Aging and Proteins

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A new frontier: protein misfolding in aging diseases

- What are proteins and what do they do?
- Protein synthesis and folding
- When folding goes wrong: misfolding, aggregation, and associated diseases
- Surviving aggregation: rescuing misfolded proteins and "shunting" aggregates to doomed cells

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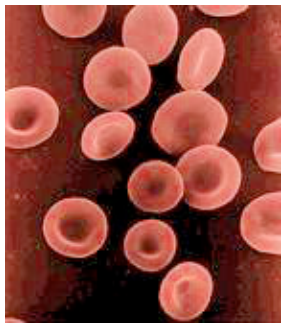
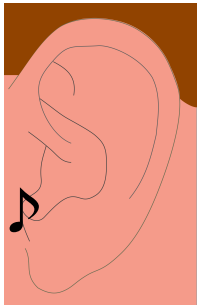
Proteins: The functional units of life

Proteins are the workhorses of the body; they perform almost all of the functions that we need to survive, including

Carrying oxygen in red blood cells to our brain, muscles, and other organs



Sensing touch, taste, sound, smell, sight



Muscle contraction

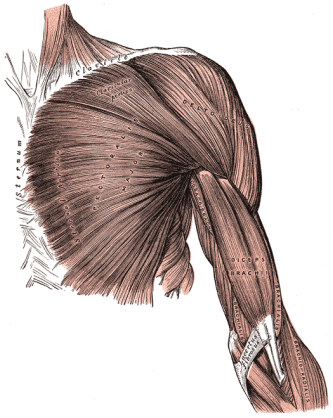


Image sources, top to bottom: Wikimedia commons users Andreas06, Pngbot; NIH

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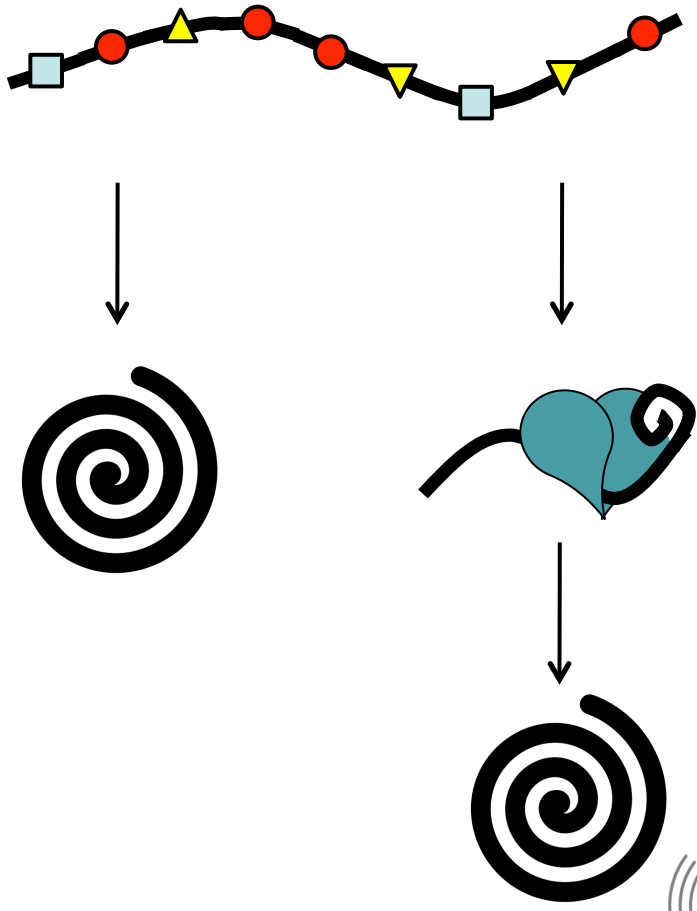
Protein synthesis and folding

- Proteins are synthesized as long chains of different "amino acids," the order of which specifies the protein
- They are then folded into a three-dimensional shape that dictates their function
- Some proteins are harder to fold than others; these require "**folding chaperones**," other proteins that help them fold



