Metabolic disorders

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Metabolic disorders

acid base balance disorders

ion and water dysbalance

small molecules disorders
(aminoacids, saccharides)

complex molecules disorders
(intracellular accumulation)

extracellular matrix disorders

organelar metabolic disorders

Intracellular accumulation of ...

Lipids

Glycogen

Proteins

Intracellular accumulation of ...

Lipids

Glycogen

Proteins

Intracellular accumulation of lipids

Steatosis

- Acquired disorder of cellular metabolism

X

Lipidosis

- Inherited disorder of cellular metabolism

Lipomatosis

- Multiplication of adipocytes in organ
  - (heart, pancreas...)

Steatosis

- Intracellular accumulation of lipids from acquired causes
- Generally reversible – sign of cellular metabolic disturbance

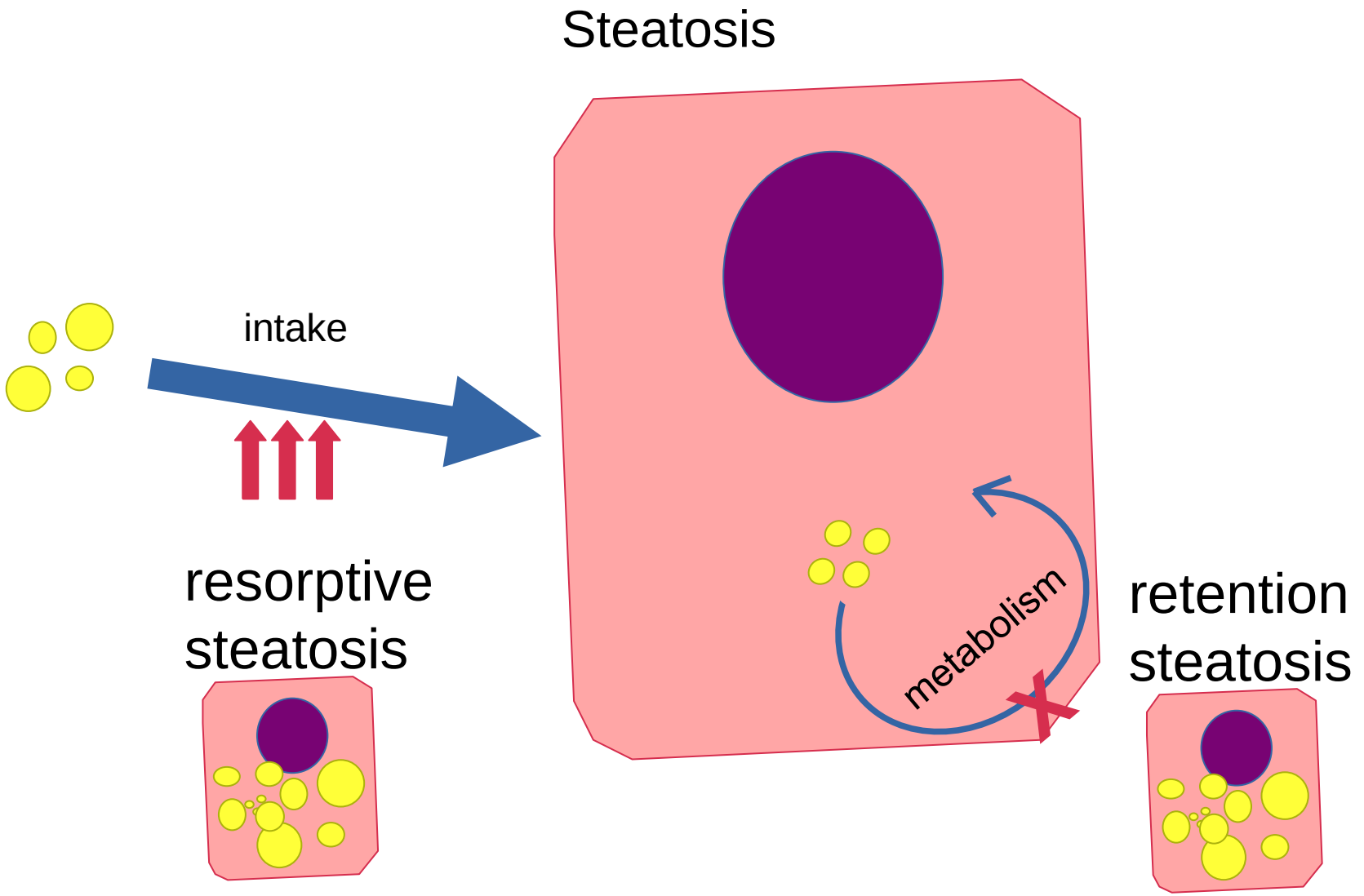
Macrovesicular

- triglycerids

Microvesicular

- glykolipids, phospholipids, cholesterol

normal liver


Steatosis
intake
resorptive steatosis
metabolism
retention steatosis

Resorptive steatosis

Chronic abscess → Membranes of degraded neutrophils → **Foamy macrophages**

= *pseudoxanthoma*

Resorptive steatosis

Cerebral infarction → Myelin sheets → **Foamy macrophages**

Resorptive steatosis

High blood level of cholesterol → High level of cholesterol in bile → **Foamy macrophages**

gallbladder cholesterolosis

Resorptive steatosis

High blood level of cholesterol → High level of cholesterol in bile → **Foamy macrophages**

gallbladder cholesterolosis

Resorptive steatosis

High blood level of cholesterol → **Foamy macrophages** in arterial intima → *Fatty streaks*

