iv. Chemistry and metabolism of Proteins and Amino acids...

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Chemistry and Metabolism of Proteins and Amino Acids

Amino Acid Structure and Classification

1. **General Structure**
   - Each amino acid has a central (α) carbon, an amino group ($-NH_2$), a carboxyl group (–COOH), a hydrogen atom, and a variable side chain (R-group).
   - At physiological pH (~7.4), the amino group is protonated ($-NH_3^+$) and the carboxyl group is deprotonated ($-COO^-$), making amino acids zwitterions.
2. **Classification**
   - **Nonpolar (Hydrophobic)**: e.g., Ala, Val, Leu, Ile, Phe.
   - **Polar, Uncharged**: e.g., Ser, Thr, Asn, Gln, Tyr.
   - **Positively Charged (Basic)**: Lys, Arg, His.
   - **Negatively Charged (Acidic)**: Asp, Glu.
3. **Essential vs. Nonessential Amino Acids**
   - Humans can synthesize some amino acids (**nonessential**); others (**essential**, e.g., Val, Leu, Ile, Lys, etc.) must be obtained from the diet.
   - Semi-essential or conditionally essential amino acids (e.g., Arg, His) may be required in certain physiological states (e.g., infancy).

Protein Turnover and Amino Acid Metabolism

1. **Protein Turnover**
   - Continuous synthesis and degradation of proteins; helps maintain amino acid pools and remove damaged or misfolded proteins.
   - **Ubiquitin–Proteasome System** and **Autophagy–Lysosome Pathway** key to selective protein degradation.
2. **Amino Acid Catabolism**
   - **Transamination**: Transfer of α-amino group to α-ketoglutarate, forming glutamate and an α-keto acid (catalyzed by transaminases).
   - **Deamination**: Removal of the amino group (e.g., oxidative deamination by glutamate dehydrogenase).
   - **Urea Cycle**: Detoxifies ammonia into urea (ornithine cycle in the liver). Dysfunction leads to hyperammonemia.
3. **Carbon Skeleton Utilization**
   - **Glucogenic** amino acids: Carbon skeletons can yield substrates for gluconeogenesis (e.g., pyruvate, TCA intermediates).
   - **Ketogenic** amino acids: Carbon skeletons form acetyl-CoA or acetoacetyl-CoA, can generate ketone bodies or lipids (e.g., Leu, Lys).
   - Some are both glucogenic and ketogenic (e.g., Ile, Phe, Tyr, Trp).

Ramachandran Plot

1. **Definition and Utility**
   - A Ramachandran plot plots the dihedral angles **ϕ (phi)** (N–Cα) vs. **ψ (psi)** (Cα–C′) for amino acid residues in a polypeptide.
   - Conformational space is restricted by steric hindrance, so only certain angle combinations are energetically allowed (e.g., α-helical, β-sheet, collagen triple helix regions).
2. **Significance**
   - Helps evaluate protein structures (e.g., from X-ray crystallography or NMR) for sterically disallowed

conformations that indicate errors.
  - Gly and Pro are exceptions: **Gly** is more flexible, **Pro** is more restricted due to its ring structure.

Levels of Protein Structure

Primary Structure

- **Definition**: The linear sequence of amino acids in a polypeptide chain, read from the N-terminus to the C-terminus.
- **Importance**: Determines how the chain folds and what higher-order structures form.
- **Peptide Bond Properties**: Partial double-bond character (resonance) restricts rotation, typically in trans configuration except for certain X–Pro bonds.

Secondary Structure

1. **α-Helix**
   - Right-handed helix stabilized by **intrachain hydrogen bonds** (C=O of residue n with N–H of residue n+4).
   - Side chains project outward. Proline disrupts α-helices; Gly can increase flexibility.
2. **β-Sheet**
   - **Extended conformation** stabilized by hydrogen bonds between backbone amides of adjacent strands.
   - Can be **parallel** or **antiparallel**. Side chains alternate above and below the sheet.
3. **Turns and Loops**
   - **β-Turns** reverse the polypeptide direction, often found on protein surfaces.
   - Essential for compact folding, connecting secondary structure elements.

Tertiary Structure

- **Definition**: The overall 3D conformation of a single polypeptide chain, including interactions among side chains (hydrophobic effects, hydrogen bonds, ionic interactions, disulfide bonds).
- **Domains**: Distinct structural/functional units within a polypeptide.
- **Stabilizing Forces**: Hydrophobic core, salt bridges, hydrogen bonds, **disulfide bonds** (covalent links between cysteine residues), metal ion coordination.

Quaternary Structure

- **Definition**: Assembly of multiple polypeptide subunits into a functional complex (e.g., hemoglobin's $\alpha 2\beta 2$ structure).
- **Forces**: Similar noncovalent interactions as tertiary structure; sometimes disulfide bonds.
- **Functional Significance**: Cooperativity, allostery, subunit regulation, structural stability.

Mechanisms and Specificity of Enzymes

Enzyme Kinetics and Catalysis

1. **Active Site**
   - Specialized pocket where substrate binding and catalysis occur. Conformational changes can enhance substrate alignment (induced fit).
2. **Transition State Stabilization**
   - Lowering activation energy (ΔG^‡) is central to catalysis. Enzymes often bind transition states more tightly than substrates, fostering product formation.
3. **Michaelis–Menten Kinetics**
   - v=Vmax[S]Km+[S]v = \frac{V_{\max} [S]}{K_m + [S]}v=Km+[S]Vmax[S].
   - **K_m** (Michaelis constant) relates to substrate affinity; **V_{\max}** is maximum rate at saturating [S].
4. **Catalytic Mechanisms**
   - Acid–base catalysis, covalent catalysis, metal ion catalysis, proximity/orientation effects.

