AL Amyloidosis

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Outline

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2. History
3. Classification
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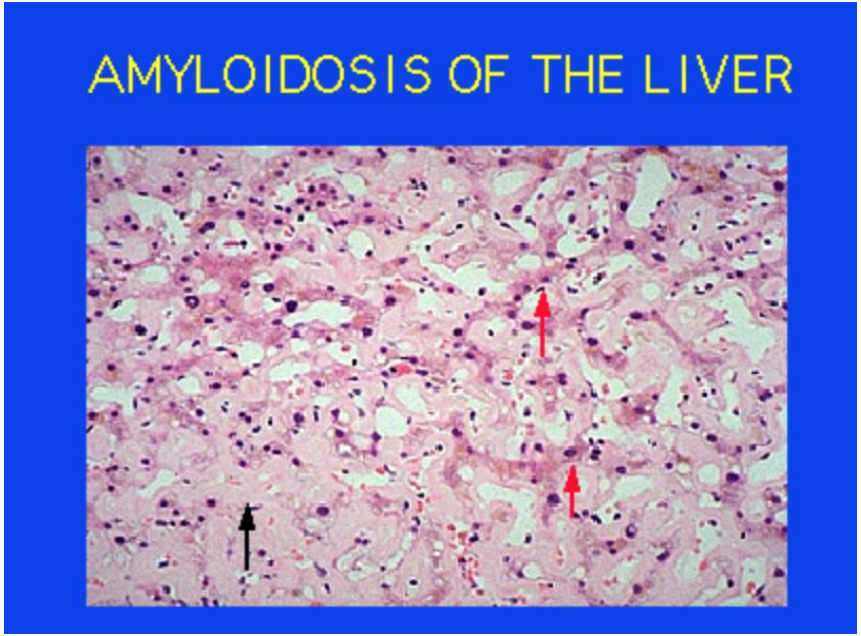
What is AL Amyloidosis?

- Bone marrow disorder
- Abnormal antibody (immunoglobulin) protein
- Formation of amyloid
- Amyloid = Aggregates of proteins allowing matching copies to stick



https://www.pathology.med.umich.edu/greensonlab/AMYLOID-HE.GIF

(Nienhuis, Bijzet & Hazenberg, 2016)

History

- 1854: Virchow uses term “amyloid” to refer to extracellular buildup in the liver (Nyirady, 2016)
- 1927: Divry and associates discover a test for identifying amyloid tissues (Congo red dye viewed under polarized light) (Beckerman, 2015)
- 1959: Cohen and Calkins discovered that amyloidosis demonstrates a fibril structure (Nyirady, 2016)

https://www.biography.com/.image/t_share/MTIwNjA4NjMzOTk5MzYxNTQ4/rudolf-virchow-9519219-1-402.jpg

Classification

- Systemic amyloidosis can be classified into:
  - Primary systemic amyloidosis
  - Amyloidosis associated with multiple myeloma
  - Secondary systemic amyloidosis

http://www.actasdermo.org/en/cutaneous-alerts-in-systemic-malignancy/articulo/S1578219013000619/

(Nyirady, 2016)

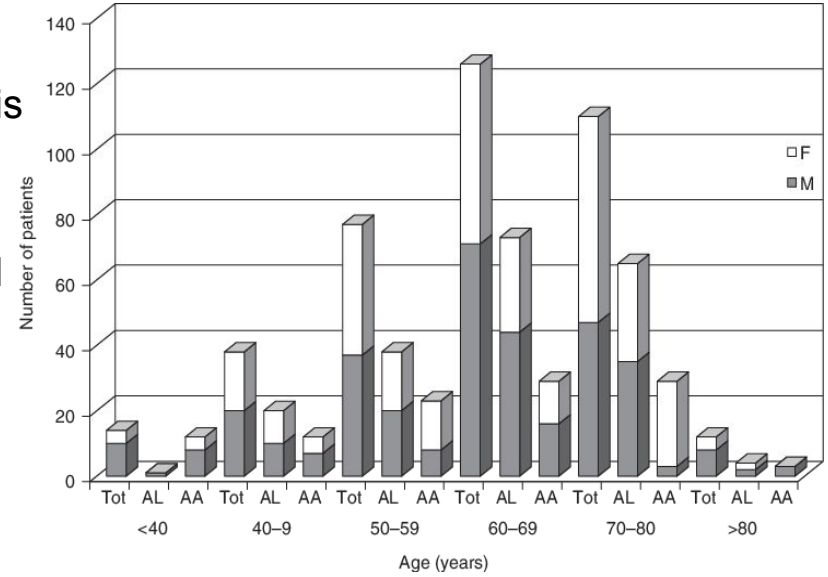
Epidemiology

- **Incidence Rates**
  - ALA most common type of systemic amyloidosis (56%)
  - 9 cases per-million inhabitants each year
  - Highest amongst adults aged 60 – 80 years old

