The Human Proteome

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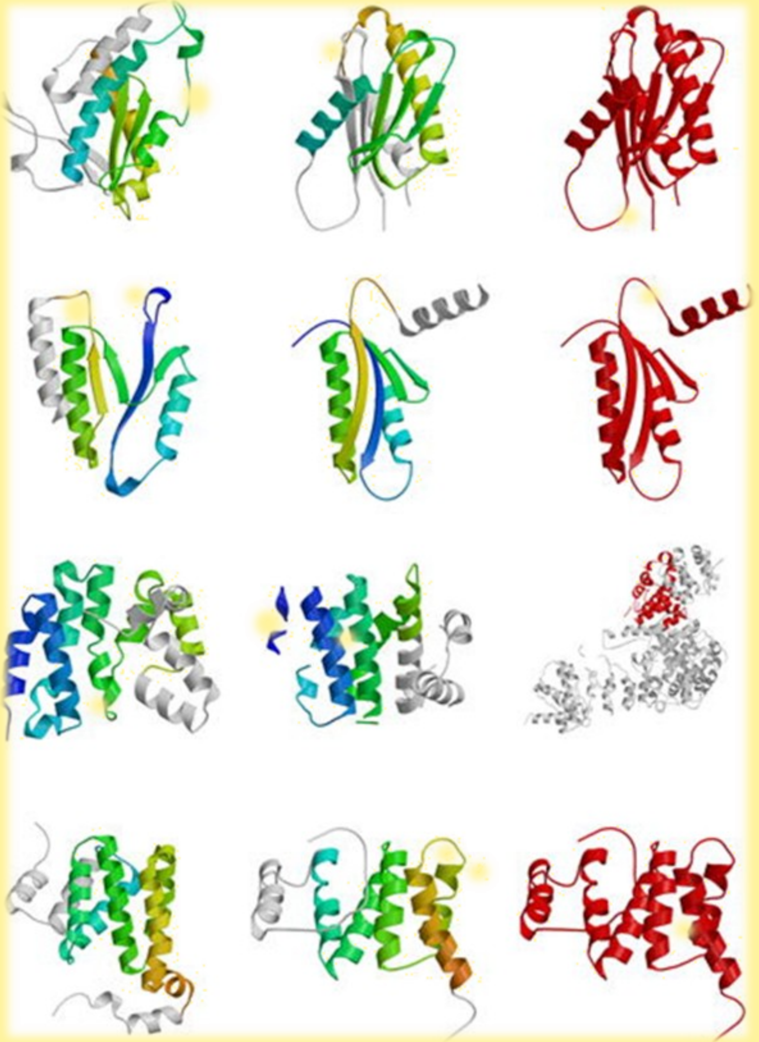
What is the human proteome?

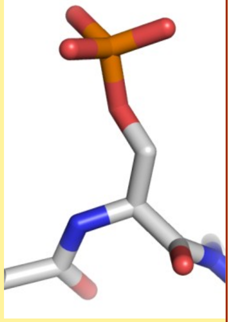
- The complete set of proteins in the human body
- Much larger than the genome due to alternative splicing and post-translational modifications
- Includes both the sequence, structure, and function of the protein
- The proteome varies with biological conditions



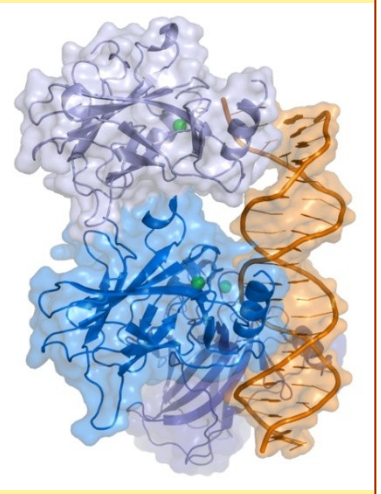
Why is it important?

