PROTEIN METABOLISM

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Nucleic acids

- The genetic code uses 4 letter nuclide alphabet: the purines adenine and guanine; the pyrimidines cytosine and thymidine.
- Glycine, aspartate, and glutamine are amino acids necessary for purine synthesis.

Purine synthesis

- Purine synthesis in 10 steps begins with ribose-5-phosphate (from the HMP pathway).
- It reacts with ATP to from PRPP. An amine group is added, releasing the pyrophosphate.
- These two are the rate-controlling reactions for the pathway.
- Glutamine pyridoxal pyrophosphate amidotransferase is the rate limiting step.
- The final product is Inosine monophosphate, which can be converted to AMP and GMP.

Pyrimidine synthesis

- Aspartate alone is necessary for pyrimidine synthesis. Uracil arises from the deamination of cytosine.
- Pyrimidine synthesis in six steps begins with the production of carbamoyl phosphate from glutamine, ATP, and bicarbonate.
- Aspartate is added and the ring is closed, producing orotic acid.
- PRPP is added and the compound decarboxylated, producing uracil monophosphate (UMP) which can be converted to cytidine triphosphate (CTP).

Pyrimidine synthesis

- UMP must be converted to dUMP and a carbon atom transferred (tetrahydrofolate reductase critical) to end with deoxy thymidine monophosphate (dTNP).
- Aspartate transcarbamylase is the rate limiting step.

Nucleic acid structure

- Nucleotides (nucleic acid plus ribose plus phosphate) are linked by 3’-5’phosphodiester bond.
- Deoxyribonucleotides are produced by reduction of ribonucleotides (lose Oxygen at the 2 position).
- ATP stimulates the reaction.
- NADH is the final reducing agent.
- DNA is largely in B form (two antiparallel strands in a right handed helix with the bases on the inside and the phosphodiester backbone on the outside).
- Proteins can interact directly with the bases in the DNA major groove.
- 10 bases per helical turn.

Nucleic acid structure

- Guanidine-cytosine base pairs contain 3 Hydrogen bonds; adenine-thymine have 2 Hydrogen bonds, less tightly bound.
- Melting temperature (denaturation) linearly related to guanidine + cytosine content.

The double helix

- Double-stranded DNA forms a helical structure.
- Bases are stacked; ring structures make them essentially flat.
- Offset nature of backbone creates major and minor grooves. (Bases more exposed in major groove.)

Transcription to Translation

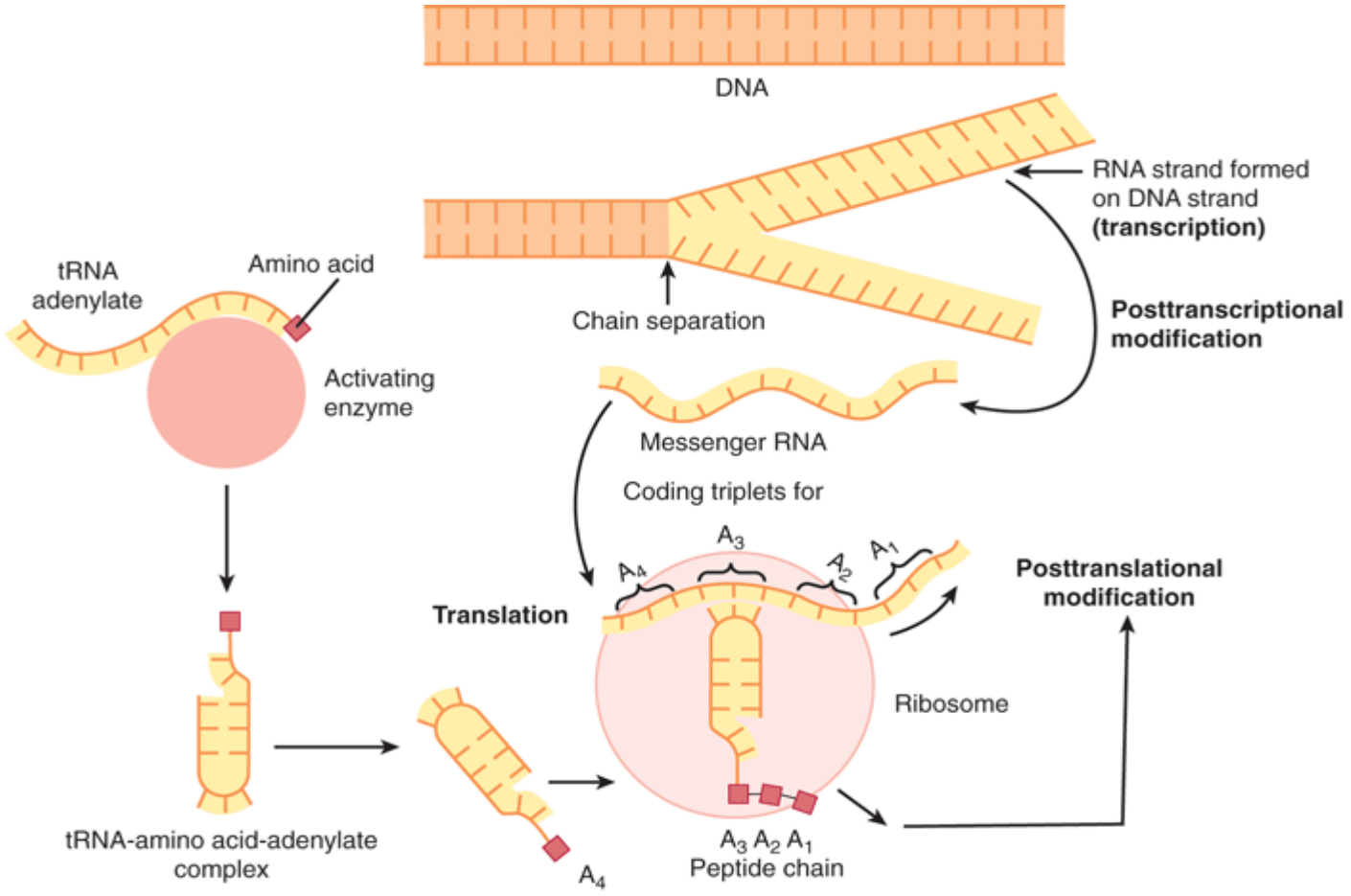


Fig. 1-15 Accessed 07/01/2010

RNA synthesis

- Pre-mRNA is generated as two exons are spliced together.
- RNA polymerase II binds to DNA promoter site with other transcription factors. mRNA is generated.
- Following transcription, mRNA is transported out of the nucleus. 5'end is capped by 7-methylguanosine. 3'end is polyadenylated.
- Messenger RNA (mRNA) transfers function coded in DNA. Uracil is substituted for Thymidine.
- Accurate base pairing is only required for the first two (of three) nucleotide positions of an mRNA codon.
- Variation in the third position will still produce the same amino acid.