(Real de Asúa et al., 2014)

- **Trends**
  - Two-thirds of all patients are male
  - No racial predilection (Africans marginal higher rates)
  - Not a hereditary disease

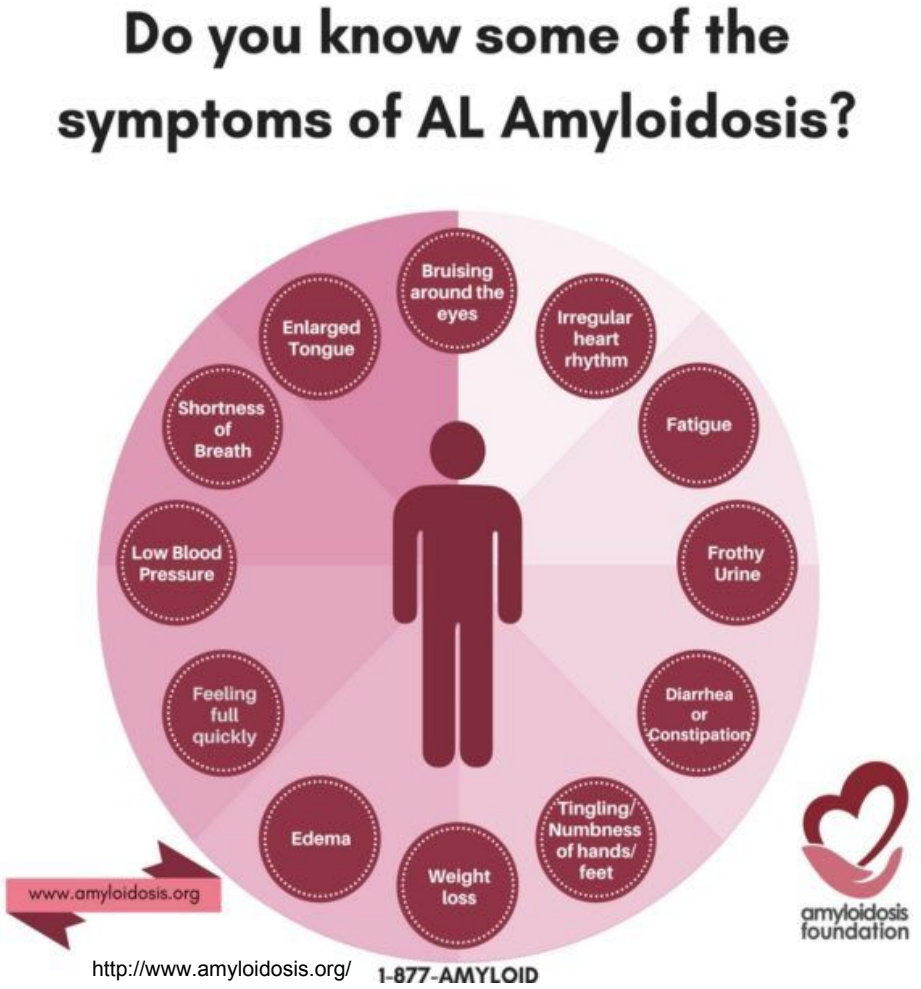
(Nienhuis, Bijzet & Hazenberg, 2016) and (Desport et al., 2012)



https://www.researchgate.net/figure/51378997_fig2_Fig-2-Frequency-of-different-types-of-amyloidosis-according-to-age-and-gender

Signs and Symptoms

- “An enlarged liver
- An enlarged tongue (macroglossia)
- An irregular heartbeat
- Diarrhea alternating with constipation
- Loss of weight
- Numbness or tingling in the hands or feet
- Severe fatigue
- Shortness of breath
- Skin changes
- Swelling of the ankles and legs
- Weakness” (Cedars-Sinai Cancer Institute, 2017)