Resorptive steatosis

High blood level of cholesterol → **Foamy macrophages** in skin → *Xanthomas*

Resorptive steatosis

Obesity, dyslipidemy, diabetes → High blood levels of cholesterol and other lipids → *Non-alcoholic fatty liver disease (NALFD)*
- one of most common liver disorders
- may progress to cirrhosis

Retention steatosis

Venostasis → Hypoxia in liver centrilobular zone → ***Nutmeg liver*** steatosis + venostasis

Retention steatosis

Venostasis → Hypoxia in liver centrilobular zone → ***Nutmeg liver*** steatosis + venostasis

Retention steatosis

Alcohol or intoxication → Liver steatosis

Lipidosis

- Intracellular accumulation of lipids from inherited causes
- Defect of enzymes for metabolism of **complex lipids**
  - Lot of different diseases, depending on type of defficient **enzyme**

- Rare diseases = *orphan diseases*
  - Only a few hundreds in Czech Republic

Lipidosis

- All cells have enzyme deficit
- X
- Disease manifests only in specific tissues
  - Spleen, liver, bone marrow – macrophages – metabolism of phagocyted membranes
  - Brain – metabolism of sphingolipids of membranes

Lipidosis
Gaucher disease

- Defect of **glucocerebrosidasis** → accumulation of glucocerebrosid
- Prevalence 1:80 000, but much more higher in Ashkenazi Jews (up to 1:500)
- **Macrophages** with *“wrinkled paper appearance”*

Lipidosis
Gaucher disease

- Accumulation of macrophages
    - Hepatosplenomegaly – spleen up to 10 kg
    - Accumulation in bone marrow
        - Inhibition of hematopoesis
            - Anaemia
            - Thrombocytopaenia
            - Leucopaenia
        - Pain
        - Fractures

Other lipidoses

Tay-Sachs disease

- Accumulation of gangliosides in *neurons*
- Rapid psychomotoric retardation – death in age of 3-4 years
- "*Cherry-red spot"* in retina – foveola centralis is the only spot in retina without lipid accumulation

Fabry disease

- XR inherited
- Visceral symptoms
  - Periferal neuropathy
  - Kidney failure
  - Myocardial hypertrophy

Other lipidoses

Niemann-Pick disease

- Types A and B
  - Deficit of sphingomyelinasis
  - Accumumulation of sphingomyelin in macrophages (spleen, liver, bone marrow)
    - CNS involvement in type A (not in type B)

- Type C
  - Defect of **transport protein** (not enzyme)
  - Heterogeneous symptomes
    - Mostly neurodegenerative

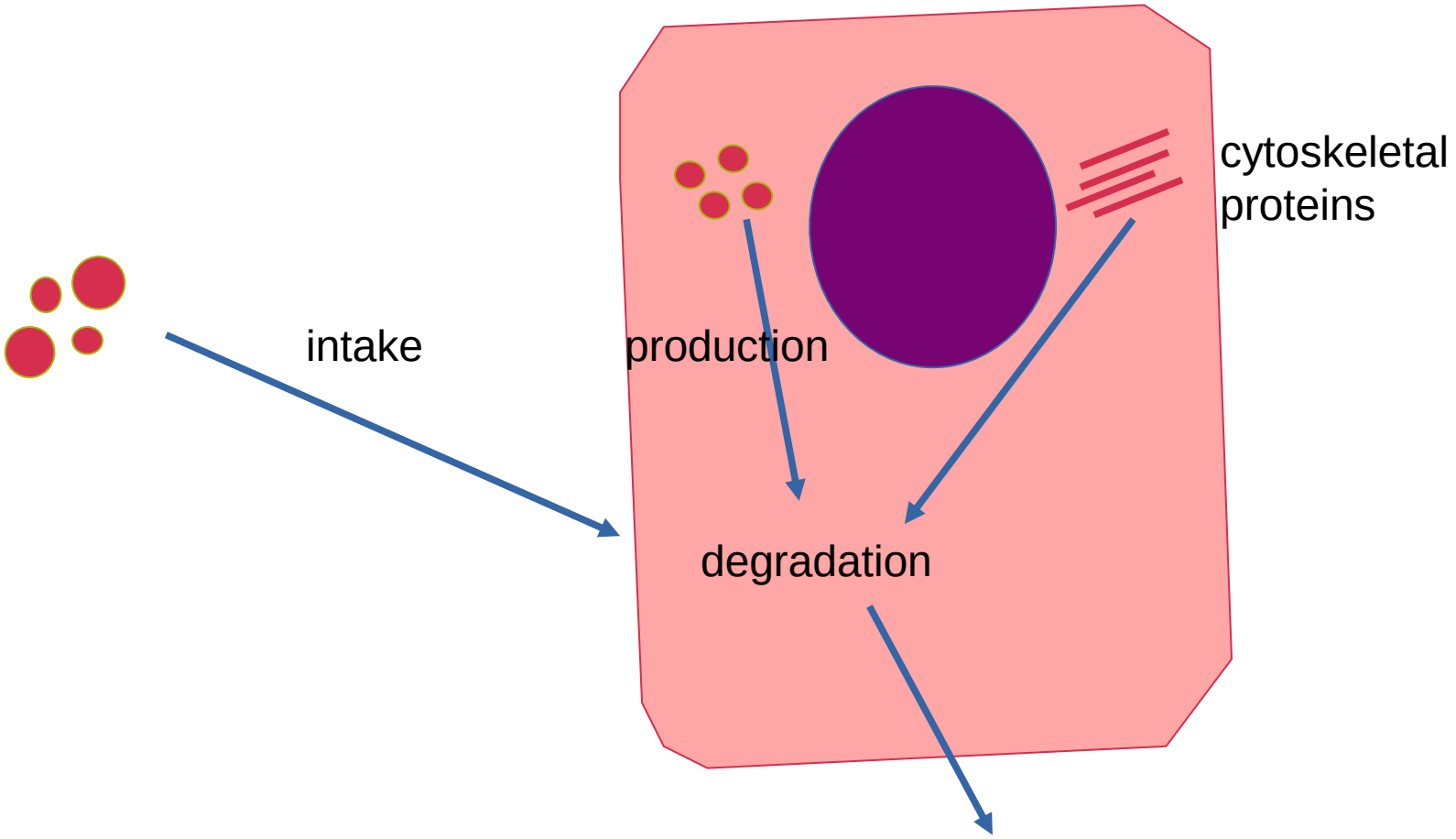
Intracellular accumulation of ...

