Other Pathways of Carbohydrate Metabolism

Gluconeogenesis
(lactate, pyruvate, glycerol, amino acids → glucose)

The Glyoxylate Pathway
(in plants, acetyl-CoA → glucose)

Biosynthesis of Oligosaccharides and Glycoproteins
(synthesis of oligosaccharides and addition to proteins)

The Pentose Phosphate Pathway
(NADPH, ribose-5-phosphate, glycolytic intermediates)

Gluconeogenesis

With fasting, 12 hour supply of glucose from glycogen stores

Gluconeogenesis provides new glucose from noncarbohydrate precursors (lactate, pyruvate, glycerol, citric acid cycle intermediates, carbon skeletons of amino acids except leucine and lysine)

All must be converted to oxaloacetate

Note: No pathway in animals for net conversion of acetyl-CoA to oxaloacetate (occurs in plants, glyoxylate cycle)

Gluconeogenesis

The gluconeogenesis pathway

Uses the glycolytic enzymes in reverse EXCEPT for pyruvate kinase, phosphofructokinase, and hexokinase (bypassed)

First bypass:

pyruvate → phosphoenolpyruvate

pyruvate carboxylase

PEP carboxykinase

Pyruvate carboxylase

$$\text{pyruvate} + HCO_3^- + \text{ATP} \rightarrow \text{oxaloacetate} + \text{ADP} + P_i$$

tetrameric protein
120-kDa subunits
biotin prosthetic group - CO_2 carrier
allosterically activated by acetyl-CoA

PEP carboxykinase (PEPCK)

oxaloacetate + GTP →

phosphoenolpyruvate + GDP + CO_2

monomeric 74-kDa enzyme

Gluconeogenesis

The gluconeogenesis pathway

Transport of phosphoenolpyruvate and oxaloacetate

Phosphoenolpyruvate is transported by specific membrane transport proteins

Oxaloacetate must be transported between mitochondrion and cytosol by use of malate-aspartate shuttle (malate dehydrogenase and aspartate aminotransferase)

Gluconeogenesis

The gluconeogenesis pathway

Second bypass:

fructose-1,6-bisphosphate → fructose-6-phosphate
fructose-1,6-bisphosphatase (FBPase-1)

Third bypass:

glucose-6-phosphate → glucose
glucose-6-phosphatase (unique to liver and kidney)

Glycolysis:

$$Glucose + 2NAD^+ + 2ADP + 2P_i \rightarrow 2pyruvate + 2NADH + 4H^+ + 2ATP + 2H_2O$$

Gluconeogenesis:

$$2Pyruvate + 2NADH + 4H^+ + 4ATP + 2GTP + 6H_2O \rightarrow glucose + 2NAD^+ + 4ADP + 2GDP + 6P_i$$

Overall:

$$2ATP + 2GTP + 4H_2O \rightarrow 2ADP + 2GDP + 4P_i$$

The cost of maintaining independent regulation of separate pathways!

Gluconeogenesis

Regulation of gluconeogenesis

Glycolysis and gluconeogenesis are reciprocally regulated to meet demands of organism

In fed state, glucose → glycogen and acetyl-CoA (fatty acid biosynthesis and fat storage)

In fasted state, glycogen and protein → glucose

Pathways are controlled by allosteric effectors and covalent modifications (hormonal control) of:

hexokinase
glucose-6-phosphatase

phosphofructokinase-2/fructose-1,6-bisphosphatase-2

pyruvate kinase
pyruvate carboxylase
PEP carboxykinase

Gluconeogenesis

The Cori cycle

Muscle (red blood cell) lactate is sent to the liver to be converted to glucose, which is then shipped back to muscle for use or storage as glycogen

The Glyoxylate Pathway

In plants, acetyl-CoA can be converted to oxaloacetate

$$2\text{Acetyl-CoA} + 2\text{NAD}^+ + \text{FAD} \rightarrow \text{oxaloacetate} + 2\text{CoA} + 2\text{NADH} + \text{FADH}_2 + 2\text{H}^+$$

involves enzymes of mitochondrion and glyoxysome

Plant specific enzymes:

isocitrate lyase
malate synthase

Biosynthesis of Oligosaccharides and Glycoproteins

Glycosidic bond - $\Delta G^{\circ\prime} = +16\ kJ \cdot mol^{-1}$

Glycosyl transferases use nucleotide sugars (UDP, GDP, CMP)

Lactose synthesis (mammary gland)

Lactose synthase (two subunits):

galactosyl transferase - catalytic unit, found in many tissues

UDP-galactose + *N*-acetylglucosamine $\rightarrow$
N-acetyllactosamine

α-lactalbumin - alters specificity of galactosyl transferase to prefer glucose as acceptor to form lactose

Biosynthesis of Oligosaccharides and Glycoproteins

Glycoprotein synthesis

Glycosylation - sorting and distribution of proteins to cellular destinations

Three groups:

1. *N*-linked oligosaccharides - attached by β-*N*-glycosidic bond to Asn residue in sequence Asn-X-Ser/Thr, where X = amino acid except Pro or Asp

2. *O*-linked oligosaccharides - attached by α-*O*-glycosidic bond to Ser or Thr (in collagen, to 5-hydroxylysine)

3. Glycosylphosphatidylinositol (GPI)-membrane anchors - attached by amide bond between mannose-6-phosphoethanolamine and carboxyl group

Biosynthesis of Oligosaccharides and Glycoproteins

Glycoprotein synthesis

N-linked glycoproteins formed in endoplasmic reticulum, processed in Golgi apparatus

