LEUKOCYTES – ONCOLOGICAL AND NON-ONCOLOGICAL DISORDERS

ANEMIAS, LEUKOPENIAS, LEUKOCYTOSIS, LEUKEMIAS, THROMBOCYTOPENIAS, THROMBOCYTOPATHY, THRMBOCYTEMIAS

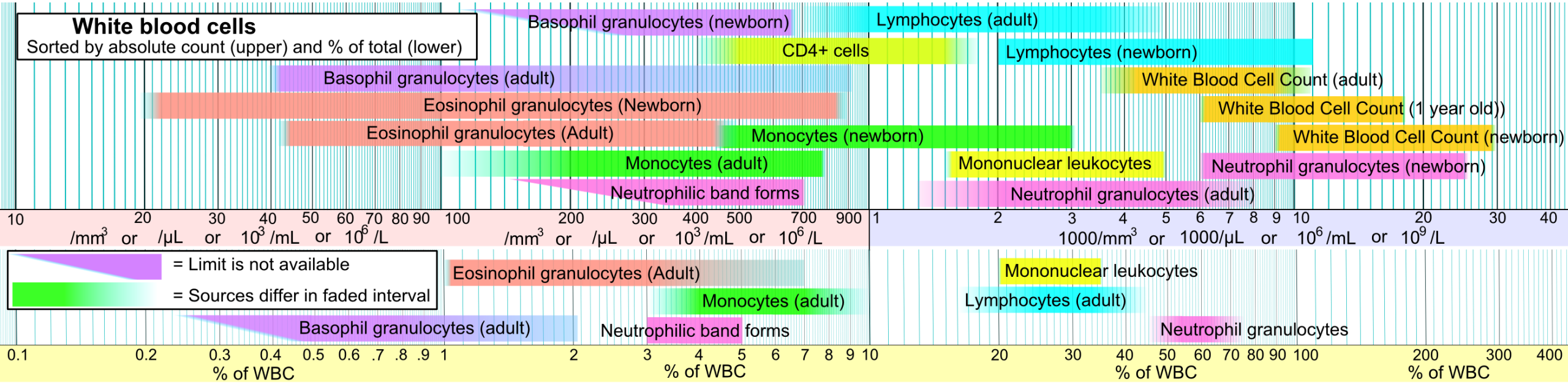
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2026/2027

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WHITE BLOOD CELLS – LEUKOPENIA, LEUKOCYTOSIS, LEUKEMIA

PHYSIOLOGICAL DATA OF WHITE BLOOD CELLS



https://upload.wikimedia.org/wikipedia/commons/b/b5/Reference_ranges_for_blood_tests_-_white_blood_cells.png

LEUKOPENIA, NEUTROPENIA, LYMPHOPENIA

- Leukopenia - <4000 cells/µl
- Neutropenia - <1500 cells/µl
- Lympho(cyto)penia – adults <1000 cells/µl (symptomatic <300 cells/µl) vs. children <3000 cells/µl

- Causes
  1. Decreased production
  2. Increased destruction or cells utilisation

When you haven't been paying attention to the lecture and the professor asks you what labs you would like to order



https://i.redd.it/44sge4vislk11.png

LEUKOPENIA

- Drop in one or more white blood cells subpopulations in peripheral blood
- It is a SYMPTOM!!!

- „Leukopenia“ and „neutropenia“ might be used interchangeably -> neutrophiles comprise 50-75 % of all leukocytes in adults

- Agranulocytosis – clinical manifestations of severe neutropenia
  - Fatigue, fever, severe to fatal course of (even mild) diseases
  - Oral cavity – mucosa ulcers –gingiva and pharynx

LEUKOPENIA CAUSES

Decreased production

- Aplastic anemia
- Genetics
- Autoimmune disorders
- Medication induced
- Onkohematologic diseases
  - Leukemias and lymphomas

Increased utilisation and/or destruction

- HIV infection
- Onkohematologic diseases
  - Leukemias and lymphomas

NEUTROPENIA AND AGRANULOCYTOSIS

- Neutrophils
  - 50–75 % of all leukocytes
  - Non-specific defense, „first-contact troops“
  - Exposure to viruses, bacteria, physical and chemical factors, malignancies
  - Functions – DEGRANULATION, phagocytosis, chemotaxy and inflammatory reponse regulation
- Neutropenia degrees
  - Mild– 1000 – 1500 cells/µl
  - Moderate – 500 – 1000 cells/µl
  - Severe - <500 cells/µl (AGRANULOCYOSIS, some sources state <100 cells/µl)
  - Critical - <100 cells/µl -> extreme morbity and mortality risk

AGRANULOCYTOSIS

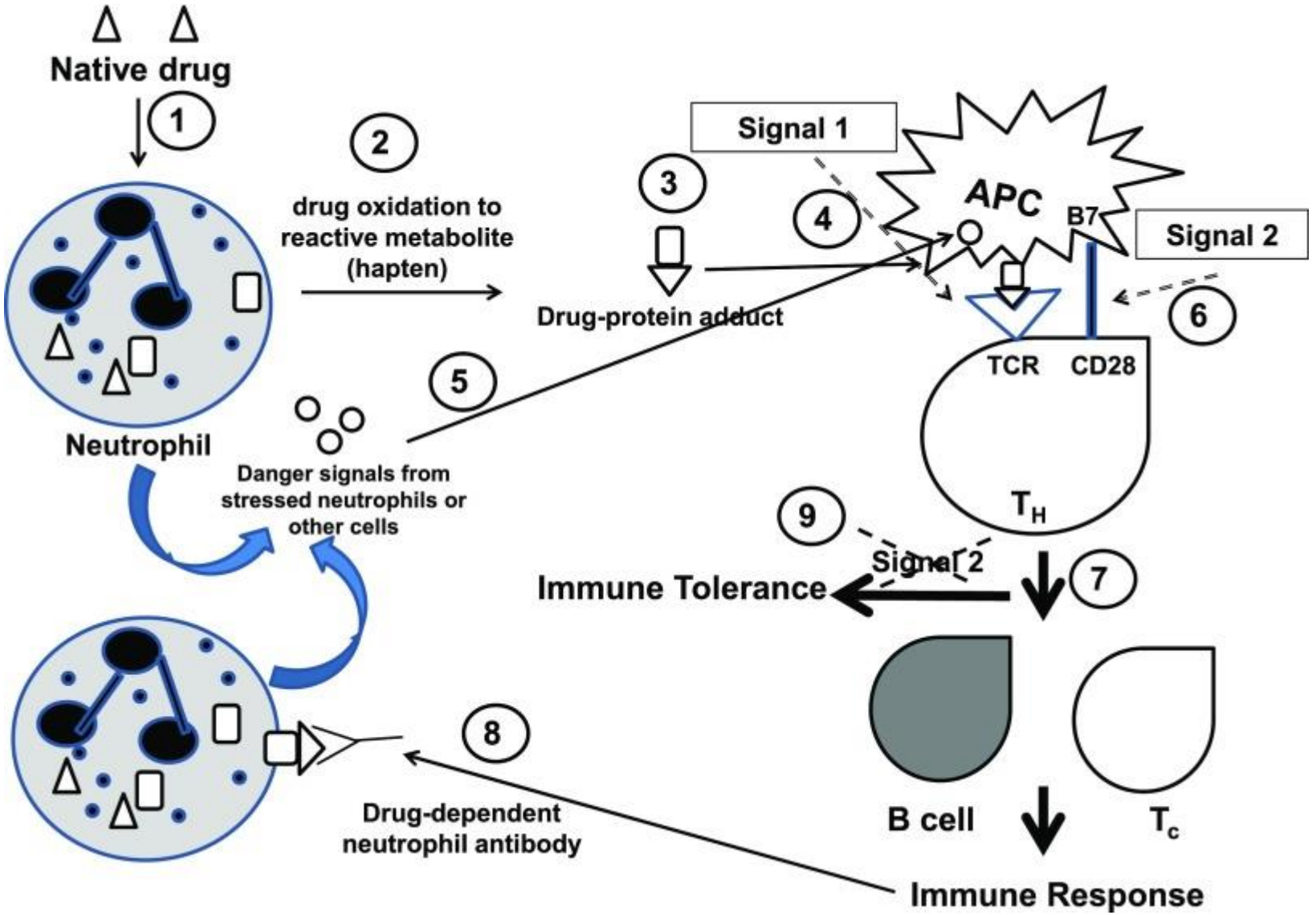
- Congenital (rare)
  - AD, ar, X-rec. – genes ELANE, HAX1, WAS (X-rec.), G6PC3, etc.
  - Autoimmune neutropenia
- Decreased production
  - Chemotherapy – destruction/"crippling" of hemopoetic stem cell – e.g. adriamycin, doxorubicin, cyclophosphamide, cisplatina, paclitaxel, carboplatina, etc.
  - Onkohematological diseases – myelodysplastic sy., leukemias, lymphomas, etc.
  - Nutrients defficiency – vit. B9, B12
- Increased destruction
  - Autoimmune diseases – e.g. systemic lupus erythematosus, Crohn disease, rheumatoid arthritis
  - Drug-induced – idiosyncratic drug reactions

ELANE – elastase, neutrophile expressed, HAX1 – proteín X1 asociovaný s hematopoeticky bunkovo-špecifickým substrátom Lyn 1, G6PC3 – katalytická podjednotka glukóza-6-fosfatázy

DRUG INDUCED (IDIOSYNCRATIC) NEUTROPENIAS

1. Hapten hypothesis
   - A condition to create a covalent bond with neutrophils surface glycoproteins
   - Drugs undergoing biotransformation -> more reactive metabolites, longer elimination half-time
   - „Allo-antigen“ established -> DDABs targetting neutrophils produced
   - „Myeloperoxidase“ hypothesis -> biotransformation process may be also in neutrophils (partial – cells affected down to promyelocyte)
2. „Danger“ hypothesis – „two signals“ hypothesis
   - A hapten – signal 1, „danger“ signal 2 – HSPs, hyaluronans fragments
     - Signal 2 as the decisive -> absence leading to immunotolerance vs. presence to neutrophiles destruction
   - „Stressed “ neutrophiles -> „danger“ signals produced
   - Drugs congujates -> inflammasome activation -> IL-1β and IL-18 produced

DDABs – drug-dependent antibodies, HSPs – heat shock proteins



https://pmc.ncbi.nlm.nih.gov/articles/PMC6142577/figure/F1/

DRUG INDUCED (IDIOSYNCRATIC) NEUTROPENIAS

- HLA antigens association -> immune system „participation“
  - Graves disease -> HLA-B*38:02 ev. HLA-DRB1*08:03.
- CAVE! – decreased neutrophils count at onset of therapy - <1500 bb/µl

NEUTROPENIA AND AGRANULOCYTOSIS SIGNS

- Repeated and prolonged infections
- Fever (severe, often >38 °C)
- Fatigue
- Pharyngitis
- Lymphadenopaties (often painful)
- Oral cavity and perianal ulcerations
- Pain, swelling and rush at infection site
- Diarrhea
- Burning sensation during urination, painful urination, urgencies; vaginal discharge, pruritus, pain

GENERAL RULES OF NEUTROPENIA/AGRANULOCYTOSIS MANAGEMENT

General rules

- Discontinuation of medication causing neutropenia/agranulocytosis (consider benefit-to-risk ratio or dosage alteration)
- Corticosteroids to contain autoimmunity to be considered
- G-CSF administration
  - Some clinical trials showed benefit (neutropenia duration decreased from cca. 9 days to 4-5 days)
  - Controversial, careful consideration

Infection prevention

- Strict hygiene rules
  - Not sharing dinnerware, hands cleaning, own towels, etc.
- Getting vaccinations available
- Gardening with gloves only
- Meat to be separated from vegetables, to be processed as the last part of meal
- To avoid animal feces (cats, dogs, bunnies, etc.) and diapers change (if necessary, gloves and a surgical mask to be used)
- Prophylactic medication administered (respiration, urogenital, probiotics!)
- Administration to hospital in case of severe agranulocytosis (strict aseptic and antiseptic protocol)

LYMPHOPENIA

- Decrease in one or more lymphocytes subpopulations under physiological levels for that certain age group
  - Adults <1000 cells/μl
  - Children below 2 years of age <3000 cells/μl
    - Adults have a neutrophils prevailing with 25 % lymphocytes only vs. 67-38 % lymphocytes in children depending on their age
- Classification
  - T-lympho(cyto)penia – CD4+ „officers and generals“ and CD8+ „melee fighters, special commandos“
  - B-lympho(cyto)penia – antibodies production, „long-range artillery“
  - NK-lympho(cyto)penia – „police“ – destruction of infected, invaded and altered cells

LYMPHOPENIA CAUSES

Acute lymphopenia

- Acute viral infection (influenza H1N1, SARS-CoV-2, hepatitis)
- Starvation
- Physical/psychical stress
- Corticoseroids administration
- Chemotherapy/radiotherapy
- Ionising radiation exposure (nuclear power plant disaster, „dirty“ bomb)

