ATP = cellular energy
How does the cell extract energy and reducing power from its environment?

How does a cell synthesize the building blocks of its macromolecules and then build the macromolecules?

Metabolism/intermediary metabolism:

Number of reactions is large but the kinds of reactions are small
5 Basic principles of metabolism:

1) Fuels are degraded and large molecules are constructed step by step in a series of linked reactions

2) The energy currency common to all life is ATP

3) The oxidation of carbon fuels powers the formation of ATP

4) Many metabolic pathways however, there are only a limited number of types of reactions

5) Metabolic pathways are tightly regulated
Phototrophs are photosynthetic organisms that obtain energy by trapping sunlight.

Chemotrophs obtain energy by oxidation of foodstuffs.

Metabolic pathways:

Some convert energy from fuels to useful forms others require energy to proceed.

1) Catabolic reactions:
2) Fuels to $\text{CO}_2 + \text{H}_2\text{O} + \text{energy}$

3) Anabolic reactions:
4) Synthesis of fats, glucose and DNA require energy
A thermodynamically unfavorable reaction can be driven by a favorable reaction:

\[
\begin{align*}
A &= B + C \quad +5 \text{ kcal} \\
B &= D \quad -8 \text{ kcal} \\
A &= C + D \quad -3 \text{ kcal}
\end{align*}
\]

By coupling the reaction to the favorable $B=D$ step this drives the overall conversion of $A$ to $C$ and $D$
ATP has a high phosphoryl-transfer potential

Adenosine triphosphate (ATP)

Adenosine diphosphate (ADP)

Adenosine monophosphate (AMP)

Figure 15.3
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Resonance stabilization of orthophosphate

ATP has a small number of such structures whereas ADP and orthophosphate have many.
Other compounds with high phosphoryl-transfer potential:

Phosphoenolpyruvate (PEP)

Creatine phosphate

1,3-Bisphosphoglycerate (1,3-BPG)

Figure 15.6
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ATP is intermediate in energy which allows it to function efficiently as a carrier of phosphoryl groups.

### Table 15.1 Standard free energies of hydrolysis of some phosphorylated compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\text{kJ mol}^{-1}$</th>
<th>$\text{kcal mol}^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphoenolpyruvate</td>
<td>$-61.9$</td>
<td>$-14.8$</td>
</tr>
<tr>
<td>1,3-Bisphosphoglycerate</td>
<td>$-49.4$</td>
<td>$-11.8$</td>
</tr>
<tr>
<td>Creatine phosphate</td>
<td>$-43.1$</td>
<td>$-10.3$</td>
</tr>
<tr>
<td>ATP (to ADP)</td>
<td>$-30.5$</td>
<td>$-7.3$</td>
</tr>
<tr>
<td>Glucose 1-phosphate</td>
<td>$-20.9$</td>
<td>$-5.0$</td>
</tr>
<tr>
<td>Pyrophosphate</td>
<td>$-19.3$</td>
<td>$-4.6$</td>
</tr>
<tr>
<td>Glucose 6-phosphate</td>
<td>$-13.8$</td>
<td>$-3.3$</td>
</tr>
<tr>
<td>Glycerol 3-phosphate</td>
<td>$-9.2$</td>
<td>$-2.2$</td>
</tr>
</tbody>
</table>

*Table 15.1
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ATP and creatine phosphate are the initial energy sources then metabolism must re-supply ATP.
ATP-ADP Cycle

Motion
Active transport
Biosyntheses
Signal amplification

ATP

Oxidation of fuel molecules or Photosynthesis

ADP
The ultimate electron acceptor in the oxidation of C is $O_2$; the more reduced a carbon is to begin with the more free energy released by its oxidation:

\[
\Delta G^{\text{red}}_{\text{ox}} (\text{kJ mol}^{-1}) = -820 \\
\Delta G^{\text{red}}_{\text{ox}} (\text{kcal mol}^{-1}) = -196
\]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Most energy</th>
<th>Least energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methane</td>
<td>$\text{H}_2\text{C}_2\text{H}_4$</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>Methanol</td>
<td>$\text{H}_2\text{C}_2\text{H}_6\text{OH}$</td>
<td>$\text{CO}_2$</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>$\text{H}_2\text{C}_2\text{H}_4\text{O}$</td>
<td>$\text{H}_2\text{O}$</td>
</tr>
<tr>
<td>Formic acid</td>
<td>$\text{H}_2\text{C}_2\text{H}_4\text{OH}$</td>
<td>$\text{H}_2\text{O}$</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>$\text{CO}_2$</td>
<td>$\text{H}_2\text{O}$</td>
</tr>
</tbody>
</table>

