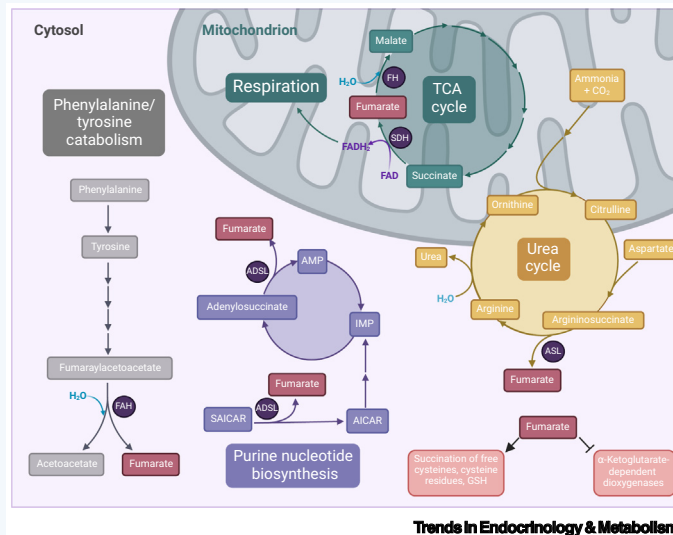


Fumarate

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In mitochondria, fumarate is generated from succinate by succinate dehydrogenase (SDH). It is converted to malate via FH.

Fumarate is produced from argininosuccinate by argininosuccinate lyase (ASL) in the urea cycle; from fumarylacetoacetate by fumarylacetoacetate hydrolase (FAH) in the final catabolic step of tyrosine and phenylalanine; and from adenylosuccinate or SAICAR by adenylosuccinate lyase (ADSL) in purine nucleotide biosynthesis.

It reacts with free cysteines and thiol groups of cysteine residues of proteins and glutathione (GSH), forming free 2-(succino)cysteine (2SC) or 2SC adducts in a process called succination.

It inhibits α-ketoglutarate (α-KG)-dependent dioxygenases due to competitive inhibition with α-KG.

Although, present in different cellular compartments, its transporters have not been identified yet in mammals, in contrast to plants and bacteria.

METABOLIC ROLE:

When oxygen is limited, it serves as a terminal electron acceptor of the electron transport chain, producing succinate, in mammals and bacteria.

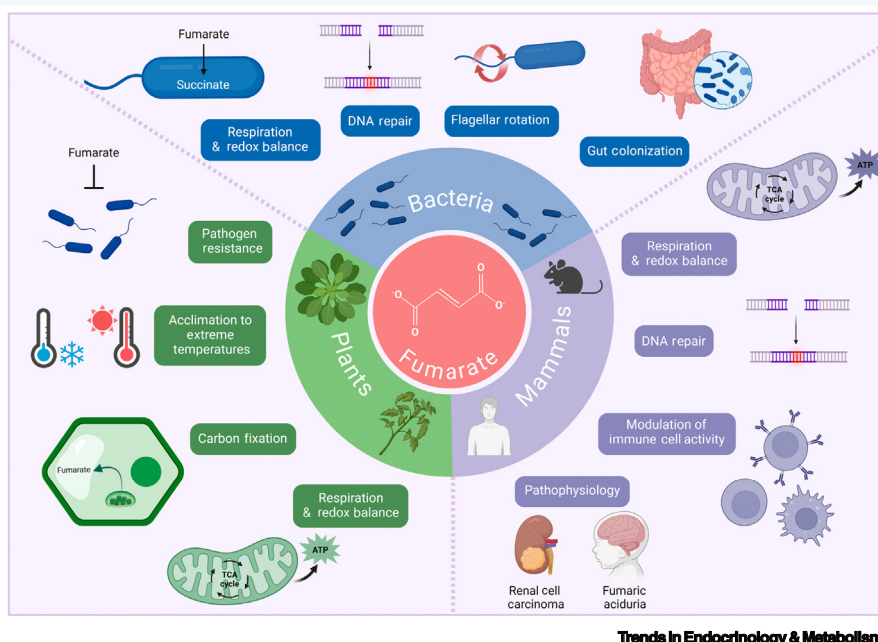
It modulates DNA repair by inhibiting α-KG-dependent histone demethylases.

Aberrant accumulation of fumarate can drive cancer transformation and progression.

In plants, it is stored in vacuoles for carbon storage and participates in temperature acclimation and pathogen resistance.

In bacteria, it alters the switching frequency and bias of the sense of rotation of the flagellar motor influencing swimming behavior and gut colonization.

Fumarate (the salt of fumaric acid) is an α,β unsaturated four-carbon dicarboxylate. It derives its name from the flowering plant *Fumaria officinalis*, where it accumulates in the leaves. Fumarate is involved in essential metabolic pathways across all organisms, from bacteria to mammals. As an intermediate of the mitochondrial pathway tricarboxylic acid (TCA) cycle, it is involved in the oxidation of carbohydrates, amino acids, and fatty acids. Fumarate is also a byproduct of the urea cycle, and amino acid and nucleotide metabolism.



In humans, the aberrant accumulation of fumarate due to the biallelic loss of the gene encoding the TCA cycle enzyme fumarate hydratase (FH), which converts it to malate, causes severe developmental delays. Inherited monoallelic mutations of *FH* followed by loss of heterozygosity predispose to renal cancer and skin and uterine fibroids. Moreover, fumarate modulates immune cell function and its esters are widely used for treating the autoimmune diseases psoriasis and multiple sclerosis.

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Declaration of interests

The authors declare no competing interests.

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