RNA synthesis

- The codon consists of a 3 letter nuclide alphabet.
- AUG is the usual start codon; UGA, UAA, UAG are the usual stop codons.
- Methionine and tryptophan alone among the amino acids are designated by a single codon.
- RNA polymerase binds to DNA promoter site with other transcription factors.
- The site is upstream (5') to the transcription start site for rRNA and mRNA genes and to the downstream (3') side of the start site for tRNA genes. (Capped)
- TATA (Hogness box) at position 25; CAAT at position 75 are promoters.

RNA synthesis

- The DNA template is read in the 3’-5’direction. Synthesis continues until a stop signal is reached.
- Non-capped protein production seen with viruses.
- RNA polymerase I (rRNA); II (mRNA); III (tRNA).
- Transcription factors have four structural motifs:
- They bind directly to the DNA in the major groove of the helix by virtue of their positive charge or basic region near the N-terminal end

RNA synthesis

- Leucine zipper:
- Every seventh amino acid is leucine
- In the protein α-helix, every other protein is leucine.
- Form dimer by binding to another leucine zipper.

RNA synthesis

- Zinc finger:
- Bind Zinc to histidine residues; facilitates DNA binding.
- Helix-turn-helix and Helix-loop-helix facilitate dimerization and binding of the protein to DNA.
- Those transcription factors that bind hormones or second messengers bind to a response element on the DNA.
- These are upstream from the transcription site and are cis-elements.
- If binding increases transcription rate, enhances; if decreases, represses.

Protein synthesis

- One transfer RNA (tRNA) for each of the naturally occurring amino acids.
- Transfer RNA (tRNA) “translates” the code.
- Translation is directional and co-linear with the mRNA.
- All tRNA’s have CCA at 3’end where the amino acid binds.
- Folded into cloverleaf structure of 4 stems and 3 loops to maximize Hydrogen bonding.

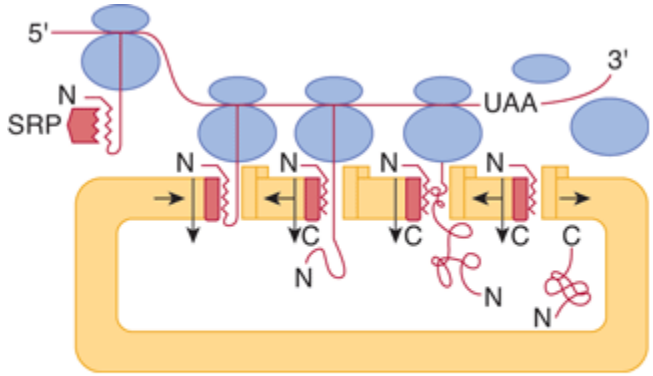
Protein synthesis

- Second loop contains three nucleotide anticodon sequence that interacts with three nucleotide codon sequence in mRNA.
- In its active form, tRNA is L-shaped.
- A charged tRNA binds to the amino acid site on the ribosome. Acylation of the tRNA uses 2ATP.

Protein synthesis

- Elongation is the stepwise formation of peptide bonds (peptidyl transferase).
- It is directed by elongation factors and requires GTP.
- Synthesis moves from N to C end of protein. Proofreading occurs with elongation.
- Translocase moves the mRNA relative to the ribosome (from the A to the P site).
- 4ATP consumed in forming each peptide bond.
- The ribosome contains only the single copy of the protein.

Translation into the Endoplasmic Reticulum



The ribosomes synthesizing a protein move along the mRNA from the 5' to the 3' end. When the signal peptide of a protein destined for secretion, the cell membrane, or lysosomes emerges from the large unit of the ribosome, it binds to a signal recognition particle (SRP), and this arrests further translation until it binds to the translocon on the endoplasmic reticulum.

N, amino end of protein; C, carboxyl end of protein.

(Reproduced, with permission, from Perara E, Lingappa VR: Transport of proteins into and across the endoplasmic reticulum membrane. In: *Protein Transfer and Organelle Biogenesis.* Das RC, Robbins PW (editors). Academic Press, 1988.) Fig. 1-18 Accessed 07/01/2010

Translation

- Polypeptide starts at amino terminus.
- Charged tRNAs aligned on mRNA by ribosome.
- Amino acids transferred from tRNA to growing polypeptide chain.
- Uncharged tRNA exits and can be attached to amino acid and be used again
- Translation terminates at the first STOP codon (UAA, UAG, UGA) in the reading frame of the mRNA.
- No tRNA with a complementary anticodon.

Translation

- Release factors bind.
- Peptidyl transferase hydrolyzes the Hydrogen bond between the polypeptide and final tRNA.
- Ribosome subunits dissociate. The uncharged tRNA moves to the elongation site and is released from the mRNA.
- Each mRNA can associate with more than one ribosome.
- This allows for faster translation overall.
- As one ribosomes translocates away from 5’ end, another can be recruited.