Chronic lymphopenia

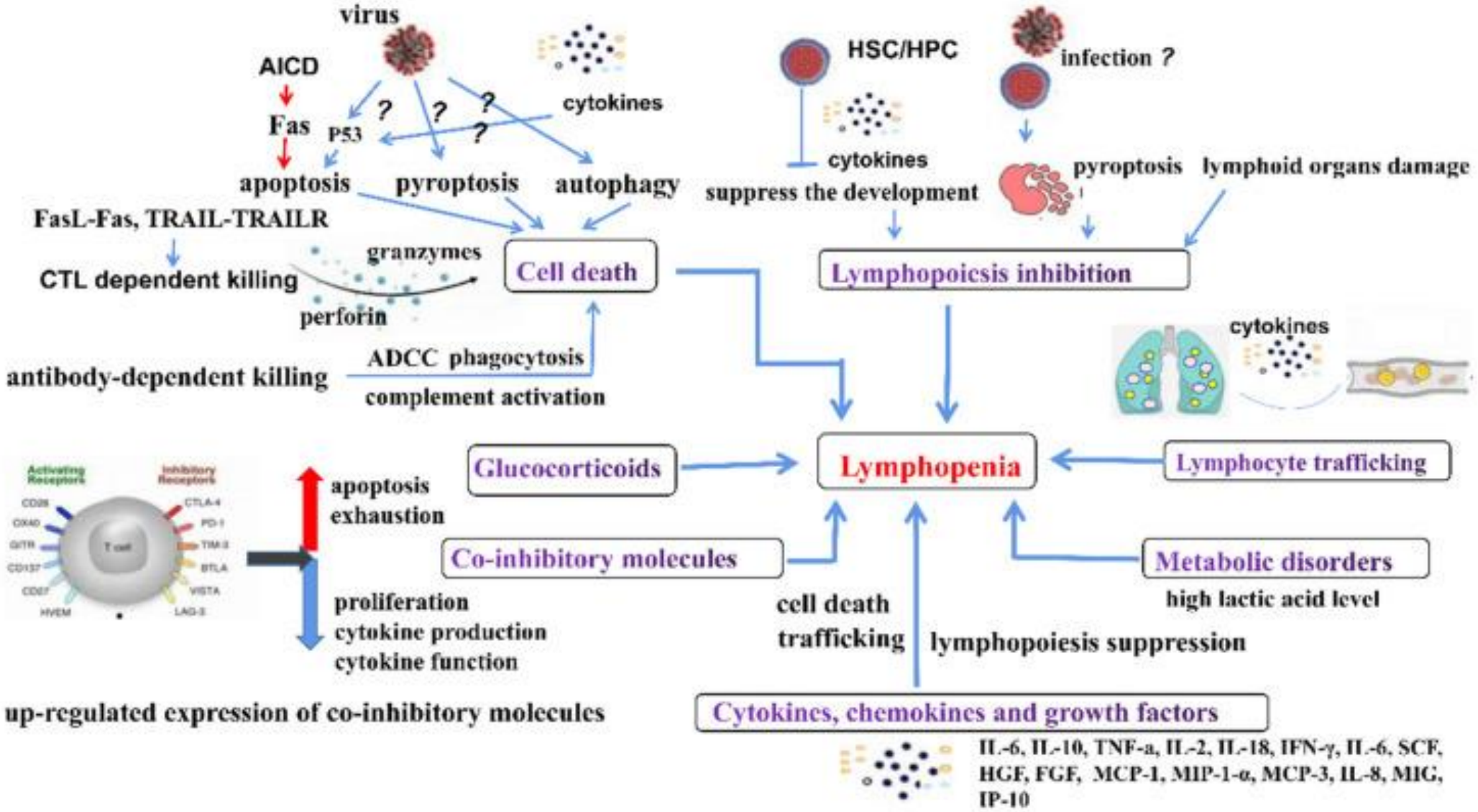
- Genetics
  - Monosomy 22q11.2 (DiGeorgeov sy), Wiscott-Aldrich sy, SCID, ataxia teleangiectatica, WHIMs
- Malnutrition
- Autoimmune diseases – e.g. lupus erythematosus, rheumatoid arthritis, myasthenia gravis
- Chronic infections e.g. HIV, miliary TBC
- Leukemias and lymphomas
- Long-term corticosteroids use, Cushing syndrome
- Sarcoidosis

SCID – severe combined immunodeficiency, WHIMs – wharts, hypogammaglobulinemia, infections and myelokathexis – mature neutrophiles and T-, B- and NK-lymphocytes retention in bone marrow; gain-of-function (?AD) CXCR4 receptor mutation (with ligand SDF-1; stroma-derived factor), for cell release into peripheral blood an inactivation of this receptor is necessary)

LYMPHOPENIA PATHOMECHANISMS (SELECTED EXAMPLES)

1. Transient lymphopenia during viral infections
   - Cytokines selection affected, lymphopoesis blocked, cell death induction
   - Possible cell death types of lymphocytes for this scenario
     - Apoptosis – direct infection e.g. MERS-CoV, HIV, measles
     - Pyroptosis – e.g. HIV, SARS-CoV-2 ->↑↑↑IL-1β
     - Autophagy – detection of gp41 in non-infected CD4+ lymphocytes in HIV+ patient
     - ADCC – viral antigens targetting antibodies attack also infected cells (surface antigen match)
     - Viral-specific CD8+ cytotoxic Ly -> FasL/FasR and TRAIL/TRAILR interaction
     - Dendritic cells – FasL/FasR – influenza virus H5N1 upregulated FasL on dendritic cells -> viral-specific CD8+ Ly destruction
     - Activation-induced cell death -> SARS-CoV-2, RSV, CDV -> FasL expression indirectly proportional to CD4+ count -> surrounding T-Ly destruction

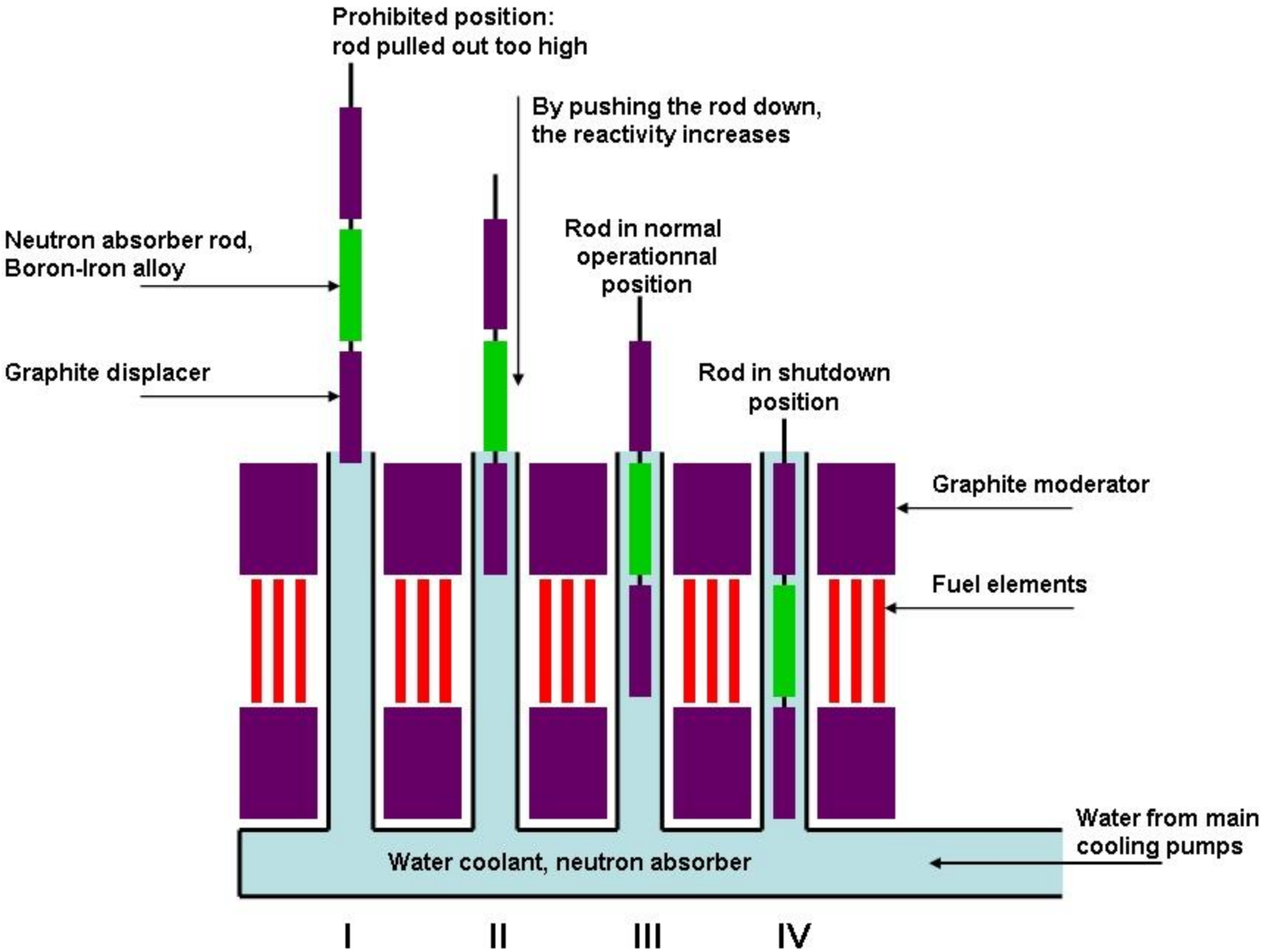
TRAIL(R) – TNF-related apoptosis inducing ligand (receptor), CDV – „canine distemper virus“


virus
AICD
Fas
P53
?
?
?
?
cytokines
apoptosis
pyroptosis
autophagy
FasL-Fas, TRAIL-TRAILR
CTL dependent killing
granzymes
perforin
Cell death
antibody-dependent killing
ADCC phagocytosis
complement activation
HSC/HPC
cytokines
suppress the development
infection ?
pyroptosis
lymphoid organs damage
Lymphopoicsis inhibition
cytokines
Glucocorticoids
Lymphopenia
Lymphocyte trafficking
Activating Receptors
Inhibitory Receptors
CD28
OX40
GITR
CD137
CD27
HVEM
CTLA-4
PD-1
TIM-3
BTLA
VISTA
LAG-3
T cell
apoptosis
exhaustion
proliferation
cytokine production
cytokine function
Co-inhibitory molecules
Metabolic disorders
high lactic acid level
cell death
trafficking
lymphopoiesis suppression
up-regulated expression of co-inhibitory molecules
Cytokines, chemokines and growth factors
IL-6, IL-10, TNF-a, IL-2, IL-18, IFN-γ, IL-6, SCF, HGF, FGF, MCP-1, MIP-1-α, MCP-3, IL-8, MIG, IP-10

CYTOKINES EFFECT ON SUPPRESION OF LYMPHOCYTES COUNT

- IL-6
  - Chronic infections, hemopoesis inhibition – STAT-3 cascade activated
- IL-10
  - T-Lymphocytes proliferation suppresion, T-lymphocytes „exhaustion“ induction, CD9+ regulatory B-lymphocytes activated
- TNF-α, interferons
  - Apoptosis induction (TNF-α, IFN-γ), lymphocytes recirculation reduction (IFN-α)
- Hemopoesis limitation with granulocytes preferred, thymus involution
- Lymphocytes redistrubuted to infected places and lymphatic nodes
- Co-inhibitory molecules upregulated – e.g. CTLA-4. PD-1 („lymphocytes exhaustion“ markers)
- CAVE! – corticosteroids in patient with initial lymphopenia may induce temporary improvement but will backfire ultimately („Chornobyl control rods“)

CTLA-4 – cytotoxic T-lymphocyte associated protein 4, PD-1 – „programmed death“ protein 1



https://i.stack.imgur.com/Ai7Yp.jpg

LYMPHOCYTES EXHAUSTION SCHEME, CYTOKINE STORM INDUCTION AND EXTENSIVE NEUTROPHILES ACTIVATION IN CORTICOSTEROIDS ADMINISTRATION DURING LYMPHOPENIA

MDSC – myeloid-derived suppresor cells

Sufficient lymphocytes count at onset

- CD4+ Lymphocytes
- CD4+ Lymphocytes
- CD8+ Lymphocytes
- CD8+ Lymphocytes
- CD4+ memory cells
- CD8+ memory cells
- B-cell memory cells

- Neutrophils
- MDSC
- Lymphocytes defficiency
- Corticosteroids
- Neutrophils

REGULATED REPONSE

Lymphocytopenia at onset

- CD4+ Lymphocytes
- CD4+ Lymphocytes
- CD8+ Lymphocytes
- CD8+ Lymphocytes
- CD4+ memory cells
- CD8+ memory cells
- B-cell memory cells

- Neutrophils
- MDSC
- Lymphocytes defficiency
- Corticosteroids
- MDSC
- Neutrophils
- Neutrophils

SIRS/CYTOKINE STORM

LYMPHOCYTES SENESCENCE AND EXHAUSTION

Senescence

- Too many lymphocytes cell divisions
- CD57 upregulated -> apoptosis-prone
- Decreased IL-2 production

- HIV+ patients contain high counts of senescent T-Ly, HIV infection effect questionable

Exhaustion

- Prolonged antigen exposure
- PD-1 upregulated
  - Also on APC, e.g. macrophages and dendritic cells
- T-lymfocytov donwregulation
- TCR (T-cell receptor) intracellular signalisation downregulation
- Immunologic memory and tollerance interference
- HIV -> ↑PD-1 in both CD4+ and CD8+ cells
- Circulating and effector memory subpopulation decrease (Ki-67+)

SYMPTOMS OF LYMPHOPENIA AND ITS MANAGEMENT

Signs and symptoms

- General – repeated bacterial, viral, parasitic, fungal infections, SIRS-prone

- HIV/malignancy -> enlarged lymphatic nodes, spleen
- Respiratory infection -> cough, catarrh, fever
- Immunity disorders -> lymphatic nodes and tonsills shrinking
- RA/SLE -> joints pain, rash

Management

- Treating the triggering cause
- Gammaglobulines when low antobodies levels detected
- Bonw marroe transplantation (hereditary conditions, oncohematologic diseases)
- HIV –> effective antiretroviral therapy

- CAVE! -> lymphopenia may aid to autoimmune disease establishment (tolerace-breaking condition)

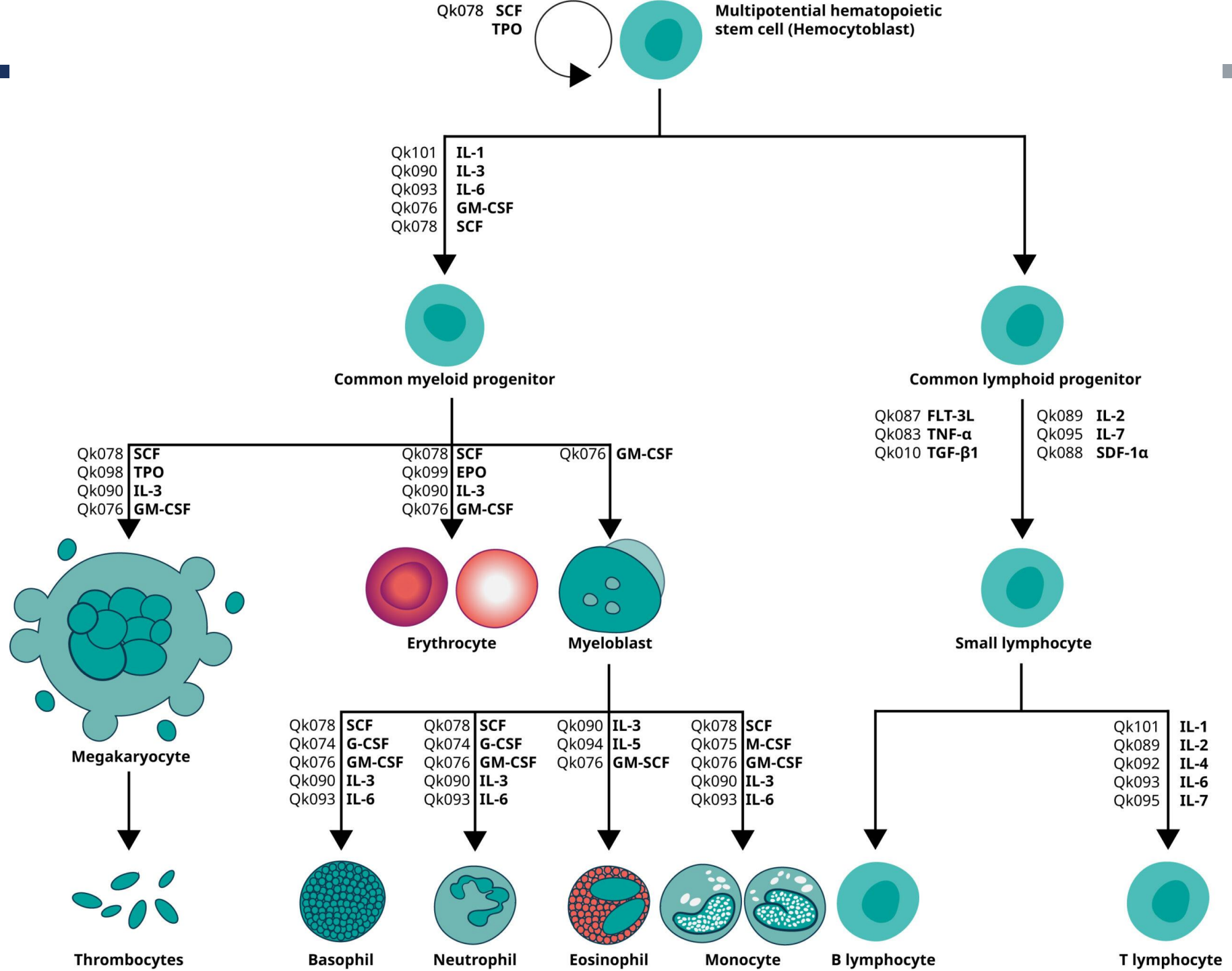
LEUKOCYTOSIS

- Elevation of leukocytes in peripheral blood >10 000 cells/μl
  - Equally or selective (neutrophilia, eosinophilia, basophilia, lymphocytosis, monocytosis)
- Causes
  - Neutrophilia – bacterial infections, pyogenic infections, sterile inflammation, MI, burns
  - Eosinophilia – allergy, parasitic infections, malignancies (Hodgkin, non-Nodgkin lymphomas), systemic autoimmune disease (SLE), vascullitis
  - Basophilia – CML (rare)
  - Monocytosis – chronic infections (TBC, bacterial endocarditis, rickettsiosis, malaria), systemic autoimmunity (SLE), IBD (ulcerous collitis), chronic myelomonocytic leukemia (immature)
  - Lymphocytosis – chronic infections (TBC, brucellosis), viral infections (hepatitis, CMV, EBV), pertusis, ALL and CLL (leukemias)
  - Immature forms – leukemias and lymphomas*