- The human genome only provides the blueprints
- Greater understanding of
  - Gene expression and regulation
  - Protein behavior after transcription
  - Signal transduction pathways
  - Protein-protein interactions
- Lead to the discovery of biomarkers for:
  - Normal biological processes
  - Diseases
  - Drug response

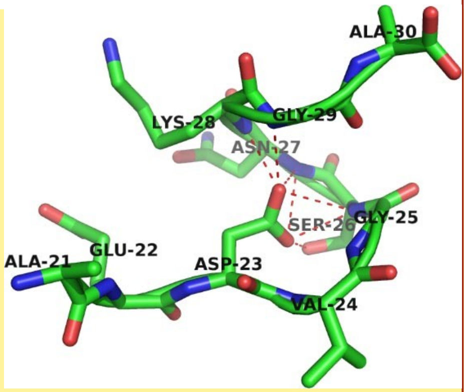
Example 1



- Phosphorylation: addition of phosphate group to protein
- Important regulatory mechanism
- p53 tumor suppressor protein has 18 phosphorylation sites
- When activated, can cause cell cycle arrest and apoptotic cell death
- Phosphorylation of n-terminus domain is critical event leading to activation



Example 2



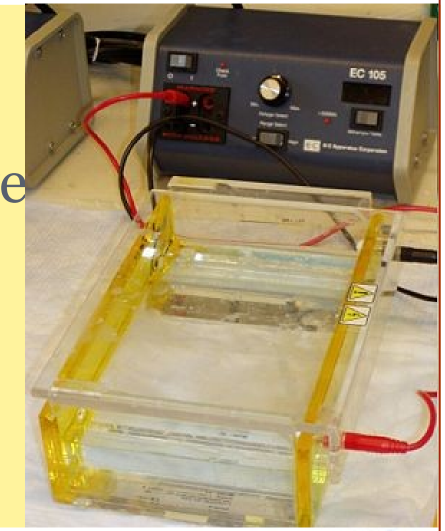
- Beta secretase produces the amyloid/ beta-protein
- Excess amyloid/beta-protein can form plaques in the brain leading to dementia
- This is thought to play a key role in Alzheimer's disease
- Use of the amyloid/beta-protein as a biomarker for Alzheimer's provides a useful diagnostic tool

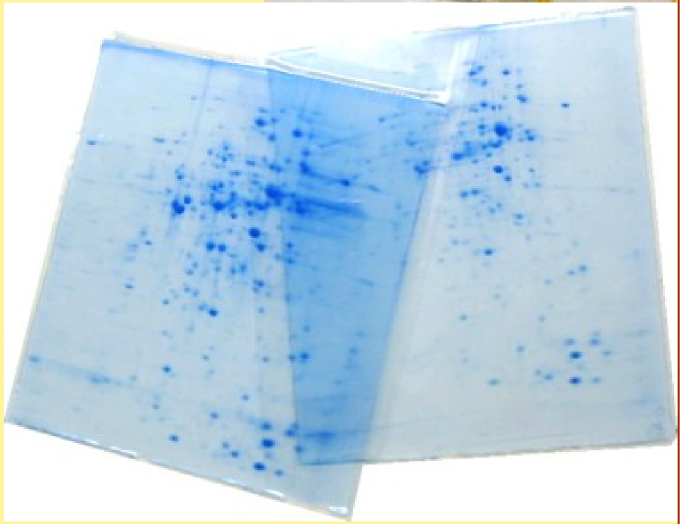
Methods 1

- Protein coding regions in the genome
  - This is a method we've looked at in class
  - By looking for various motifs and comparing it to databases of known protein sequences, protein coding regions can be identified
  - Protein sequence databases include:
    - Blast
    - InterPro
    - Blocks
    - Etc.

Methods 2

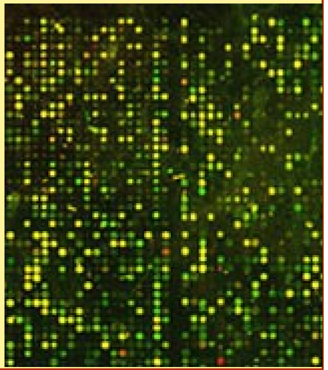
- 2-D gel electrophoresis
  - Gel electrophoresis uses electrical charge to move proteins through a polymer matrix
  - This can be used to separate DNA and proteins by mass
  - 2-D gel electrophoresis separates proteins proteins along two axis using two physical properties
  - In addition to mass, the isoelectric point can be used (the pH at which a molecule has no charge)





