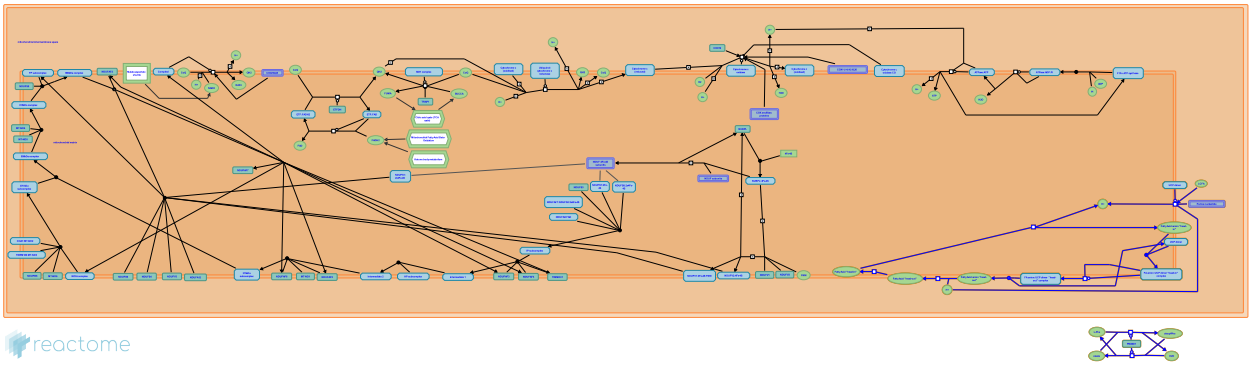
Mitochondrial Uncoupling



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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

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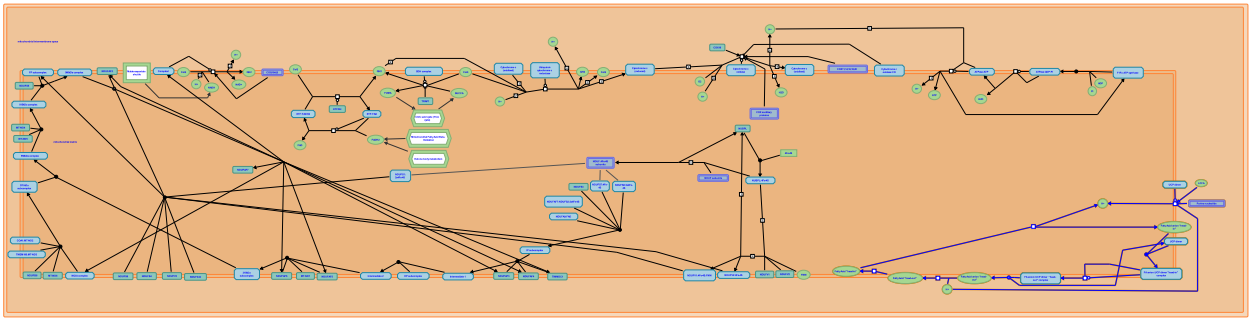
Mitochondrial Uncoupling ↗

Stable identifier: R-HSA-166187



Uncoupling proteins (UCPs) are members of the mitochondrial transport carrier family, and have been implicated in a wide range of physiological and pathological conditions. Physiological conditions include thermogenesis, fatty acid metabolism and protection against free radicals and ageing; pathological conditions include involvement in obesity, diabetes and degenerative, neurological and immunological diseases.

The UCPs share general structural features with the other mitochondrial transport carriers. They have a tripartite structure, consisting of three homologous sequence repeats of approximately 100 residues. The carriers also have a signature motif, which is repeated in all members of the family and in all three repeats. The transmembrane arrangement of UCPs is 6 alpha-helix regions (2 regions per repeat) spanning the lipid bilayer with the amino and carboxyl termini facing the cytosolic side. The crystal structure of one member of the family, the adenine nucleotide translocase, is known, and UCPs can be successfully folded into this structure to indicate their probable 3D arrangement (Pebay-Peyroula et al. 2003, Kunji 2004, Esteves & Brand 2005).

The most studied member of the family, UCP1, catalyzes adaptive thermogenesis (i.e. heat generation) in mammalian brown adipose tissue. It does so by promoting a leak of protons through the mitochondrial inner membrane, which uncouples ATP production from substrate oxidation, leading to fast oxygen consumption and ultimately to heat production. The thermogenic activity of UCP1 in brown adipose tissue plays an important role when the organism needs extra heat, e.g. during cold weather conditions (for small rodents), the cold stress of birth or arousal from hibernation. UCP1 homologs have been found in lower vertebrates such as fish, where their role is unclear (Cannon & Nedergaard 2004, Jastroch et al. 2005).