Post-translational modifications

TYPE	AMINO ACIDS	EXAMPLE
Carboxylation	Glu	Coagulation cascade
Hydroxylation	Pro, Lys	Collagen stability
Phosphorylation	Ser, Thr, Tyr	Enzyme activity
Glycosylation	Ser, Asn	Secretion, membrane
Fatty acylation		Membrane anchor
Prenylation		Membrane anchor
ADP-ribosylation		Enzyme activity

Protein synthesis

- Large ribosomes are synthesized in the nucleolus; smaller subunits are synthesized in the nucleus.
- They are assembled in the nucleus and are transported to the cytoplasm through nuclear pores.
- Free ribosomes are involved in the synthesis of structural proteins and of enzymes destined for the nucleus, peroxisomes, or mitochondria.
- Peroxisomes contain a number of enzymes that transfer protons from organic substrates (urate, d-amino acids, fatty acids containing >24 Carbons atoms) to molecular Oxygen with the formation of hydrogen peroxide (degraded by cytoplasmic catalase).

Protein targeting

- Proteins for secretion, membranes, organelles are often modified in ER and Golgi.
- Synthesized by ribosomes of rough ER.
- Signal peptide of nascent protein binds signal recognition particle (SRP).
- Docks with receptor on ER.
- Protein enters ER lumen via pore, can be modified and enter secretion pathway.

Protein synthesis

- Peroxisomes are the site of phospholipid exchange, converting phosphatidylserine and phosphatidylethanolamine.
- It is also the site for production of bile acids.

Protein synthesis

- The Golgi apparatus distributes proteins (and lipids) from the rough endoplasmic reticulum (RER, continuous with the outer nuclear membrane and containing ribosomes) to secretory vesicles and lysozomes.
- N-linked oligosaccharides are attached in the RER.
- That of asparagine is modified in the Golgi apparatus.
- O-oligosaccharides are added to serine and threonine residues in the Golgi as well.

Protein synthesis

- Mannose-6-phosphate is added to specific lysosomal proteins in the Golgi.
- Proteoglycan assembly as well as sulfation of sugars in proteoglycans and of selected protein tyrosine residues also occurs in the Golgi.
- The smooth endoplasmic reticulum (SER) is continuous with the RER, but contains no ribosomes, and is involved in steroid production in the adrenals and gonads, excitation-contraction mechanisms of muscle, fat absorption in the intestine, and in cholesterol and lipid metabolism and drug detoxification in the liver.

Protein synthesis

- Glycosylation occurs in the Golgi apparatus and in the (RER). The protein is released from the RER.
- Amino acids are made from intermediates of the citric acid cycle.
- The amino group of glutamine can be transferred to many α-keto acids in transamination reactions.
- Pyridoxal phosphate (vitamin B6) is a cofactor.
- Ten amino acids essential for function are not produced in the body and must be consumed:
- Leucine, Lysine, Isoleucine, Phenylalanine, Tryptophan, Methionine, Threonine, Valine, Arginine, Histidine.
- Only L forms are found in proteins.

Essential amino acids

- Even though glycine, serine, cysteine and alanine are all non-essential, vitamin deficiencies can make some amino acids essential.
- Folate is needed for one-Carbon transfer operations.
- Required for serine conversion to glycine (and heme metabolism).
- Vitamin B_6 is required for transamination reactions.
- Threonine to glycine is a minor pathway.
- Tryptophan to alanine (and to pyruvate) is a minor pathway.
- Serine to phosphoglycerate and cysteine to pyruvate also require vitamin B_6.

Amino acid transport

- Luminal transport is Na^+ dependent; contra-luminal transport is Na^+ independent.
- The four transporters are:
- Small aliphatic (alanine, serine, threonine)
- Large aliphatic and aromatic (isoleucine, leucine, valine, tyrosine, tryptophan, phenylanaline)
- Basic (arginine, lysine, cysteine, ornithine)
- Acidic (glutamate, aspartate)

Amino acid derivatives

- Phenylalanine: tyrosine, thyroxine, dopa, catechols Mg^{+} required), melanin
- Tryptophan: niacin, NAD, serotonin, melatonin
- Histidine: histamine
- Glycine: porphyrin, heme
- Arginine: creatine, urea, nitric oxide
- Serine: glutamate, GABA
- Threonine: component of vitamin B_{12}
- Aspartate, Cysteine: components of Co A

Urea cycle

- Transaminases remove the amino group from one amino acid and transfer it to an α-keto acid.
- α-ketoglutarate and glutamate are the most common pair involved in transaminase reactions.
- The reactions are reversible (used in both synthesis and degradation of amino acids).
- Pyridoxal phosphate is employed as a cofactor.
- Glutamate deydrogenase removes an amine from the amino acid (NAD or NADP as cofactor).
- The reaction is reversible.
- Free ammonia is generated.
- Glutaminase and asparaginase remove an amide from the amino acid. Free ammonia is generated.

Urea cycle

- Free ammonia receives a proton to form NH_4^+.
- Purine degeneration also generates NH_4^+.
- The Nitrogen atoms of amino acids and of purines are converted to urea in the liver.
- Bacteria in the liver degrade urea to free ammonia.
- Other sources of ammonia are the serine (to pyruvate) and threonine (to α-ketobutyrate) degradation pathways whose dehydratase reactions require pyridoxal phosphate as well as the conversion of histone to urocanate.