*as for teaching purposes leukemias and lymphomas are stated separately

LEUKOCYTOSIS DEVELOPMENT MECHANISMS

1. Increased bone-marrow synthesis and „storage pools“ release
   - Metamyelocyt lost mitotic ability -> „band“ transformation -> 3–5 % of circulating neutrophils
2. Decreased leukocytes adhesions to blood vessel walls
   - 50 % neutrophils circulate and 50 % adhering during physiological conditions
3. Decreased leukocytes extravasation
4. Increased bone-marrow precursors count
   - More efficient reaction to G-CSF, GM-CSF, cytokines effect, e.g. TNF-α, IL-2, IL-7, TGF-β1;, IL-1, IL-3, IL-4, IL-5, IL-6



https://421795589.r.directcdn.net/wp-content/uploads/2024/05/Hematopoiesis-graphic-final-scaled.jpg

LEUKEMOID REACTION

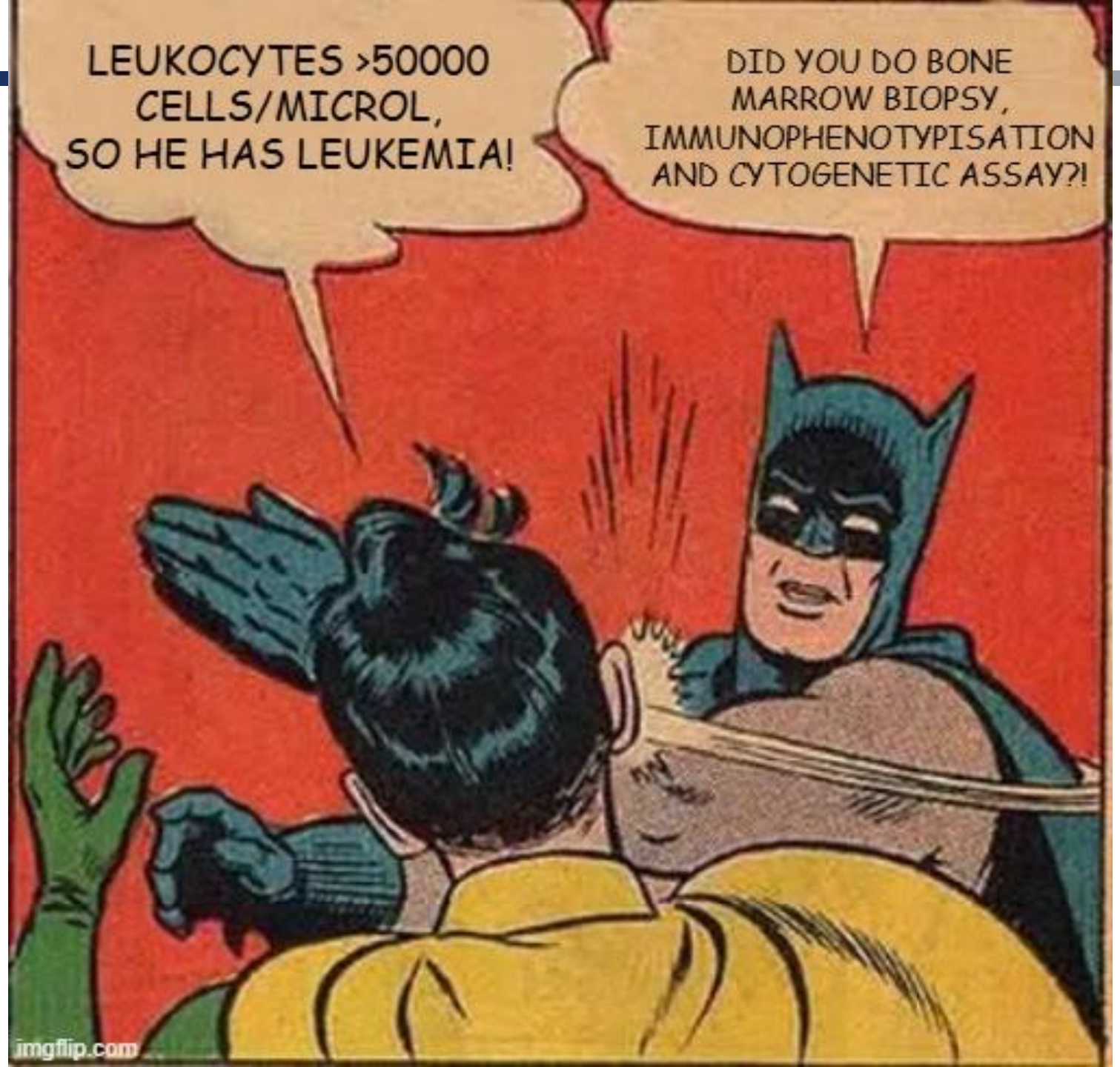
- Elevation of peripheral leukocytes >50 000 bb/µl
- Temporary condition mostly
- Causes
  - Severe infections – *C. difficile,* miliary TBC, Shigellosis (*S. dysenteriae*)
  - „Hyperinflammation“ - ↑↑IL-6
  - Terapeutic (iatrogenic) – e.g. corticosteroids therapy, minocyclin, G-CSF, GM-CSF
  - Rare – mesenteric inflammatory pseudotumor (benign neoplasia), alkoholic steatohepatitis, hemorrhage (massive, retroperitoneal)
  - Correlation/unclear causality – ATRA-therapy, asplenia, diabetic ketoacidosis, hepatic necrosis, trsomy of ch. 21 (cca. 10 % incidence), paraneoplastic syndrome (extremely rare)

ATRA – all-*trans*-retinoic acid

LEUKEMOID REACTION

- Characteristics
  - Peripheral blood - POLYCLONAL neutrophils (also less mature forms – metamyelocytes, „bands“)
    - Chronic myeloid leukemia - monoclonal neutrophils (immunophenotypisation assessed)
    - Lymphoid leukemoid reaction also possible
  - ↑S-ALP (leukemias - ↑ - CNL but ↓ - CML)
  - Vit. B12 in physiological range (leukemias and G-CSF administration - elevated – liver supplies mobilised)
  - Bone-marrow biopsy - hypercellular, yet physiological
    - Leukemias and oncohematologic disorders – monoclonal pathologic occupation mostly

- CAVE! – leukemoid reation means no oncohematological disease usually but observation is necessary (possible leukemia onset)!



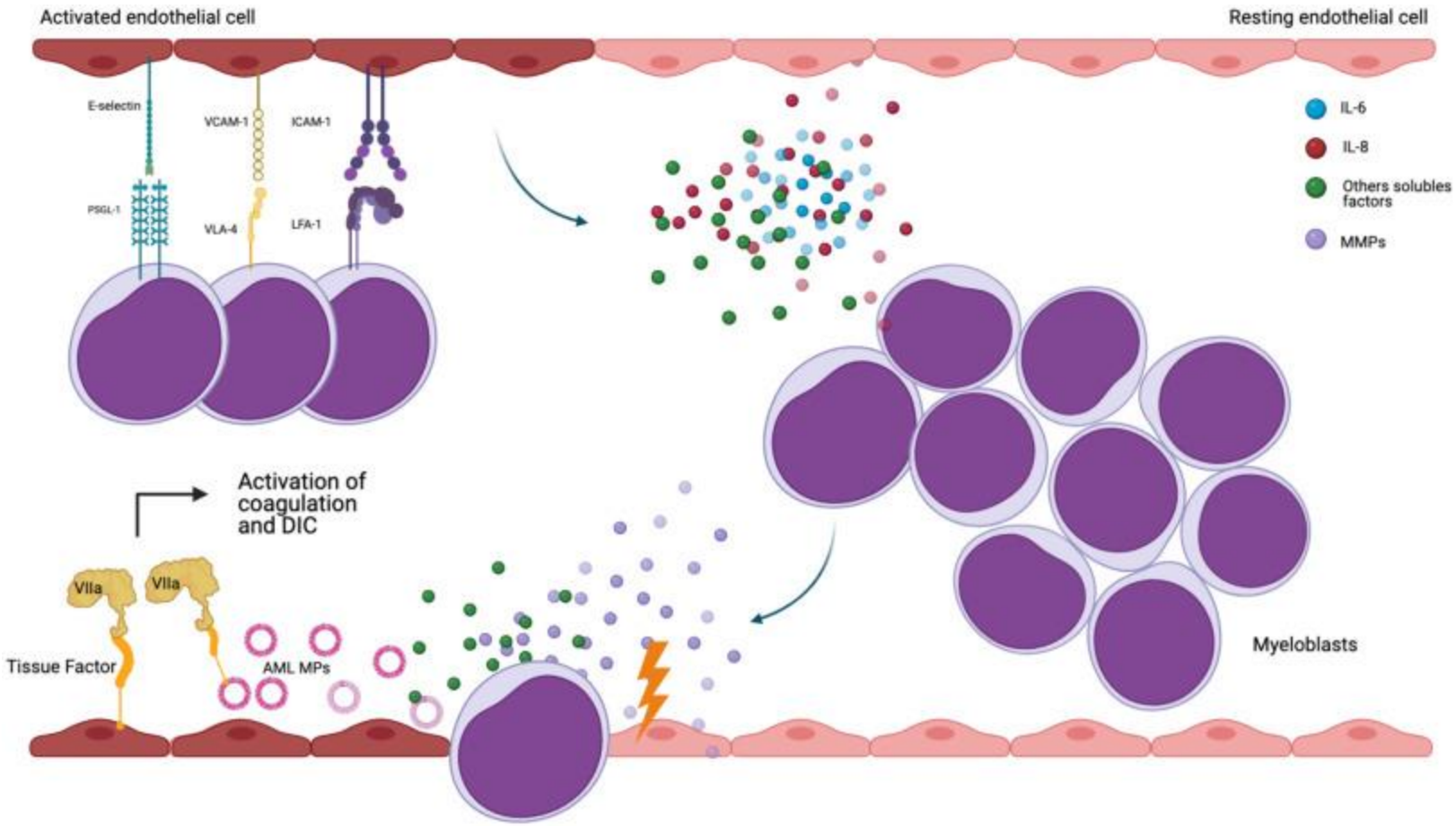
Source: author‘s work ☺

LEUKOSTASIS (ALIAS SYMPTOMATIC HYPERLEUKOCYTOSIS)

- Leukocytes and immature precursors rise in peripheral blood >100 000 cells/μl (hyperleukocytosis definition)
  - Acute myeloid leukemia (AML) may manifest these symptoms even with lower counts (from 30 000 cells/μl) -> larger leukemic cells (volume)
- Always states leukemia or oncohematological disease presence (leukemisation)!
  - Present during diagnostics
    - AML (10–20 %), ALL (20–30 %)
    - CML (rare, symptoms may not manifest even at 200 000 – 300 000 cells/μl), (CLL (?, rare) -> frequent hyperleukocytosis
- Severe to life-threatening condition – immediate admińistration to hospital and intervention necessary
  - Poor prognosis – mortality 20–40 % when untreated (pulmonar complications, transitory ischemic attack, stroke (mainly ischemic), CVS collapse)