Figure 15.9

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Fats are more efficient fuel source than carbohydrates because the carbon in fats is more reduced:

Glucose

Fatty acid
G3P is a metabolite of glucose and oxidation of this aldehyde to the acid releases energy.

Glyceraldehyde 3-phosphate  $\rightarrow$  3-Phosphoglyceric acid
The formation of ATP from G3P occurs in two steps; the first oxidation step requires NAD+ and HPO$_4^{2-}$ resulting in a phosphorylated intermediate 1,3-BPG:

\[
\text{Glyceraldehyde 3-phosphate (GAP)} \quad \overset{+ \text{NAD}^+ + \text{HPO}_4^{2-}}{\longrightarrow} \quad \text{1,3-Bisphosphoglycerate (1,3-BPG)}
\]
The second step ADP is phosphorylated to ATP with the 1,3-BGP phosphate group:

\[
\begin{align*}
\text{O} & \quad \text{OPO}_3^{2-} \\
\text{H} & \quad \text{C} \quad \text{OH} \\
\text{CH}_2\text{OPO}_3^{2-} & \quad + \quad \text{ADP} \quad \rightarrow \quad \text{H} & \quad \text{C} \quad \text{OH} \\
& \quad \text{CH}_2\text{OPO}_3^{2-} & \quad + \quad \text{ATP}
\end{align*}
\]

1,3-Bisphosphoglycerate \quad 3-Phosphoglyceric acid
Proton Gradients across membranes are created by the oxidation of carbon fuels pumping protons out resulting in the influx of protons through an ATP-synthesizing enzyme (red complex) and the synthesis of ATP from ADP.
The digestion of food results in the generation of a few simple units that play a key role in metabolism.
NAD is a major electron carrier in the oxidation of fuels

NAD\(^+\) Nicotinamide adenine dinucleotide R=H

NADP Nicotinamide adenine dinucleotide phosphate R=P

Figure 15.13
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In the oxidation of a substrate, the nicotinamide ring of NAD+ accepts a hydrogen ion and two electrons generating the reduced form as NADH. This is a dehydrogenation reaction.
The other major electron carrier is the coenzyme flavin adenine dinucleotide FAD and FADH$_2$. 

![Chemical diagram showing the reaction of a molecule with FAD to produce FADH$_2$.]
FAD consists of a flavin mononucleotide (blue) and an AMP unit (black)
The electrons and protons are carried by the isoalloxazine ring component of FAD:

**Oxidized form (FAD)**

**Reduced form (FADH₂)**

Figure 15.15
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Reductive biosynthesis uses NADPH as the electron donor not NADH which is used for ATP generation.
Coenzyme A is a carrier of acetyl groups through a thioester bond.
The hydrolysis of the acetyl group generates -7 kcal
It is used in the catabolism of fatty acids and the synthesis of membrane lipids
NADH, NADPH and FADH2 react slowly with $O_2$
Likewise ATP and acetyl CoA are hydrolyzed slowly without a catalyst
The stability of these molecules allow them to control the flow of free energy and reducing power

