

Chem 452 - Lecture 2

Protein Structure

Part 4

Question of the Day: How is online video game-playing is being used to help find cures for diseases?

Protein Folding

† The primary structure determines the other levels of structure.

- Christian Anfinsen demonstrated this in the 1950's

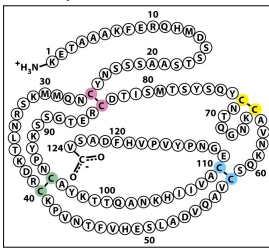


Christian Anfinsen
1972 Nobel Prize in Chemistry

Chem 452, Lecture 2 - Protein Structure 2

Protein Folding

† Anfinsen's Experiment

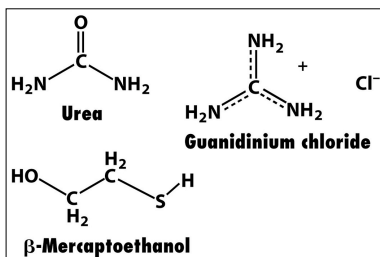


Bovine Ribonuclease A

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Protein Folding

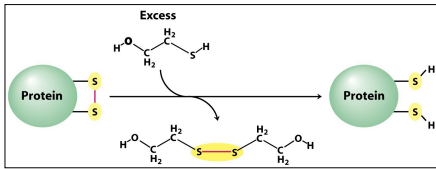
† Anfinsen's Experiment



Chem 452, Lecture 2 - Protein Structure 4

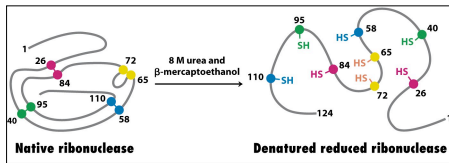
Protein Folding

+ Anfinsen's Experiment



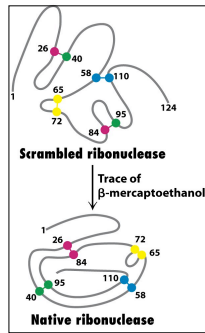
Protein Folding

+ Anfinsen's Experiment



Protein Folding

+ Anfinsen's Experiment



Protein Folding

+ The primary structure determines the other levels of structure.

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Christian Anfinsen
1972 Nobel Prize in Chemistry

Protein Folding

...we have occasionally called (9) the "thermodynamic hypothesis." This hypothesis states that the three-dimensional structure of a native protein in its normal physiological milieu (solvent, pH, ionic strength, presence of other components such as metal ions or prosthetic groups, temperature, and other) is the one in which the Gibbs free energy of the whole system is lowest; that is, that the native conformation is determined by the totality of interatomic interactions and hence by the amino acid sequence, in a given environment. ...



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1972 Nobel Prize in Chemistry

Protein Folding

DNA proposed structures

♦ Watson & Crick's DNA structure also made biological sense:

- ♦ "However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined?"
- ♦ "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material."



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1972 Nobel Prize in Chemistry

Protein Folding

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Protein Folding

♦ The primary structure determines the other levels of structure.

... In terms of natural selection through the "design" of macromolecules during evolution, this idea emphasized the fact that a protein molecule only makes stable, structural sense when it exists under conditions similar to those for which it was selected—the so-called physiological state.



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Protein Folding

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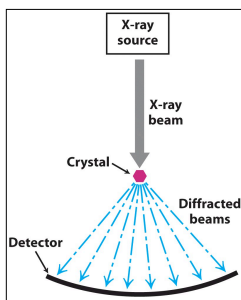
Christian Anfinsen
1972 Nobel Prize in Chemistry

Protein 3-Dimensional Structures

† The first proteins to have their 3-D structures determined were determined in the late 1950's myoglobin and hemoglobin.

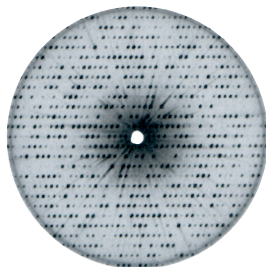
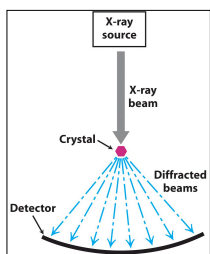
Protein 3-Dimensional Structures

† X-ray crystallography (Section 3.6)