Lipids

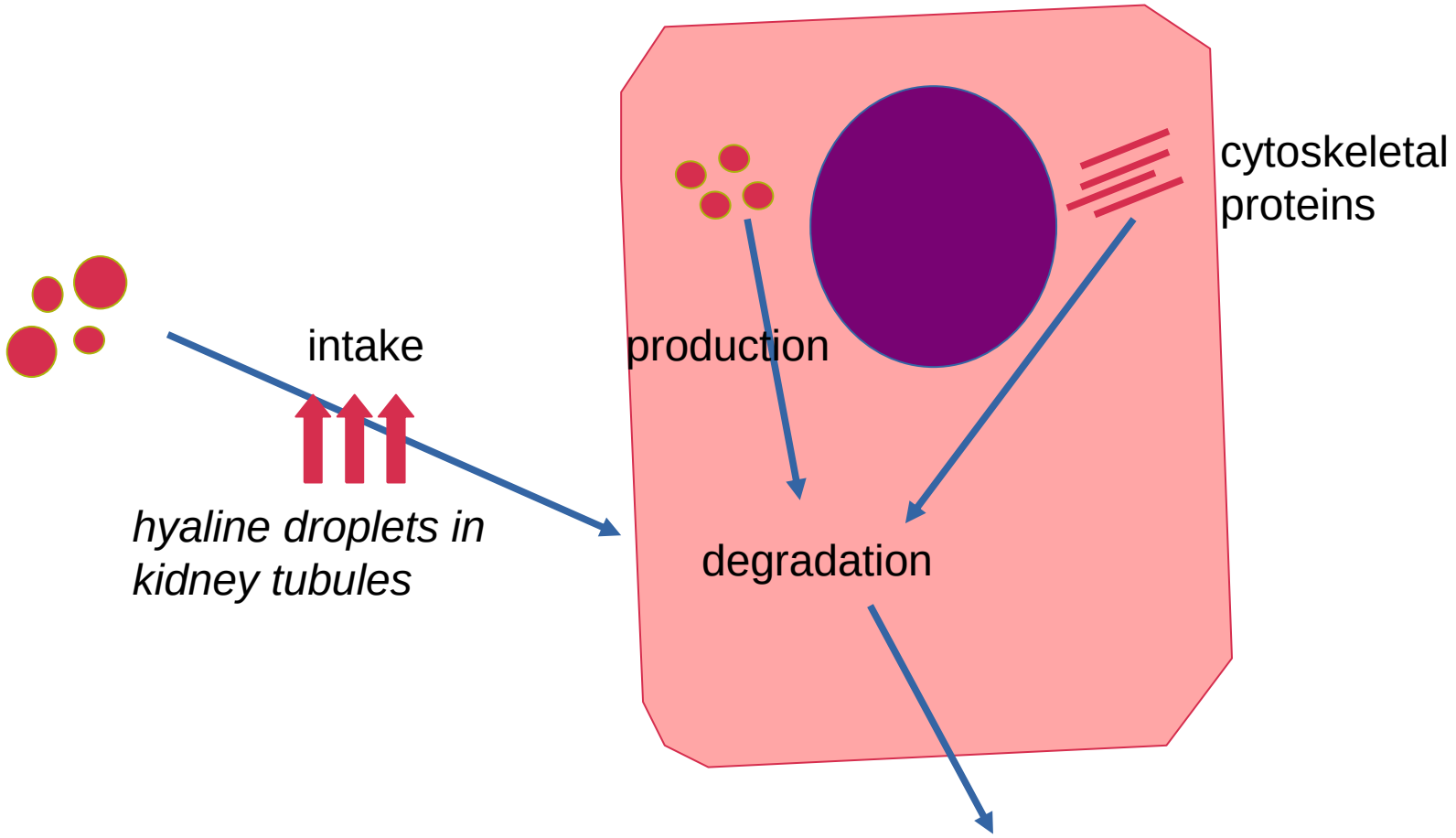
Glycogen

Proteins

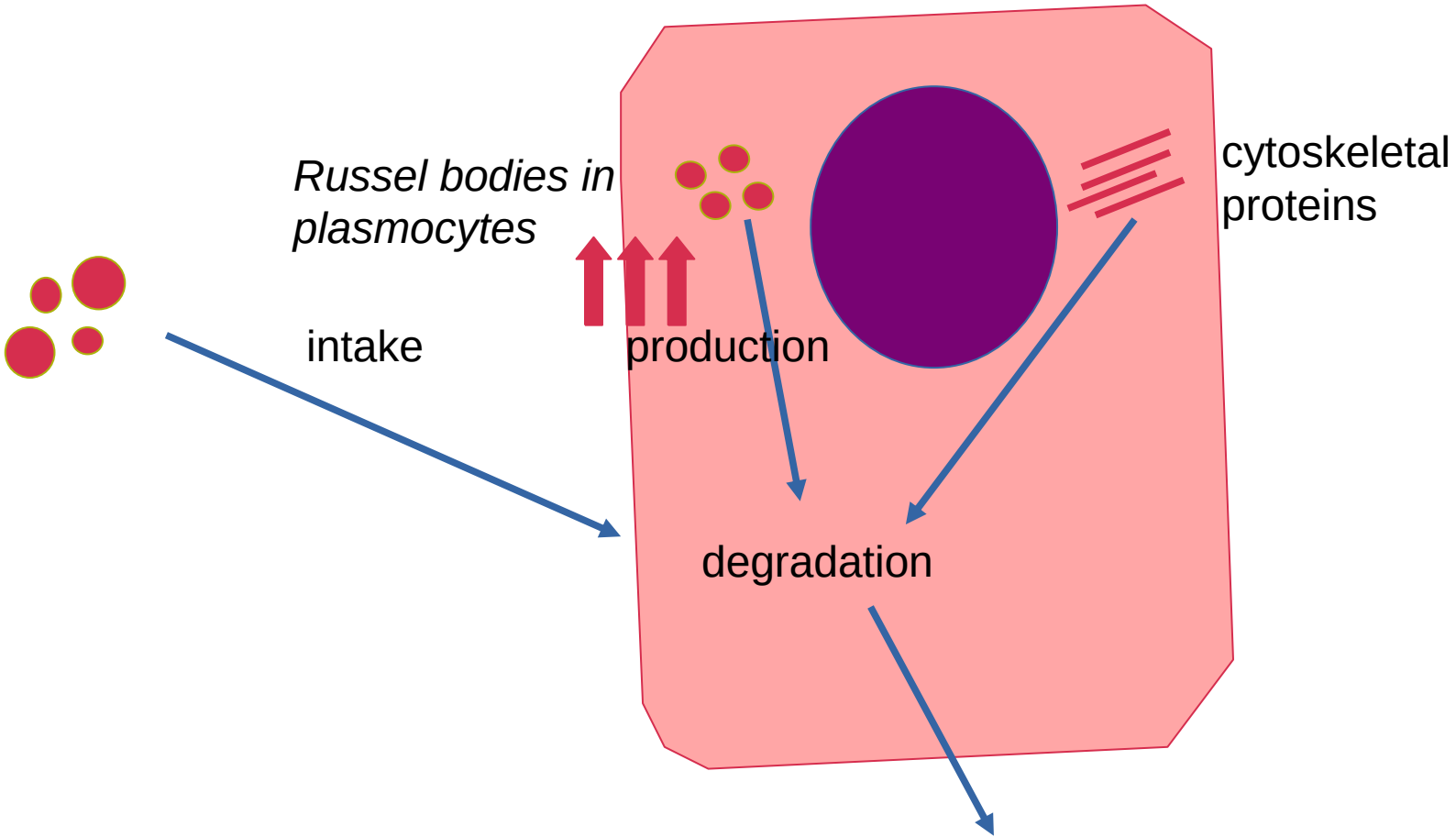
Intracellular accumulation of proteins



