HM/CH-1/L-11

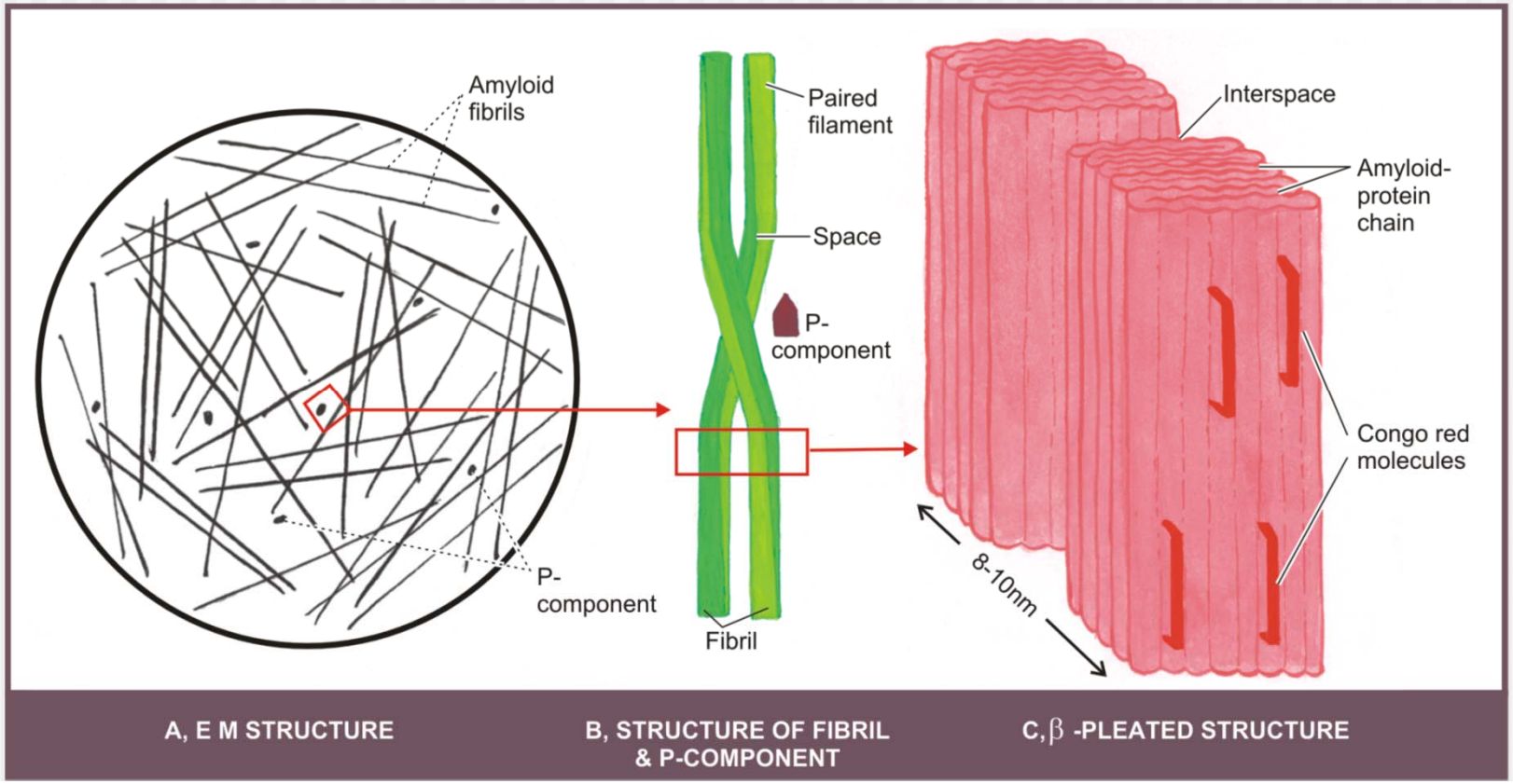
AMYLOIDOSIS

Definition, history, nomenclature

- Extracellular deposition of fibrillar proteinaceous material with common morphologic and staining characters but different protein (chemical) composition
- Rokitansky, 1842; Virchow named it (amylon=starch); C/S brown with iodine and violet on adding dil. H_2SO_4
- Nomenclature: prefix A for amyloid, postfix of specific protein type

Physical & chemical nature

- FIBRIL PROTEINS (95%)
- NON-FIBRILLAR COMPONENTS (5%)



FIBRIL PROTEINS

- Twin filaments (7-9 nm), cross-β pleated; birefringence; β-fibrillosis

TYPES:

- AL proteins
- AA proteins
- Other proteins

AL protein

- Derived from amino-terminal segment of Ig light chain and part of C region
- Lambda (λ) >>kappa (κ) light chain
- Aminoacid sequence homology
- Production from Ig-secreting cells
- Examples: Primary amyloidosis in plasma cell dyscrasias

AA protein

- Protein with mol wt 8.5-kD, derived from larger precursor protein SAA with mol wt 12.5 kD
- No sequence homology
- SAA circulates with HDL_3
- Synthesis in liver as acute phase reactant
- Examples: Secondary amyloidosis in chronic inflammation, traumatic conditions

Other proteins

- Transthyretin (TTR): trans-thy-retin (AFp)
- $A\beta_2$-microglobulin ($A\beta_2M$)
- β-amyloid protein (Aβ)
- Immunoglobulin heavy chain amyloid (AH)
- Amyloid from hormone precursor proteins (ACal, AIAPP, AIns, APro,AANF, ALac)
- Amyloid of prion proteins (APrP)
- Miscellaneous heredofamilial forms: AApoA1, AGel, ALys, AFib, ACys