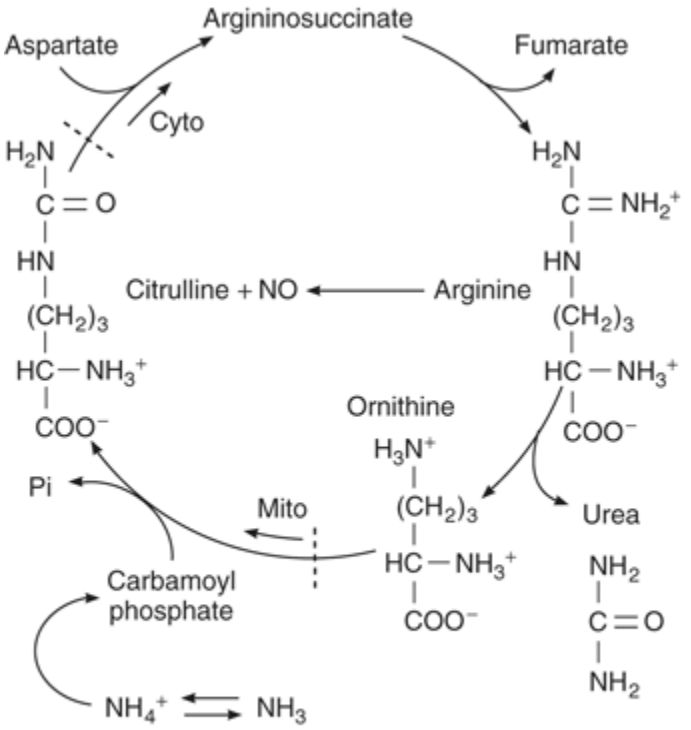
Urea cycle

- Glutamate is the amino acid pivotal for amino acid synthesis and degradation.
- Glutamate collects Nitrogen atoms from other amino acids through transaminase reactions of glutamate dehydrogenase and transfers them to other amino acids through transaminase reactions. (synthesis)
- The Nitrogen atoms collected from other amino acids may be released as NH_4^+ (glutamate dehydrogenase) or transferred to oxaloacetate to form aspartate.
- In either path, they enter the urea cycle.

Urea cycle

- Ornithine is produced from glutatmate (to arginine) and serves as a Nitrogen carrier that is regenerated in the cycle.
- High ammonia production stimulates urea formation.
- High protein diet and fasting both stimulate urea formation.
- Arginine stimulates the formation of N-acetylglutamate, a positive allosteric effector of carbamoyl phosphate synthetase 1.

Urea Cycle



The overall reaction in the urea cycle consumes 3 ATP.

Fig. 1-20 Accessed 07/01/2010

Secondary structure

- With the sole exception of glycine, the α-carbon of amino acids is chiral.
- As glycine is the smallest amino acid, it can be accommodated in places inaccessible to other amino acids. Thus, it often occurs where peptides bend sharply.
- The hydrophobic R groups of alanine, valine, leucine, and isoleucine and the aromatic R groups of phenylalanine, tyrosine, and tryptophan typically occur primarily in the interior of cytosolic proteins.

Secondary structure

- Free rotation is possible about only two of the three covalent bonds of the polypeptide backbone:
- The α-carbon to the carbonyl carbon (CO) bond, and the α-carbon to the nitrogen bond.
- The partial double-bond character of the peptide bond that links CO to the nitrogen requires that the carbonyl carbon, carbonyl oxygen, and nitrogen remain co-planar, thus preventing rotation.
- All peptide sequences have bonds in a trans configuration.

Secondary structure

- The charged R groups of basic and acidic amino acids stabilize specific protein conformations via ionic interactions, or salt bridges.
- These interactions also function in "charge relay" systems during enzymatic catalysis and electron transport in respiring mitochondria.
- Histidine plays unique roles in enzymatic catalysis.
- The pK_a of its imidazole proton permits it to function at neutral pH as either a base or an acid catalyst.

Secondary structure

- The primary alcohol group of serine and the primary thioalcohol (-SH) group of cysteine are excellent nucleophiles and can function as such during enzymatic catalysis.
- However, the secondary alcohol group of threonine, while a good nucleophile, does not fulfill an analogous role in catalysis.
- The —OH groups of serine, tyrosine, and threonine also participate in regulation of the activity of enzymes whose catalytic activity depends on the phosphorylation state of these residues.

Tertiary structure

- The stability of a helix arises primarily from hydrogen bonds formed between the oxygen of the peptide bond carbonyl and the hydrogen atom of the peptide bond nitrogen of the fourth residue down the polypeptide chain.
- The ability to form the maximum number of hydrogen bonds, supplemented by van der Waals interactions provides the thermodynamic driving force for the formation of an helix.

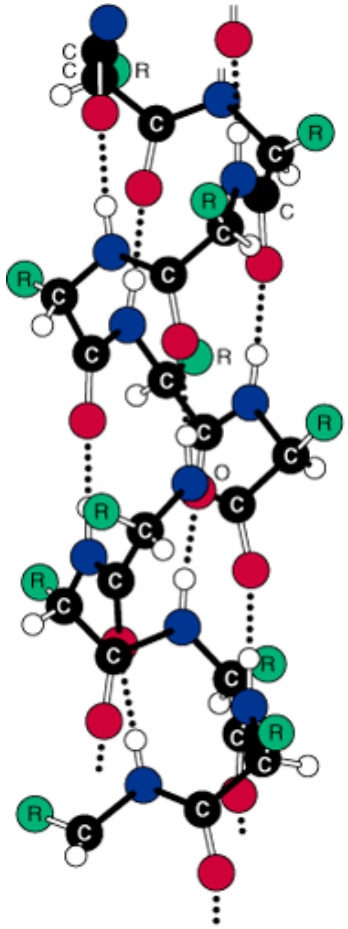
Tertiary structure

- As the peptide bond nitrogen of proline lacks a hydrogen atom to contribute to a hydrogen bond, proline can only be stably accommodated within the first turn of an helix.
- When present elsewhere, proline disrupts the conformation of the helix, producing a bend.
- Because of its small size, glycine also often induces bends in helices.

Tertiary structures

- α helix.
- Each turn covers approximately 3.6 amino acid residues.
- Stabilized by almost linear hydrogen bonds between amine and carboxyl groups.
- Intramolecular H-bonding occurs between parts of the same chain as in the α-helix. (α-keratin, hair, forms a D-α helix)
- L-β helix.
- Each turn covers approximately 3.3 amino acid residues.
- Stabilized by association of three helices to form a triple helix. (collagen)

α-helix



Hydrogen bonds (dotted lines) formed between H and O atoms stabilize a polypeptide in an -helical conformation. The side chains (R) are on the outside of the helix. The van der Waals radii of the atoms are larger than shown here; hence, there is almost no free space inside the helix.