Prognosis

Amyloid Type	Systemic Amyloidosis	
Subtype	AL	AA
Protein Deposited	Light chain	Amyloid A
Disease Etiology	Plasma cell dyscrasia with ↑ light chains	Systemic autoimmune or infections
Specific Features	Kidney, heart and liver affected	Renal dysfunction
Median Survival	1-3 years	11 years

http://circ.ahajournals.org/content/133/3/245

- Median survival is 1-3 years
  - Slowly progressive and fatal if untreated (Ma & Ra, 1994; Papadakis & McPhee, 2017)
- Chemotherapy medicine with autologous stem cell transplantation (Shiel, & Balentine, 2017; Papadakis & McPhee, 2017)
  - Median survival approaches **5** years
  - ~ **10** years = hematologic remission

Targeted Organs - Mortality

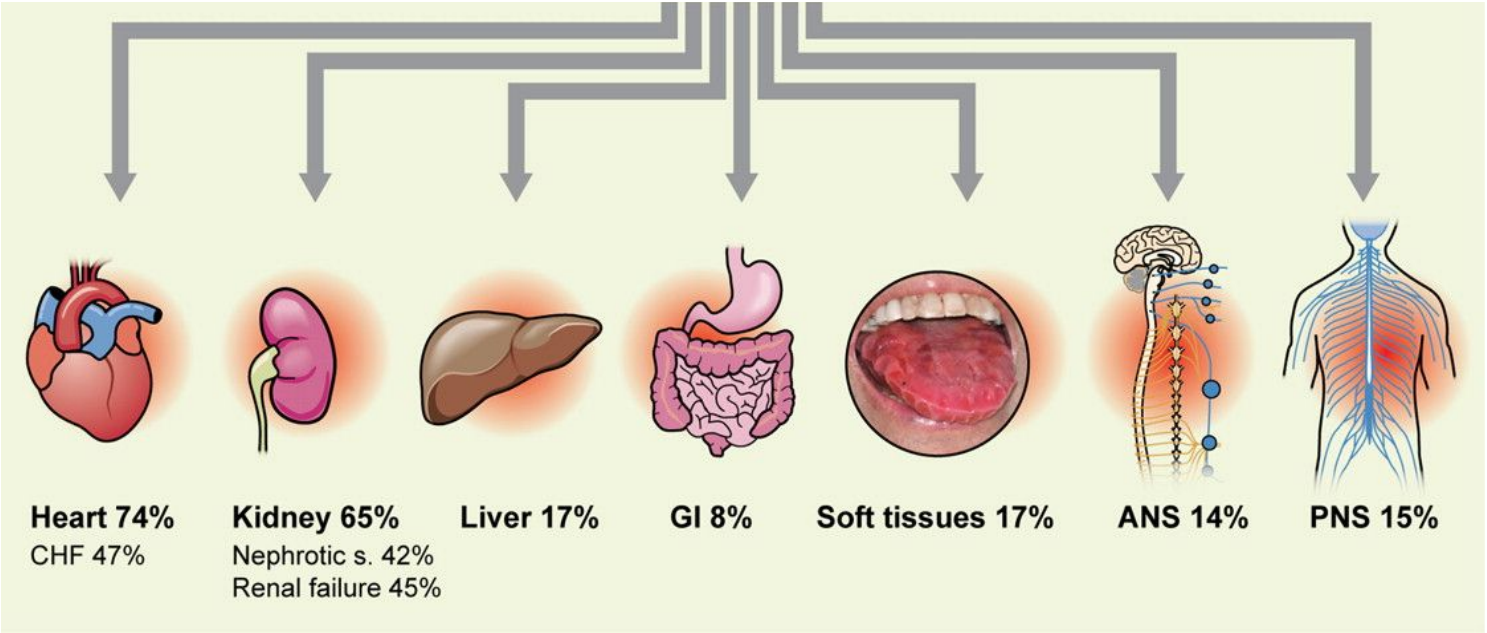
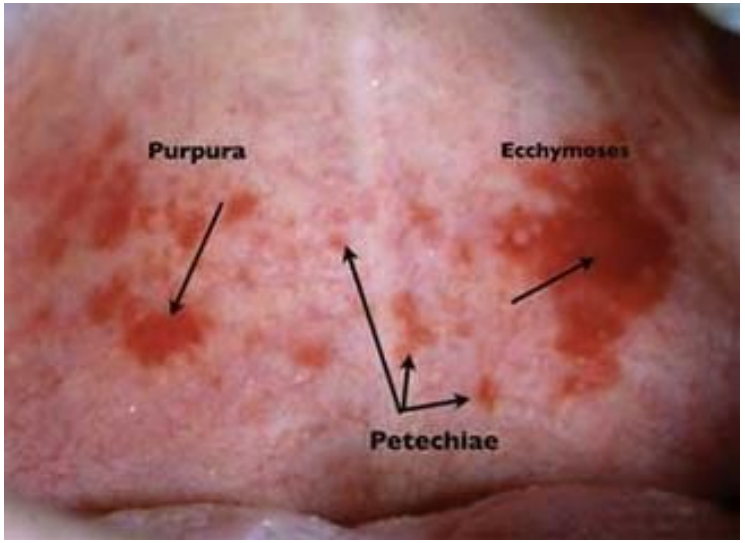


