

Signalling Regulation of Mevalonate Pathway by Reversible Phosphorylation of HMGCR

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The importance of cholesterol in health and disease is commonly understood since many studies have correlated increase detection of cholesterol in blood with many diseases such as cardiovascular disease or elevated blood pressure. In this study we investigate the activation/inactivation mechanism of cholesterol synthesis in response to AMP/ATP ratio. The link step between energy need and inactivation of cholesterol synthesis is mediated by AMP activated protein kinase (AMPK) through phosphorylation of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), the enzyme catalysing the committing step in cholesterol synthesis.

Besides the fact that this system is known for years and is one of the first AMPK regulated pathways identified, the full pathway involved in this regulation has not been caught clearly in literature. There are numerous studies referring to AMPK regulated pathways but not a concrete piece of work combining the newly retrieved knowledge on AMPK regulation as well as the antagonized effects of HMGCR dephosphorylation. In order to produce a clear and easily understood description of the pathway we decided to create a map depiction of the system. After careful manual curation of the relative papers and taking advantage of the SBGN notation, a community driven system notation with computational potentials, we constructed a map depicting the well characterized interactions of proteins involved in this system, particular in human organism.

The aim of this project is the collection of the available information, characterization of the relation between pathway players and the production of a map that would be a helpful tool in identifying potential drug targets and generally improve the understanding of the regulation mechanism.

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The Genomics and Pathway Biology MSc programme started in 2003 and has had a number of supervisors and contributors. Profs Peter Ghazal and Douglas Roy have supervised the programme throughout. Other supervisors include Dr Stuart Moodie (2004-5), Dr Kevin Robertson (2004-7), Prof Tom Freeman (2006-7), Dr Steven Watterson (2008-10), Dr Alexander Mazein (2009-11) and Dr Kai Kropp (2010-11).

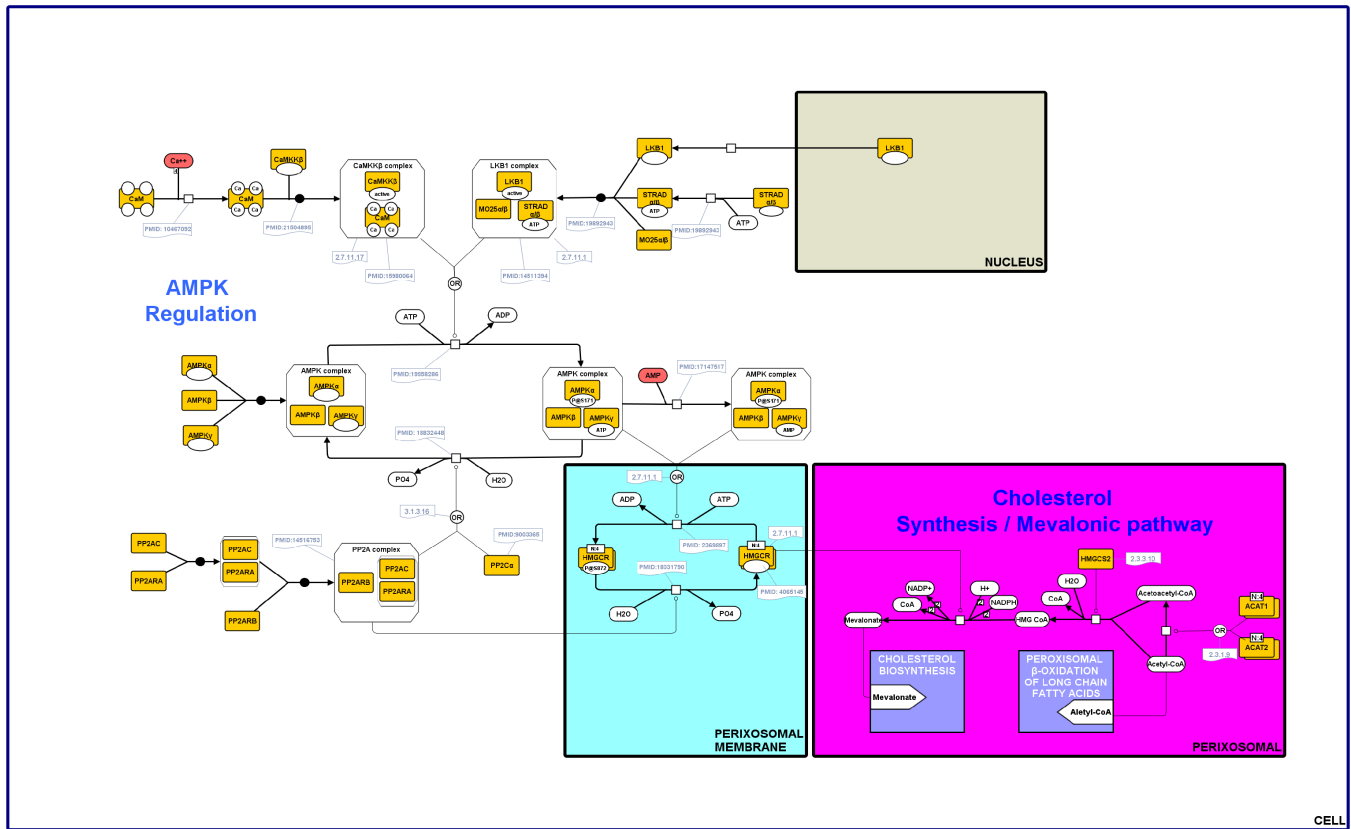


Figure 7. The AMPK regulated HMGR pathway, we can see proteins in yellow, organelles are in collared squares (light blue for peroxisome membrane, violet for peroxisome and grey for nucleus) the compounds are uncoloured except of the Ca²⁺ and AMP that are stimuli for the pathway and are collared orange.

