Misfolded Proteins

Misfolded proteins are aberrantly folded proteins that fail to achieve their functional three-dimensional structure. This misfolding disrupts their normal function and often leads to aggregation, which is a hallmark of many neurodegenerative diseases.

Protein Folding Basics

- Proteins must fold into specific three-dimensional shapes to perform their biological functions.
- Folding is guided by:
    1. **Amino acid sequence** (primary structure).
    2. Interactions such as hydrogen bonding, hydrophobic interactions, and ionic bonds.
- Assisted by **chaperone proteins** to prevent misfolding and aggregation.

Causes of Protein Misfolding

1. **Genetic Mutations**: Single-point mutations can destabilize protein folding (e.g., mutation in **SOD1** in ALS).
2. **Post-translational Modifications**: Aberrant phosphorylation, glycation, or oxidation (e.g., hyperphosphorylated tau in Alzheimer's).
3. **Cellular Stress**: Oxidative stress, inflammation, or changes in pH.
4. **Aging**: Decline in protein quality control mechanisms, including chaperones and proteasomes.

Consequences of Protein Misfolding

1. **Loss of Function**: Misfolded proteins cannot perform their normal roles (e.g., prion protein in Creutzfeldt-Jakob disease).
2. **Gain of Toxic Function**: Misfolded proteins form toxic aggregates that interfere with cellular processes (e.g., beta-amyloid plaques in Alzheimer's).
3. **Aggregation and Inclusion Bodies**:
    1. Alzheimer's disease: Beta-amyloid plaques and tau tangles.
    2. Parkinson's disease: Alpha-synuclein aggregates (Lewy bodies).
    3. Huntington's disease: Mutant huntingtin protein aggregates.

Mechanisms of Toxicity

- **Membrane Damage**: Misfolded proteins disrupt cell membranes, causing ion leakage and cellular stress.
- **Disruption of Cellular Processes**: Inhibit proteasome activity, autophagy, and mitochondrial function.
- **Neuroinflammation**: Activation of microglia and astrocytes exacerbates damage.

Protein Quality Control Systems

To maintain proteostasis (protein homeostasis), cells employ:

1. **Molecular Chaperones**: Help proteins fold correctly (e.g., heat shock proteins).
2. **Ubiquitin-Proteasome System (UPS)**: Tags misfolded proteins with ubiquitin for degradation.
3. **Autophagy-Lysosomal Pathway**: Degrades aggregated proteins and damaged organelles.
4. **Endoplasmic Reticulum-Associated Degradation (ERAD)**: Clears misfolded proteins from the ER.

Misfolded Protein-Related Neurodegenerative Diseases

Disease	**Misfolded Protein**	**Aggregation Type**		
Alzheimer’s disease	Beta-amyloid, Tau	Plaques, Neurofibrillary tangles		
Parkinson’s disease	Alpha-synuclein	Lewy bodies		
Huntington’s disease	Mutant huntingtin	Polyglutamine inclusions		
ALS	SOD1, TDP-43, FUS	Cytoplasmic inclusions		
Prion diseases	Prion protein (PrP	**Sc**	**)**	Amyloid plaques

Therapeutic Approaches

1. **Reducing Misfolding**: Chaperone-based therapies (e.g., HSP inducers).
2. **Promoting Clearance**: Enhancing autophagy or proteasome activity (e.g., ambroxol for Parkinson’s).
3. **Preventing Aggregation**:
    1. Monoclonal antibodies against misfolded proteins (e.g., lecanemab for beta-amyloid in Alzheimer’s).
4. **Small Molecule Stabilizers**: Stabilize the native conformation of proteins (e.g., tafamidis for transthyretin amyloidosis).
5. **Gene Therapy**: Correcting genetic defects.
6. **Immunotherapy**: Vaccines targeting misfolded proteins to stimulate clearance.

Emerging Research

1. **Structural Biology**: Advanced imaging techniques (e.g., cryo-EM) to study protein aggregates.
2. **Artificial Intelligence**: Predicting misfolding patterns and designing interventions.
3. **Gene Editing**: Correcting mutations associated with misfolding (e.g., CRISPR).