HYPOTHESES, MECHANISM AND MANIFESTATION OF LEUKOSTASIS

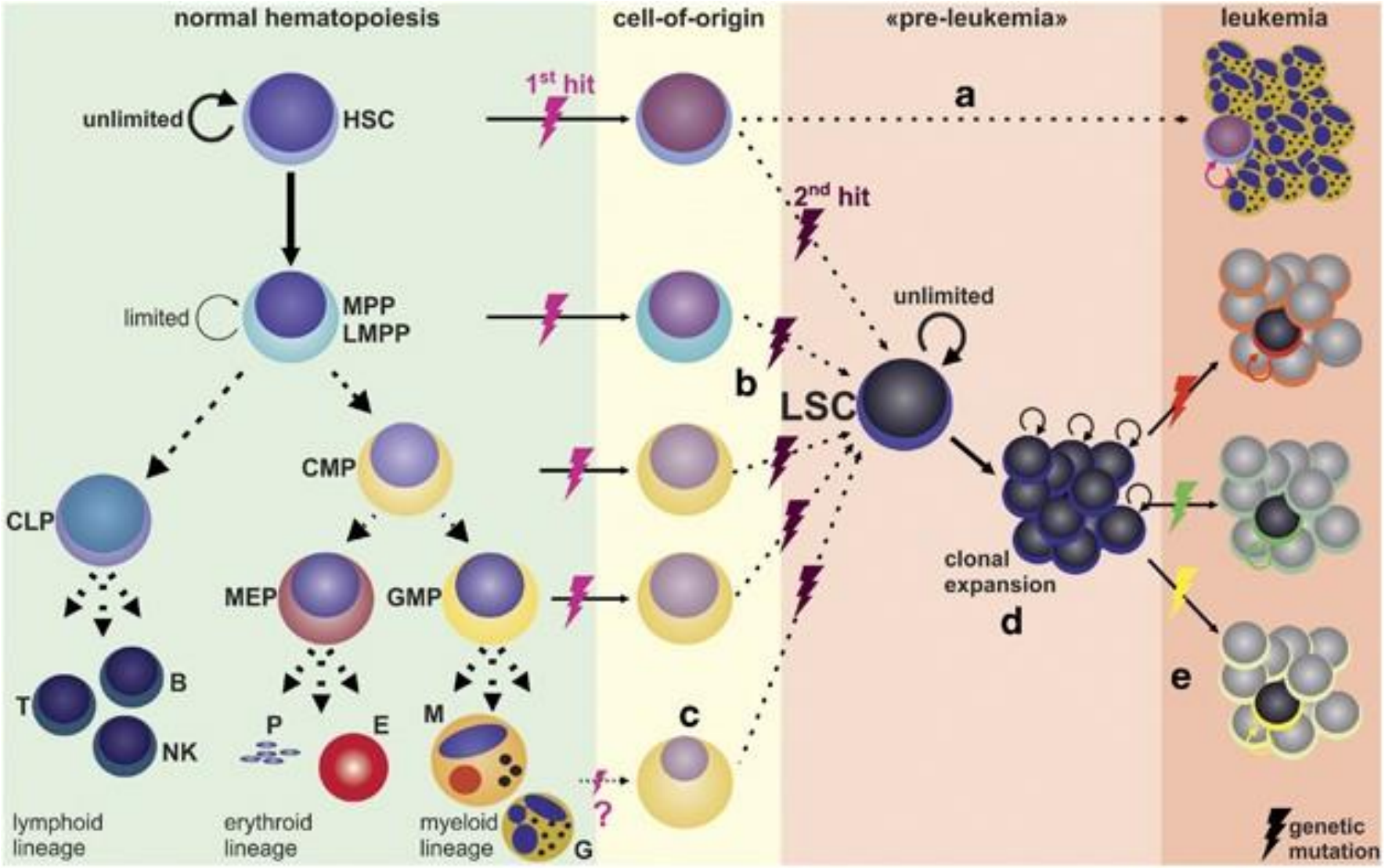
- Hypotheses
  1. Elevation of rigid blasts count -> microcircullation obstruction
  2. „Hypoxic theory“ – tissue hypoxia -> ↑mitotic blasts activity -> ↑cytokínov production -> endothelial damage and subsequent hemorragies -> ↑blasts migration to capillaries
- Mechanism – capillaries obstruction and tissue hypoxia emergence
- Manifestation
  - Pulmonary – dyspnoe, cough, hypoxia (arteficial ventillation often necessary); Chest X-ray – diffuse alveolar or interstitial infiltrates, stetoscopic - rumbles
  - CNS – confusion, blurred vision, vertigo, ataxia, tinnitus, headache, disorder of consciousness (somnolence to coma); seizures, focal neurologic functions defficiency (e.g. arm)
  - Ophtalmology – retinal edema and hemorrhages, blood vessels dilation
  - Tissue – pain in various body parts, (?)fever
  - Rare – priapism (erection without stimulation or lasting for hours after cessation of stimuli)



https://ars.els-cdn.com/content/image/1-s2.0-S0268960X22000066-gr3.jpg

LEUKEMIAS AND LYMPHOMAS – GENERAL CHARACTERISTICS

- Oncohematologic diseases
- „Founder cell“ – monoclonal
- Bone marrow occupation and destruction -> hemopoesis decreased
- Non-specific symptoms usually
  - Fatigue, tiredness, repeated subfevers and fevers (ev. „night chills“ or periodic fever), unexplained weight loss or cachexia
  - Frequent infections
  - Anemia – normocytic normochromic (anemic hypoxia)
  - Thrombocytes functions affected – petechias, purpuras, ecchymoses, bleeding manifestations
  - Lymfadenopathy (one or more groups)
- BONE MARROW BIOPSY IS DECISIVE FOR DIAGNOSIS CONFIRMATION!



https://media.springernature.com/full/springer-static/image/art%3A10.1038%2Fcdd.2014.89/MediaObjects/41418_2015_Article_BFcdd201489_Fig1_HTML.jpg

Pathophysiology Behind the Leukemias

https://calgaryguide.ucalgary.ca/wp-content/uploads/2020/01/Pathophysiology-Behind-the-Leukemias.jpg

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Point Mutation (in DNA)

Chromosomal Abnormality (duplication, loss, recombination error)

Combinations of these genetic defects causes reduced tumor suppressor gene expression and/or increased oncogene expression

In White Blood Cells and their precursors:
- Lack of cell growth inhibition and / or apoptosis.
- Over stimulation of cell division/growth

Neoplastic blood cell incapable of regulated cell division

Neoplastic cells uncontrollably divide in a monoclonal way: one neoplastic cell originates all successive cells

Genes regulating differentiation/maturation <u>disrupted</u>, affected neoplastic cells are incapable of further differentiation/maturation

Specific mutations cause slower disease progression

CML: Chronic Myeloid Leukemia

Degeneration during CML's "blast crisis"

Specific mutations cause rapid division and buildup of existing neoplastic cells → Acute/rapid disease progression.

<u>ALL</u>: Acute Lymphoblastic Leukemia
<u>AML</u>: Acute Myeloid Leukemia

Genes regulating maturation remain <u>intact</u> (affected neoplastic cell is capable of further differentiation/maturation)

Some neoplastic cells <u>take time to mature</u> further → **less rapid disease progression** (more indolent disease); cells don't die

<u>CLL</u>: Chronic Lymphoid Leukemia

	Initiating Mutational Event
ALL	Any combination of mutations, chromosomal alterations, or other genetic abnormalities that creates a neoplastic cell (incapable of regulating cell growth/division).
AML	
CLL	
CML	Translocation between Chr 9 and Chr 22 → Philadelphia chromosome (abnormal Chr 22) → BCR-ABL1 oncogene (along with other genetic abnormalities)

Note:
Although it is tempting to group the leukemias together for study purposes, it is best to learn the 4 main types of leukemias independently of one another, as they have a uniquely different pathophysiology and clinical presentation

CC BY NC SA

LEUKEMIAS AND ONCOHEMATOLOGICAL DISEASES CLASSIFICATION

Leukemias

1. Acute myeloid leukemia
2. Chronic myeloid/myelocytic leukemia
3. Acute lymphocytic/lymphoblastic leukemia
4. Chronic lymphocytic leukemia

Lymphomas and other

- Hodkgin lymphoma
- Non-Hodgkin lymphoma

- Myelodysplastic syndrome
- Polycytemia vera rubra
- Essential thrombocytemia
- Myelofibrosis
- Mastocytosis

ACUTE MYELOID LEUKEMIA

- Onkohematological disease from immature myeloid precursors in bone marrow and peripheral blood
  - Include states with overt production of red blood cells, platelets and their precursors - megykaryocytes
- Epidemiology and statistics
  - Cca. 22 000 pacients dg. per rok 2025 estimated in USA (cca 11 000 deaths)
    - 217 new cases in Slovakia in 2023 (incidence 2,6/100000 inhabitants/year)
  - Men affectedy slightly more
  - Age of onset usually >45 years
  - 33 % of leukemias (although 1 % of malignancies)

AML PATHOMECHANISM

- Multistep process
  - „Preleukemický HSPC“ creation (NPM1, TET2, SMC1A) -> driver and key mutations acquired -> leukemic hemopoesis

- Genetic preconditioning
  - Low genetic burden compared to other leukemias however with high penetrance!
    1. Somatic mutations (acquired during life)
    - Signal and kinase cascades (FLT3, „RASopatie“), epigenetic modifiers (DNMT3A, TET2, IDH1, -2, MLL/KMT2A), transcription factors (CEBPA, RUNX1), RNA-splicing factors (SRSF2), tumor-suppressor genes (-TP53) and nucleophosmin (NPM1)
    2. Gametic/“germline
    - M. Down (GATA1 gene), RUNX1, DDX41

FLT3 – Fms-like tyrosin kinase 3, DNMT3A – DNA-methyltransferase 3α, TET2 – Tet methylcytosinedioxygenase 2, IDH1, 2 – isocitrate dehydrogenase 1, 2; MLL/KMTA2 – mixed lineage leukemia/histone-lysine N-methyltransferase 2A, CEBPA – CCAAT/enhancer-binding protein alpha, RUNX1 – Runt-related transcription factor 1, SRSF2 – serine/arginine-rich splicing factor 2
Note – examples are stated here, complete gene list is more extended, suggested further reading - https://link.springer.com/content/pdf/10.1007/s11864-022-01021-8.pdf

AML PATHOMECHANISM

- Epigenetic mechanisms
  - Methylation dysregulation - DNA – DNMT3A^{R882H} hypomethylated with „dominant phenotype “, TET2 „loss-of-function“, MLL fused gene hypomethylation (CpG sequences)
  - Non-coding RNA alterations
    - Micro-RNA – miR-145 and miR-146 deletion, miR-9 and miR-155 upregulated -> selective advantage for clones, adaptation and inflammatory response adjusted in favour of blasts
    - Long non-coding RNA (LncRNA) – conformation affect, may be as „oncogenes/TSG“ - HOTAIR (*cis*-HOTAIRM1), RUNXOR (RUNX1 promotor to enhancer interactions and translocations, chromosomal „looping“)
- Microenvironment alteration
  - Dicer1 deletion, VEGF-A secretion, interleukines secretion, CXCL12 reduced, GAS6 upregulated, WNT-ligands upregulated

GAS6 – growth arrest signal 6, Dicer1 – dsRNA endoribonuclease

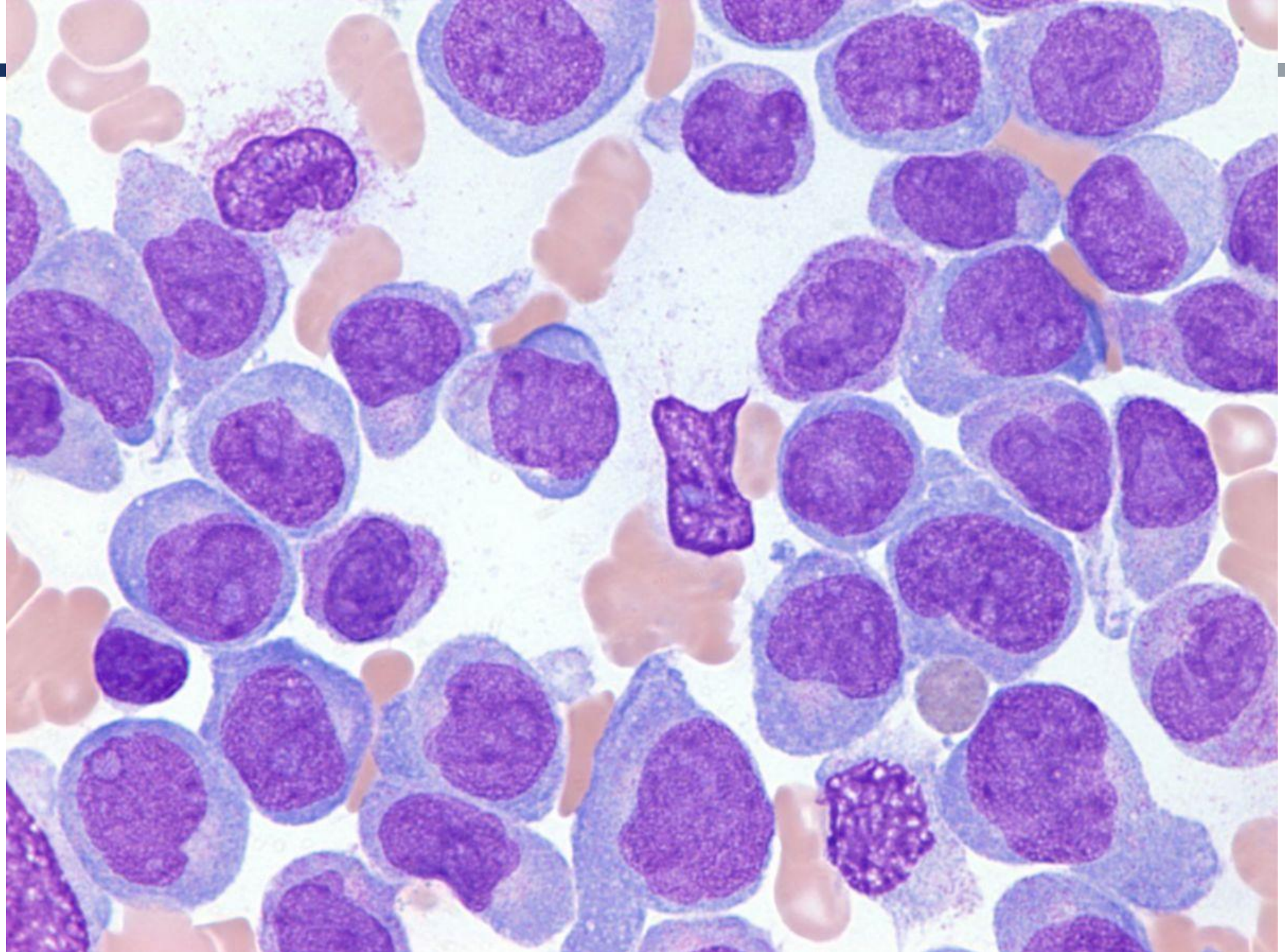
AML THERAPY EVASION

- Blasts acquiring resistance to chemotherapy -> selection pressure -> chemoresistant AML established

1. Fatty acids-rich microenvironment -> leukemic stem cells (LSC) homing to gonadal adipose tissue
   - Scavenger receptor CD36 and FABP4 expression -> oxidative metabolism
2. Endosteal region migration of chemoresistnent LSCs
   - E-selektínu and CXCL12/SDF-1 expressed, adhesion molecules CD44, expression, VLA4-VCAM1 axis upregulation, CXCL12R and CXCL4R upregulation

- Prognosis
  - Complete remission - 50–80 % paatients (relaps within 3 year usually, 60 % in favourable prognosis types, 85 % in poor prognosis types)
  - 5-year survival – cca 29,5 % (adults) vs. 66 % (children and teenagers <19 years of age)