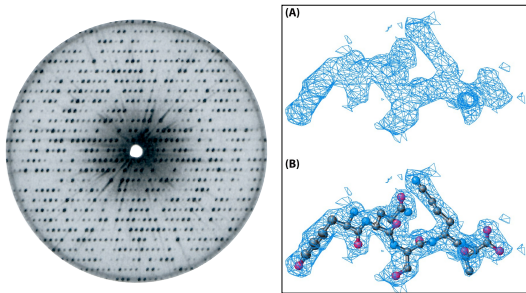
Protein 3-Dimensional Structures

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Protein 3-Dimensional Structures

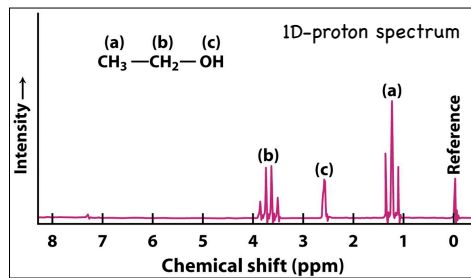
+ X-ray crystallography (Section 3.6)



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Protein 3-Dimensional Structures

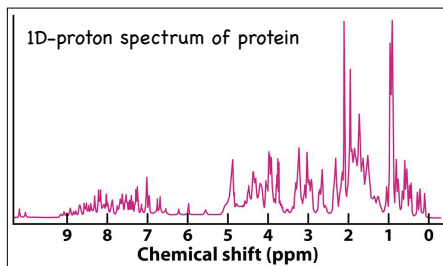
+ NMR Spectroscopy (Section 3.6)



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Protein 3-Dimensional Structures

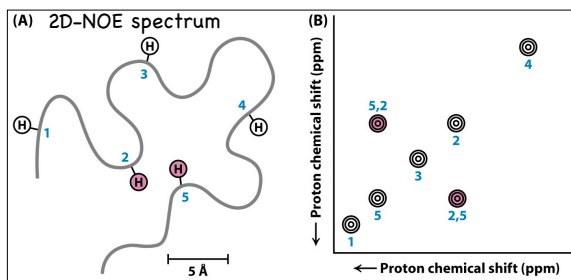
+ NMR Spectroscopy (Section 3.6)



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Protein 3-Dimensional Structures

+ NMR Spectroscopy (Section 3.6)

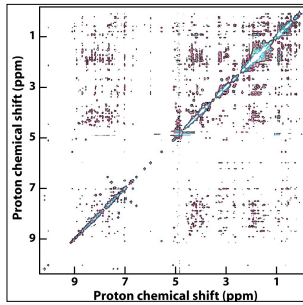


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Protein 3-Dimensional Structures

+ NMR Spectroscopy (Section 3.6)

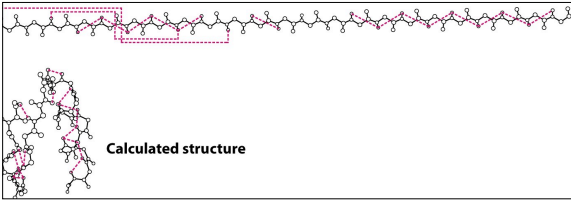
2D-NOE spectrum



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Protein 3-Dimensional Structures

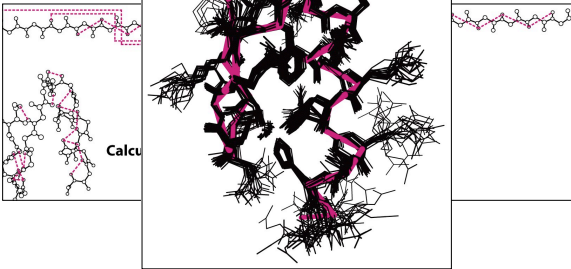
+ NMR Spectroscopy (Section 3.6)



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Protein 3-Dimensional Structures

+ NMR Spectroscopy (Section 3.6)



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Protein 3-Dimensional Structures

+ Prediction from amino acid sequence

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Protein 3-Dimensional Structures