Intracellular accumulation of proteins

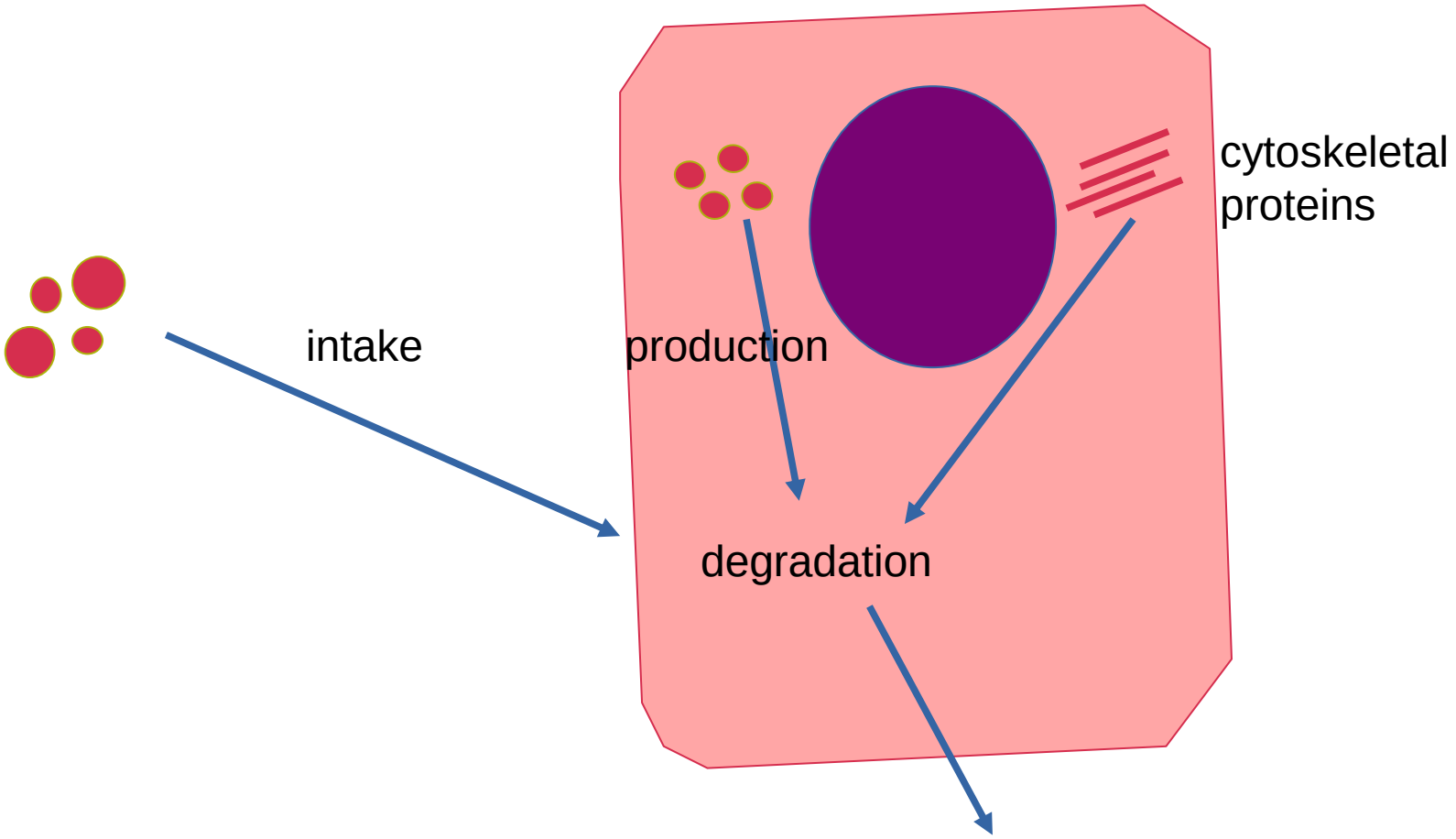


Intracellular accumulation of proteins