Figure 1: Percentages referring to mortality rate (death within 3 years) upon development of AL Amyloidosis

http://www.bloodjournal.org/content/119/19/4343?sso-checked=true

Diagnosis

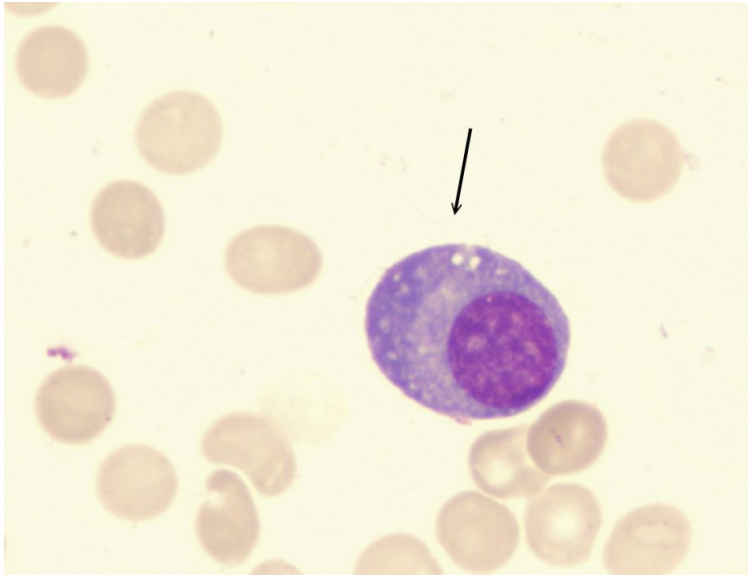
- Considered in patients with (Sanchorawala, 2006):
  - Proteinuria
  - Cardiomyopathy
  - Neuropathy
  - Hepatomegaly
  - Myeloma
- Diagnosis requires two criteria (Sanchorawala, 2006):
  - Amyloid in the tissue
  - Plasma Cell Dyscrasia
- Skin signs (Nyirady, 2016)



http://www.rdhmag.com/articles/print/volume-29/issue-4/columns/oral-exams/petechiae-ecchymoses-or-purpura.html

Pathophysiology

- **BRIEF OVERVIEW**
  - Plasma cell dyscrasia (Zhang, Huang & Li, 2017)
  - Abnormal, over-proliferative plasma cells (PC) mass produce Ig antibodies (Ramirez-Alvarado, 2013; ,Zhang, Huang & Li, 2017)
  - Once in blood circulation, Ig light chains unfold, bind to other light chains, and deposit as insoluble amyloid fibrils in ECM of tissues & organs (Ramirez-Alvarado, 2013)