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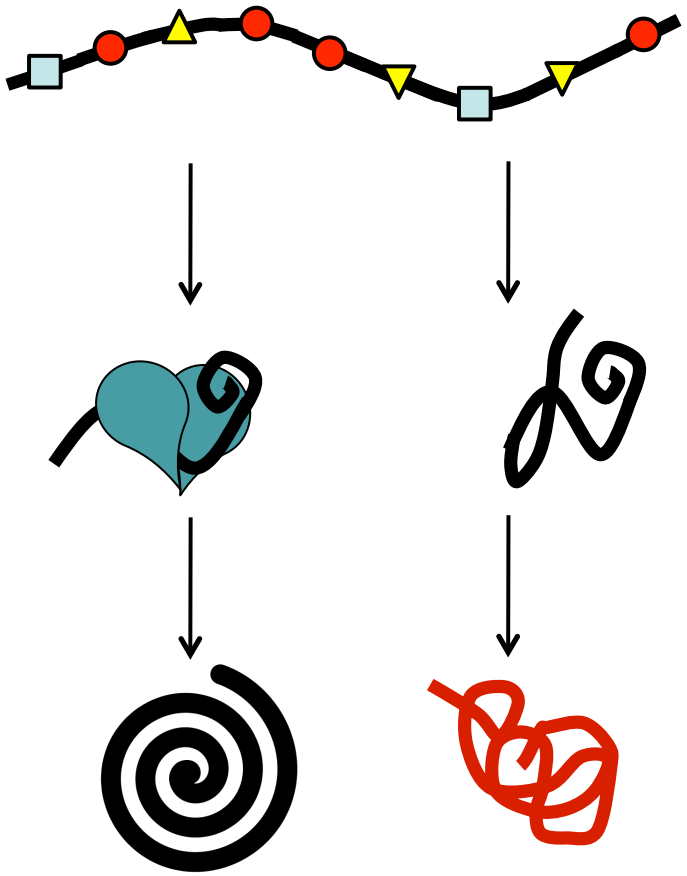
Spiral courtesy of Wikimedia Commons user Bayo

When folding goes wrong: Misfolded proteins

- When chaperones aren't accessible to proteins that need them for folding, they can **misfold**
- Misfolded proteins are nonfunctional!



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An analogy: misfolded proteins and the zombie apocalypse

- Just as zombies can bite and transmit their disease to those that they interact with, misfolded proteins can induce other happily folded proteins to misfold
- Like zombies, misfolded proteins tend to stick together. These "clumps" are called **aggregates**
- Aggregation increases as we get older

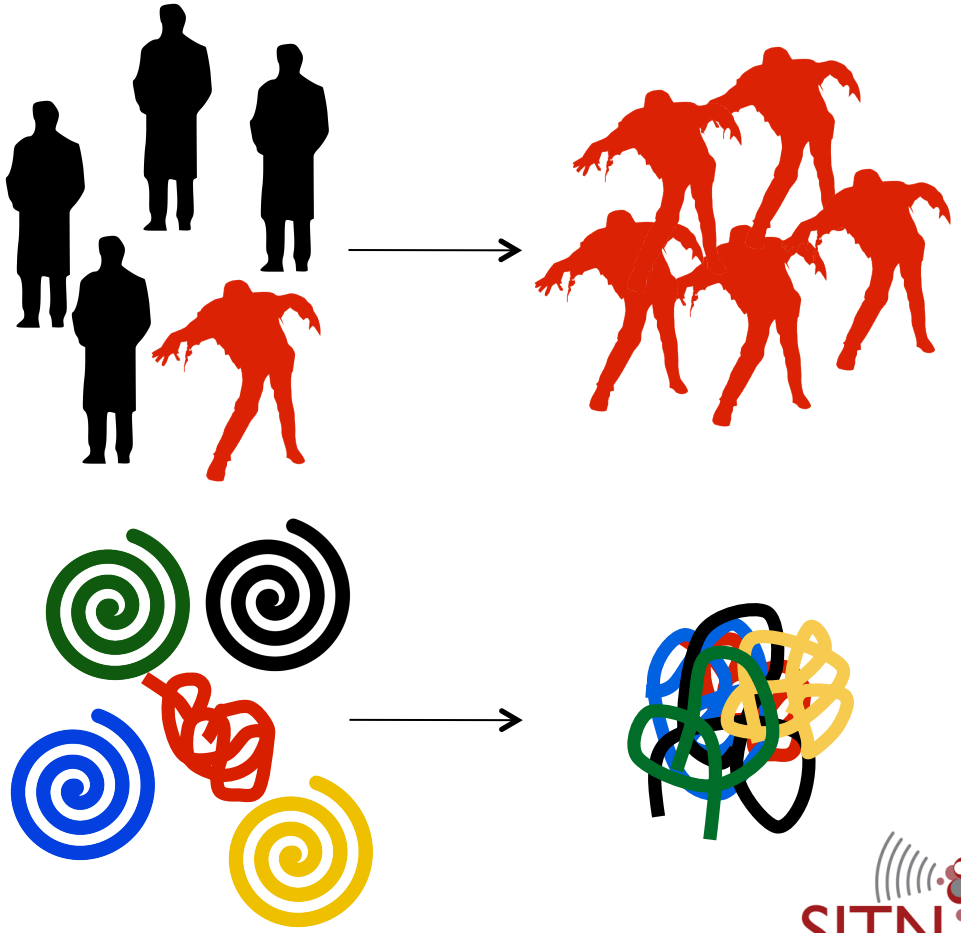

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Image sources: Normal person silhouette, Wikimedia commons user LiftArn; Zombie, user Jovianeye

So what?