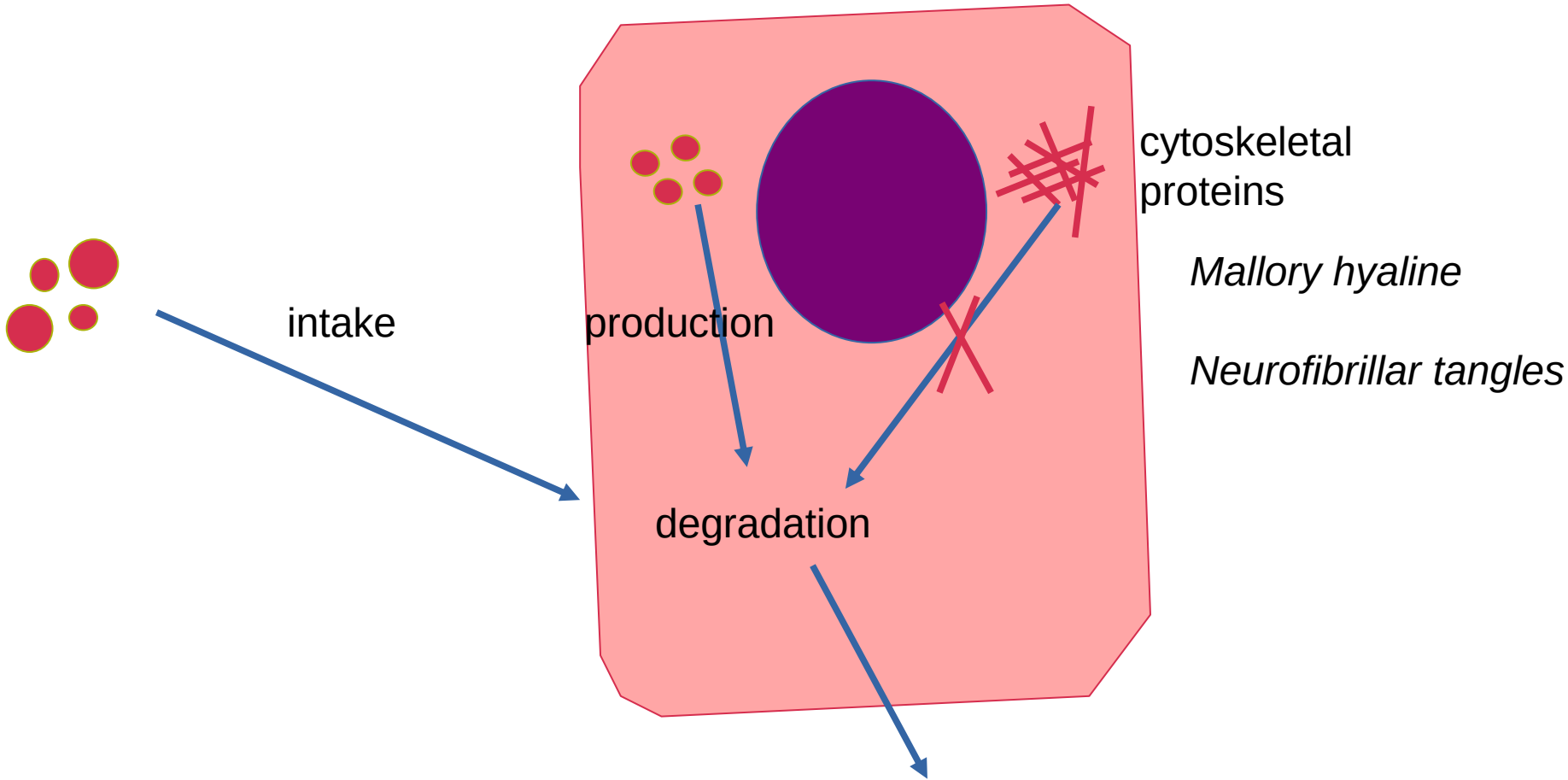


Russel bodies
- accumulation of immunoglobulines produced in plasmocytes
- chronic inflammation or plasmocytoma