The proton conductance of UCP1 in brown adipose tissue is tightly controlled. It is strongly inhibited by physiological concentrations of purine nucleotides. This inhibition is overcome by fatty acids, which are released from intracellular triacylglycerol stores following adrenergic activation in response to cold or overfeeding. Other activators include superoxide, retinoic acid, the retinoid 4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetra-methyl-2-naphtalenyl)-1-propenyl]benzoic acid (TTNPB) and reactive alkenals, such as hydroxynonenal.

UCP2 and UCP3 have high amino acid sequence homology to UCP1 (59 and 57% amino-acid identity respectively). UCP2 has been identified in lung, spleen, pancreatic beta-cells and kidney, whereas UCP3 is found in brown adipose tissue and skeletal muscle. Homologs of UCP2 and UCP3 are found in marsupials, birds, fish and plants.

Despite a low level of sequence homology with UCP1-3, UCP4 and UCP5 share their functional properties (Hoang et al. 2012).

There is strong evidence that the regulated uncoupling caused by these proteins attenuates mitochondrial reactive oxygen species production, protects against cellular damage, and (in beta-cells) diminishes insulin secretion. There are also untested suggestions that their transport of fatty acids may be physiologically important (Brand & Esteves 2005, Esteves & Brand 2005, Krauss et al. 2005). The modest depolarization brought about by UCP activation is thought to diminish superoxide generation without significantly compromising ATP production, creating a protective, negative-feedback system that complements enzymatic defences against reactive oxygen species.

There is some evidence that this mechanism is important in the etiology of Parkninson's Disease. Deletion of Park7 (DJ-1) decreased the abundance of Ucp5 and Ucp4 mRNA and compromised mitochondrial uncoupling in response to oxidant stress (Guzman et al. 2010). This may explain the unusual accumulation of mitochondrial DNA mutations with age in SNc dopaminergic neurons (Bender et al. 2006). These mutations, which are attributable to accumulated superoxide exposure, diminish mitochondrial competence and promote phenotypic decline, proteostatic impairments and death (Nicholls 2008).

A number of models have been proposed for the molecular mechanism by which fatty acids lead to increased proton conductance by UCP1 in brown adipose tissue mitochondria, and presumably by the other UCPs as well. These are the "fatty acid cycling" model and the "proton buffering" model.

Studies of mouse models and of cultured human cells have suggested that oleoyl-phenylalanine, synthesized by extracellular PM20D1, may play a role in uncoupling independent of the action of UCPs (Long et al. 2016). Its synthesis and hydrolysis are annotated here.

Literature references

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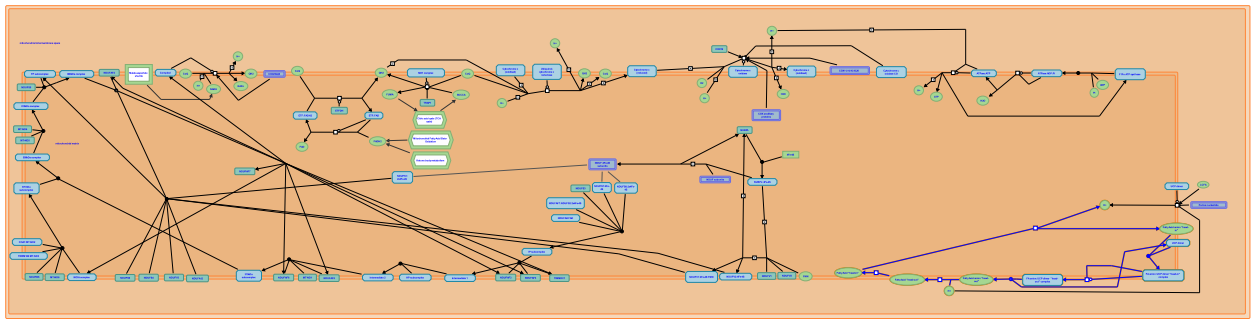
Editions

2005-11-09	Authored	Jassal, B., Esteves, TC., Brand, MD.

The fatty acid cycling model ↗

Location: Mitochondrial Uncoupling

Stable identifier: R-HSA-167826



The "fatty acid cycling" hypothesis proposes that protonated fatty acids flip-flop in the membrane and deliver a proton to the matrix side. UCP1 catalyses the return of the fatty acid anion to the cytosolic side of the membrane, resulting in net proton transport catalysed by the protein.

