arginine, threonine, and lysine exist at a subunity interface.[3] The protein when extracted from R. spheroids contains 1600-folds and weighs about 80,000 daltons.[4] Enzymatic activity varies for different sources of the enzyme.[5]

Reaction Mechanism

The active sites of ALAS utilize three key amino acid side chains: Arg-85 and Thr-430 and Lys-313. Although these three amino acids have been identified to allow this reaction to proceed, they would be inactive without the addition of cofactor pyridoxal 5’-phosphate (PLP) whose role in this synthesis is detailed in the image above. Before the reaction can begin, the PLP cofactor binds to the lysine side chain to form a Schiff base that promotes attack by glycine substrate,.[6][7][8][9] Lysine acts as a general base during this mechanism,.[10][11] In the detailed reaction mechanism, the hydronium atoms that are added in come from a variety of residues in that offer hydrogen bonds to facilitate ALA synthesis.[12] ALA synthase removes the carboxyl group from glycine and the CoA from the succinyl-CoA by means of its prosthetic group pyridoxal phosphate (a vitamin b6 derivative), forming δ-aminolevulinic acid (dALA), so called because the amino group is on the fourth carbon atom in the molecule. This reaction mechanism is particularly unique relative to other enzymes that use the PLP cofactor because Glycine is initially deprotonated by a highly conserved active site lysine, leading to condensation with succinyl-CoA and loss of CoA. Protonation of the carbonyl group of the intermediate by an active site histidine leads to loss of the carboxyl group. The last intermediate is finally reprotonated to produce ALA. Dissociation of ALA from the enzyme is the rate limiting step of the enzymatic reaction and was shown to be depended upon a slow conformational change of the enzyme. The function of pyridoxal phosphate is to facilitate the removal of hydrogen, by utilizing the electrophilic pyridinium ring as an electron sink.



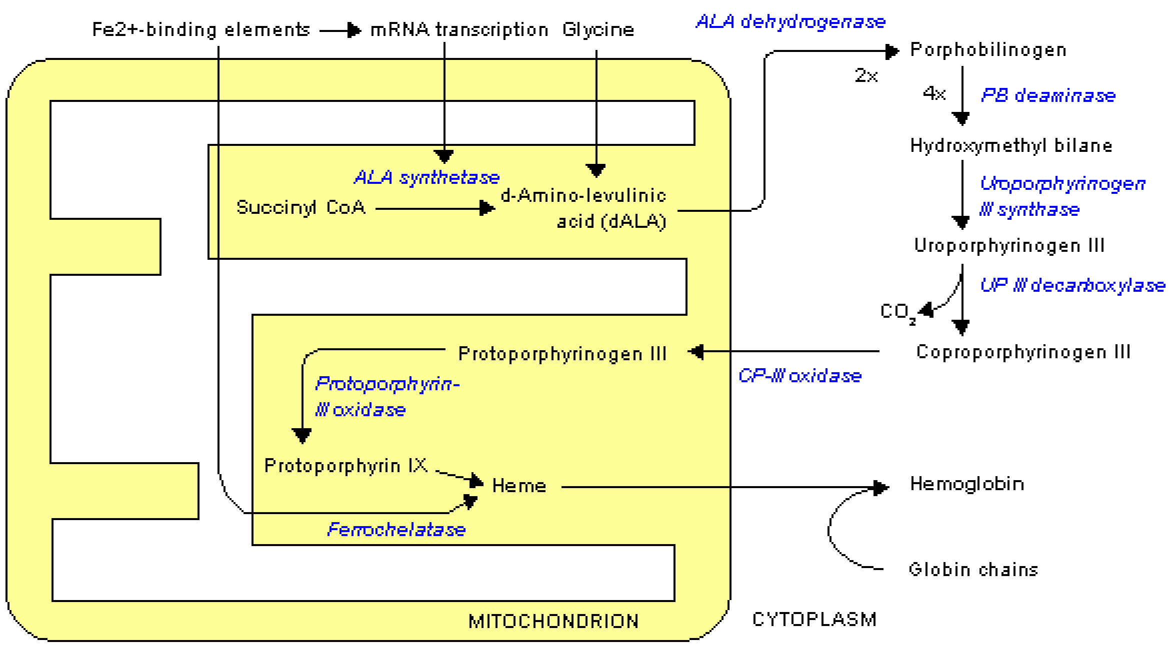
The location of this enzyme in biological systems is indicative of the feedback that it may receive. ALA Synthase has been found in bacteria, yeast, avian and mammalian liver and blood cells and bone marrow. The location of this enzyme in animal cells is within the mitochondria.[13] Since the enzyme appears to be located near its source of succinyl-CoA and the end of the heme pathway indicates that the starting and end points of heme biosynthesis serves as feedback for ALA Synthase.[14] ALA synthase is also inhibited by hemin andglucose.[15]



Heme synthesis

Biological Function

ALAS1 and ALAS2 catalyze the first step in the process of heme synthesis. It is the first irreversible step and is also rate limiting. This means that the beginning of the formation of hemes is very intentional and subject to a variety of areas of feedback. For example, the two substrates, oxaloacetate and glycine, are highly produced by and utilized in other essential biological processes such as glycolysis and the TCA cycle. The image below illustrates the heme synthesis pathway and the role ALAS plays.



Heme synthesis—note that some reactions occur in the cytoplasm and some in the mitochondrion (yellow)

Disease Relevance

Aminolevulinic Acid Synthase Deficiency results in a lack of ability to create heme since its job is to catalyze the first step in the process. These deficiencies are often a result of genetic mutation that can result in a variety of diseases. One such disease is s-linked sideroblastic anemia which results in the appearance red blood cells in the bone marrow.[16] This disease is linked specifically with mutations in the genes that encode for ALAS2.[17]

Photodynamic Therapy is a special treatment using a photosensitizing agent called Levulan (5 aminolevulinic acid HCL 20%) which is activated with the correct wavelength of light. This treatment removes sun damaged precancerous zones and spots called actinic keratosis. There is also a positive effect on sun damaged skin, fine lines, and blotchy pigmentation. It has the ability to minimize pores and reduce oil gland production. Levulan also is a great way to effectively treat stubborn acne vulgaris, acne rosacea , and improves the appearance of some acne scars.

The appointment will last approximately 1½ hours, most of which is an incubation period. To achieve maximal improvement of the skin, more than one treatment may be required. Additional treatments can be done at periodic intervals in the future to maintain the rejuvenated appearance of the skin.

Following Photodynamic Therapy, the treated areas will appear red with some peeling for 2 - 12 days. Some patients have an exaggerated response and experience marked redness of their skin. Temporary swelling of the lips and around your eyes can occur for a few days. Darker pigmentation patches can become temporarily darker and then peel off, leaving normal, rejuvenated skin which can take 7 - 12 days.

Patients should avoid exposure of the areas treated with Levulan to sunlight, bright windows, and bright indoor light for 40 hours after treatment. Exposure may cause redness, swelling of the skin, and prolong the recovery process. Patients should protect their skin from the sun and bright light by wearing a wide brimmed hat or similar head covering and by keeping a thick coat of sun-blocking agent, such as zinc-oxide, on the skin until after the peeling has occurred. Some actinic keratosis, especially thicker lesions, may need additional treatment with liquid nitrogen, topical cream, or photodynamic therapy. When used to treat acne and rosacea, a series of treatments are often needed to obtain optimal results. A follow-up appointment will be scheduled to assess the progress of your skin condition.