Specificity and Regulation

1. **Substrate Specificity**
   - Determined by shape, charge, polarity of the active site.
   - **Lock-and-key** vs. **Induced fit** models.
2. **Allosteric Regulation**
   - Effector molecules bind sites other than the active site, altering enzyme activity.
   - Sigmoidal kinetics typical of cooperative enzymes (e.g., ATCase in pyrimidine synthesis).
3. **Covalent Modification**
   - Phosphorylation, methylation, acetylation modulate enzyme activity.
   - Zymogen activation by proteolytic cleavage (e.g., trypsinogen → trypsin).

Coenzymes and Cofactors

1. **Definition**
   - **Cofactors**: Non-protein chemical compounds (metal ions or organic molecules) required for enzymatic activity.
   - **Coenzymes**: Organic cofactors (often derived from vitamins) that transiently associate with the enzyme (e.g., NAD^+ from niacin).
2. **Examples**
   - **Metal Ions**: Fe^{2+}, Zn^{2+}, Mg^{2+} in various enzymes (e.g., iron in cytochromes).
   - **Vitamins**: B vitamins → coenzyme forms (e.g., Thiamine pyrophosphate (B1), FAD (B2), NAD^+ (B3), CoA (B5), Pyridoxal phosphate (B6), Biotin (B7), Folate derivatives (B9), Cobalamin (B12)).
3. **Function**
   - Participate in redox reactions, group transfers, electron carriers, assisting in enzyme conformational changes.
   - **NAD^+/NADH** and **FAD/$FADH_2$** vital for oxidative metabolism.
   - **CoA** for acyl group transfers, etc.

Disorders Associated with Protein and Amino Acid Metabolism

Amino Acid Metabolic Defects

1. **Phenylketonuria (PKU)**
   - Deficiency of **phenylalanine hydroxylase** or tetrahydrobiopterin cofactor. Elevated phenylalanine → neurological damage if untreated.
   - Dietary phenylalanine restriction essential.
2. **Maple Syrup Urine Disease (MSUD)**
   - Defect in branched-chain α-ketoacid dehydrogenase complex. Accumulation of Leu, Ile, Val and their α-keto acids leads to neurological symptoms.
   - Control via dietary restriction of branched-chain AAs.
3. **Alkaptonuria**
   - Defect in **homogentisate oxidase**, leading to buildup of homogentisic acid. Characterized by dark urine on standing, ochronosis (pigmentation in cartilage).
4. **Homocystinuria**
   - Often due to **cystathionine β-synthase** deficiency. High homocysteine can cause cardiovascular and connective tissue problems.
   - B6 supplementation, dietary methionine/homocysteine management.

Urea Cycle Disorders

- **Ornithine Transcarbamylase (OTC) Deficiency**: X-linked, leads to hyperammonemia, elevated orotic acid.
- Other enzyme defects (e.g., carbamoyl phosphate synthetase I deficiency) also cause hyperammonemia, neurotoxicity.

Protein Misfolding and Aggregation

- **Neurodegenerative Diseases**: Alzheimer's (β-amyloid), Parkinson's (α-synuclein), prion diseases (PrP^{Sc}).
- Protein quality control failures (chaperones, proteasome) implicated in pathology.

Proteomics

Definition and Approaches

1. **Proteomics**: The large-scale study of the entire set of proteins (proteome) expressed by a cell, tissue, or organism, including their modifications, interactions, and functions.
2. **Techniques**
    - **2D Gel Electrophoresis**: Separate proteins by isoelectric point (pI) and molecular weight.
    - **Mass Spectrometry**: Identify proteins/peptides (e.g., MALDI-TOF, LC-MS/MS).
    - **Protein Microarrays** or **Affinity-based methods**: Assess protein–protein or protein–ligand interactions.

Biological and Clinical Significance

1. **Biomarker Discovery**
    - Proteomic profiles in diseases (e.g., cancer) can reveal diagnostic or prognostic markers.
2. **Functional Proteomics**
    - Identification of protein–protein interaction networks, post-translational modifications (phosphorylation, glycosylation, etc.).
3. **Systems Biology Integration**
    - Proteomics complements genomics and metabolomics to yield a holistic view of cellular function and disease mechanisms.

Concluding Remarks

Proteins and amino acids are central to life's chemistry, fulfilling roles in **enzymatic catalysis**, **structural frameworks**, **signaling**, and **transport**. Their **primary** sequence determines higher-level folding (secondary, tertiary, quaternary), governed by **steric constraints** (Ramachandran plot) and diverse **intermolecular interactions**. **Enzymes** exemplify the sophistication of **specificity and catalysis**, often reliant on **cofactors** and **coenzymes** derived from dietary vitamins and minerals.

Disorders in **protein/amino acid metabolism**—from enzymatic defects (e.g., PKU, MSUD, urea cycle deficiencies) to misfolded protein aggregation—underscore the delicate balance required for normal physiology. Finally, **proteomics** offers an unparalleled lens through which to interrogate protein expression, modifications, and interactions on a systems-wide scale, paving the way for **precision medicine** and deeper insights into the molecular underpinnings of health and disease.