Intracellular accumulation of proteins



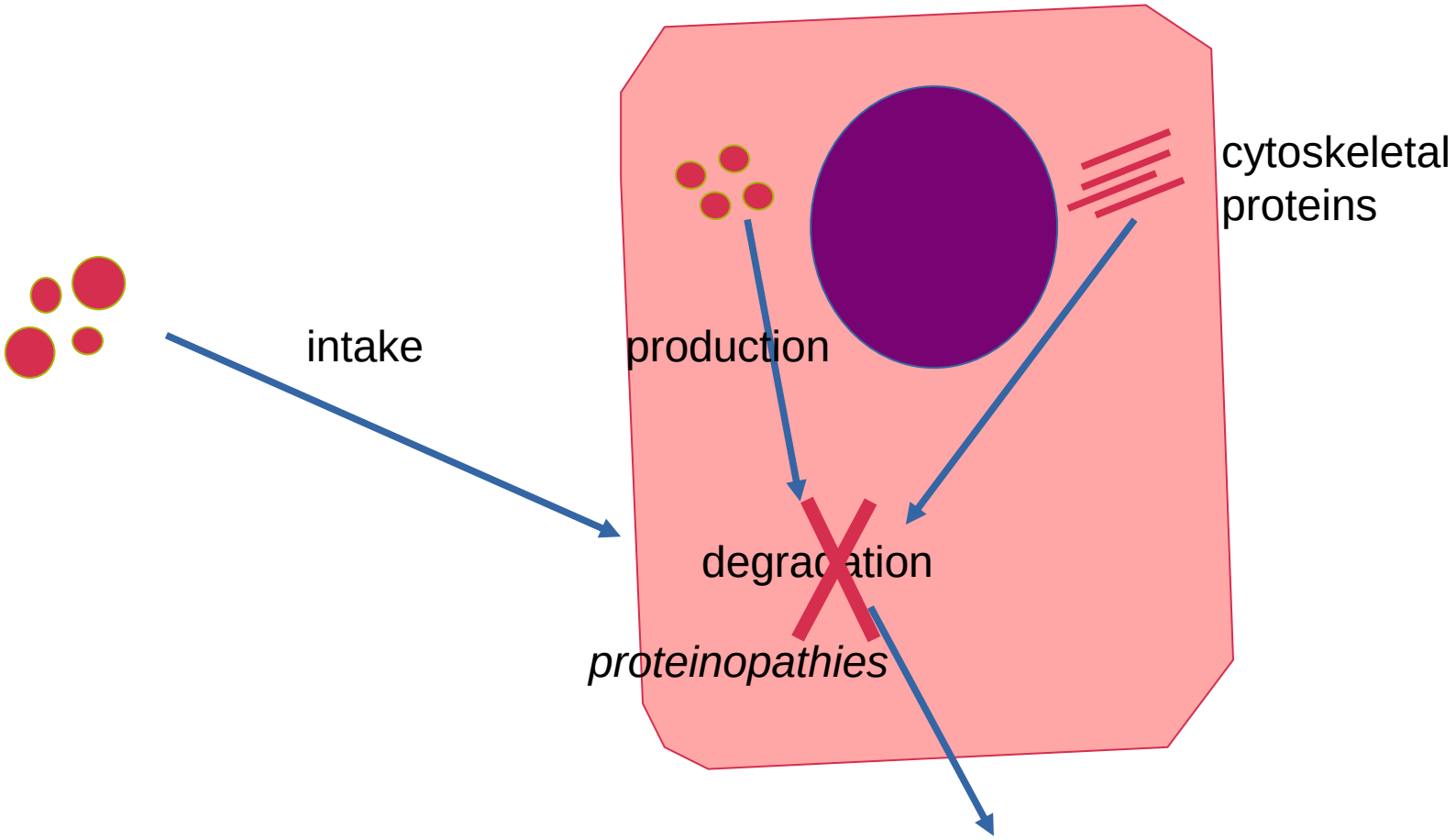
Intracellular accumulation of proteins



Mallory hyaline
- liver
- accumulated cytokeratines damaged by alcohol

Neurofibrillar tangles
- brain
- Alzheimer disease

Intracellular accumulation of proteins



Proteinopathies

Protein misfolding disorders

- abnormal conformations of alpha-helix and beta-sheets (more beta-sheets)

Misfolded proteins are

- unable to be degraded by enzymes
- not immunogenous
- leading the cell to apoptosis

- ...also loss of normal protein function (i.e. alpha1-antitrypsine)

Proteinopathies

Etiology

Gene mutation
- familiar type of *Creutzfeldt-Jakob disease*
- inherited *alpha1-antitrypsine defficiency*

Acquired disorders of protein folding – toxic damage or senescence
- *Alzheimer disease*
- *Parkinson disease*

Chaperonopathies
(chaperones – cytoplasmatic structures protecting protein folding)

Intracellular accumulation of ...