TABLE 2.3 Relative frequencies of amino acid residues in secondary structures

| Amino acid | α helix | β sheet | Reverse turn |
|------------|----------------|---------------|--------------|
| Glu | 1.59 | 0.52 | 1.01 |
| Ala | 1.41 | 0.72 | 0.82 |
| Leu | 1.34 | 1.22 | 0.57 |
| Met | 1.30 | 1.14 | 0.52 |
| Gln | 1.27 | 0.98 | 0.84 |
| Lys | 1.23 | 0.69 | 1.07 |
| Arg | 1.21 | 0.84 | 0.90 |
| His | 1.05 | 0.80 | 0.81 |
| Val | 0.90 | 1.87 | 0.41 |
| Ile | 1.09 | 1.47 | 0.47 |
| Tyr | 0.74 | 1.45 | 0.76 |
| Cys | 0.66 | 1.40 | 0.54 |
| Trp | 1.02 | 1.35 | 0.65 |
| Phe | 1.16 | 1.33 | 0.59 |
| Thr | 0.76 | 1.17 | 0.96 |
| Gly | 0.43 | 0.58 | 1.77 |
| Asn | 0.76 | 0.48 | 1.34 |
| Pro | 0.34 | 0.31 | 1.22 |
| Ser | 0.57 | 0.96 | 1.22 |
| Asp | 0.99 | 0.39 | 1.24 |

NOTE: The amino acids are grouped according to their preference for α helices (top group), β sheets (second group), or turns (third group).
SOURCE: T. E. Creighton, *Proteins: Structures and Molecular Properties*, 2d ed. (W. H. Freeman and Company, 1992), p. 256.

Protein 3-Dimensional Structures

- + Predicting a 3-D structure (tertiary structure) by analyzing the amino acid sequence (primary structure)
- By comparison to structures found in the protein data bank.

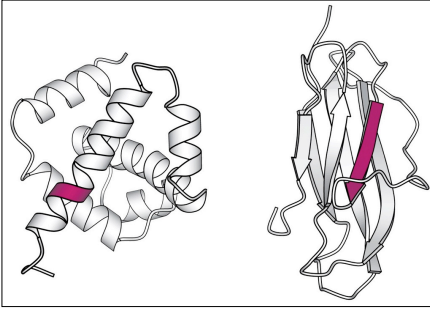
Protein 3-Dimensional Structures

The screenshot shows the PDB website interface. At the top, there's a search bar with 'PDB-101' entered. Below the search bar, there are navigation options like 'All Categories', 'Author', 'Molecule', 'Sequence', and 'Ligand'. The main content area features a 'Biological Macromolecular Resource' section with a 'Full Description' and 'Structural View of Biology' options. A 'Molecule of the Month' section highlights the 'Pyruvate Dehydrogenase Complex'. The page also includes a sidebar with 'New Structures', 'New Features', and 'SOAP Service Retirement in 2013'.

Protein 3-Dimensional Structures

- + Predicting a 3-D structure (tertiary structure) by analyzing the amino acid sequence (primary structure)
- By comparison to structures found in the protein data bank.

Protein 3-Dimensional Structures



The sequence VDLLKN

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Protein 3-Dimensional Structures

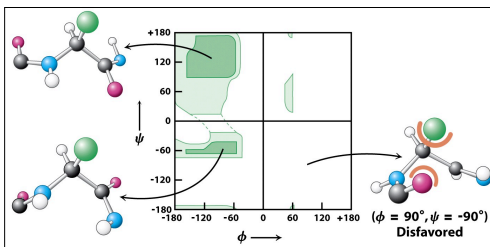
+ Predicting a 3-D structure (tertiary structure) by analyzing the amino acid sequence (primary structure)

- By comparison to structures found in the protein data bank. Text†
- By searching for the structure with the lowest free energy.
- Rosetta@Home

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Protein 3-Dimensional Structures

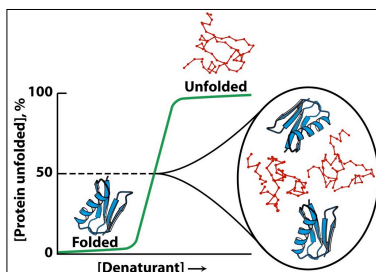
+ The Levinthal Paradox



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Protein Folding

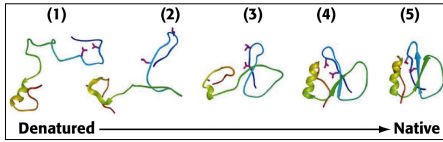
+ Proteins folding is highly cooperative



Chem 452, Lecture 2 - Protein Structure 24

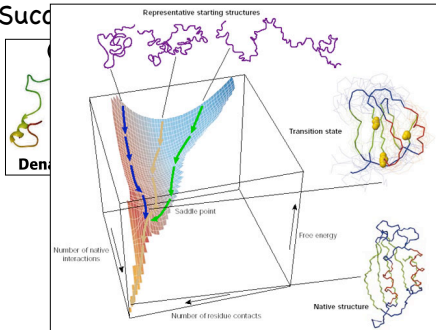
Protein 3-Dimensional Structures

+ Successive Stabilization



Protein 3-Dimensional Structures

+ Succ



Protein 3-Dimensional Structures

+ Predicting a 3-D structure (tertiary structure) by analyzing the amino acid sequence (primary structure)

