ATP homeostasis is essential for cellular functions

Energy expenditure:
Maintain membrane potential, cellular integrity, trafficking, movement
Synthesis of macromolecules, protein, RNA, DNA
Storage, fat, glycogen

Energy production:
Hydrolysis of carbohydrates
Fatty acid oxidation
Amino acids

ATP is the cellular energy currency

\[
\text{ATP} \rightarrow \text{ADP} \rightarrow \text{AMP}
\]

\[
\text{ADP + ADP} \leftrightarrow \text{ATP + AMP}
\]

\[
\text{ATP} \gg \text{AMP}
\]
AMPK is a key cellular energy sensor

AMPK, AMP activated protein kinase
Regulated by the ratio of AMP/ATP
Phosphorylates a large numbers of proteins
Regulates cellular energy homeostasis
AMPK is activated by phosphorylation

AMPK is a trimer
The gamma subunit binds AMP or ATP
AMP and ATP binding are mutually exclusive
AMP allosterically activates AMPK
A major effect of AMP is to inhibit dephosphorylation of AMPK
PP1C is the likely phosphatase responsible for AMPK inactivation

AMPK

CaMKK
LKB1

Ca^{2+} \rightarrow T172 \rightarrow [AMP]:[ATP]

\beta \rightarrow \text{Energy production}
\gamma \rightarrow \text{Energy expenditure}

\alpha \rightarrow \text{Restore energy balance}
Mutation in \( \gamma \) subunit causes cardiomyopathy and hypertrophy

- Residues mutated in WPW syndrome, mutations affect AMP binding
Active AMPK promotes energy production by stimulating Glucose uptake, Glycolysis, Fatty acid oxidation, and Mitochondrial biogenesis.
AMPK promotes glucose uptake and glycolysis

**Anaerobic conditions**

- AMP/ATP
- AMPK
  - AS160 → pAS160
  - Rab-GTP → Rab-GDP
  - GLUT4in → GLUT4pm
- PFK-2 → pPFK-2
  - Fructose 2,6 bisphosphate
  - PFK-1
- Glucose out → Glucose in
  - F6P → F1,6P → Lactate
- ATP
AMPK stimulate GLUT4 translocation to plasma membrane
AMPK inhibits energy consuming pathways

AMPK decreases energy expenditure by inhibiting
Fatty acid synthesis
Sterol synthesis
Glycogen synthesis
Protein synthesis
Cell growth
Cell proliferation
AMPK inhibits protein synthesis

AMP/ATP → AMPK → TSC2 → Rheb → mTOR → S6K, 4EBP1, S6 → Ribosome, Initiation → Translation

AMPK → eEF2 Kinase → eEF2 → Elongation
Major effects of AMPK activation on glucose and lipid metabolism in liver, muscle, and adipose tissue. Pathways stimulated by AMPK are shown with thick arrows, those inhibited by thin arrows with thick bars across them. Effects of AMPK on pyruvate oxidation are mediated by upregulation of mitochondrial biogenesis, whereas effects on fatty acid oxidation are mediated by both phosphorylation of ACC2 and activation of fatty acid entry into mitochondria, as well as upregulation of mitochondrial biogenesis.
AMPK function in hypothalamus to regulate appetite
<table>
<thead>
<tr>
<th>Protein target</th>
<th>Effect on protein function</th>
<th>Pathway</th>
<th>Tissue</th>
<th>Effect on pathway</th>
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</thead>
<tbody>
<tr>
<td><strong>Lipid metabolism</strong></td>
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<td></td>
</tr>
<tr>
<td>ACC1</td>
<td>↓ activity</td>
<td>Fatty acid synthesis</td>
<td>All cells?</td>
<td>↓ fatty acid synthesis</td>
</tr>
<tr>
<td>ACC2</td>
<td>↓ activity</td>
<td>Fatty acid oxidation</td>
<td>Muscle, liver</td>
<td>↑ fatty acid oxidation</td>
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<tr>
<td>HMGCR</td>
<td>↓ activity</td>
<td>Isoprenoid synthesis</td>
<td>Liver</td>
<td>↓ cholesterol synthesis</td>
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<tr>
<td>HSL</td>
<td>↓ activity</td>
<td>Lipolysis</td>
<td>Adipose tissue</td>
<td>↓ lipolysis</td>
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<tr>
<td><strong>Carbohydrate metabolism</strong></td>
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</tr>
<tr>
<td>AS160</td>
<td>↓ Rab-GAP?</td>
<td>GLUT4 trafficking</td>
<td>Muscle</td>
<td>↑ glucose uptake</td>
</tr>
<tr>
<td>Glycogen synthase</td>
<td>↓ activity</td>
<td>Glycogen synthesis</td>
<td>Muscle</td>
<td>↓ glycogen synthase</td>
</tr>
<tr>
<td>PFK2 (cardiac isoform)</td>
<td>↑ activity</td>
<td>Glycolysis</td>
<td>Heart</td>
<td>↑ glycolysis</td>
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<tr>
<td>PFK2 (inducible isoform)</td>
<td>↑ activity</td>
<td>Glycolysis</td>
<td>Monocytes, macrophages</td>
<td>↑ glycolysis</td>
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<tr>
<td><strong>Protein metabolism (translation)</strong></td>
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<tr>
<td>EF2K</td>
<td>↑ activity</td>
<td>Protein synthesis</td>
<td>All cells?</td>
<td>↓ translation elongation</td>
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<tr>
<td>TSC2 (tuberin)</td>
<td>↑ Rheb-GAP</td>
<td>Regulation of TOR</td>
<td>All cells?</td>
<td>↓ translation initiation, ↓ cellgrowth, ↓ protein synthesis</td>
</tr>
<tr>
<td><strong>Cell signalling</strong></td>
<td></td>
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<td></td>
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<tr>
<td>eNOS</td>
<td>↑ activity</td>
<td>Nitric oxide production</td>
<td>Endothelial cells</td>
<td>↑ nitric oxide, ↑ increased blood flow?</td>
</tr>
<tr>
<td>IRS1</td>
<td>↑ PI3-kinase</td>
<td>Insulin signalling</td>
<td>All cells?</td>
<td>↑ insulin signalling?</td>
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<tr>
<td><strong>Transcription</strong></td>
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<td></td>
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<tr>
<td>p300</td>
<td>↓ interaction</td>
<td>Gene expression</td>
<td>All cells?</td>
<td>↓ transcription by nuclear receptors</td>
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<tr>
<td>HNF4-α</td>
<td>↓ DNA binding, ↑ degradation</td>
<td>Gene expression</td>
<td>Liver, others</td>
<td>↓ transcription</td>
</tr>
<tr>
<td>ChREBP</td>
<td>↓ DNA binding</td>
<td>Gene expression</td>
<td>Liver</td>
<td>↓ transcription of lipogenic genes</td>
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<tr>
<td>TORC2</td>
<td>↑ cytoplasmic translocation</td>
<td>Gene expression, localization</td>
<td>Liver</td>
<td>↓ transcription of gluconeogenic genes</td>
</tr>
<tr>
<td><strong>Ion transport/ion balance</strong></td>
<td></td>
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</tr>
<tr>
<td>CFTR</td>
<td>↓ channel opening</td>
<td>Ion transport, fluid secretion</td>
<td>Airway, gut epithelium</td>
<td>↓ ion transport, ↓ fluid secretion</td>
</tr>
</tbody>
</table>