Methods 3

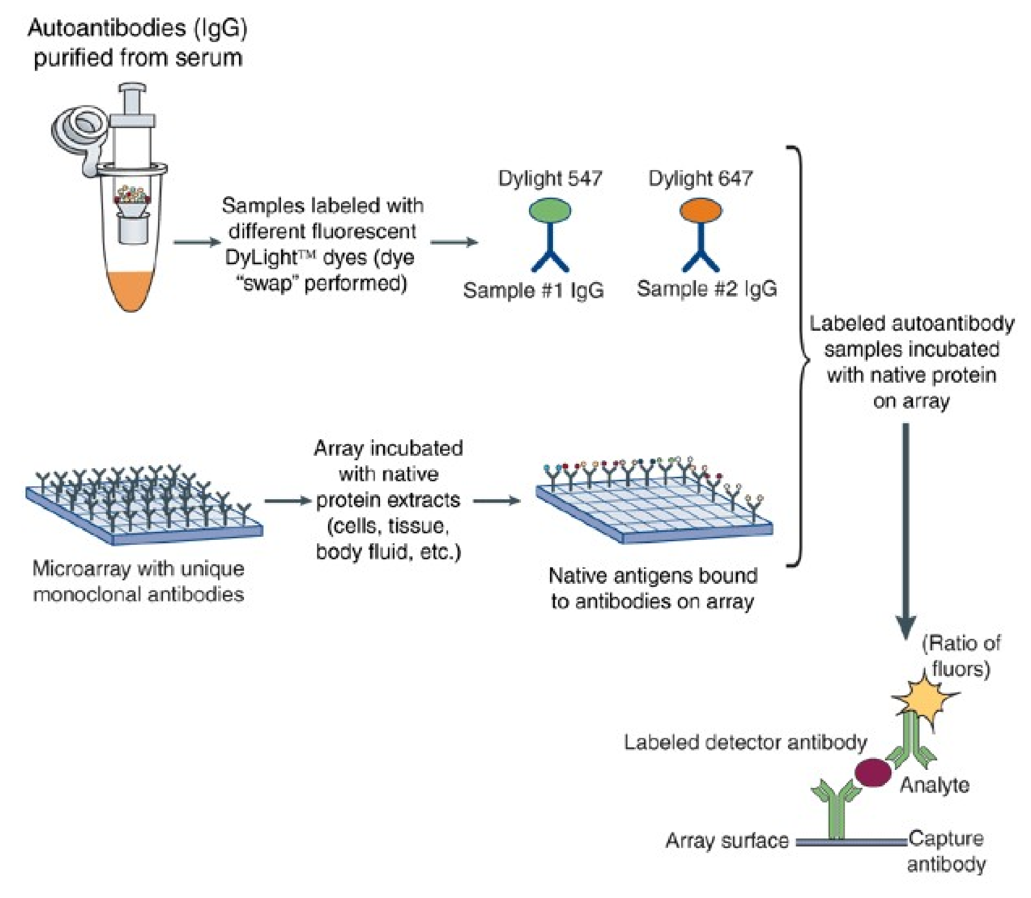
- Protein microarrays
  - Piece of glass is affixed with different proteins at different locations to form an array
  - These proteins are used to capture other proteins and thereby reveal different protein-protein interactions
  - The most common type of protein microarray is an antibody array
  - This can be used to detect the presence and quantity of proteins in biological samples
  - The results are then measured via fluorescence detection methods



Example 3

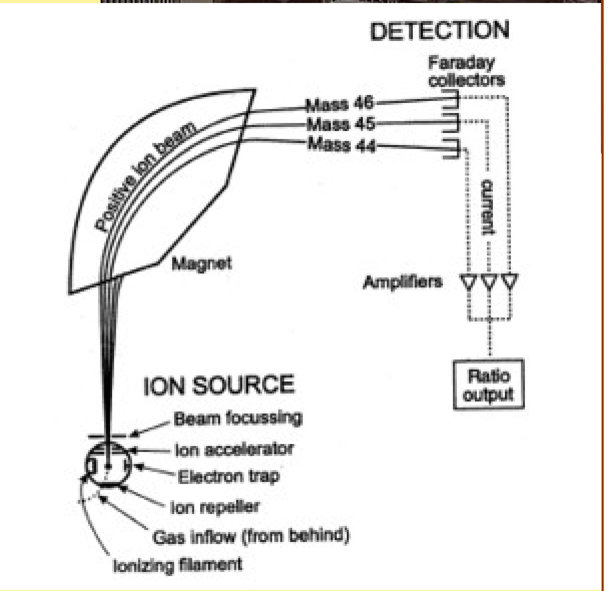
- Human autoantibodies are antibodies targeted at the individual's own proteins
- Utz lab attempting to create autoantigen microarrays that could detect autoantibodies
- Consist of a combination of peptides, proteins, nucleic acids, and protein complexes
- Would be very useful in diagnosing and understanding autoimmune diseases