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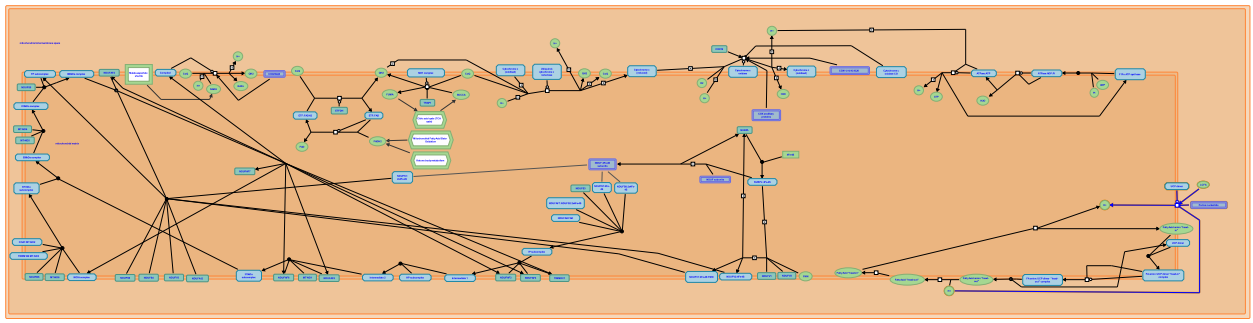
The proton buffering model ↗

Location: Mitochondrial Uncoupling

Stable identifier: R-HSA-167827



The "proton buffering" model proposes that UCP1 is intrinsically a proton carrier, and that fatty acid acts as a prosthetic group during proton transport. Fatty acid penetrates from the lipid phase, with its carboxyl group oriented to the proton translocation path. Here, it works as a donor-acceptor of protons between the residual carboxyl groups of UCP1. Ultimately, protons are extruded to the matrix side of the membrane.
Rial et al (2004) suggest fatty acids are inducers of proton transport by UCP by allowing themselves to become substrates for UCP and activation of the proton buffering mechanism itself. Binding of nucleotides to UCP inhibits it's proton transport capability. UCP accepts purine ribose tri- and di- nucleotides; GTP, ATP, GDP and ADP. The monophosphates GMP and AMP are poor ligands for UCP binding.

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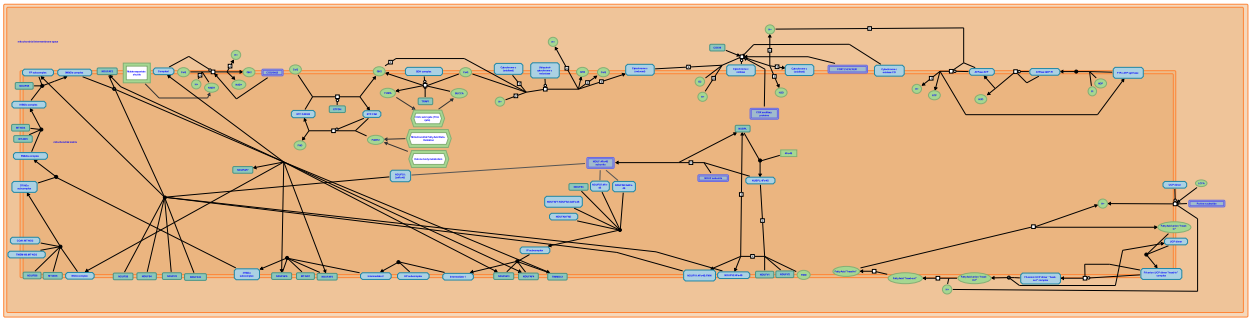
Oleoyl-phe metabolism ↗

Location: Mitochondrial Uncoupling

Stable identifier: R-HSA-9673163

Compartments: extracellular region



Extracellular PM20D1 (N-fatty-acyl-amino acid synthase/hydrolase PM20D1) catalyzes the reversible condensation of L-phenylalanine (L-phe) and oleate ((9Z)-octadecenoate) to form oleoyl-phe (N-(9Z-octadecenoyl)-L-phenylalanine) and water. In addition to the condensation of phe with oleate ((9Z)-octadecenoate) annotated here, purified human PM20D1 protein in vitro can catalyze the condensation of leucine and isoleucine with oleate and with other long-chain unsaturated fatty acids including arachidonate, with lower efficiencies. Although the reverse (hydrolysis) direction of this reaction is thermodynamically favored, expression of PM20D1 protein in mice or in cultured cells was associated with elevated levels of oleoyl-phe in serum and culture media, respectively. Treatment of cultured mouse brown adipose tissue adipocytes and of isolated mitochondria with oleoyl-phe induced uncoupled respiration independently of UCP1 (uncoupling protein 1). Photolabeling studies of isolated mitochondria identified the ADP/ATP symporters SLC25A4 and SLC25A5 as possible targets of oleoyl-phe. Consistent with these observations, expression of PM20D1 and elevated blood levels of oleoyl-phe in mice were associated with increased energy expenditure and improved glucose homeostasis. These results suggest a physiological role for PM20D1 and its condensation reaction product in thermogenesis and raise the possibility that oleoyl-phe and related molecules might have a clinical role in treatment of obesity (Long et al. 2016).

Literature references

Jedrychowski, MP., Spiegelman, BM., Gygi, SP., Lokurkar, IA., Lin, H., Svensson, KJ. et al. (2016). The Secreted Enzyme PM20D1 Regulates Lipidated Amino Acid Uncouplers of Mitochondria. *Cell, 166*, 424-435. ↗

Editions

2020-01-06	Authored, Edited	D'Eustachio, P.
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