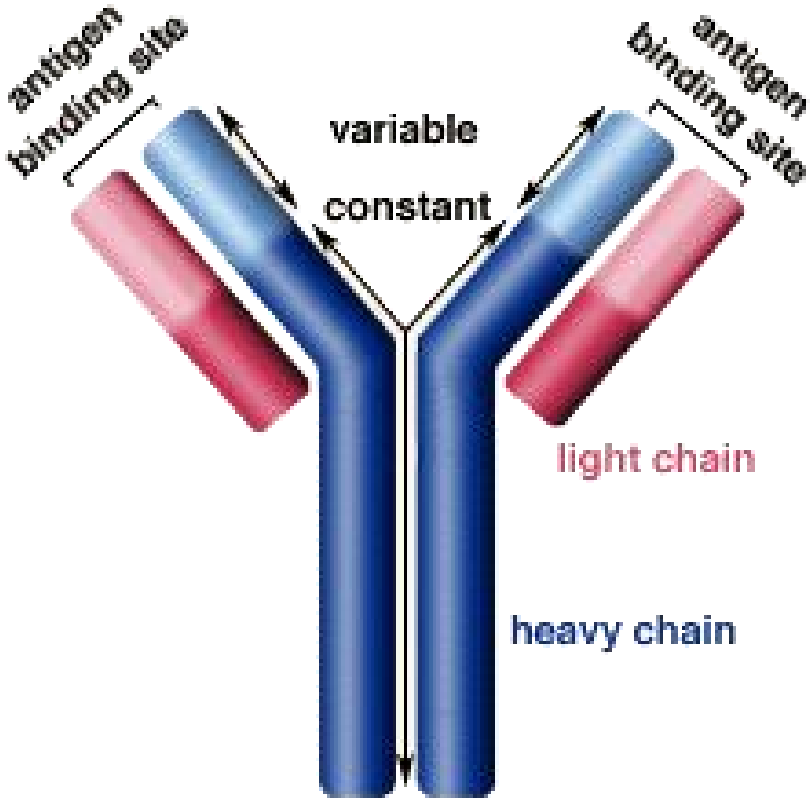


https://theadventuresofbecky.files.wordpress.com/2010/03/plasma-cell-100x-website-arrow.jpg

https://www.youtube.com/watch?v=bTcWtVpBcgA

Ig Antibodies

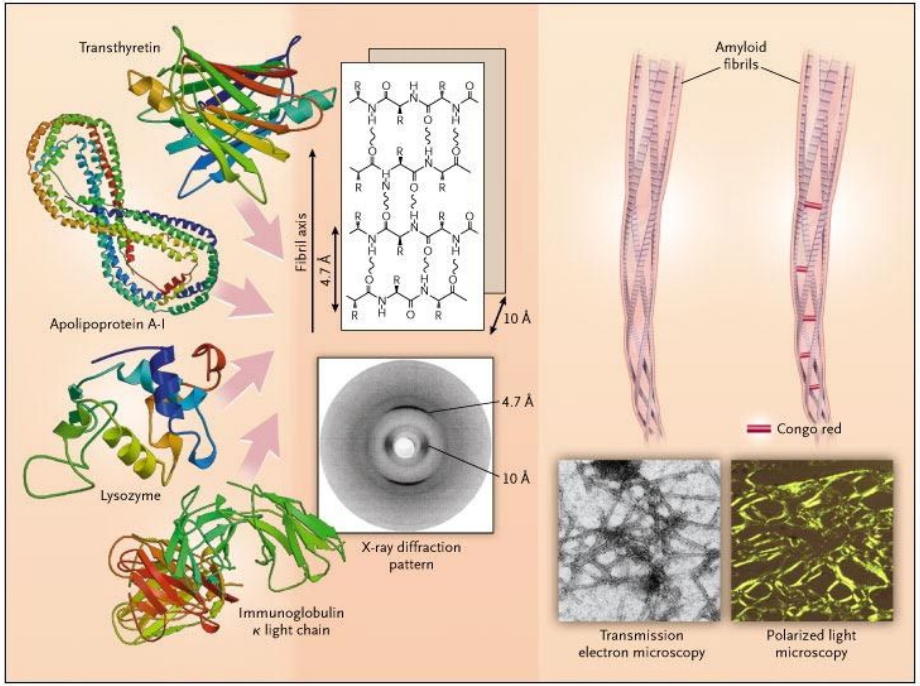
- Composed of
  - Two light chains
    - Kappa (k)
    - Lambda (λ)
  - Two heavy chains (Ramirez-Alvarado, 2013)
- Tendency to develop fibrillogenesis depends on primary structure of light chains (Zhang, Huang & Li, 2017)
- Normally, k:λ = 2:1
- AL amyloidosis, k:λ = 1:4 (Weiss, Wong & Comenzo, 2016; .Zhang, Huang & Li, 2017)
- Variable regions of light chains are highly mutated (Perfetti et al., 1998)