Example 3 cont'd

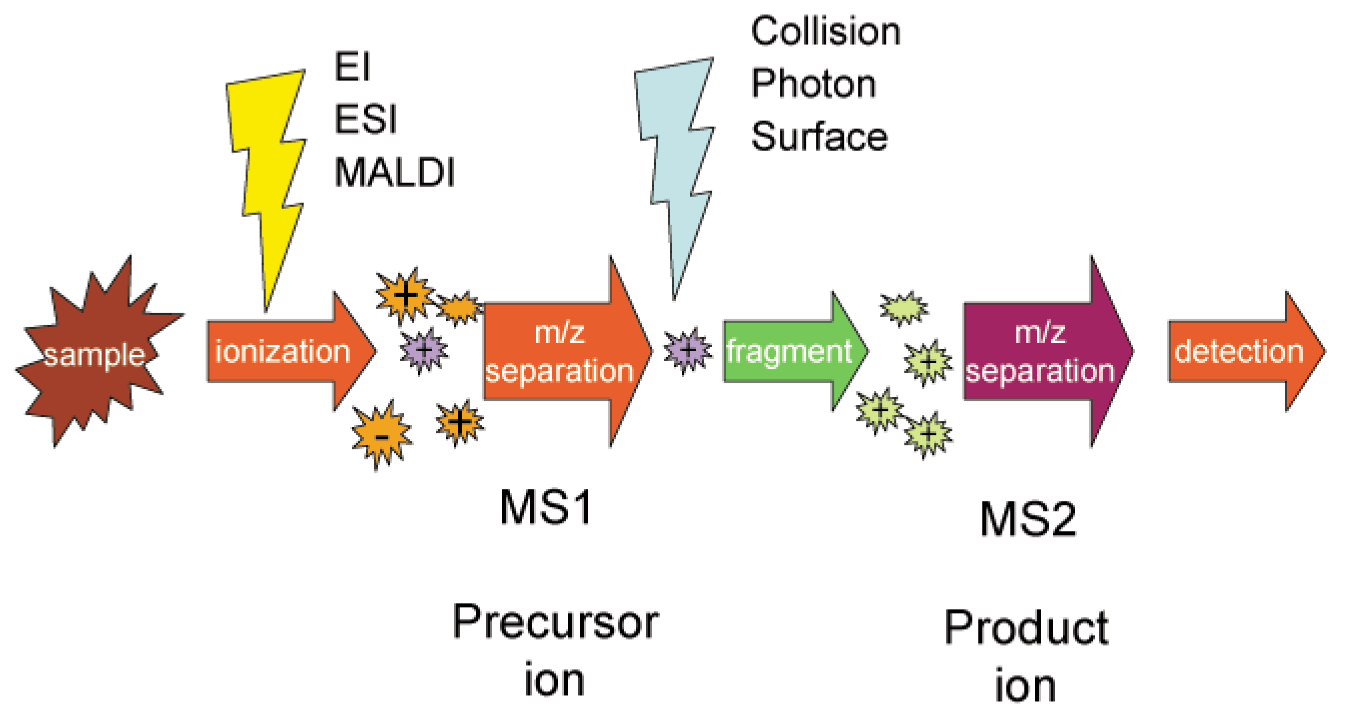


Methods 4

- Tandem mass spectrometry
  - Mass spectrometry subjects compounds to an electro-magnetic field whereby it separates them by their mass-to-charge ratio
  - These separated compounds are then measured by a detector
  - Tandem mass spectrometry involves several steps of mass spectrometry with a fragmentation step in between
  - This can be used to fragment proteins over multiple steps to determine composition and structure



Method 4 cont'd



Current efforts

- Human Proteome Organization (HUPO)
  - Founded in 2001
  - International collaboration between eleven different proteomic research initiatives
- Human Proteome Initiative (HPI)
  - Attempts to annotate all known human protein sequences
  - The database of protein information is known as swiss-prot
- Human Proteome Folding Project
  - Attempts to use known data on proteins to model folding and determine protein structure
  - This requires vast amounts of computation and the project is attempting to spread the work across a grid of computers

Implications for Medicine

- New drug targets
- Biomarkers to track the presence and progression of diseases
- Genome can provide information about predispositions to various diseases, but knowledge of person's current proteome would give information about current biological conditions

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