The existence of a recurring set of activated carriers in all organisms is a unifying theme in biochemistry
<table>
<thead>
<tr>
<th>Carrier molecule in activated form</th>
<th>Group carried</th>
<th>Vitamin precursor</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP</td>
<td>Phosphoryl</td>
<td>Nicotinate (niacin)</td>
</tr>
<tr>
<td>NADH and NADPH</td>
<td>Electrons</td>
<td>Riboflavin (vitamin B&lt;sub&gt;2&lt;/sub&gt;)</td>
</tr>
<tr>
<td>FADH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Electrons</td>
<td>Riboflavin (vitamin B&lt;sub&gt;2&lt;/sub&gt;)</td>
</tr>
<tr>
<td>FMNH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Electrons</td>
<td>Riboflavin (vitamin B&lt;sub&gt;2&lt;/sub&gt;)</td>
</tr>
<tr>
<td>Coenzyme A</td>
<td>Acyl</td>
<td>Pantothenate</td>
</tr>
<tr>
<td>Lipoamide</td>
<td>Acyl</td>
<td></td>
</tr>
<tr>
<td>Thiamine pyrophosphate</td>
<td>Aldehyde</td>
<td>Thiamine (vitamin B&lt;sub&gt;1&lt;/sub&gt;)</td>
</tr>
<tr>
<td>Biotin</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Biotin</td>
</tr>
<tr>
<td>Tetrahydrofolate</td>
<td>One-carbon units</td>
<td>Folate</td>
</tr>
<tr>
<td>S-Adenosylmethionine</td>
<td>Methyl</td>
<td></td>
</tr>
<tr>
<td>Uridine diphosphate glucose</td>
<td>Glucose</td>
<td></td>
</tr>
<tr>
<td>Cytidine diphosphate diacylglycerol</td>
<td>Phosphatidate</td>
<td></td>
</tr>
<tr>
<td>Nucleoside triphosphates</td>
<td>Nucleotides</td>
<td></td>
</tr>
</tbody>
</table>

Note: Many of the activated carriers are coenzymes that are derived from water-soluble vitamins.
Many activated carriers are derived from vitamins

Vitamins are organic molecules that are needed in small amounts in the diets of higher animals as higher animals have lost the capacity to synthesize these molecules during the course of evolution.

E. Coli can thrive on glucose and organic salts, humans require at least 12 vitamins in their diet. The biosynthesis of vitamins is often complex requiring many steps; it is easier to acquire these nutrients in the diet than to synthesize them de novo.
<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Coenzyme</th>
<th>Typical reaction type</th>
<th>Consequences of deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamine (B₁)</td>
<td>Thiamine pyrophosphate</td>
<td>Aldehyde transfer</td>
<td>Beriberi (weight loss, heart problems, neurological dysfunction)</td>
</tr>
<tr>
<td>Riboflavin (B₂)</td>
<td>Flavin adenine dinucleotide (FAD)</td>
<td>Oxidation-reduction</td>
<td>Cheliosis and angular stomatitis (lesions of the mouth), dermatitis</td>
</tr>
<tr>
<td>Pyridoxine (B₆)</td>
<td>Pyridoxal phosphate</td>
<td>Group transfer to or from amino acids</td>
<td>Depression, confusion, convulsions</td>
</tr>
<tr>
<td>Nicotinic acid (niacin)</td>
<td>Nicotinamide adenine dinucleotide (NAD⁺)</td>
<td>Oxidation-reduction</td>
<td>Pellagra (dermatitis, depression, diarrhea)</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>Coenzyme A</td>
<td>Acyl-group transfer</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Biotin</td>
<td>Biotin–lysine adducts (biocytin)</td>
<td>ATP-dependent carboxylation and carboxyl-group transfer</td>
<td>Rash about the eyebrows, muscle pain, fatigue (rare)</td>
</tr>
<tr>
<td>Folic acid</td>
<td>Tetrahydrofolate</td>
<td>Transfer of one-carbon components; thymine synthesis</td>
<td>Anemia, neural-tube defects in development</td>
</tr>
<tr>
<td>B₁₂</td>
<td>5’-Deoxyadenosyl cobalamin</td>
<td>Transfer of methyl groups; intramolecular rearrangements</td>
<td>Anemia, pernicious anemia, methylmalonic acidosis</td>
</tr>
</tbody>
</table>
Vitamin B₅
(Pantothenate)

Vitamin B₂
(Riboflavin)

Vitamin B₃
(Niacin)

Vitamin B₆
(Pyridoxine)
Not all vitamins function as coenzymes; those with letter designation have a diverse array of functions.