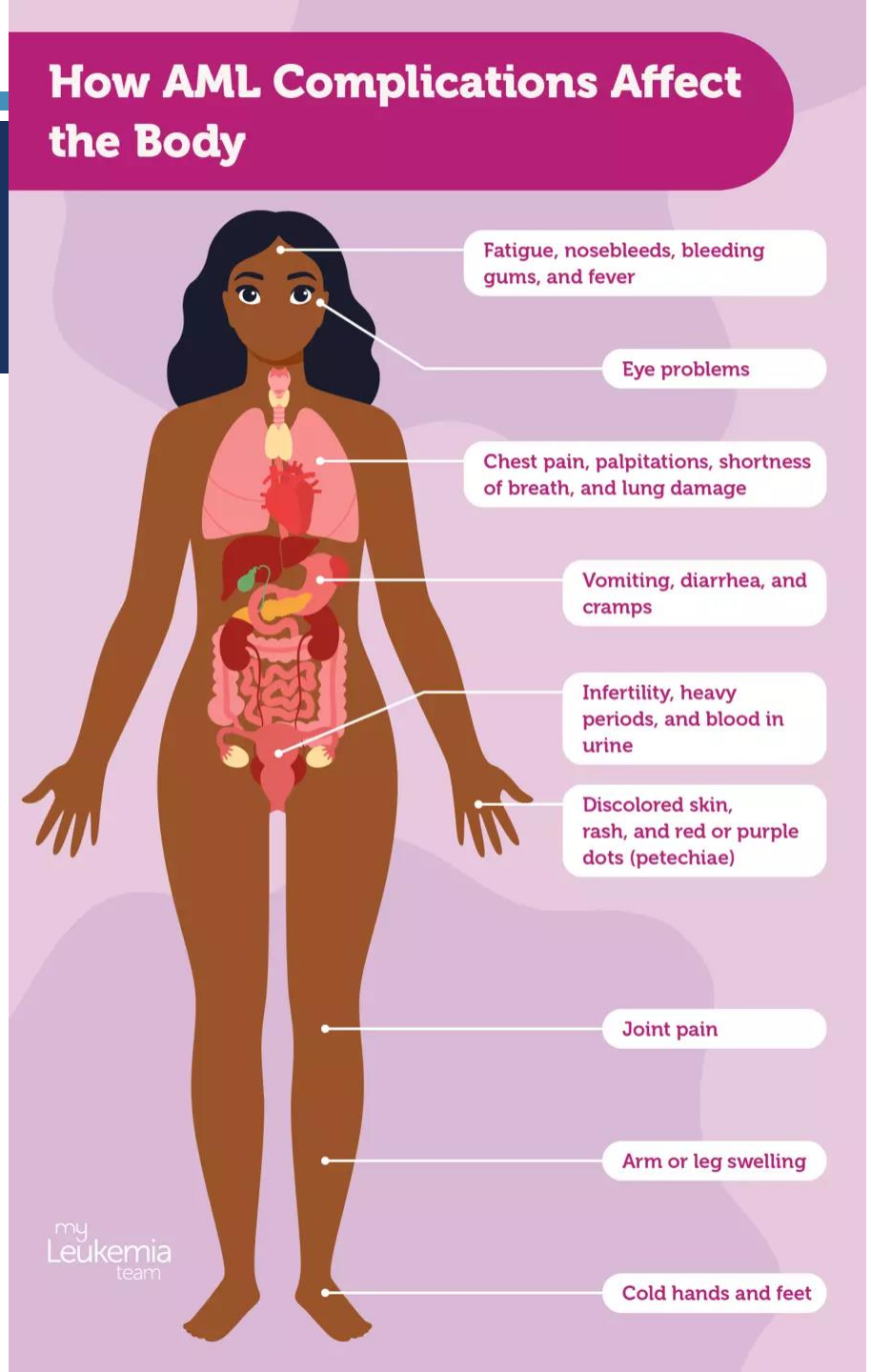
CXCL12/SDF-1 – CXC-motif chemokine 12/stromal cell derived factor-1, VLA4 - integrin



https://stjude.scene7.com/is/image/stjude/aml-leukemia-bm-m4?fit=crop,1&wid=1200

AML SYMPTOMS AND MANIFESTATIONS

- Hemopoesis disorders
  - Normocytic normochromic anemia
  - Leukocytosis with functional leukopenia
    - Prone to bacterial, fungal infections of skin and mocosa
  - Trombocytopenia -> bleeding manifestations
  - DIC risk – blasts presence
- Leukemic invasion
  - Hepatomegaly, splenomegaly, lymphadenopathy
- Leukostasis symptoms



https://cdn.myhealthteams.com/graphic/65086ee7fe9c0e0a2fc68441/woriginal/MyLeukemiaTeam_ComplicationsFromAcuteMyeloidLeukemia_Graphic-8aa00c4332a348bf15e8bec3c81763cc.webp?1695051492

ACUTE LYMPHOCYTIC/LYMPHOBLASTIC LEUKEMIA

- Onkohematological disease typical with elevation of immature lymphocytes form in bone marrow and peripheral blood
- Epidemiology and statistics
  - Peak – 2–5 years of age (USA – 2025 estimate – incidence 6100 cases, mortality 1400 cases)
    - 2015 – 7.7/100000 children vs. 1/100000 adults per year (CZE)
  - Men affected slightly more
  - Prognosis
    - Children – favourable (60 % of all ALL)
    - Adults – poor (80 % deaths to ALL despite 40% of ALL cases)

FACTORS LEADING TO ALL DEVELOPMENT

- Genetics
  - Children – hyperploidy (51 – 65 chromosomes in blasts - 25 % children vs 11 % adults), t(12,21)/TEL-AML1 (ETV6-RUNX1 – 20–25 % children vs <3 % adults)
    - These mutations are with favourable prognosis
  - Adults – Ph+ (Philadelphia chromosome, t(9,22 – BCR-ABL – 25 % adults vs 5 % children), hypoploidy (<46 Ch in cells – 5 % adults vs. 5 % children)
    - These mutations are associated with poor prognosis
- Environmental factors
  - Children – unknown, genetics (Down sy, Klinefelter sy, Fanconi anemia, neurofibromatosis, ataxia teleangiectatica, Bloom syndrome, Li-Fraumeni sy – one allele p53 loss inherited)
  - Adults – chemical (benzene), biological (HTLV-1, EBV), radiation, malignancy treatment in early age (chemotherapy)

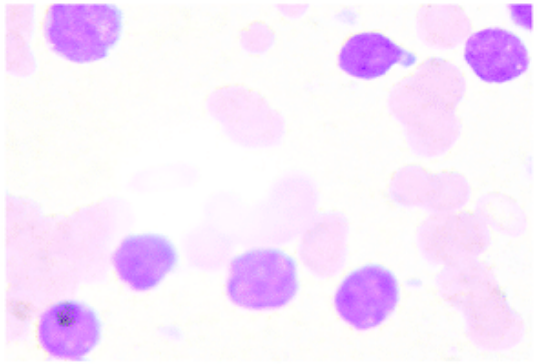
ETV6 – Ets-leukemia virus 6

ALL MECHANISM AND ITS PROGRESS

1. Genetic abnormalities accumulation in B- and T-cells precursors
2. „Founder cell“ transformation -> leukemic stem cells (LSCs) -> bone marrow invasion and destruction
3. Physiological hemopoesis suppression -> leukocytosis (even normal count or leukopenia) with functional pancytopenia
4. Peripheral blood invasion
5. Lymphatic nodes migration and spleen occupation -> lymphadenopathy and splenomegaly
6. High turnover of tumour cells -> ↑LDH

CAVE! – possible blast migration to CNS -> intracranial bleeding, seizures, neuropathies, leukoencephalopathy, thrombosis, meningitis (even lethal!), long-term cognitive functions defficiency -> intrathecal chemotherapy as a prophylaxis and treatment

FAB classification of lymphoblastic leukaemia



L1 Lymphoblastic leukaemia with homogeneous structure

Frequency:

Between 25% and 30% of cases in adults, and 85% of cases in children.

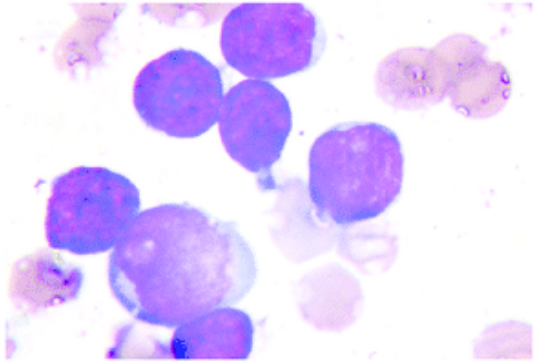
Morphology:

Blasts are homogeneous, nucleus is regular, chromatin is homogeneous, small or no nucleoli, scanty cytoplasm, and mild to moderate basophilia.

Immunophenotype

B:	T:
• CD19	•CD3
•CD22	•CD7
•CD79a	•CD5
•CD10	•CD2
•CD20	•CD4

•Cytoplasmic or superficial immunoglobulin



L2 Lymphoblastic leukaemia with varied structure

Frequency:

Accounts for 70% of cases in adults, and 14% in children.

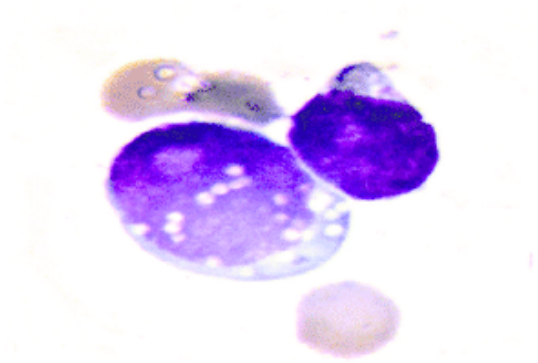
Morphology:

Nucleus is irregular, heterogeneous chromatin structure, large nucleoli.

Immunophenotype

B:	T:
•CD19	•CD3
•CD22	•CD7
•CD79a	•CD5
•CD10	•CD2
•CD20	•CD4

•Cytoplasmic or superficial immunoglobulin



L3 Burkitt's leukaemia

Frequency:

Rare subtype, accounting for less than 1% to 2% of cases.

Morphology:

Large blasts, prominent nucleoli, stippled homogeneous chromatin structure, abundant cytoplasm, abundant cytoplasmic vacuolation (bubble type) covering the nucleus.

Immunophenotype

B:	T:
•CD19	•CD3
•CD22	•CD7
•CD79a	•CD5
•CD10	•CD2
•CD20	•CD4

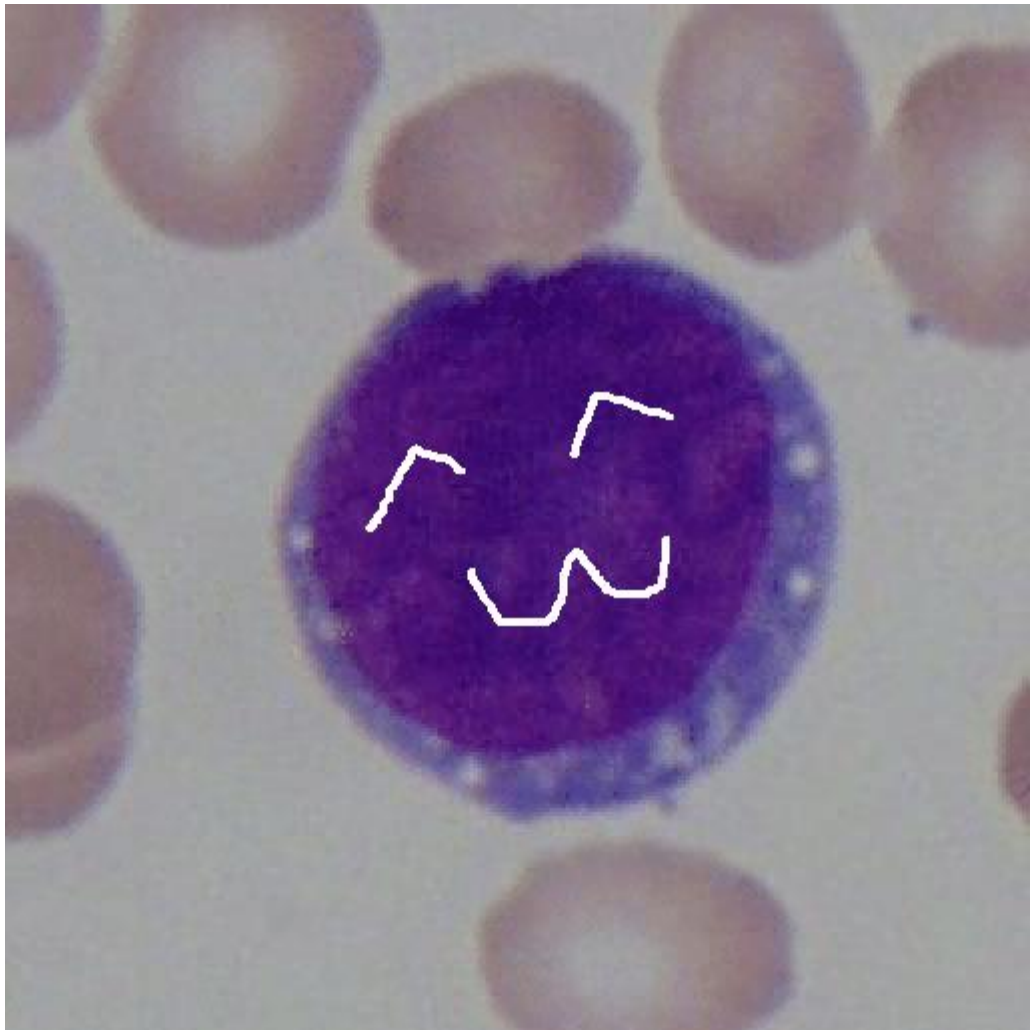
•Cytoplasmic or superficial immunoglobulin

ALL according to cells origin	ALL percentage
B-cell precursors	80–85 %
T-cell precursors	10–15 %
NK-cells precursors	0–1 %

2015

https://www.researchgate.net/profile/Adrian-Santoyo-Sanchez/publication/284069311/figure/fig1/AS:401297940193303@1473363459583/French-American-British-FAB-classification-of-acute-lymphoblastic-leukaemia-FAB.png

THOSE TYPOS... – „A CUTE LYMFOCYTIC LEUKEMIA“



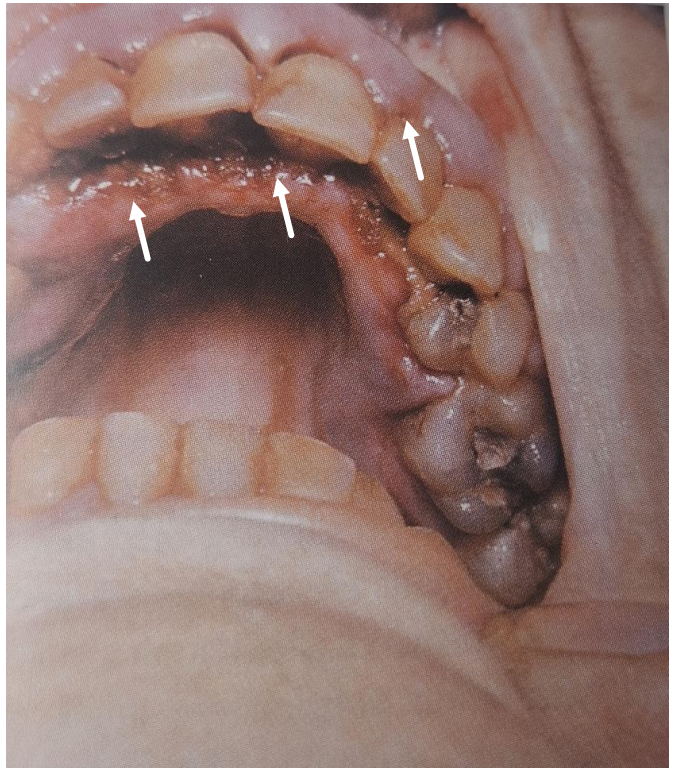
ALL MANIFESTATIONS

- Hemopoesis affected
  - >20 % blasts in peripheral blood and bone marrow
  - Functional pancytopenia -> anemia; prone to infections; bleeding manifestations (skin, GIT)
  - DIC imminent! – blasts in peripheral circulation
  - Bone pain – bone marrow invasion
- Lymphadenopathy (multiple groups together)
- Hepato- and splenomegaly
- „Night chills“, subfevers, fevers