- By comparison to structures found in the protein data bank.
- By searching for the structure with the lowest free energy.
- + Rosetta@Home

Protein 3-Dimensional Structures

+ Predicting a 3-D structure (tertiary structure) by analyzing the amino acid

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Protein 3-Dimensional Structures

Join Rosetta@home

1. Read and install
2. Submit your first puzzle
3. Download, install, and run Rosetta
4. & Complete your first puzzle

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Protein 3-Dimensional Structures

+ Predicting a 3-D structure (tertiary structure) by analyzing the amino acid sequence

- By using Rosetta@home
- By using Foldit

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Protein 3-Dimensional Structures

+ Taking Rosetta one step further with Foldit, by turning structure prediction into an online video game!!

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foldit
Solve Puzzles for Science

GET STARTED: DOWNLOAD

Windows 32-bit
Mac OS X
Linux

RECOMMEND FOLDIT

USER LOGIN

Username *

Password *

Log in

Create new account
Request new password
Sign in using Facebook

What's New

Small Update

We've posted a small update today that should improve some of the introductory 'tutorials'.

(Sun, 09/25/2011 - 01:25) | 8 comments | Share

Puzzle deadlines extended, global chat help

We have extended the deadline for the Beginner Puzzle and Puzzle 439 by 3 days (due to all the new visitors to the site).

Again, welcome to all the new Foldit players. We are working on improving the server response time. If you are having trouble with global chat, you may need to use an IRC client to access chat: http://tost.wiki.com/wiki/268_8 IRC_chat_information

(Thu, 09/22/2011 - 10:25) | 2 comments | Share

Server status

Due to the high volume of new visitors to the site, response times from the server are slow and some features of the site are disabled. We're working on improving the server response time. Thanks to your patience!

(Mon, 09/19/2011 - 19:37) | 3 comments | Share

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Protein 3-Dimensional Structures

• The Protein Data Bank (PDB) is an online database of 3-dimensional structures.

- It includes not only proteins, but other biological structures, such as nucleic acids and even whole virus particles.

Protein 3-Dimensional Structures

www.rcsb.org

PROTEIN DATA BANK

Search

Biological Macromolecular Resource

Holecule of the Month

Pyruvate Dehydrogenase Complex

A multienzyme complex involved in the catabolism of pyruvate to acetyl-CoA. The complex performs a central step in energy production, catalyzing the reaction that links glycolysis with the tricarboxylic acid cycle. The reaction is performed in three separate steps by three separate enzymes, but all three enzymes are linked efficiently together into one large multienzyme complex.

Full Article

Bacterial Phosphotransferase System

Bacteria are strictly cells. They often live in anaerobic environments, and many live in places with no oxygen, so their options for generating energy are limited. So, bacteria have developed their own means of living off of substrate available, and expanding these resources to their best advantage. The bacterial phosphotransferase system, often abbreviated as 'ptg', is a perfect example of both the opportunistic nature of bacterial life, and their flexible use of resources.

Full Article / Archive / PDB Structural Biology Knowledgebase

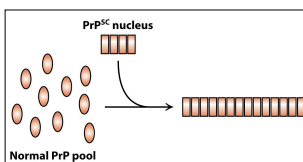
Protein Misfolding

• What happens when a protein misbehave and misfold.

- Prions
 - Mad Cow Disease (Bovine spongiform encephalopathy, BSE)
 - Creutzfeld-Jakob disease (CJD)
 - Scrapies
 - Chronic Wasting Disease (CWD)
- Alzheimer's Disease