Many diseases, most of which are associated with aging, are driven by protein aggregation!

Disease	Primary aggregated protein	Symptoms
Parkinson's Disease	α-synuclein	Loss of motor control, tremor
Alzheimer's Disease	APP (Amyloid Precursor Protein) and Tau	Loss of motor control, dementia
Huntington's Disease	Huntingtin	Loss of motor control, seizures, dementia
ALS (Lou Gehrig's Disease)	Many	Loss of motor control, muscle loss

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Recovering from protein misfolding

Younger cells are able to recover from low levels of protein misfolding in two ways:

1. Refolding misfolded proteins

2. Active asymmetric segregation of aggregates during cell division

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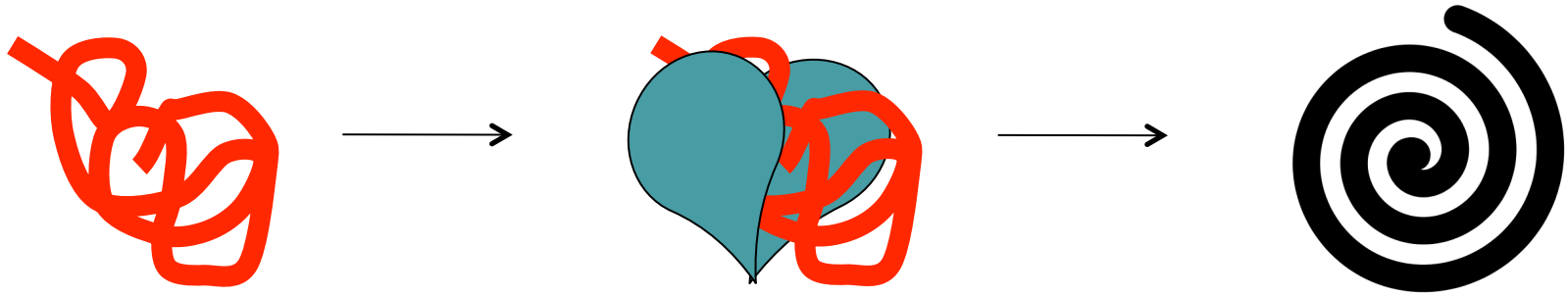
Protein refolding

Chaperones can destroy or refold individual misfolded proteins into their normal, functional form



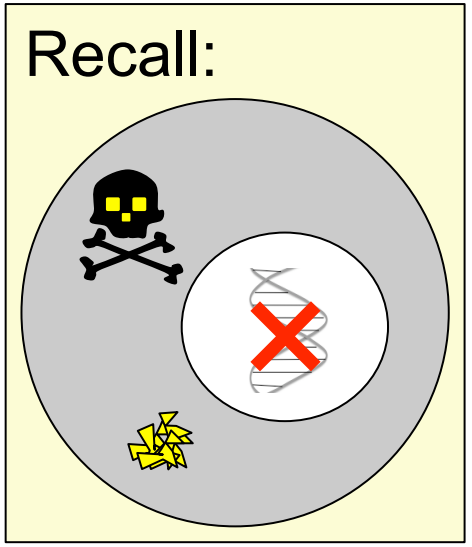
This process fails as we age as chaperones cannot keep up with the rate of protein misfolding.

Why don't we just make more chaperones as we age?

As we age, our cells encounter all kinds of damage:

- DNA damage from chemicals, UV light, and other sources

- Damage accumulated while responding to our environment (extreme heat or cold, starvation, disease)



We just can't keep up with everything!!