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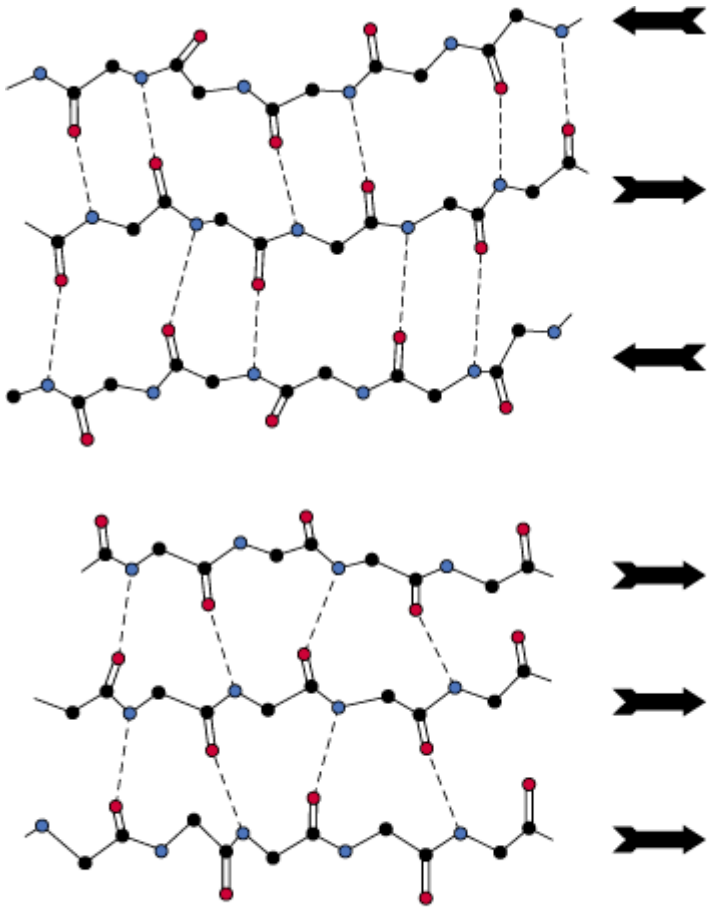
Fig 5-4 Accessed 08/01/2010

Tertiary structures

- β-pleated sheets.
- α-Carbon atoms occupy highest and lowest points.
- Side chains point either up or down.
- Stabilized by almost linear hydrogen bonds between sheets.
- Intermolecular H-bonding occurs between different chains as in a β-pleated structure .
- β-turns enable peptide to reverse direction. 4 amino acid residues.
- The structure of the peptide bond imposes restrictions on the ways proteins fold.

β-sheets



Top: Antiparallel β sheet. Pairs of hydrogen bonds alternate between being close together and wide apart and are oriented approximately perpendicular to the polypeptide backbone. Bottom: Parallel β sheet. The hydrogen bonds are evenly spaced but slant in alternate directions.

Fig. 5-5 Accessed 07/01/2010

Tertiary structure

- Turns and bends refer to short segments of amino acids that join two units of secondary structure, such as two adjacent strands of an anti-parallel sheet.
- Loops are regions that contain residues beyond the minimum number necessary to connect adjacent regions of secondary structure.
- Helix-loop-helix motifs provide the oligonucleotide-binding portion of DNA-binding proteins such as repressors and transcription factors.
- Many loops and bends reside on the surface of proteins (epitopes).

Domain

- A domain is a section of protein structure sufficient to perform a particular task such as binding of a substrate or other ligand.
- They are generally modular, contiguous in both primary sequence and three-dimensional space
- Not all domains bind substrates.
- Hydrophobic membrane domains anchor proteins to membranes or enable them to span membranes.
- Localization sequences target proteins to specific subcellular or extracellular locations.
- Regulatory domains trigger changes in protein function in response to the binding of allosteric effectors or covalent modifications. .

Enzyme regulation

- Allosteric change
- Hemoglobin as an example
- Covalent modification
- Muscle glycogen phosphorylase as an example
- Protein-protein interaction
- Calmodulin and monomeric G-proteins as examples

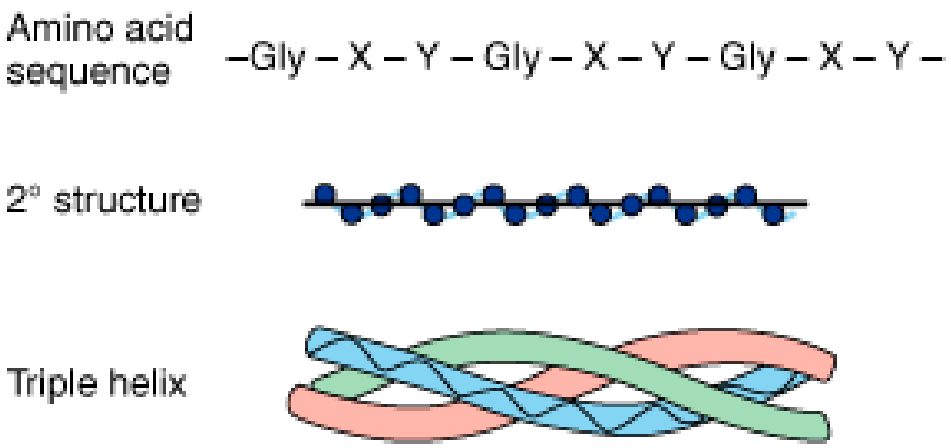
Tertiary structure

- Domains are physically independent regions within the overall tertiary structure of a large, complex protein.
- Generally domains are visually obvious, different regions within the molecule.
- SIRT1, 3, and 6 genes lead to NAD^+-dependent deacetylation of proteins, stabilizing chromosome

Primary structure variation

- Polymorphisms
- Single amino acid changes as in hemoglobin A, S, C
- Isoforms (isoenzymes
- Protein families
- Hemoglobin, myoglobin
- Serine proteases
- Development variation

Structural relation



Bonds are in trans position.