Lipids

Glycogen

Proteins

Glycogen storage diseases

Liver

- Degradation of glycogen for regulation of glucose blood level

Muscles

- Glycogen for own metabolism
- Hyperaccumulated glycogen impairs muscle function

Predominantly **hepatal** glycogen storage diseases

von Gierke disease (GSD I)

- Defficiency of glucose-6-phosphatase → normally changes glucose-6-phosphate into free glucose, possible to transfer in blood

- Hypoglycemia
  - After stress or physical activity
  - Hypoglycemia of newborns in most serious cases
- Hepatomegalia
  - Accumulation of glycogen

Predominantly **muscular** glycogen storage diseases

Pompe disease (GSD II)

- Defficiency of alpha-1,4-glucosidase (acidic maltase) – lyzosomal enzyme
- Curable with enzyme replacement therapy

- *Infant type*
  - Cardiomyopathy, hypotonia etc. in first year of life

- *Late onset type*
  - Myopathy – predominantly in proximal muscles

McArdle disease (GSD V)

- Defficiency of muscle phosphorylase – cutting glucose-1-phosphate from glycogen
- Muscle weakness, cramps and myoglobinuria

Organelar metabolic disorders

Lysosomes

Peroxisomes

Mitochondria

Organelar metabolic disorders

Lysosomes

Peroxisomes

Mitochondria

Lysosomal disorders

Lysosomes are normally part of heterophagy (phagocytosis, endocytosis) and autophagy.

- Accumulation of metabolic intermediate product
  - May be toxic
  - May cause defficiency of end product

- Secondary accumulation
  - Impaired autophagy due to lysosomal dysfunction

Lysosomal disorders

- Lipidoses
  - Gaucher disease
  - Tay-Sachs disease
  - Fabry disease
  - Niemann-Pick disease

- Glycogenosis – only Pompe disease (GSD II)

- Mucopolysacharidoses
  - Disorders of extracellular matrix
    - Hurler syndroma
    - Hunter syndroma
    - Morquio syndroma

Therapy of lysosomal disorders

Historically untreatable fatal diseases.
New ways of treatment available:

- *Enzyme replacement therapy*
  - substitution of defficient enzyme
    - Gaucher disease
    - Pompe disease
    - Hurler syndrome
    - etc.

- *Molecular chaperon therapy*
  - Helps the defficient protein to fold correctly
    - i.e. Gaucher disease

- *Substrate reduction therapy*

Organelar metabolic disorders

Lysosomes

Peroxisomes

Mitochondria

Peroxisomal disorders

Peroxisomes normally metabolise very long chain fatty acids (VLCFA).

- Multiorgan disorder with neurological symptoms, liver dysfunction, craniofacial dysmorphy and other bone deformities.

- *Zellweger syndrome*
- *X-linked adrenoleukodystrophy*

Organelar metabolic disorders

Lysosomes

Peroxisomes

Mitochondria

Mitochondrial disorders

Maternal hereditability
Heteroplasmia
Threshold effect

Symptoms in most energetically dependent tissues

- CNS
- Muscles
- Kidneys
- Heart

- - lactate acidosis

- MELAS syndrome
  - *Myopathy, Encephalopathy, Lactate Acidosis, Stroke-like events*
- MERRF syndrome
  - *Myoclonical Epilepsy and Ragged-Red Fibres*
- Leber’s hereditary optical neuropathy

Extracellular matrix disorders

collagen

fluids

mucopolysaccharids

Extracellular matrix disorders

collagen

mucopolysaccharids

Acquired extracellular matrix disorders

Fibrosis
Sclerosis/hyalinisation

collagen

mucopolysaccharids

Fibrinoid change
Myxoid change

Inherited extracellular matrix disorders

elastin

collagen

mucopolysaccharids

Inherited extracellular matrix disorders

elastin

collagen

mucopolysaccharids

Inherited disorder of elastin
Marfan syndrome

Mutation of fibrilin gene → impaired elastin synthesis

- High astenic body, long members, long thin fingers
- Joint hypermobility
- Lens subluxation
- Cardiovascular disorders
  - Mitral valve prolaps
  - ***Cystic medionecrosis*** *of aorta* – prone to rupture and disection

Inherited disorder of colagen
Ehlers-Danlos syndrome

Mutation of gene for some colagen subunit

- Joint hypermobility
  - Subluxations
  - Arthrosis
- Vessel wall fragility

Inherited disorder of mucopolysaccharides = *mucopolysaccharidoses*

Lysosomal disorders

Gene defect of lysosomal enzymes => impaired degradation of extracellular matrix mucopolysaccharides => accumulation in phagocyting cells

- **CNS damage**
  - Accumulation in microglia => long time inflammatory stress => secondary destruction of neurons – *“neuroinflammation”*
- Eye damage
  - Accumulation in cornea – opacity and loss of transparency => blindness
- **Skeletal deformations**
  - Accumulation in chondrocytes => impaired enchondral ossification => disorder of long bones growth
- **Soft tissues deformities**
- Cardiovascular disorders
  - Mitral valve regurgitation
  - Intimal fibrosis

Inherited disorder of mucopolysaccharides = *mucopolysaccharidoses*

Hurler syndrome (MPS type I)

- Defficiency of *alpha-L-iduronidase* => accumulation of heparan-sulphate and dermatan sulphate
- ***Gargoylism***
- Cognitive impairment
- Cardiovascular complications – death arround 10 years

Inherited disorder of mucopolysaccharides = *mucopolysaccharidoses*

Hunter syndrome (MPS type II)

- X-linked disorder
- Milder clinical course than MPS type I

Morquio syndrome (MPS type IV)

- AR disorder
- May have quite normal cognitive functions

Another acquired disorders of extracellular matrix

fluids

collagen

mucopolysaccharids

+ deposits of pathological substances

calcifications

amyloid

Calcification

Dystrophic

In **pathologically altered** tissues.