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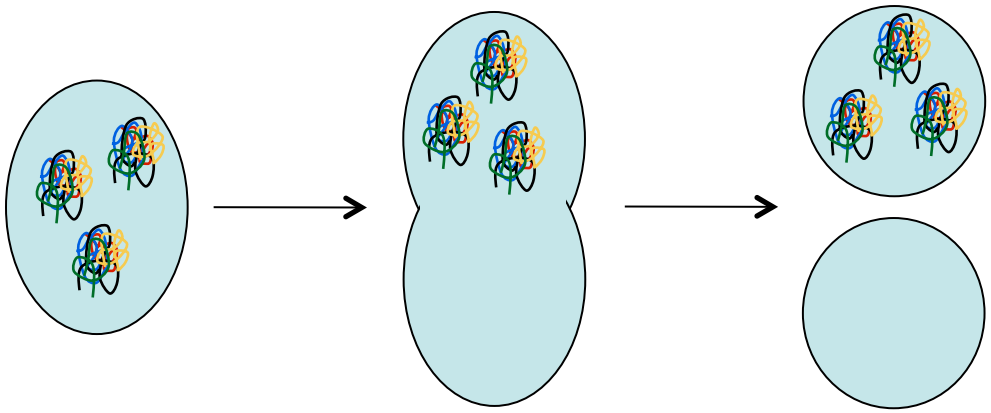
Asymmetric Segregation

Aggregates can collect in one daughter cell during cell division, freeing the other cell from aggregrates



As we age our cells can collect too many aggregates to partition them all to one cell during division, invalidating this recovery mechanism.

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Questions currently being asked about aging-related aggregation

1. Why do these diseases primarily affect the brain?

2. Why do older cells respond less effectively to aggregation?

3. What can we do to fight aging-related protein aggregation?

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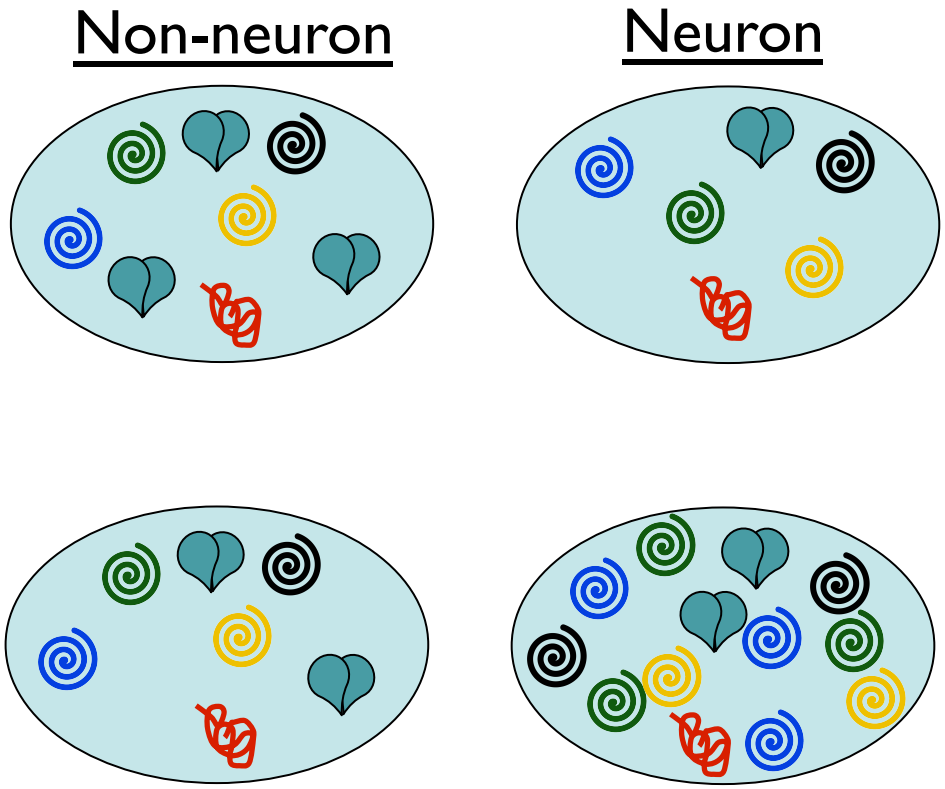
Why do these diseases primarily affect the brain?

- Brain cells (**neurons**) may have fewer refolding chaperones
- Neurons may be more tightly packed with proteins



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Why do older cells respond less effectively to aggregation?

- As with neurons, older cells are believed to have fewer chaperones

- Older cells are more likely to have accumulated aggregates at some point in their life, making recovery an uphill battle

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What can we do to fight aging-related protein aggregation?

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Returning to the question of programmed aging…

Does our inability to clear protein aggregates as we age support the idea that we may be programmed to age?

- Our inability to respond to increasing aggregation is most likely due to a limit of our cells' ability to fight damage

- Human cells only intentionally collect aggregates to improve the fitness of other cells (and the organism as a whole)

No, increasing protein aggregation during aging and in disease doesn't give evidence for programmed aging in humans.

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Next up: Phil

- Using genetics to study aging
- Research regarding genetic programs that regulate aging

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