Fig. 5-11 Accessed 07/01/2010

Protein life cycle

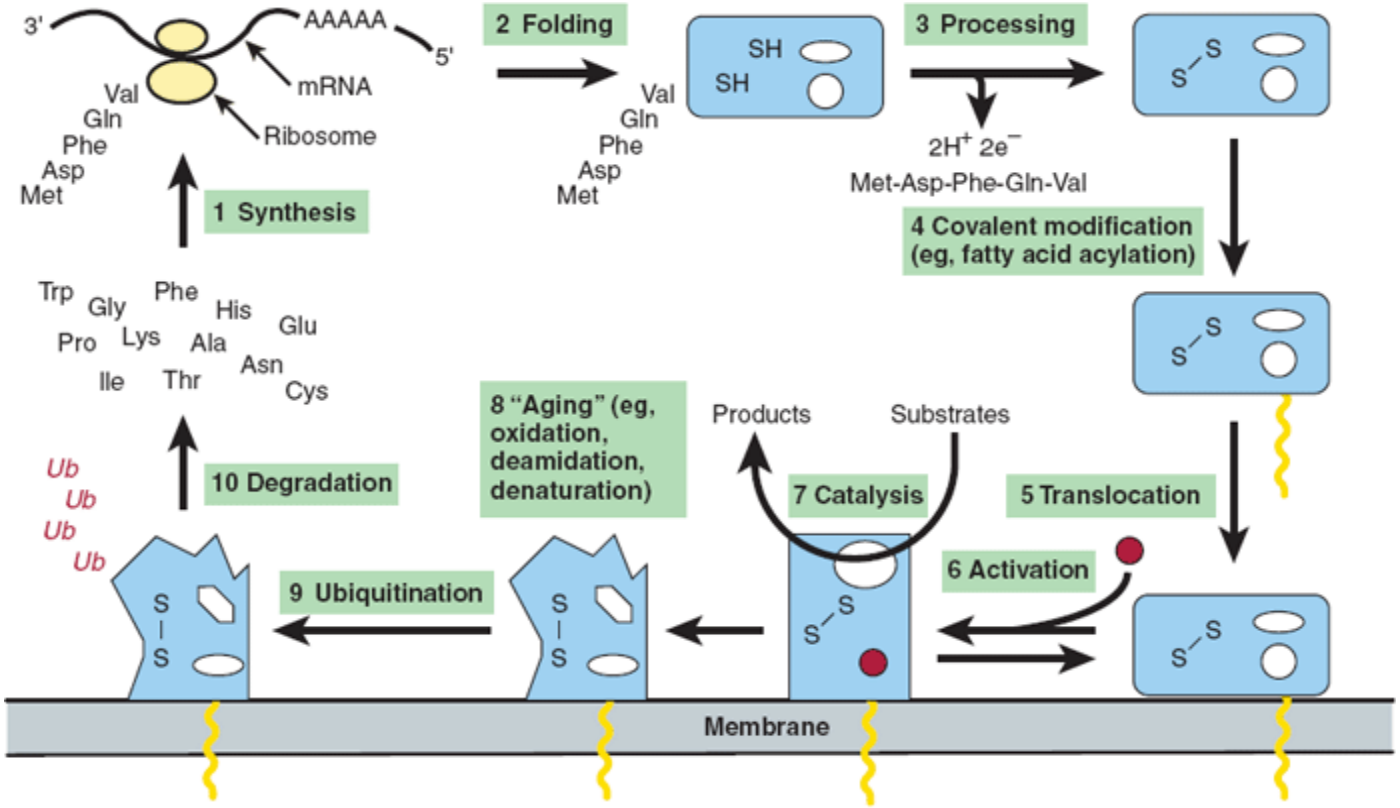


Fig. 4-1 Accessed 07/01/2010

Ubiquitin

- Ubiquitin molecule consists of 76 amino acids and contains 7 lysine residues.
- An enzyme cascade whose combination of E2-E3 that controls ubiquination of protein directs protein use or disposal.
- Poly-ubiquination of a protein at the lysine at position 6 is a DNA damage response
- at 11, proteasomal degradation results
- at 27, mitophagy (transcriptional regulation)
- at 29, regulating kinase activities
- at 33, also regulating T-cell receptor signaling
- at 48, proteasomal degradation

Ubiquitin

- Mono- or poly-ubiquination at lysine 63 leads to autophagy
- Polyubiquination at that site, however, may lead to endocytosis

Proteasomal degradation

- A proteasome is a large multi-20S subunit structure that binds to proteins tagged with ubiquitin.
- The tagged protein is unfolded and digested sequentially. Ubiquitin released to be used again.
- Deubiquinating enzymes are proteases that remove ubiquitin for reuse once proteins fate decided.
- Hydrolysis requires ATP.

Nucleotide catabolism

- Purines are salvaged by direct reaction with PRPP.
- Adenosine becomes AMP.
- Guanine and hypoxanthine are converted to GMP and IMP.
- Purines are degraded by removal of the sugar, removal of amino groups, and oxidation of the ring.
- Xanthine oxidase oxidizes the resulting bases hypoxanthine and xanthine to uric acid.

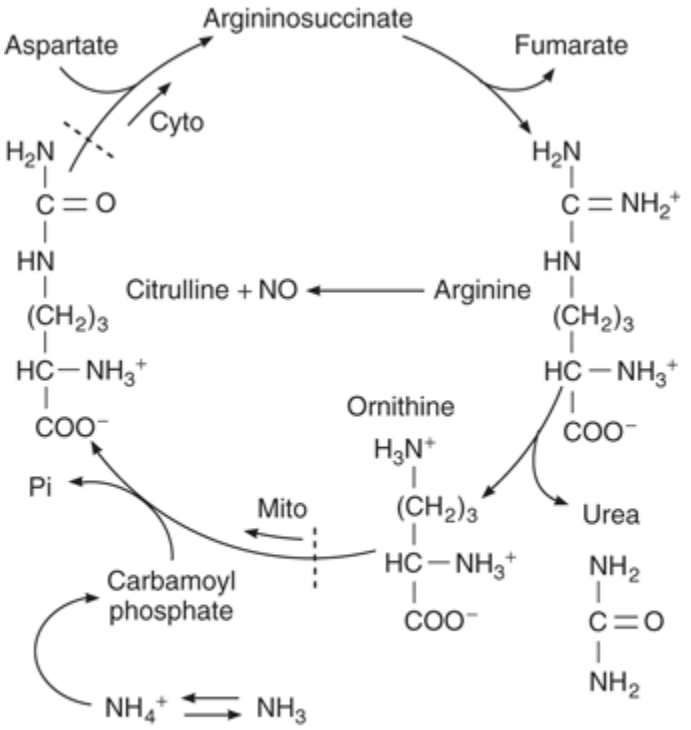
Nucleotide catabolism

- Pyrimidine salvage takes place in two steps:
- Base to nucleoside to nucleotide.
- Pyrimidine degradation consists of removal of the sugar, deamination, and opening of the ring.
- β-alanine (from uridine and cytosine) and β-aminoisoutyric acid (from thymidine) are the major products.