ACC1, acetyl-CoA carboxylase-1; ACC2, acetyl-CoA carboxylase-2; AS160, AKT substrate of 160 kDa; CFTR, cystic fibrosis transmembrane conductance regulator; ChREBP, carbohydrate-response element-binding protein; EF2K, elongation factor-2 kinase; eNOS, endothelial nitric oxide synthase; GLUT4, glucose transporter type-4; HMGCR, 3-hydroxy-3-methylglutaryl coenzyme A reductase; HNF4-α, hepatocyte nuclear factor-4α; IRS1, insulin receptor substrate-1; PKF2, 6-phosphofructo-2-kinase; PI, phosphatidylinositol; Rab-GAP, Rab GTPase-activating protein; Rab-GD, Ras homologue enriched in brain GTPase-activating protein; TOR, target of rapamycin; TORC2, transducer of regulated CREB (cyclic AMP-responsive element binding) activity; TSC2, tuberous sclerosis-2. *Detailed references can be found elsewhere*. 
The mammalian target of rapamycin (mTOR) is a cellular nutrient rheostat

- Rapamycin is a drug for immunosuppression, restenosis, and renal cancer
- mTOR is a protein kinase, forms two distinct TOR complexes, TORC1 and TORC2
- TORC1 is activated by growth factors, energy sufficiency, and nutrients
- TORC1 is inhibited by stress conditions
- TORC1 regulates translation, cell growth, and cell size
- Activation of TORC1 is associated with human cancer
TSC1/TSC2 function as GTPase activating protein (GAP) towards Rheb
TORC1 phosphorylates and suppresses the inhibitory activity of 4E-BP1 towards eIF4E.

eIF4E binds to CAP in eukaryotic mRNA to initiate translation.
Implication of energy response in disease

- Diabetic drug metformin and rosiglitazone activate AMPK
- Mutations in AMPK cause Wolf-Parkison-Whie syndrome, Mutation in the AMPK gamma2 subunit, cardiomyopathy with hypertrophy
- Germline mutations of LKB1 cause Peutz-Jeghers Syndrome, hamartoma in gastrointestinal track
- LKB1 is mutated in ~50% of sporadic non-small cell lung cancers

A possible mechanism for the energy sensing pathway to act as tumor suppression

![Diagram of energy sensing pathway involving LKB1, AMPK, TSC1, TSC2, Rheb, and cell growth](image)
Metformin, the most common diabetes drug

- The first-line drug for type 2 diabetes
- One of the most prescribed drugs in US, > 35 million/year
- Increase insulin sensitivity
- Increase glucose uptake and utilization
- Reduce LDL and triglyceride
- Activate AMPK
Rapamycin as a drug for immunosuppressant and cancer

- Used to prevent rejection of organ transplantation, such as kidney
- Prevent restenosis after balloon angioplasty
- For late stage renal cancer
- Inhibit mTORC1 but not mTOR2
- Bind FKBP12, then bind mTOR