

Protein Folding and Human Diseases

Proteins are by far the most abundant class of macromolecules in cells (approximately 50% of dry mass) and are involved in nearly all aspects of cell structure and physiology. Protein (or polypeptides) is assembled from a set of 20 different amino acids, each linked to its neighbor through a chemical “peptide” bond. Initially, proteins are translated as linear polypeptide chains. However, to perform their intended functions, these chains must first fold into precise three-dimensional configurations. The process of protein folding requires assistance from proteins collectively referred to as the “protein folding machinery”. The critical nature of protein folding capacity is underscored by several human genetic disorders (eg. cystic fibrosis, type 2 diabetes) where this process is mis-regulated. In this class, we will be reading various papers describing how protein folding affects human health and causes varieties of human diseases.

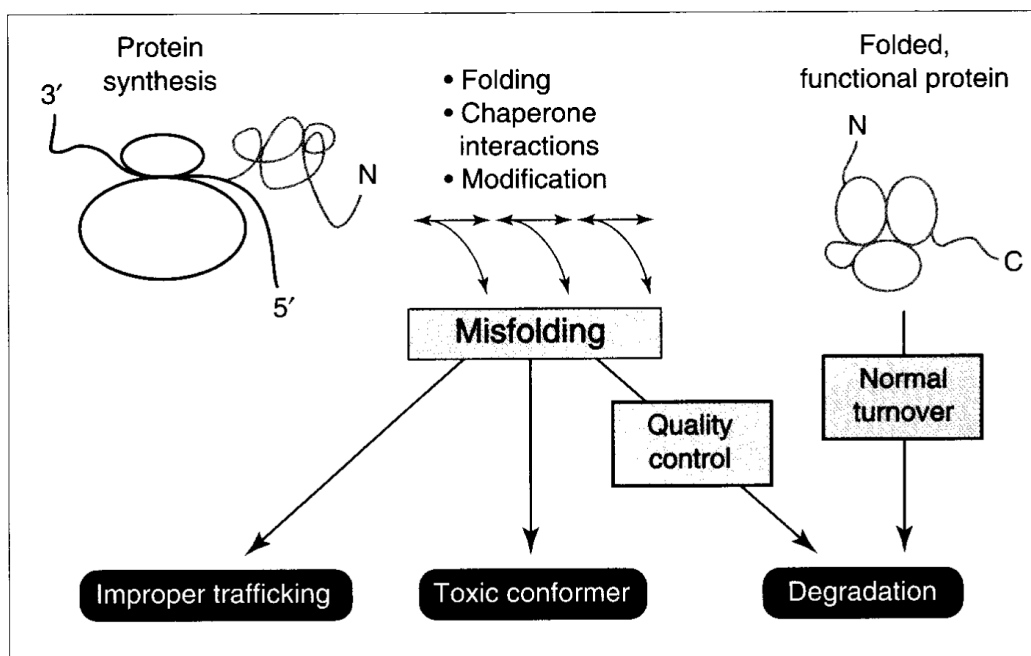


Figure 1

Diversity of protein misfolding in disease. The ability of a protein to perform its function in the cell depends upon its ability to assume a functional conformation. Thus, mutations and environmental changes that destabilize the native state, or divert proteins from their normal folding pathway, underlie several human diseases. For example, alteration of the thermodynamic stabilities of the native state and crucial folding intermediates may prevent folding into the functional conformation on a biological time scale. The cell's quality control apparatus must then recognize the misfolded and partially folded products and mark them for recycling. Off-pathway traps can be caused by aggregation, mistargeting into an inappropriate cellular location, or proteolysis of the polypeptide. Proteins and peptides that are aggregated into amyloid plaques are often resistant to degradation. Furthermore, the formation of these deposits, rather than the lack of native protein, may be responsible for the cellular pathology. (*TIBS 20, 456, 1995*)

Overview of the class:

Presentation Sign Up

You will sign up to present a scientific paper as a small group (2 people). A list of papers and dates will be posted on the website during the first week on the class website (see below) and you can sign up after the 2nd lecture (1/10/2011). The papers for each week will be posted on the website as well.

Midterm and Final Exams

We will not have mid-term or final exams but you are graded based on both your attendance & **participation** and evaluation on your presentation.

In addition to attendance and presentation of the paper, your final grade will be determined based on your participation including asking questions or participation in discussion during the class.

How to prepare for presentation:

1. Based on the sign up, I will announce a schedule of presenters during the 2nd week (on 1/13/2011) on the class website
2. Presentation does not have to be a powerpoint presentation but the classroom has a set-up for both powerpoint and overhead presentation.

*Mac users will need to bring an adaptor for projector. Note that different Mac uses different adaptor.
3. Office Hour: During the preparation of presentation, I will meet with you (as a group) upon request.

Before you make an appointment, however, I would like you to do the following:

- (1) Read the paper carefully
- (2) Get together with your fellow presenter(s) to discuss the paper and prepare the presentation.
- (3) After that, if you wish, one of you will e-mail me to make an appointment. For example, I prefer meeting with you either Thursday or Friday afternoon. This way, your group will have time to complete your preparation over the weekend before your presentation on Monday.
4. Evaluation: After each presentation, I will give everybody in the class an evaluation form to fill out. I will make the evaluation available to the presenters and you can read about what your classmates thought of your

presentation. In addition, if you would like, I will meet with you for my evaluation upon request. Please make an appointment with me.

5. For each paper, I would like you to discuss the following issues.
 - a. Brief overview-----What was the point of the paper?
 - b. Introduction-----I would like you to discuss specific biological process (or mechanism) that the paper is discussing. For example, if the paper is generally talking about regulation of translation, I would like you to discuss briefly mechanism (or steps) of translation, components or regulatory steps known to take place during translation, and what is the specific question(s) being asked in the paper?
 - c. Question(s)-----What is the question(s) that the authors wanted to address? And why such question is important for human health?
 - d. Results section-----I would like you to discuss results of the experiments described in each figures. If there are multiple panels, discuss individually. I will discuss this in detail during the 2nd (1/10/2011) lecture.

Important points to consider:

- *What did the authors want to demonstrate?
 - *What was the experimental method?
 - *What were the results (which band(s) on the gel or which signals in the microscope picture demonstrate their conclusion?)
 - *What was the conclusion(s) drawn from each figure? Do you agree with their conclusion? --(Is the data convincingly clear? Or can you see the same changes (or no change) that the authors claim?)
 - *Is there other experimental method to demonstrate the same issue? And if so, why one may be better than the other?
- e. Discussion-----
 - *What were the overall conclusion(s) drawn from the entire paper?
 - *Do you agree with the authors conclusions overall? And why?
 - *What other questions need to be addressed or what is next? --Is there anything missing from the paper?