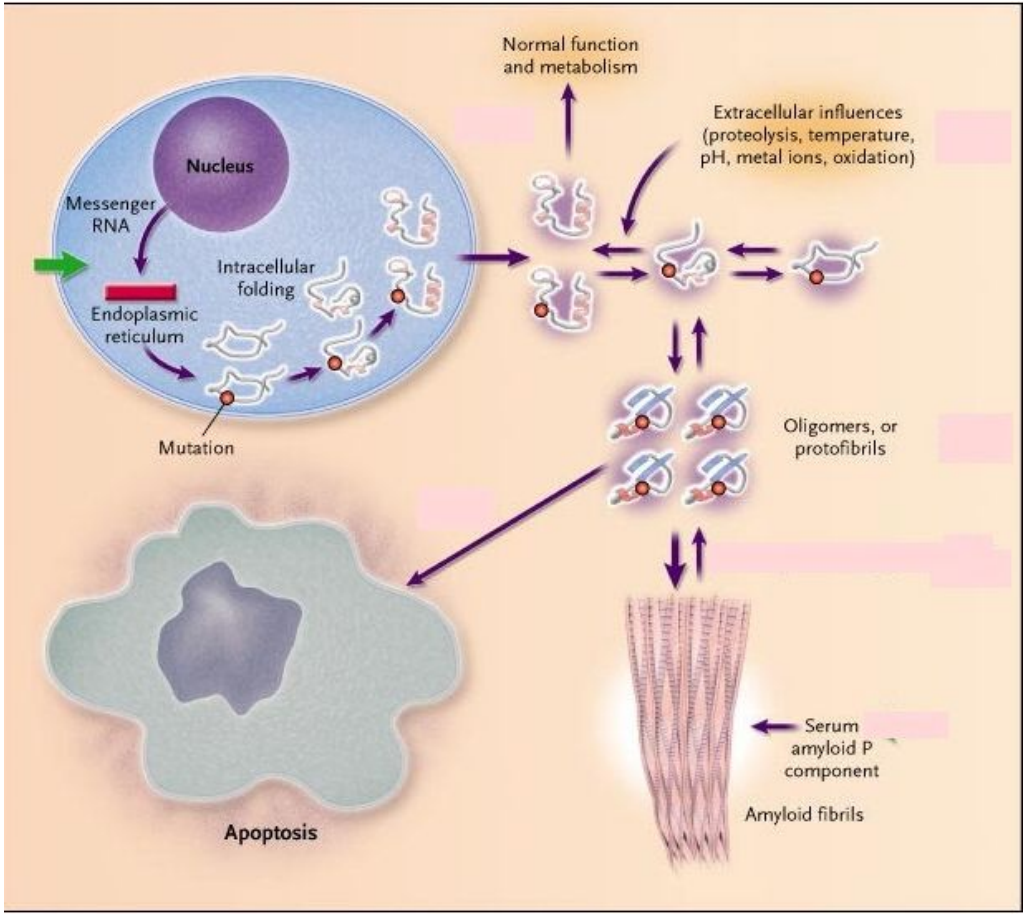
http://www.biology.arizona.edu/immunology/tutorials/antibody/structure.html

Amyloid Fibrils

- Matrix components + Ig light chains form β-super-secondary structure
  (Perfetti et al., 1998)
- Protofilaments wind around each other, forming fibrils
  (Merlini & Belloti, 2003)



http://www.nejm.org/doi/full/10.1056/NEJMra023144



http://www.nejm.org/doi/full/10.1056/NEJMra023144

How Do Fibrils Form?

- Amyloid precursors are secreted as native proteins but escape intracellular quality control system (Merlini & Bellotti, 2003)
- Reach eqbm between fully folded and partially folded state (Merlini & Bellotti, 2003)
- Low pH
- Oxidation
- rise in temperature
- Limited proteolysis

Shift eqbm to partially folded state

- Oligomers or protofibrils cause cellular toxicity by activating apoptosis (Merlini & Bellotti, 2003)

Factors Influencing Fibrillogenesis

- **Plasma cells**
  - Cytogenetic abnormalities
    - translocation of chromosome 14q32, monosomy 13, trisomies 9, 15, 11 and 3

(Warsame et al., 2015; Zhang, Huang & Li, 2017,18)

- **Post translational modifications**
  - Glycosylation: alters protein solvation energy, increases binding strength at certain regions and protects some sites from protease degradation

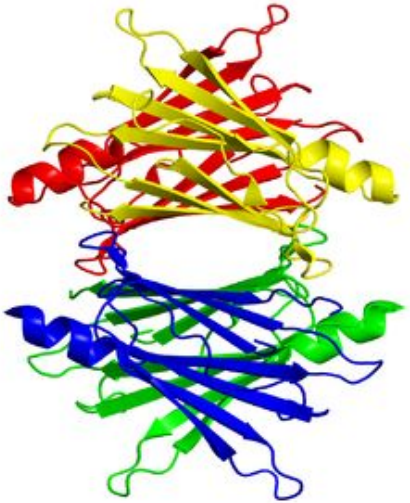
(Schachter, 1984; Petukhov et al., 1999; Zhang, Huang & Li, 2017)

Factors Influencing Fibrillogenesis

- **Extracellular Matrix Components**
  - Serum amyloid P: protects amyloid fibrils from proteolytic degradation (Tennent, Lovat & Pepys, 1995; Zhang, Huang & Li, 2017)
  - Heparan Sulfate proteoglycans (HSPG): interact with ligands and promote protofilament assembly into mature fibrils (McLaurin, Franklin, Zhang, Deng & Fraser, 1999; Ren et al., 2010; Zhang, Huang & Li, 2017)
- **Extracellular Chaperones**
  - Bind to amyloid fibrils and protect them from protease degradation (Zhang, Huang & Li, 2017)