- Necrosis
  - Caseous necrosis (TBC)
- Newly formed fibrous tissue in inflammation
  - *Pericarditis petrosa*
  - *Porcelain gallbladder*
- Hyaline degenerated fibrous tissue
  - Mitral valve calcification
- Atherosclerotic plates
- Tumors
  - Leiomyoma

Metastatic

In **normal** tissues during **hypercalcemia**.

Hypercalcaemia

- Parathyroideal adenoma
- Paraneoplastic production of parathormone in other tumor
- Plasmocytoma
- Sarcoidosis

- Tissues producing acidic metabolites =>
- => having alcalic stroma
  - **Lungs**
  - **Kidneys**
  - **Stomach**

Calcification

Tuberculosis

Calcification

Low grade glioneural tumor

Calcification

Lung – metastatic calcification

Calcification

Kidney – metastatic calcification

Amyloidosis

Accumulation of amorphic protein material in **extracellular** matrix.

Amyloidosis

Accumulation of amorphic protein material in **extracellular** matrix.

Amyloidosis

Kongo red staining

Amyloidosis

Kongo red staining in *polarized light*

Amyloid

Lot of different types of proteins (nowadays 37 suspitious proteins) are able to form amyloid.

Changed protein structure – majority of beta sheets =>

=> Unable to be degradated => Accumulation

Amyloidosis

- Accumulation in various locations

- Vessel walls
- Kidneys (mainly in glomeruli)
- Spleen
  - Red pulp – *“ham-like spleen”*
  - White pulp – *“sago spleen”*
- Heart – myocardium
- Muscles – tongue
- GIT mucosa
- Adipose tissue – good material for diagnostics

- Amyloid is *toxic* for neighbouring cells.
- Impaired diffusion through thickened vessel walls.
- Mechanical obstruction.

Amyloidosis

- Generalised amyloidoses
  - AL amyloidosis
  - AA amyloidosis
- Localised amyloidoses
  - Endocrine amyloidosis
  - Senile (ATTR) amyloidosis
  - Amyloidosis of chronicly dialised patients
- Hereditary amyloidoses
  - Hereditary transthyretin amyloidosis
  - Familiar mediterrean fever

AL amyloidosis

- So called *primary amyloidosis*.

- Associated with hemathological malignity – ***plasmocytic myeloma*** or MGUS
  - Tumor cells differentiate to plasmocytes – producing immunoglobulines – monoclonal production (physiological is polyclonal) -
    - - only one type of *kappa* or *lambda* light chains

- Immunoglobuline light chains can aggregate into amyloid
  - Immunohistochemical visualisation

- TREATMENT
  - Treat the hemathological malignity

AA amyloidosis

- So called *sedondary amyloidosis*
- ***Serum amyloid protein A*** (SAA protein) – one of proteins of acute inflammatory phase

- Associated with chronic inflammation
  - Chronic infections
    - Osteomyelitis
    - Tuberculosis
  - Autoimmune diseases
    - Revmatoid arthritis
    - Crohn disease
    - Psoriasis
    - Bechterev disease

- TREATMENT
  - Treat the cause of chronic inflammation
    - Antibiotical therapy for chronic infections
    - Immunosuppresive therapy for autoimmune diseases

Other amyloidoses

Endocrine amyloid

- Medullary carcinoma of thyroid gland
- Insulinoma

Senile amyloidosis

- Predominantly in heart
- Transthyretin as precursor of amyloid

Amyloidosis of chronically dialised patients

- Beta-2 microglobulin – ineffectively eliminated by hemodialisis
- Affinity to osteoarticular system – arthropaties, carpal tunel syndrome

Alzheimer disease

- A-beta amyloid

Hereditary amyloidoses

Hereditary transthyretine amyloidosis
= *familiar amyloid polyneuropathy*

- Mutated transthyretine – prone to accumulation and amyloidogenesis
- TREATMENT
  - Liver transplantation

Familiar mediterrian fever

- Mutation of gene for *pyrin* – pathologicaly activated pyrin activates hyperproduction of IL-1 => *persistent inflammation*
- Hyperproduction of SAA => AA amyloidosis

Recapitulation

Recapitulation

Intracellular accumulation of metabolites

Lipids
- steatosis
X
- lipidosis
- lysosomal diseases

Proteins
- hyperproduction, increased intake
- misfolding

Glycogen
- glycogen storage diseases

Recapitulation

Organelar metabolic disorders

Lysosomes
- lipidoses
- Pompe disease
- mucopolysacharidoses

Peroxysomes
- Zellweger syndrome
- VLCFA metabolism

Mitochondria
- different hereditability
- MELAS
- MERRF

Recapitulation

Extracellular matrix disorders

	Acquired	**Inherited**
Normal components	Fluids + -	Marfan syndrome – elastin
	Collagen	Ehlers-Danlos syndrome – collagen
	Mucopolysacharides	Mucopolysaccharidoses - Hurler syndrome - Hunter syndrome - Morquio syndrome
Pathological components	Calcifications - dystrophic - metastatic	
	Amyloidosis - AL - AA	