Protein catabolism

- The methylated and otherwise modified nucleotides and bases in tRNA are excreted intact without further metabolism.
- Amino acids cannot be stored and the excess are catabolized in the urea cycle.
- Ammonium ion (from amino acid cytosolic degradation) and carbon dioxide are phosphorylated in the mitochondrion to carbamoyl phosphate.
- This enters the cytosol and is used in the conversion of ornithine to citrulline which is then joined with aspartate to form arginosucinate.
- It is the rate limiting step.

Urea Cycle



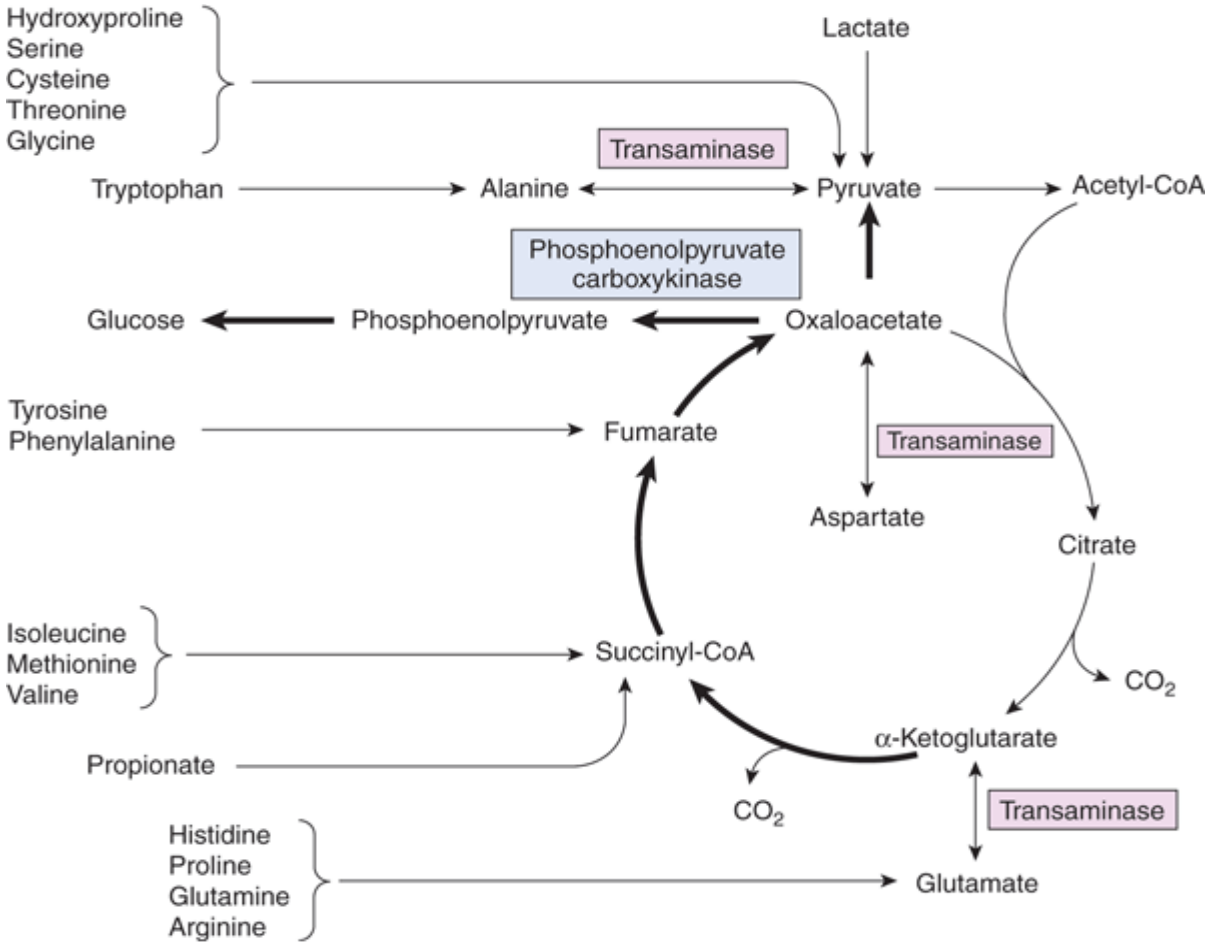
The overall reaction in the urea cycle consumes 3 ATP.

Fig. 1-20 Accessed 07/01/2010

Protein catabolism

- Further catabolism to arginine and fumarate occurs.
- Arginine is deaminated, producing ornithine and urea.
- Urea is then excreted.
- Fumarate then enters the TCA cycle.

Tricarboxylic acid cycle (Krebs cycle, citric acid cycle)



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

Fig. 1-19 Accessed 07/01/2010

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Protein assay techniques

Technique	Sample
Southern blot	DNA
northern blot	RNA
western blot	protein
ASO	DNA
ELISA	protein
microarray	RNA or cDNA

ELISA and microarray techniques do not employ gels.

Urea cycle disorders

- Dminiished ammonium ion excretion, arginine production.
- Lethargy, coma result.
- Carbamoyl phosphate synthetase (CPS1 gene)
- Accumulate N-acetyl glutamic acid in the mitochondrion.
- Orotic acid increases.
- Muscular hypotonia common
- Presents shortly after birth
- Ornithine transcarbamoylase (OTC). Most common defect. X-linked. Unable to convert to citrulline (in mitochondrion). Orotic acid increases.
- Argininosuccinate synthetase (ASA).