Protein Misfolding

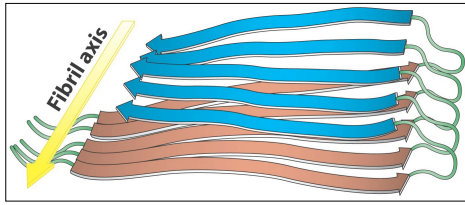
• Prions



Stanley Prusiner
1997 Nobel Prize in Medicine

Protein Misfolding

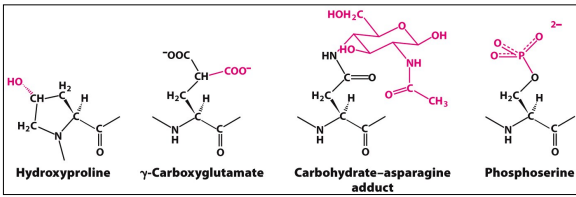
+ Alzheimer's Disease



Amyloid β -fibrils

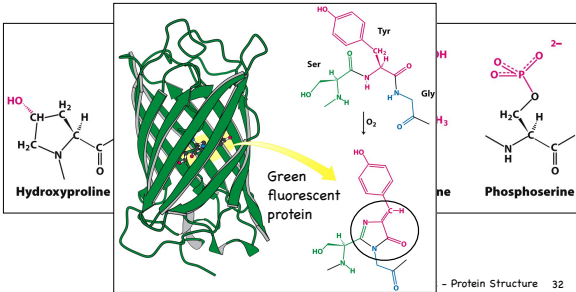
Modifications to the Primary Structure

+ Many proteins and peptides undergo post translational modifications



Modifications to the Primary Structure

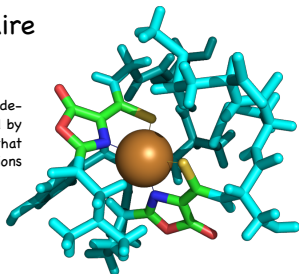
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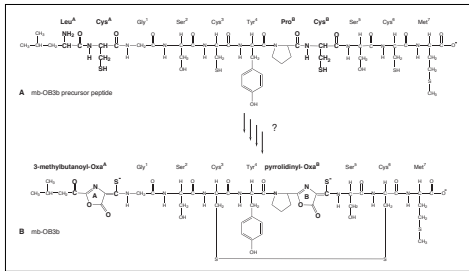
+ Some post translational modifications that we have discovered here at UW-Eau Claire

Methanobactins are peptide-derived molecules produced by methane oxidizing bacteria that are scavengers for copper ions



Modifications to the Primary Structure

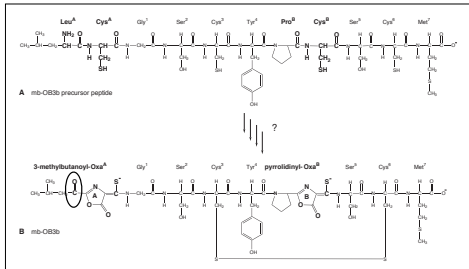
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Modifications to the Primary Structure

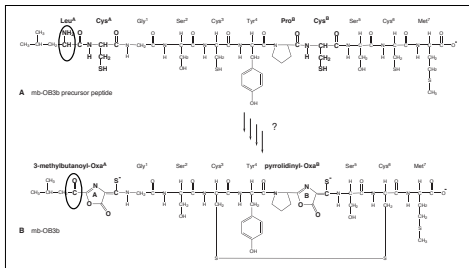
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Modifications to the Primary Structure

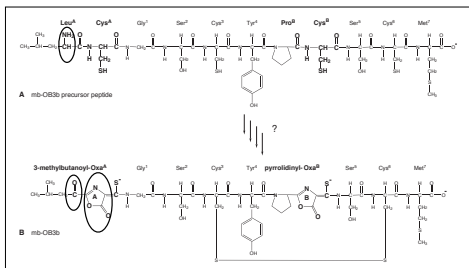
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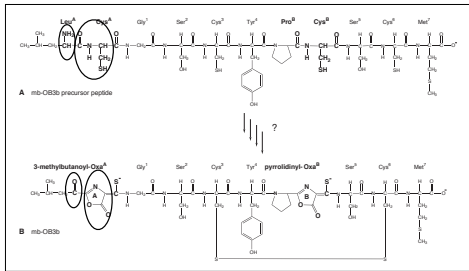
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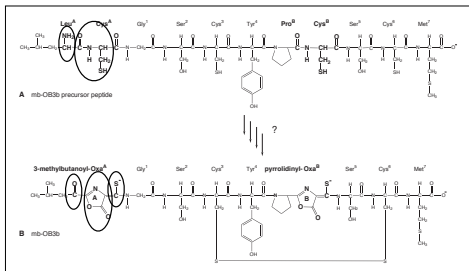
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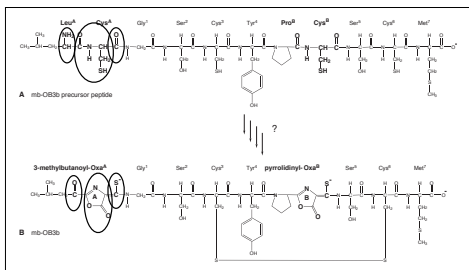
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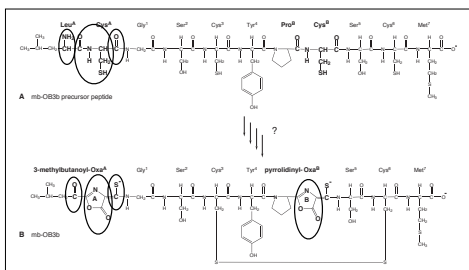
Modifications to the Primary Structure