**Table 15.4 Noncoenzyme vitamins**

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Function</th>
<th>Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Roles in vision, growth, reproduction</td>
<td>Night blindness, cornea damage, damage to respiratory and gastrointestinal tract</td>
</tr>
<tr>
<td>C (ascorbic acid)</td>
<td>Antioxidant</td>
<td>Scurvy (swollen and bleeding gums, subdermal hemorrhaging)</td>
</tr>
<tr>
<td>D</td>
<td>Regulation of calcium and phosphate metabolism</td>
<td>Rickets (children): skeletal deformities, impaired growth Osteomalacia (adults): soft, bending bones</td>
</tr>
<tr>
<td>E</td>
<td>Antioxidant</td>
<td>Inhibition of sperm production; lesions in muscles and nerves (rare)</td>
</tr>
<tr>
<td>K</td>
<td>Blood coagulation</td>
<td>Subdermal hemorrhaging</td>
</tr>
</tbody>
</table>
Figure 15.18

Vitamin K<sub>1</sub>

Vitamin A (Retinol)

Vitamin E (α-Tocopherol)

Vitamin D<sub>2</sub> (Calciferol)
There are thousands of metabolic reactions, but they can be subdivided into six types:

<table>
<thead>
<tr>
<th>Type of reaction</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidation–reduction</td>
<td>Electron transfer</td>
</tr>
<tr>
<td>Ligation requiring ATP cleavage</td>
<td>Formation of covalent bonds (i.e., carbon–carbon bonds)</td>
</tr>
<tr>
<td>Isomerization</td>
<td>Rearrangement of atoms to form isomers</td>
</tr>
<tr>
<td>Group transfer</td>
<td>Transfer of a functional group from one molecule to another</td>
</tr>
<tr>
<td>Hydrolytic</td>
<td>Cleavage of bonds by the addition of water</td>
</tr>
<tr>
<td>Addition or removal of functional groups</td>
<td>Addition of functional groups to double bonds or their removal to form double bonds</td>
</tr>
</tbody>
</table>

Table 15.5
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Oxidation-reduction reactions

\[
\text{Succinate} + \text{FAD} \leftrightarrow \text{Fumarate} + \text{FADH}_2 \tag{1}
\]

\[
\text{Malate} + \text{NAD}^+ \leftrightarrow \text{Oxaloacetate} + \text{NADH} + \text{H}^+ \tag{2}
\]
Ligation reactions

\[
\text{Pyruvate} + \text{CO}_2 + \text{ATP} + \text{H}_2\text{O} \leftrightarrow \text{Oxaloacetate} + \text{ADP} + P_i + H^+ \quad (3)
\]
Isomerization reactions

Citrate $\rightleftharpoons$ Isocitrate

Unnumbered 15 p444a
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Group-transfer reactions

Glucose + ATP ↔ Glucose 6-phosphate (G-6P) + ADP
Hydrolytic reactions

\[
\text{Product} + \text{H}_2\text{O} \rightleftharpoons \text{Product} + \text{Product}
\]
Functional groups may be added to double bonds to form single bonds or removed from single bonds to form double bonds. The enzymes that perform this step are called lyases.

\[
\begin{align*}
\text{Fructose 1,6-bisphosphate (F-1,6-BP)} & \quad \iff \quad \text{Dihydroxyacetone phosphate (DHAP)} + \text{Glyceraldehyde 3-phosphate (GAP)} \\
\end{align*}
\]
A critical step in glycolysis a dehydration reaction

\[
\begin{align*}
\text{2-Phosphoglycerate} & \quad \leftrightarrow \quad \text{Phosphoenolpyruvate (PEP)} \\
\text{H} - \text{C} - \text{OPO}_3^{2-} & \quad \leftrightarrow \quad \text{H} - \text{C} = \text{C} - \text{OPO}_3^{2-} + \text{H}_2\text{O}
\end{align*}
\]
Metabolism is controlled by:

1) The amount of enzymes

2) Their catalytic activities

3) The accessibility of substrates
ADP is an ancient module in metabolism

Figure 15.20
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