Prevention

- Alzheimers: Transthyretin prevents amyloid formation (Schwarzman et al., 1994)
- Familial Mediterranean fever: Colchicine (Zemer et al., 1986)

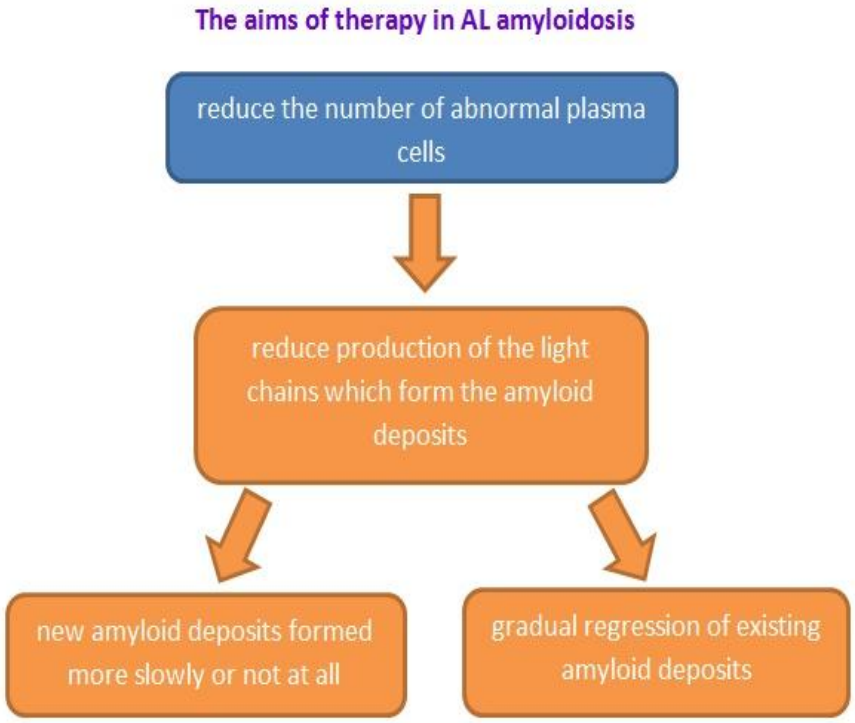


https://en.wikipedia.org/wiki/Transthyretin

http://www.davipharm.info/dv/en/product/musculo-skeletal-system/colchicine.html

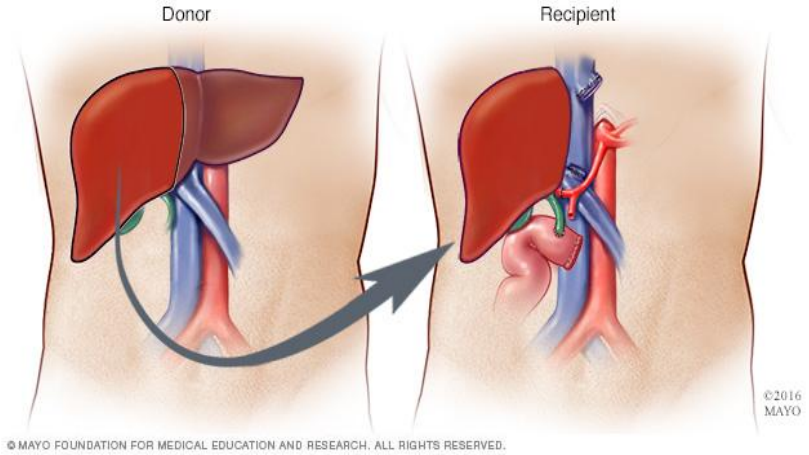
Treatment/Management

1. **High-dose chemotherapy medicines with autologous stem cell transplantation** (Palladini et al., 2004; Derrer, 2015; Shiel, & Balentine, 2017; Papadakis, & McPhee, 2017)
    - Common chemotherapy medication is melphalan
    - Not all the patients can do autologous stem cell transplantation due to high toxicity



http://www.amyloidosis.org.uk/al-amyloidosis/treatment/

Treatment/Management



http://www.mayoclinic.org/tests-procedures/liver-transplant/details/what-you-can-expect/rec-20211848