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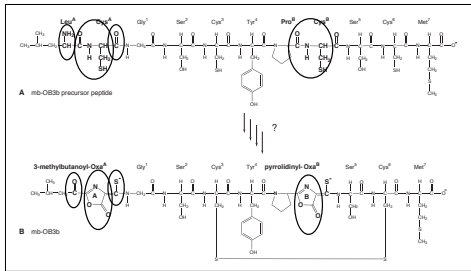
Modifications to the Primary Structure

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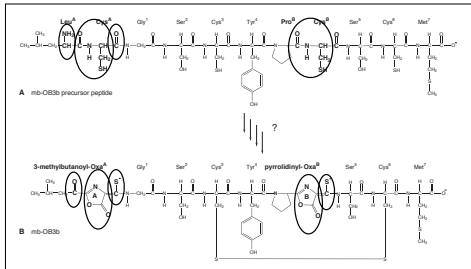
Modifications to the Primary Structure

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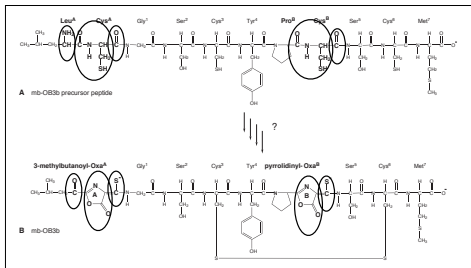
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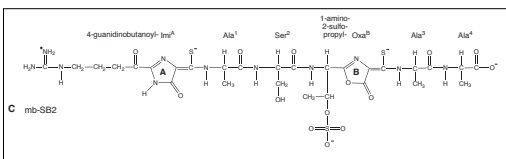
Modifications to the Primary Structure

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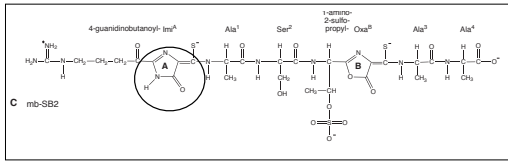
Modifications to the Primary Structure

- Many proteins and peptides undergo post translational modifications



Modifications to the Primary Structure

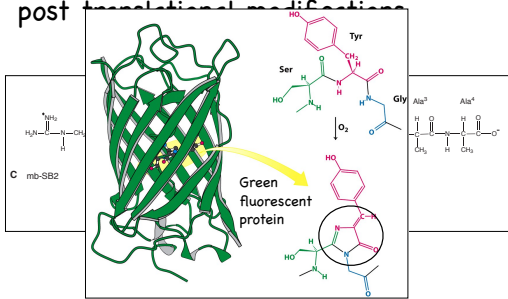
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Modifications to the Primary Structure

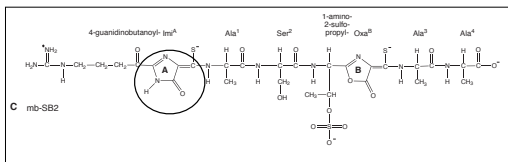
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Modifications to the Primary Structure

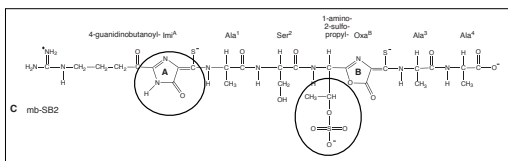
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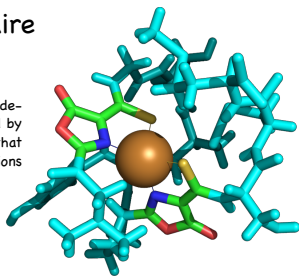


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Modifications to the Primary

+ Some post translational modifications that we have discovered here at UW-Eau Claire

Methanobactins are peptide-derived molecules produced by methane oxidizing bacteria that are scavengers for copper ions



Chem 452, Lecture 2 - Protein Structure 36

Next up

+ Hemoglobin and Myoglobin.

Chem 452, Lecture 2 - Protein Structure 37