AML AND ALL MANIFESTATIONS IN ORAL CAVITY

- Gum swelling
  - Lack of functional leukocytos to contain low-grade infections, blasts infiltration
- Mucosal ulcers
  - Immunodefficiency (e.g. HSV) + cytotoxoc drugs (e.g methothrexate)
- Leukemic deposits
  - Blasts deposited in oral cavity and salivary glands
- Purpura
  - Gums bleeding, purple spots and flashes, hemorrhagic blisters
  - Prolonged healing of extraction socket due to blasts infiltration
- Anemia
  - Pale mucosa
  - Warning sign in children – anemia from other causes rarely
- Cervical lymphadenopathy
  - ALL mainly, other types also possible

AML AND ALL MANIFESTATIONS IN ORAL CAVITY



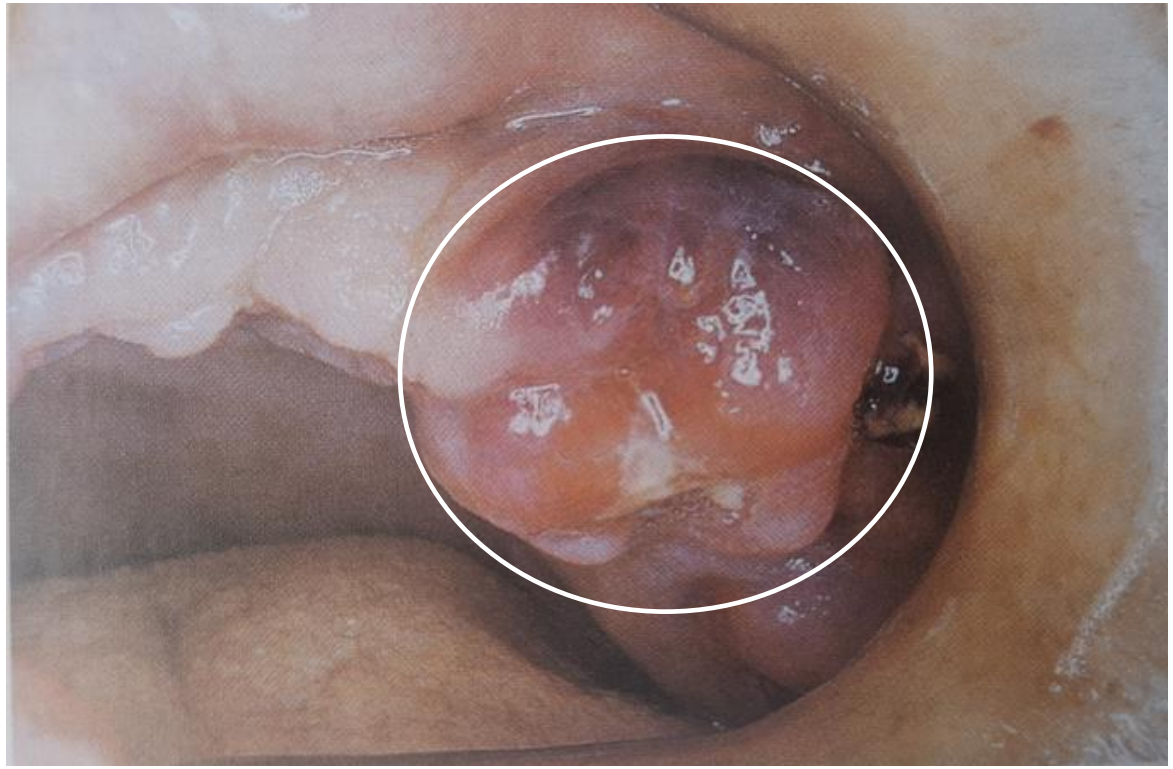
Acute myeloid leukemia – swollen, purple gums and palate ulcerations – possible infections entry



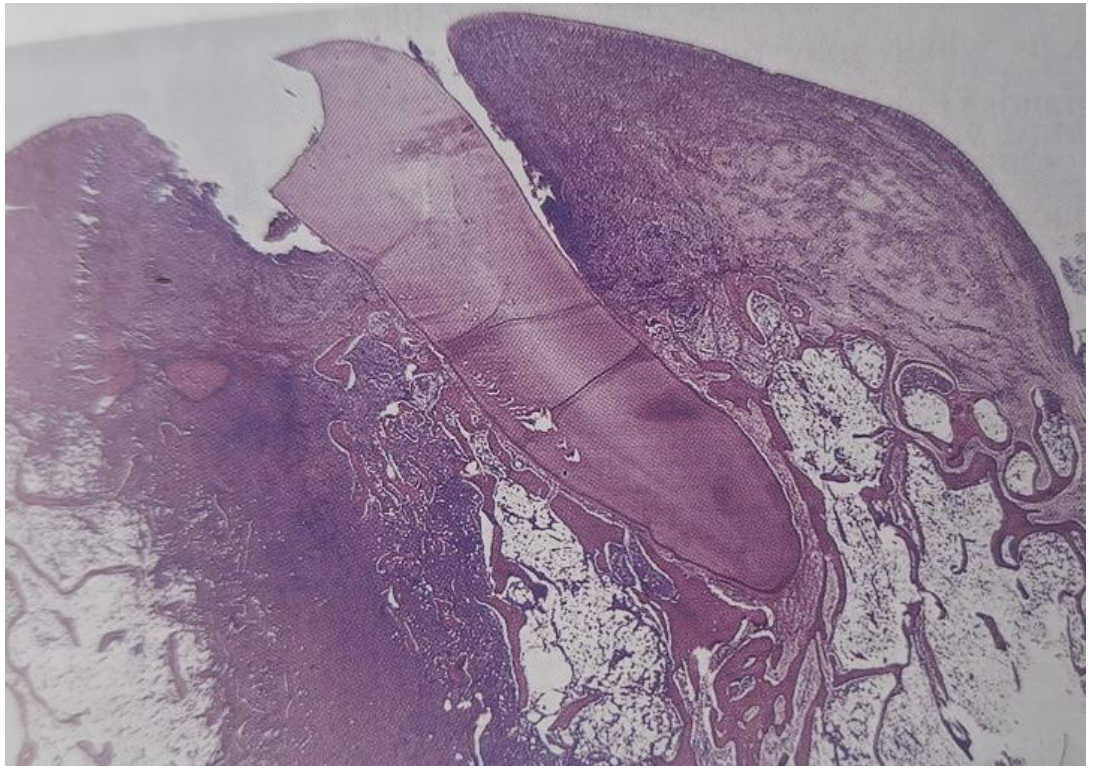
Interdental bone marrow and gums infiltration by blasts

Lawson, R. A., Odell, E. W.: Oral Pathology and Oral Medicine, Churchill Livingstone, Londýn, Veľká Británia, 2008, 484 s., ISBN: 978-0443101250.

AML AND ALL MANIFESTATIONS IN ORAL CAVITY



AML – ulcerated tumorous mass caused by blastic tissue migration



AML – massive gum and extraction socket infiltration by blasts – prevention of wound healing

Lawson, R. A., Odell, E. W.: Oral Pathology and Oral Medicine, Churchill Livingstone, Londýn, Veľká Británia, 2008, 484 s., ISBN: 978-0443101250.

CHRONIC MYELOID LEUKEMIA

- Oncohematological disease typical with increase in myeloid precursors of higher maturity degree compared to AML
- Epidemiology
  - USA 2025 estimate – incidence 9 500 cases, mortality cca 1 300 cases
  - 50 % patients aged 65+, rarely in children or <40 years of age
- Fusion gene BCR-ABL1 establishment typical
  - T(9;22)(q34;q31)
  - Chromosome 22 contain several points of possible breaks and translocations – variations e13a2 and e14a2 (210 kDa)
    - Variations 190 kDa (e1a2 – B-cell-ALL), resp. 230 kDa (chronic leukemias)
  - This gene solely allows leukemic transformation

CML PATHOMECHANISM

1. BCR-ABL1 fusion gene -> protein
   - Tyrosin kinase activity
   - Cascades JAK/STAT, PI3K/AKT, RAF, MYC and RAS/MEK stimulated -> proliferation, cell survival and resistance to apoptosis cell advantage
   - BCR-ABL negative CML -> SETBP1, ASXL1, NRAS/KRAS, SRSF2, CSF3R, U2AF1 gene mutations, etc.
2. Leukemic stem cells development -> chronic phase

SETBP1 – Set binding protein 1, ASXL1 – additional sex chromatine human homologue 1, NRAS – neuroblastoma RAS viral homologue, KRAS – Kirsten rat sarcoma virus, SRSF2 – serin/arginin-rich splicing factor 2
U2AF1 – U2 small nuclear RNA auxilliary factor 1

CML COURSE

1. Chronic phase (3–5 years, 85 % patients during dg.)
   - <10 % bone marrow blasts, possible anomalies in peripheral blood (↑Tr, ↑Leu - ↑Neu, ↑Ba, ↑Eo, „left“ shift)
   - „Myelocyte bulge“ – myelocytes prevail over mature metamyelocytes
   - Asymptomatic patient or non-specific symptoms – weight loss, fever/“night chills“, weakness, splenomegaly
2. *Accelerated phase (7–12 months without treatment)*
   - *Additional mutations acquired – p53-; CDKN2A-; GATA2-; RUNX1; IKZF1; ASXL1; WT1*
   - *Additive cytytogenetic abnormalilites (ACA) mark worse prognosis and increasing severity (5–10 % in chronic phase vs. 80 % v blastic phase)*
   - *Anemia development, symptoms from chronic phase more intense of starting to manifest*

CDKN2A –cycline-dependentkinase inhibitor 2A; GATA2 – GATA-binding protein 2; RUNX1 –Runt-related transcription factor 1; IKZF1 – Ikarus family zinc finger 1; ASXL1 – Additional sex chromatine human homologue 1; WT-1 – Wilms tumor 1

CML COURSE

3. Blastic phase (blastic crisis; 3–6 months; survival median 1.8 years)
   - Bone-marrow and peripheral blasts >20 %
   - High cells turnover -> ↑K^+, ↑LDH, ↑uric acid
   - Organs infiltration -> lymphadenopathy, splenomegaly, bone pain
   - Sternal bone „softening“ -> hemopoesis bone marrow expansion to phylogenetic older locations
   - AML/ALL transformation

Chronic Myeloid Leukemia (CML): *Pathogenesis and Clinical Presentation*

Authors:
Yan Yu
Katie Lin
Reviewers:
Jennifer Au
Crystal Liu
Danielle Chang
Lynn Savoie*
**Indicates faculty member at time of initial publication*

Translocation of a Chr 9 segment onto Chr 22, creating a Philadelphia chromosome (Chr 22) containing the BCR-ABL1 fusion gene

Mutations from ionizing radiation

Other genetic abnormalities

These genetic abnormalities accumulate in the earliest cell of the blood cell differentiation sequence: the pluripotent hematopoietic stem cell

Hematopoietic stem cell division in the bone marrow becomes unregulated → Multifactorial causes, most with unclear mechanisms → Weight loss, malaise, fever/ chills, night sweats

https://calgaryguide.ucalgary.ca/wp-content/uploads/2015/05/CML.jpg

1. Chronic Stage (85% of clinical presentation): Hematopoietic stem cell division/differentiation in the bone marrow results in ↑ production of multiple blood cell lines (detectable on CBC, but patients are usually asymptomatic at this stage)

- Neoplastic division of platelet precursor cells → Thrombocytosis
- Neoplastic division of WBC precursor cells, especially neutrophil precursors → **Leukocytosis:**
  · Neutrophilia, basophilia, & eosinophilia
  · "Left shift": ↑ neutrophil & band production
  · Disorderly WBC differential: i.e. "myelocyte bulge"
  → Trapping of WBC's in the spleen enlarges the spleen → **Splenomegaly:**
  · Left upper quadrant pain
  · Early satiety (large spleen compresses the stomach)
  · Associated hepatomegaly (if spleen is overfilled & WBCs spill over into liver)

Acquired ↑ genetic abnormalities

2. Accelerated Stage
More and more immature precursor cells ("blasts") divide and accumulate in bone marrow (where 10-19% of blood cells are "blasts".) Blasts start to spill over into the peripheral blood

Dividing "blasts" limit the space and resources available for RBC synthesis → Anemia → *↓ oxygenation of blood means blood is less red & body tries to compensate* → Pallor, Dyspnea, Tachycardia

Acquired ↑ genetic abnormalities

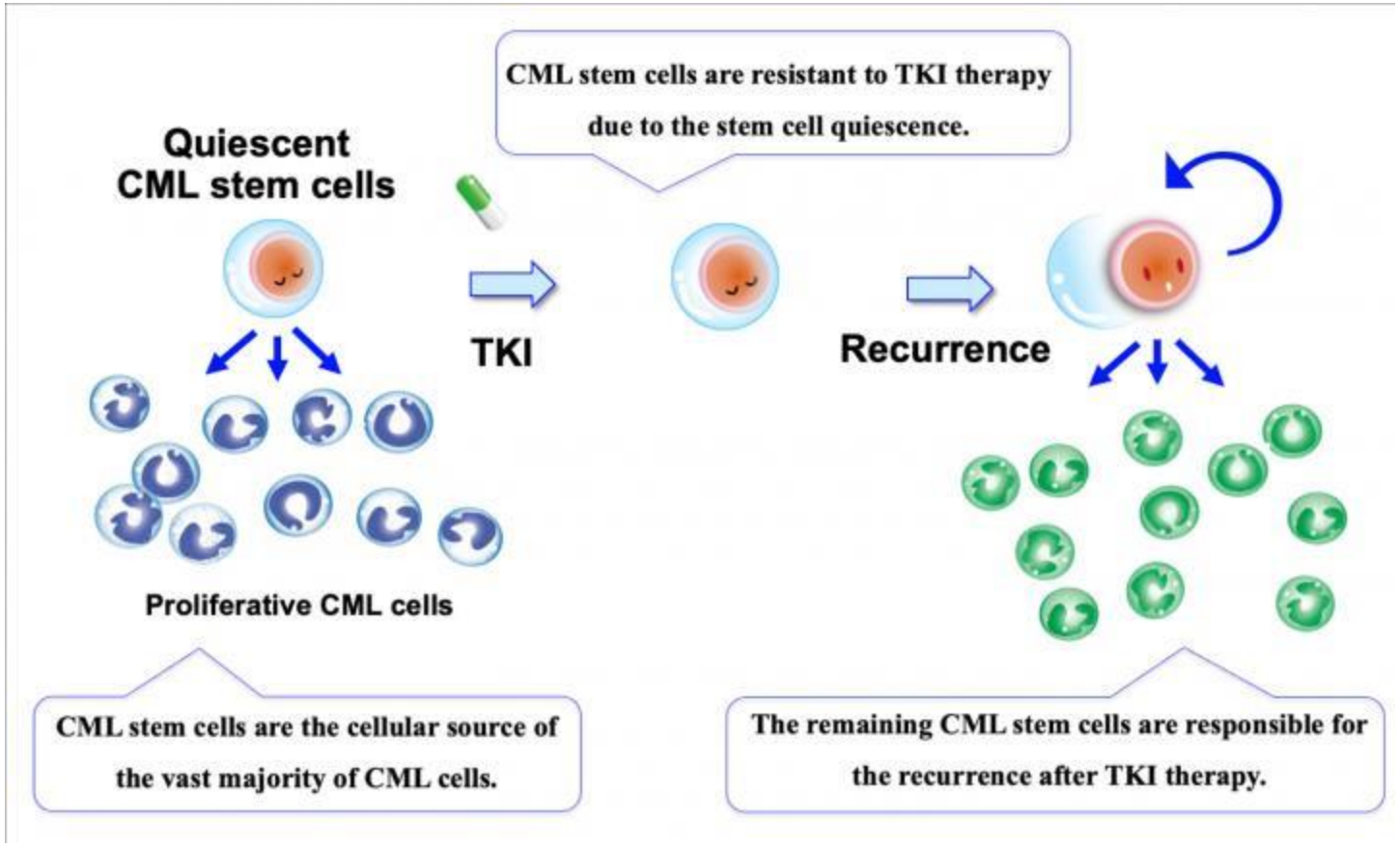
3. Blast crisis (transformation into AML/ALL)
Neoplastic blast cells have filled up the bone marrow (where >20% of blood cells are blasts). More blasts spill out into the peripheral blood.