2. **Liver, Kidney or Heart transplant**
   - The vital organs failure

3. **Diuretic medicines (kidney problem**
   - Remove excess water from the body

(Derrer, 2015; Shiel, & Balentine, 2017; Papadakis, & McPhee, 2017)

Social Implications

- **Amyloidosis Not Well Known by Society**
  - Misconceptions and wrongful information
  - Difficult disease to understand
  - Ongoing research
- **The Amyloidosis Foundation**
  - Raising money (Yearly Runs)
  - Spreading Awareness
  - Providing grants for research

http://www.amyloidosis.org/

amyloidosis foundation

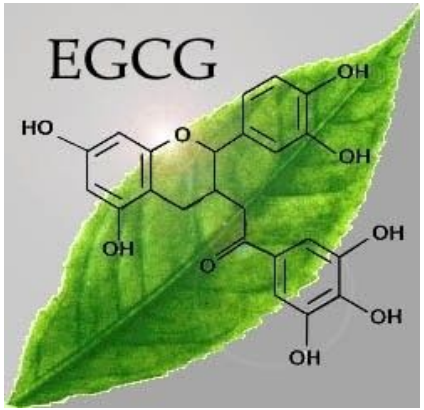
http://www.amyloidosis.org/

(Amyloidosis Foundation, 2017)

Further Research/Applications/Implications

- **Study of Gene Expression Changes/Mutations** (Zhou et al., 2012)
  - Studying proteins, mutations and gene expressions
  - Large scale characterization currently being conducted
  - Identify structures used to diagnose patients earlier and/or target as treatment

- **Epigallocatechin-3-Gallate (EGCG)** (Andrich et al., 2016)
  - Most abundant catechin in tea
  - Suggested that EGCG specifically inhibits the aggregation phase



http://toptestosteronesupplements.com/epigallocatechin-gallate-egcg-ingredient-breakdown/

Further Research/ Applications/ Implications

- **Clear Amyloid Protein Deposits (Immunotherapy / Physical)** (Rosenzweig et al., 2017)
  - Clearing amyloid protein deposits directly was before seen as impossible
  - Scavenger cells recognize and engulf amyloid deposits
  - New immunotherapy treatments accelerate functionality of scavenger cells

http://www.iran-daily.com/News/129235.html

- **Other** (Gertz et al., 2016; Wechaleka et al., 2016; Sanchorawala et al., 2017)
  - **Antibiotics** = Interfere with amyloid deposit formation
  - **Targeting of SAP Protein** = Potential new treatment target
  - **Vaccines** = Protect vital organs from amyloid formation

https://www.swan.wa.gov.au/files/assets/public/image-resources/lists/people/children/ph_immunisation.jpg?w=480

Conclusion

- Bone marrow disorder
  - Abnormal antibody light-chains
  - Formation of lethal amyloid
  - Disrupt tissues and organs

https://tctechcrunch2011.files.wordpress.com/2016/08/thats-all-folks.png?w=1279&h=727&crop=1

- AL amyloidosis is still rather lethal - be aware and stay educated

(Nienhuis, Bijzet & Hazenberg, 2016)

- The ALA foundation website is a great source for more information
- Researchers believe ALA will no longer be a threat in 10 years!

Multiple Choice #1:

Which of the following statements is INCORRECT.

a) AL Amyloidosis incidence rate is highest for adults age 50 to 60.
b) Epigallocatechin-3-Gallate (EGCG) is a potential future treatment for AL Amyloidosis.
c) Amyloid formation is most lethal when formed in the heart.
d) Misfolded Light Chains is the cause of amyloid formation in AL Amyloidosis .
e) 56% of all Systemic Amyloidosis cases are of AL variety

Multiple Choice #1: (Answer)

Which of the following statement is INCORRECT.

a) AL Amyloidosis incidence rate is highest for adults age 50 to 60. ##
b) Epigallocatechin-3-Gallate (EGCG) is a potential future treatment for AL Amyloidosis.
c) Amyloid formation is most lethal when formed in the heart.
d) Misfolded Light Chains is the cause of amyloid formation in AL Amyloidosis .
e) 56% of all Systemic Amyloidosis cases are of AL variety

Multiple Choice #2:

Which of the following does NOT influence fibrillogenesis?

a) Plasma cells
b) Intracellular Matrix Components
c) Extracellular Chaperones
d) Post translational Modifications
e) Extracellular Matrix Components

Multiple Choice #2: (Answer)

Which of the following does NOT influence fibrillogenesis?

a) Plasma cells
b) Intracellular Matrix Components ##
c) Extracellular Chaperones
d) Post translational Modifications
e) Extracellular Matrix Components

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