Urea cycle disorders

- Arginase deficiency
- ARG1 gene
- Poor growth
- Spasticity
- Mental retardation
- 1-3 years-of-age
- May be precipitated by high protein meal
- Urea not produced

Urea cycle disorders

- Arginosuccinic aciduria
- ASL gene at
- Newborns
- Arginosuccinate lysase deficiency
- Aspartic acid accumulates in cytoplasm
- Lethargy
- Poor temperature control
- Seizures

Urea cycle disorders

- Carbamoyl phosphate synthetase deficiency
- CPS1 gene at
- Accumulate N-acetyl glutamic acid in the mitochondrion.
- Orotic acid increases.
- Muscular hypotonia common
- Presents shortly after birth

Urea cycle disorders

- Ornithine transcarbamoylase
- OTC gene at X
- Most common defect.
- Unable to convert to citrulline (in mitochondrion).
- Glutamine levels elevated in serum
- Pyloric stenosis
- Splenomegaly
- Failure to thrive in newborn

Urea cycle disorders

- Type I citrullinemia
- ASS1 gene at
- Type II citrullinemia
- SLC25A13 gene at
- Neonatal onset
- (ornithine translocase deficiency)
- Adult onset
- Hepatic steatosis
- N-acetylglutamate synthase deficiency
- NAGS gene at

Amino acid transport disorders

- Cystinuria
- Cystine is 2 cysteines with disulfide bond.
- Three types of defects known.
- Each affects brush border amino acid b° transporter (basic amino acids).
- High levels of lysine, arginine, and ornithine in urine.
- Limit methionine ingestion.
- Cystine is least soluble of amino acids; can form kidney stones.

Amino acid transport disorders

- Cystinosis involves a defective transporter for lysozymes.
- Alkalinization and use of penicillamine chelation to control stone formation.
- Hartnup's disease results from defects in transporters of neutral amino acids.
- Loss of tryptophan.

Amino acid disorders

- Hyperhomocysteinemia
- Caused by enzyme defects in the methionine metabolism pathway
- Caused by either folate or B12 deficiency.
- Can also be caused by a defect in the enzyme that produces the N^5-methyl-FH_4.
- The N^5-methyl-tetrahydrofolate (N^5-CH_3-FH_4) gives its methyl group to B12, which then transfers it to homocysteine to turn it into methionine.

Homocystinuria

- Autsomal recessive.
- Cystathionine synthase deficiency.
- Increase dietary folate and B12 to ameliorate
- Or diminished affinity of cystathionine synthase for pyridoxal phosphate.
- Increase vitamin B6 in diet to ameliorate
- Or homocysteine methyltransferase deficiency.
- Mental retardation, osetoporosis, tall stature, kyphosis, downward and inward lens subluxation, accelerated atherosclerosis, arterial and venous thrombosis.
- Homocysteine in urine

Lesch-Nyhan syndrome

- Affects male children by the age of 2 years.
- Poorly coordinated, mentally retarded, extremely hostile, compulsive self-destructive tendencies.
- No treatment for the neurological symptoms.
- Elevated uric acid levels.

Lesch-Nyhan syndrome

- Hypoxanthine-Guanine phospho-ribosyl transferase deficiency increases hypoxanthine and guanine concentrations.
- Increased PRPP promotes de novo synthesis of purines.
- Increased uric acid production results.
- While hypoxanthine and xanthine can also produce crystals, it is the deposition of uric acid crystals and consequent inflammation that leads to tissue damage.
- Alleviate with allopurinol administration.

Orotic aciduria

- Orotate phosphoribosyl transferase deficiency leads to failure of generation of uracil monophosphate (from aspartate) and, thus, cytosine and thymidine phosphorylated nucleotides.
- Failure to thrive, developmental retardation.
- Sparse hair, cardiac malformations, bilateral strabismus, inability to sit unaided.
- Megaloblastic anemia and stone formation.
- Abnormalities of immune function.

Orotic aciduria

- Depletion of CDP-ethanolamine and CDP-choline, necessary for phospholipid synthesis as well as depletion of UDP sugars necessary for galactose utilization and glycogen formation proposed as the basis for the skeletal muscle weakness noted.

Other clinical disorders

- Purine nucleoside phosphorylase deficiency increases deoxyguanosine which is converted back to dGTP.
- Synthesis of dCTP and dTTP is blocked.
- T cell function is impaired.

Other clinical disorders

- Adenosine deaminase deficiency increases deoxyadenosine and this is converted back to dATP.
- Synthesis of dCTP, dUTP, dGTP is blocked.
- 2'-deoxyadenosine also inhibits S-adenosylhomocysteine hydrolase which decreases methylation reactions vital to normal cell function.
- T and B cell function is impaired.

Phenylketonuria

- Phenylalanine hydroxylase gene defect.
- Autosomal recessive
- No conversion to tyrosine.
- Increase tyrosine in diet to ameliorate
- High phenylalanine levels disrupt protein synthesis, brain myelination.
- Eventually produces retardation.
- Decreased melanin formation (eye, skin lesions).
- Oxidized homogentisate discolors urine and deposits in joints, causing arthritis.
- Musty body order.

Phenylketonuria

- Phenylalanine is essential.
- Tyrosine is not essential except in phenylalanine deficiency.
- Hydroxylation of phenylalanine requires tetrahydrobiopterin (THB), a co-enzyme made from GTP.
- A defect in THB synthesis will also cause a pheynylketonuria type illness.
- Also needed for nitric oxide synthase (pain).
- Products are fumarate (glucogenic) and acetyl-CoA (ketogenic).
- THB deficiency will not respond to dietary therapy.

Other disorders

- Alkaptonuria (ochronosis).
- Autosomal recessive.
- Deficiency of homogentisic acid oxidase in degradative pathway of tyrosine.
- Dark connective tissue; pigmented sclera.
- Urine turns black on standing.
- Albinism.
- Autsomal recessive.
- Deficiency of tyrosinase (inability to synthesize melanin) or tyrosine transporters.
- Ocular albinism is an X-lined recessive disorder.

Maple syrup urine disease

- The carbons of the essential amino acids valine and isoleucine can be converted to Succinyl-CoA. (glucogenic).
- Isoleucine and leucine produce Acetyl-CoA (ketogenic)
- A defect in branched chain α-ketodehydrogenase. High levels of α-ketogenic acids contribute to neurological deficit.
- Urine smells like maple syrup.