- High turnover of these cancerous cells → excess cell lysis → Release of intracellular contents (uric acid, K+, LDH) into plasma
  - · Hyperkalemia
    · High (LDH) → Gout
  - Hyperuricemia → Acute Kidney Injury
- Expanding marrow pushing on bone → Bone pain
- Bone marrow expands into sternum → Sternal tenderness

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

Re-Published **June 15, 2019** on www.thecalgaryguide.com

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https://genengnews.com/wp-content/uploads/2020/09/Sep18_2020_KazuhitoNaka_CMLstemcells.jpg

CHRONIC LYMFOCYTIC LEUKEMIA

- Oncohematologic disease typical with leukocytes increase in bone-marrow and periphjeral blood (also organs infiltration often) – monoclonal B-cells
  - Partial preservation of signalisation, B-cell receptor (BCR) including
  - Packing of monoclonal B-cells -> oppression of healthy cells, defective defensive functions, CD5+, CD23+
- Classification
  - Slowly progressing CLL (indolent)
  - Fast progressing CLL (aggresive)
- Epidemiology and statistics
  - USA 2025 estimate – incidence 24 000, mortality 4 500 cases
  - Average age during diagnosis - 70 years of age, rarely <40 years of age

CLL PATHOMECHANISM

1. Monoclonal-B-lymphocytosis – „pre-leukemic condition“
   - Definition – „low-grade“ (<500 MBLy-Ly/μl) vs „high-grade“ (500 – 5000 MBLy/μl)
   - Genetics - „first hit“
     - Classic factors (SNP, partial monosomies) – locus 13q21.33-22.2, m-del q11, m-delq13, m-del p17; 47, XX/XY,+12;
     - NOTCH1, BIRC3, SF3B1, MYD88, ATM a TP53 factors mutations
     - V(D)J components mutations – e.g. IVGH4-59/61 („low-grade“) vs. IGHV1-69, IGH2-5, IGHV3-23, etc. („high-grade“) -> genomic transformation failure (antobodies production necessity) -> „second hit“
   - Environmental factors influence (benzene; EBV; chemotherapy in medical history)
   - Packed MBLy in bone marrow and their release into periphery
   - Asymptomatic, average CLL/SLL transfromation time is 6.4 years

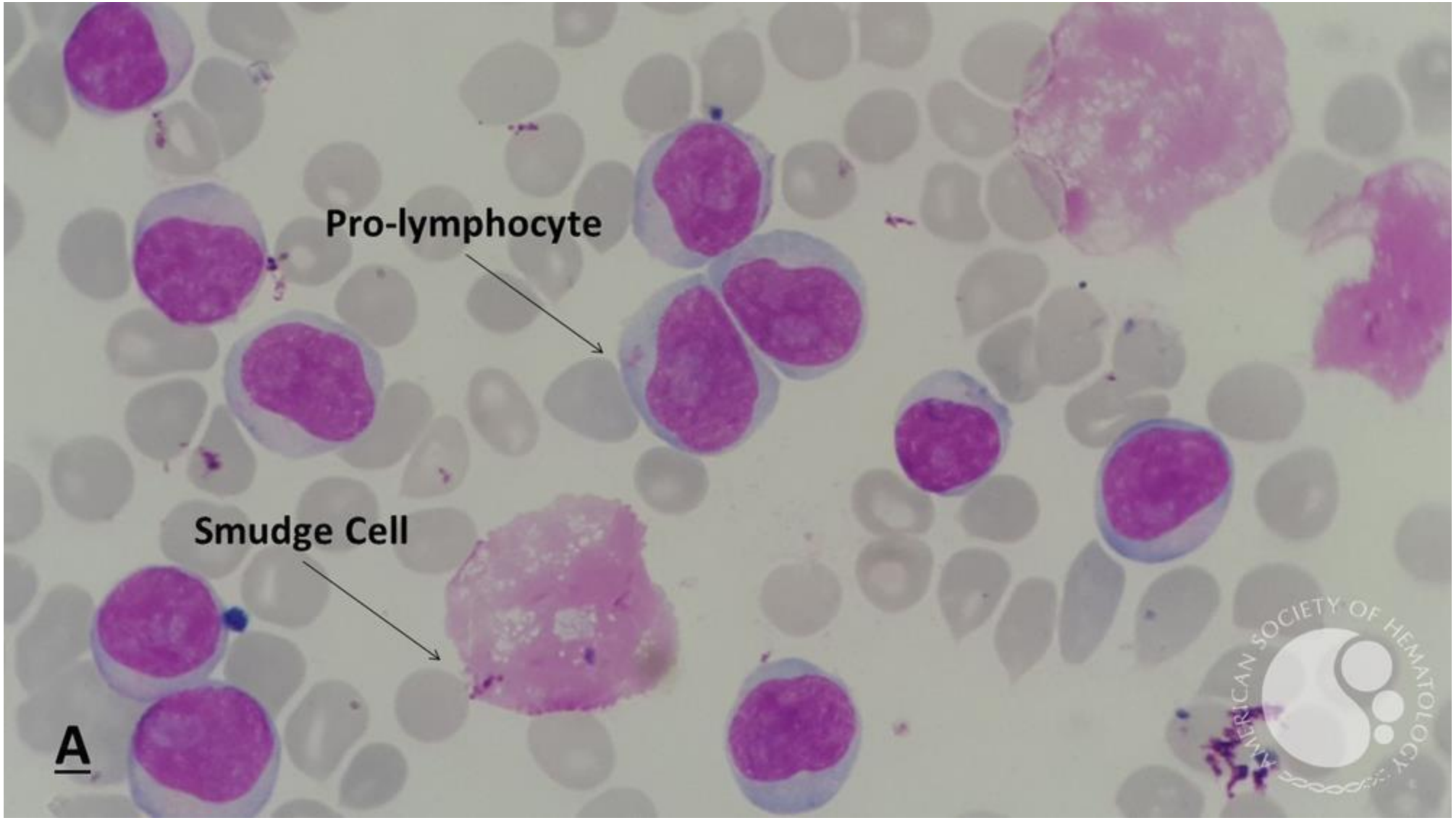
„m-“ marking partial monosomy, SLL – small-cell lymphoma

CLL PATHOMECHANISM

2. CLL transition
   - CLL may start even without MBLy
   - Genetic and epigenetic abnormalities accumulation -> bone-marrow microenvironment change
   - Enviromental factors – as in MBLy + insecticides, Agent Orange, radiation
   - Survival cascades regulation -> „Goldilocks and three bears“ -> BCR, NF-κB
   - Bone-marrow occupation, „immunosuppression“ established -> malignant B-Ly with leukocytosis
   - Asymptomatic for a long time -> MBLy in peripheral blood, „smudge/basket“ cells, hypogammaglobulinemia

CLL MANIFESTATIONS

- Long-term asymptomatic
- Decresed functional leukocytes + hypogammaglobulinemia – frequent infections
- Inflammatory cytokines production -> fever, „night chills“, weight loss, appetite loss
- Splenomegaly, lymphadenopathy
- ↓Ery -> normocytic normochromic anemia
- ↓Tr – bleeding manifestations



https://imagebank.hematology.org/getimagebyid/62207?size=3

CHRONIC LEUKEMIAS MANIFESTATION IN ORAL CAVITY – GINGIVAL HYPERTROPHY (LEFT) AND ULCERS (RIGHT)





https://figures.semanticscholar.org/bcf5c8ac3d24aa15203a2a3e2fd9682e40bd75ad/2-Figure1-1.png
https://post.medicalnewstoday.com/wp-content/uploads/sites/3/2022/05/Leukemia-rash-slide11.jpg

LYMPHOMAS

- Oncohematological diseases from peripheral lymphocytes of various maturation degrees (B-, T-, NK-cells)
- Heterogenic disease groups (progression and malignancy degree varying)
- Possible start both in bone marrow and peripheries
  - Leukemic transformation possible -> ALL mostly
- Classification
  - Hodgkin lymphomas
    - Nodular sclerosis Hodgkin lymphoma, mixe cellularity HL, lymfocyte-rich HL, lymphocyte-depleted HL
    - Nodular lymphocyte-predominant Hogdkin lymphoma -> different pathomechanism, to be treated as a separate entity
  - Non-Hodgkin lymphomas

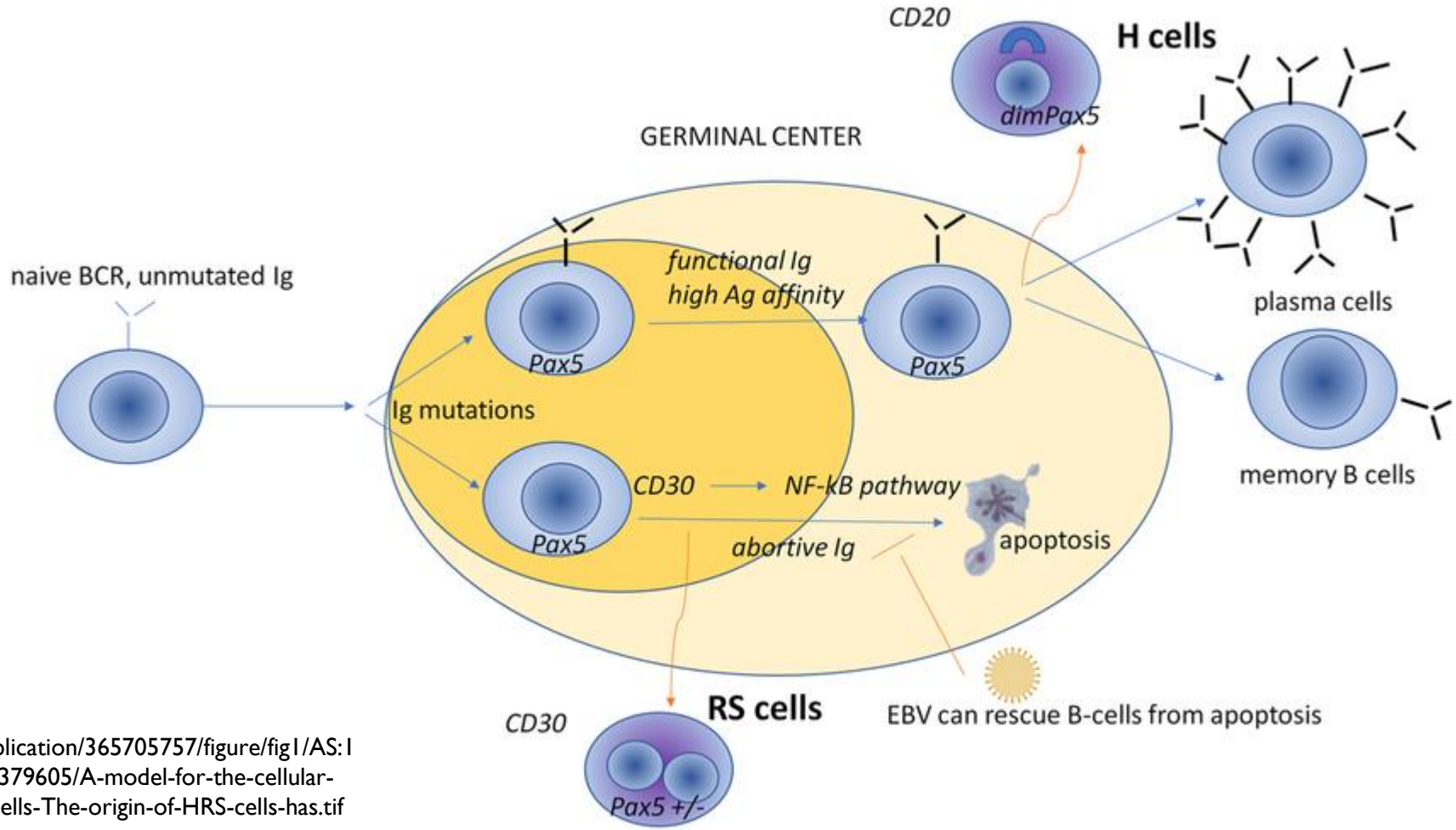
LYMPHOMAS

- Epidemiology and statistics (cca 5 % of all malignancies)
  - Hodgkin lymphoma
    - USA 2025 estimate – incidende 8 700 cases, mortality 1 150 cases
    - Peak (age groups) – 15–19 years of age and 55+ years of age
  - Non-Hodgkin lymphomas
    - USA 2025 estimate – incidence 80 400 cases, mortality 19 400 cases
    - Peak (age groups) – risk increasing with age, 50 % case in 65+years of age