Non-fibrillar components

- Amyloid P component (AP)
- Apolipoprotein-E (apo-E)
- Sulfated glycosaminoglycans (GAGs)
- α-1 anti-chymotrypsin
- Protein X
- Other components (complement, proteases, membrane constituents)

Pathogenesis (Amyloidogenesis)

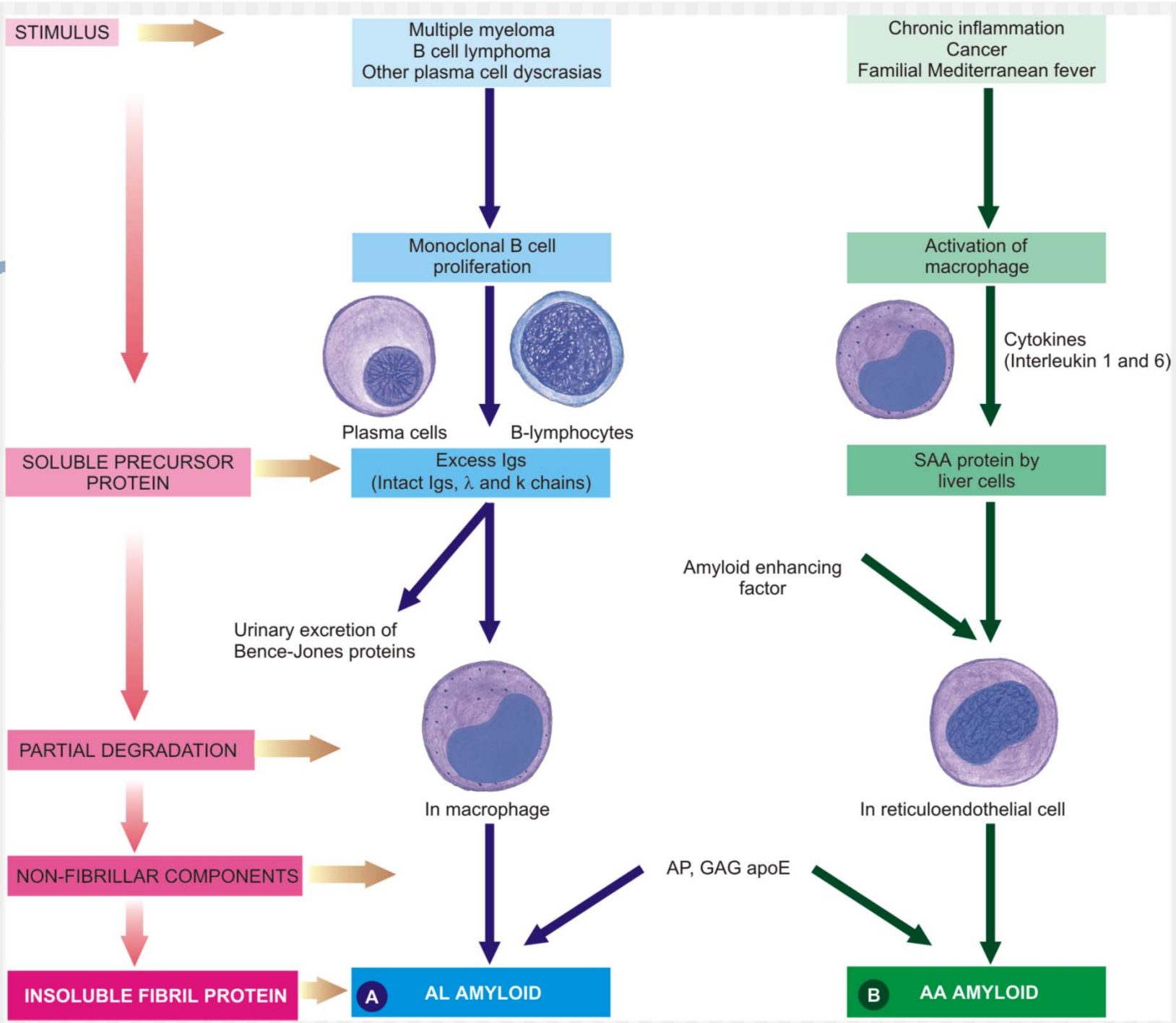
- Pool of amyloidogenic precursor protein
- A nidus for fibrillogenesis
- Partial degradation or proteolysis in macrphages, RE cells
- Exceptions to generalisation (ATTR, $A\beta_2M$, prionosis)
- Role of non-fibrillar components (AP, apoE, GAGs)

Deposition of AL amyloid

- Disorders of Ig synthesis
- Excessive Ig synthesis by monoclonal gammopathy
- Partial degradation
- Non-fibrillar components

Deposition of AA amyloid

- Raised SAA levels
- Increaded synthesis of SAA by liver in response to cytokines, IL1 & IL6
- Partial degradation
- Amyloid enhancing factor (AEF)
- Role of AP and GAGs


STIMULUS
Multiple myeloma
B cell lymphoma
Other plasma cell dyscrasias
Chronic inflammation
Cancer
Familial Mediterranean fever
Monoclonal B cell proliferation
Activation of macrophage
Cytokines (Interleukin 1 and 6)
Plasma cells
B-lymphocytes
SOLUBLE PRECURSOR PROTEIN
Excess Igs (Intact Igs, λ and k chains)
SAA protein by liver cells
Amyloid enhancing factor
Urinary excretion of Bence-Jones proteins
PARTIAL DEGRADATION
In macrophage
In reticuloendothelial cell
NON-FIBRILLAR COMPONENTS
AP, GAG apoE
INSOLUBLE FIBRIL PROTEIN
A
AL AMYLOID
B
AA AMYLOID