Pathway	Subpathway	Reaction equation	EC	Protein Name	Protein ID (UniProt)	Subcellular Location	Organism	PMID (reaction exists)	Reference2 (enzyme catalyzes this reaction)	Reference3 (enzyme subcellular localization)
Lipid Metabolism	Sterol/isoprenoid Synthesis	LKB1+PKA+cAMP+ ATP→ P-LKB1 +ADP +PKA	2.7.11.11	cAMP-dependent protein kinase catalytic subunit	P22694/ P17612 / P22612	Cytoplasm, Cell membrane, Nucleus	human	11297520	10642527	17482549
Lipid Metabolism	Sterol/isoprenoid Synthesis	LKB1+PKCζ+ATP→ P-LKB1 +ADP +PKCζ	2.7.11.13	Protein kinase C zeta type	Q05513 Q15418/ Q15349/ P51812/ O75582/ Q9UK32	Cytoplasm, nucleus, Endosome, Cell junction.	human	16407220	21835890	12244101
Lipid Metabolism	Sterol/isoprenoid Synthesis	LKB1+RSK+ATP→ P-LKB1 +ADP +RSK	2.7.11.1	Ribosomal protein S6 kinase	O75582/ Q9UK32	Nucleus, Cytoplasm.	human	17040210	21220320	17965187
Lipid Metabolism	Sterol/isoprenoid Synthesis	LKB1+MOD25+STRAD+ ATP→ LKB1 complex				Cytoplasm	human	14511394	14985505	19892943
Lipid Metabolism	Sterol/isoprenoid Synthesis	LKB1 complex + AMPK complex + ATP → P-AMPK complex + ADP + LKB1 complex	2.7.11.1	Serine/threonine-protein kinase STK11	Q15831	Nucleus, Cytoplasm, Membrane, Mitochondrion.	human	16407220	14511394	19187764
Lipid Metabolism	Sterol/isoprenoid Synthesis	Ca+2 + CaM + CaMKKbeta → CaMKKbeta complex				Cytoplasm	human	21504895	17157809	10467092
Lipid Metabolism	Sterol/isoprenoid Synthesis	CaMKKbeta complex + AMPK complex + ATP → P-AMPK complex + CaMKKbeta complex + ADP	2.7.11.17	Calcium/calmodulin-dependent protein kinase kinase 2	Q96RR4	Cytoplasm	human	15980064	16054095	16054096
Lipid Metabolism	Sterol/isoprenoid Synthesis	P-AMPK complex + AMP → P-AMPK complex				Cytoplasm	human	10698692	17147517	8549768
Lipid Metabolism	Sterol/isoprenoid Synthesis	HMGCR + ATP + P-AMPK complex → P-HMGCR + ADP + P-AMPK complex	2.7.11.1	AMPK subunit alpha 1/2	Q13131/ P54646	nucleoplasm, cytosol	human	6307348	2369897	4065145
Lipid Metabolism	Sterol/isoprenoid Synthesis	P-HMGCR + H2O + PP2A → HMGCR +PPi + PP2A	3.1.3.16	Serine/threonine-protein phosphatase 2A catalytic subunit	P67775/ P62714	Cytoplasm, cytoskeleton, spindle pole	human	6324764	18031790	17086192
Lipid Metabolism	Sterol/isoprenoid Synthesis	(S)-3-hydroxy-3-methylglutaryl-CoA + 2 NADPH + 2H+ → (R)-mevalonate + CoA + 2 NADP+	1.1.1.34	3-hydroxy-3-methylglutaryl-coenzyme A reductase, HMG-CoA reductase, HMGCR	P04035	Endoplasmic reticulum membrane, Peroxisome membrane	human	624722	6305342	10698924 brain, thymus, spleen and kidney
Lipid Metabolism	Sterol/isoprenoid Synthesis	PP2A + P-AMPK complex + H2O →AMPK complex + PP2A + PPI	3.1.3.16	Serine/threonine-protein phosphatase 2A catalytic subunit	P67775/ P62714	Nucleus, Chromosome, centromere, Cytoplasm, cytoskeleton, spindle pole	human	14516753	20957029	18832448
Lipid Metabolism	Sterol/isoprenoid Synthesis	PP2Ca + P-AMPK complex + H2O →AMPK complex + PP2Ca + PPI	3.1.3.16	Protein phosphatase 1A	P35813	Nucleus, cytosol, protein serine/threonine phosphatase complex	human	9003365	9003365	9003755

Compound Name	KEGG CID	ChEBI	Comments
3',5'-Cyclic AMP, cAMP	C00575	17489	message for PKA activation
Adenosine 5'-triphosphate, ATP	C00002	15422	energy for phosphorylation
Adenosine 5'-diphosphate, ADP	C00008	16761	
Calcium cation, Ca ²⁺	C00076	3311	cofactor of CaMKK
Diphosphate, P _{pi}	C00013	18361	
water, H ₂ O	C00001	15377	
Adenosine 5'-monophosphate, AMP	C00020	16027	activates AMPK
(S)-3-Hydroxy-3-methylglutaryl-CoA, HMG-CoA	C00356	15467	
Hydron, H ⁺	C00080	15378	
Coenzyme A, CoA	C00010	15346	
(R)-Mevalonate	C00418	36464	
Reduced nicotinamide adenine dinucleotide phosphate, NADPH	C00005	16474	energy
Nicotinamide adenine dinucleotide phosphate, NADP ⁺	C00006	18009	