Four stages to *N*-linked glycoprotein carbohydrate portion:

1. Synthesis of lipid-linked oligosaccharide precursor, dolichol carriers. Stepwise addition of monosaccharide units by specific glycosyl transferases, formation of "core" structure

2. Transfer of precursor to amino group of Asn residue on polypeptide, membrane-bound oligosaccharide-transferring enzyme

3. Removal of some precursor's sugar units, 3 glucose and 1 mannose enzymatically removed, then transported to Golgi apparatus (cis and trans Golgi network)

4. Addition of sugar residues (*N*-acetylglucosamine, galactose, fucose, sialic acid) to remaining core oligosaccharide

(N-acetylglucosamine)$_2$(mannose)$_3$

Biosynthesis of Oligosaccharides and Glycoproeins

Glycoprotein synthesis

Classified as three groups:

1. High-mannose oligosaccharides - 2 to 9 mannose residues appended to pentasaccharide "core"
2. Complex oligosaccharides - variable amound of *N*-acetyllactosamine as well as sialic acid and/or fucose linked to "core"
3. Hybrid oligosaccharides - elements of both high-mannose and complex chains

Antibiotics tunicamycin and bacitracin inhibit bacterial wall synthesis

Biosynthesis of Oligosaccharides and Glycoproteins

Glycoprotein synthesis

O-linked glycoproteins are posttranslationally formed in Golgi apparatus

(Blood group antigens and cell-cell recognition)

Transfer of *N*-acetylgalactosamine from UDP-GalNAc to Ser or Thr(no common sequence) by GalNAc transferase

Stepwise addition of galactose, sialic acid, *N*-acetyl glucosamine, and fucose by specific glycosyl transferases

Biosynthesis of Oligosaccharides and Glycoproteins

Glycoprotein synthesis

GPI (glycosylphosphatidylinositol)-linked proteins anchor proteins to exterior surface of eukaryotic plasma membrane

Core GPI structure synthesized on lumenal side of endoplasmic reticulum

The Pentose Phosphate Pathway

hexose monophosphate shunt
phosphogluconate pathway

$3\text{Glucose-6-phosphate} + 6\text{NADP}^+ + 3\text{H}_2\text{O} \Leftrightarrow$
$6\text{NADPH} + 6\text{H}^+ + 3\text{CO}_2 + 2\text{fructose-6-phosphate} +$
glyceraldehyde-3-phosphate

NADH and NADPH not metabolically interchangeable!
NADPH is used in endergonic reductive biosynthesis

Three stages:

1. Oxidation reactions (NADPH production)

$3\text{Glucose-6-phosphate} + 6\text{NADP}^+ + 3\text{H}_2\text{O} \rightarrow$
$6\text{NADPH} + 6\text{H}^+ + 3\text{CO}_2 + 3\text{ribulose-5-phosphate}$

2. Isomerization and epimerization reactions (pentose sugars for nucleotide biosynthesis)

$3\text{Ribulose-5-phosphate} \Leftrightarrow$
$\text{ribose-5-phosphate} + 2\text{xylulose-5-phosphate}$

3. Carbon-carbon bond cleavage and formation reactions (generation of glycolytic intermediates)

$\text{Ribose-5-phosphate} + 2\text{xylulose-5-phosphate} \Leftrightarrow$
$2\text{fructose-6-phosphate} + \text{glyceraldehyde-3-phosphate}$

The Pentose Phosphate Pathway

Oxidation reactions of NADPH production:

Glucose-6-phosphate dehydrogenase - hydride transfer from C1 of glucose-6-phosphate to NAD^+ to form 6-phosphoglucono-δ-lactone, inhibited by NADPH

$$\Delta G = -17.6\ kJ \cdot mol^{-1}$$

6-Phosphogluconolactonase - hydrolysis of 6-phosphoglucono-δ-lactone to 6-phosphogluconate

Phosphogluconate dehydrogenase - oxidative decarboxylation of 6-phosphogluconate to ribulose-5-phosphate and CO_2 (similar to isocitrate dehydrogenase reaction)

The Pentose Phosphate Pathway

Isomerization and epimerization reactions of ribulose-5-phosphate:

Ribulose-5-phosphate isomerase - occurs through enediolate intermediate

Ribulose-5-phosphate epimerase - occurs through enediolate intermediate

The Pentose Phosphate Pathway

Carbon-carbon bond cleavage and formation reactions:

Transketolase - thiamine pyrophosphate cofactor, structure similar to pyruvate dehydrogenase

Transaldolase - aldol cleavage, Schiff base formation

Overall conversion:

$$C_5 + C_5 \Leftrightarrow C_7 + C_3$$

$$C_7 + C_3 \Leftrightarrow C_6 + C_4$$

$$C_5 + C_4 \Leftrightarrow C_6 + C_3$$

$$3\ C_5 \Leftrightarrow 2\ C_6 + C_3$$

The Pentose Phosphate Pathway

Control of the pentose phosphate pathway:

In specific tissues, glucose-6-phosphate can be completely oxidized to CO_2

$$\text{Glucose-6-phosphate} + 12NADP^+ + 7H_2O \rightarrow 6CO_2 + 12NADPH + 12H^+ + P_i$$

Flux through pentose phosphate pathway is controlled by rate of glucose-6-phosphate dehydrogenase reaction, which is regulated by substrate $NADP^+$

Glucose-6-phosphate dehydrogenase deficiency

NADPH is required by cells for reduction of glutathione disulfide to glutathione (glutathione reductase)

Lack of enzyme predisposes cells to oxidative stress induced by drugs (primaquine)