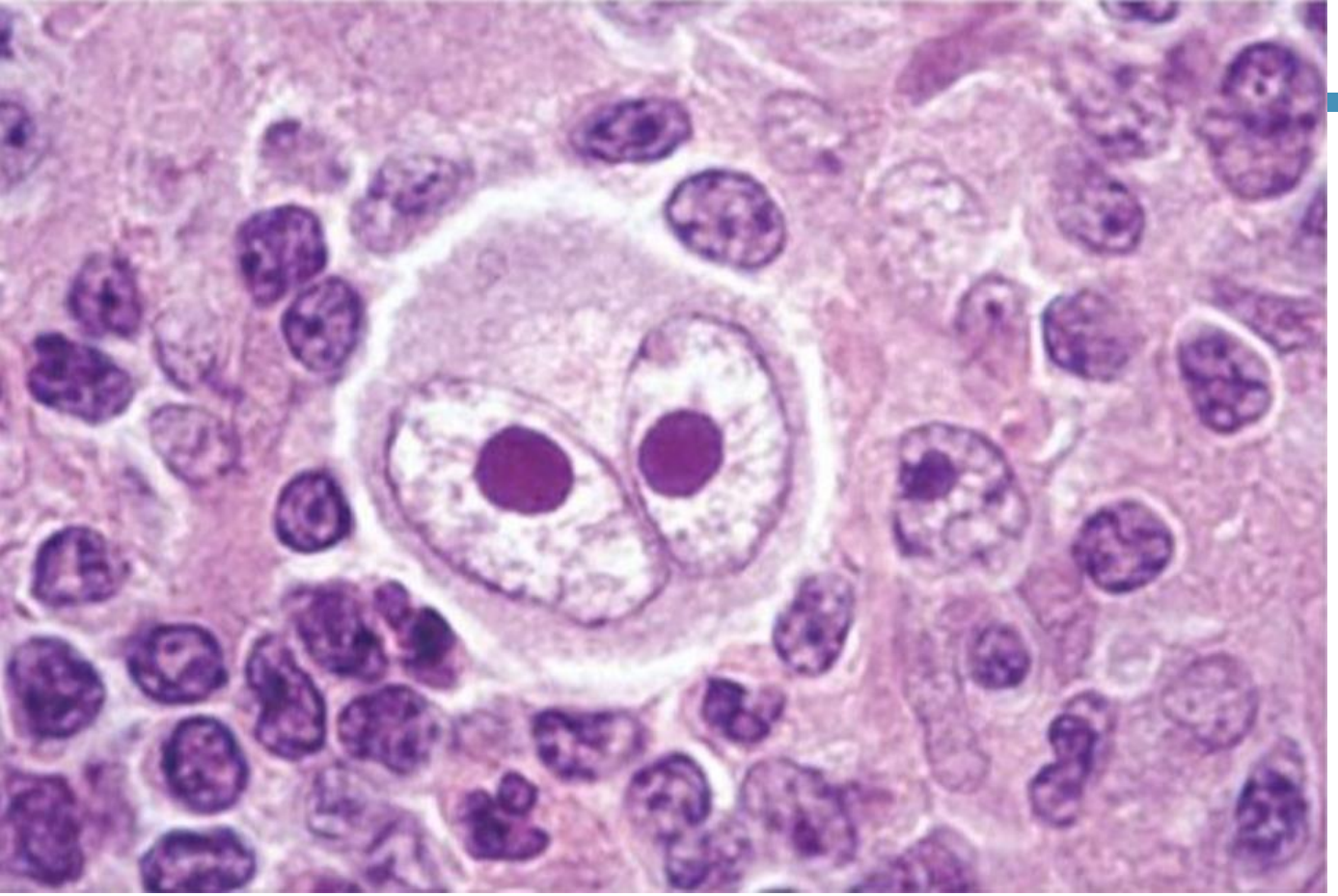
LYMPHOMAS PATHOMECHANISM

- Hodgkin lymphoma
  - B-cell to plasmocyte transformation failure -> Ig genes mutations and apoptosis escape
  - Genetic factors unknown – even monozygotic twins do not have increased risk
  - EBV viral effect -> apoptosis escape („cell dame fortune“)
- Non-Hodgkin lymphomas
  - Genetics – various anomalies
    - B – t(14;18)/Bcl2, t(11,14)/Cycline D1, t(8;14)/c-MYC, Bcl6
    - T – RASopathies, mutations in PIK3R1, PIK3CA, PTEN, monosomies (45, X0; m-del-3p, Y-deletion, aneuploidies +3, +7, +21, +X, +Y), TCRδ genes translocation (14q32) and TCRα translocation (14q11)
  - Environmental influence – oncogenic viruses (HTLV-1, EBV, HIV), chemical (benzene, chemotherapy), physical (radiation), etc.
  - „Two“ to „three“ hypothesis theory – according to lymphoma type
  - Frequent „bystander“ cells role -> lymphocytes activated without Ag stimulation (intercellular communication)

HODGKIN LYMPHOMA



https://www.researchgate.net/publication/365705757/figure/fig1/AS:11431281258505454@1720099379605/A-model-for-the-cellular-germinal-center-origin-of-HRS-cells-The-origin-of-HRS-cells-has.tif



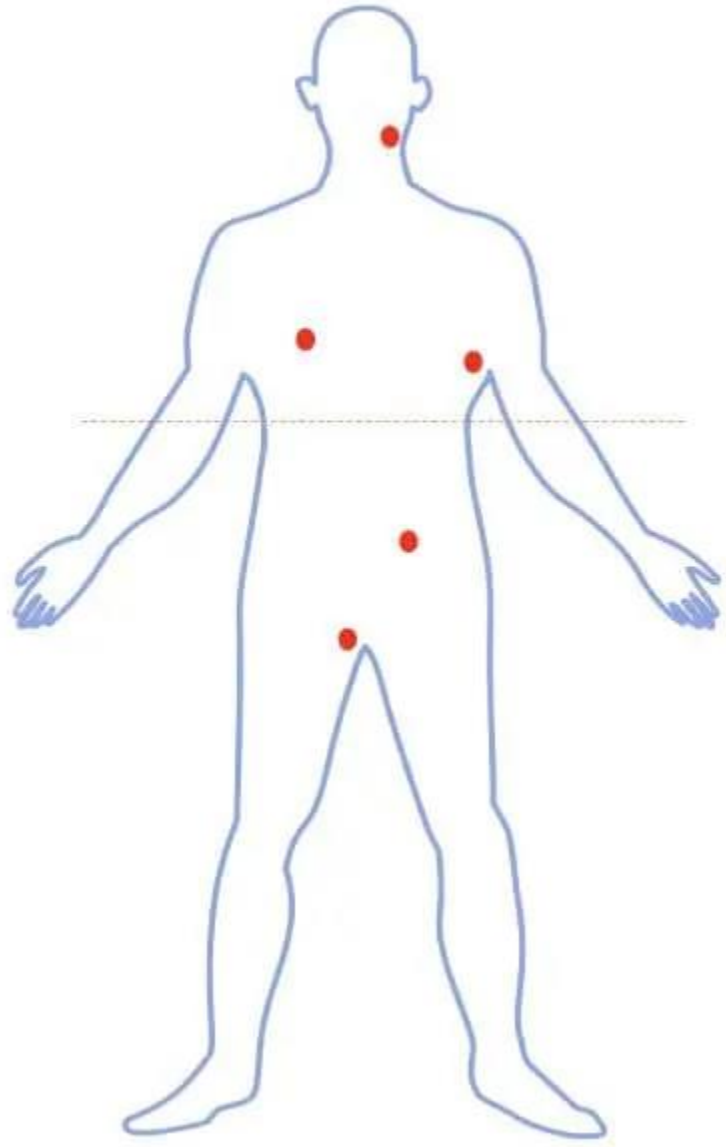
Reed-Sternberg cells -> note the two nuclei „owl eyes/orphan Annie“ sign

DESCRIPTION	APPEARANCE
Large cells (20 to 60 µm in diameter) Abundant eosinophilic cytoplasm Nucleus: Typically two large nuclei -"mirror image" Prominent eosinophilic nucleolus surrounded by a halo	 Classic RS cell
Single, large, round nucleus with a large eosinophilic inclusion-like nucleolus May be seen in any subtypes of CHL	 Mononuclear cell variant (Hodgkin cell)
Abundant, lightly acidophilic or water-clear cytoplasm Large folded or multilobed nucleus One or more prominent eosinophilic nucleoli Seen in nodular sclerosis of CHL	 Lacunar cell variant
Dark eosinophilic cytoplasm with pyknotic nuclei Strongly indicate HL but not diagnostic	 Mummified cell variant
Highly pleomorphic cells Large bizarre hyperchromatic nuclei Commonly found in lymphocyte-depleted CHL	 Anaplastic/pleomorphic variant
Abundant pale cytoplasm with popcorn nucleus Specific to the nodular lymphocyte predominance type of HL	 Lymphocyte predominant cell (LP cell)/popcorn cell

https://news.weill.cornell.edu/sites/default/files/styles/news_story_featured_image/public/story_featured_images/cesarman_hodgkin_lymphoma.png?itok=qpdgrkKe&c=82e5cd098a063437ef400c1dd9278924
https://i0.wp.com/pathologymcq.com/wp-content/uploads/2023/12/IMG_6219.jpeg?resize=493%2C622&ssl=1

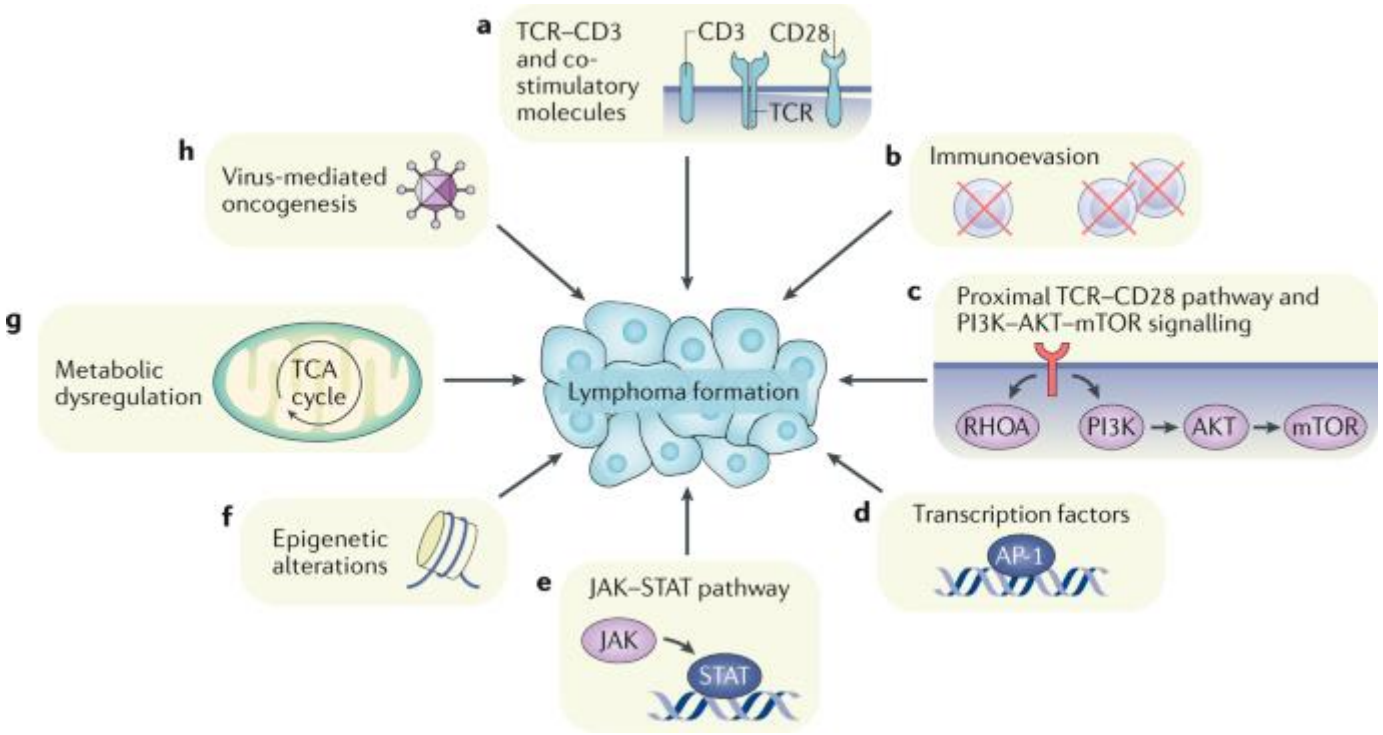
Ann-Arbor classification of Hodgkin lymphoma progress

Stage	
I	Single lymph node region (I) or single extranodal organ or site (I_E)
II	≥ 2 lymph node regions on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extralymphatic organ or tissue (II_E)
III	Lymph node regions on both sides of the diaphragm (III), including organs or area near the lymph nodes or the spleen (III_E)
IV	Dissemination to ≥ 1 extralymphatic organs or tissues, with or without involvement of nearby lymph nodes
Modifying features	
A	Asymptomatic
B	Unexplained fever (>38C); night sweats; loss of >10% body weight in 6 months
E	Involvement of a single, contiguous or proximal extranodal site
X	Bulky disease (>10 cm; >0.33) of transtthoracic mediastinal diameter



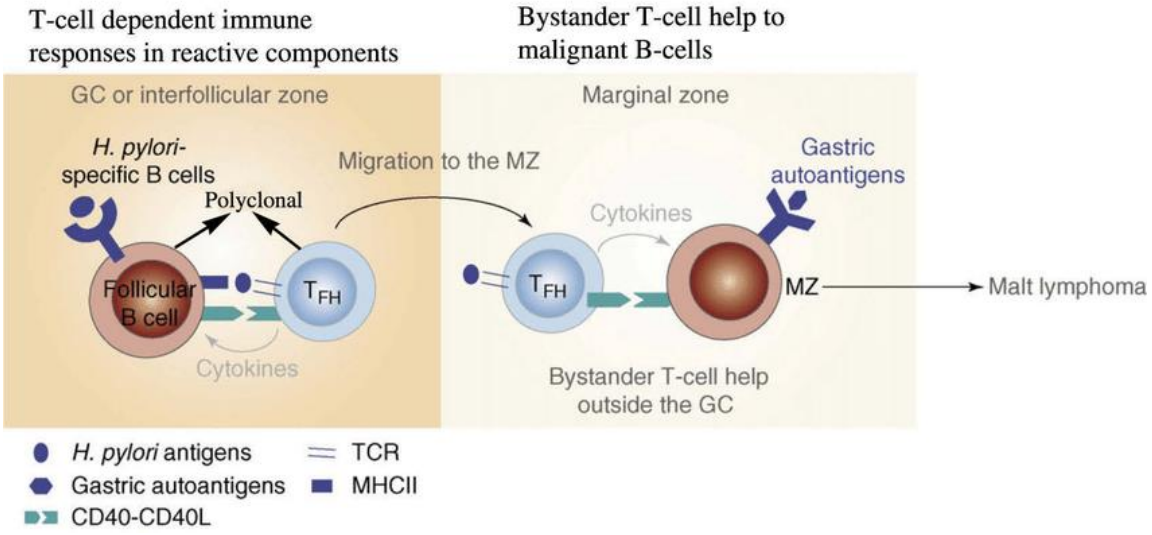
https://myhematology.com/wp-content/uploads/2023/11/Hodgkin-Lymphoma-staging.jpg

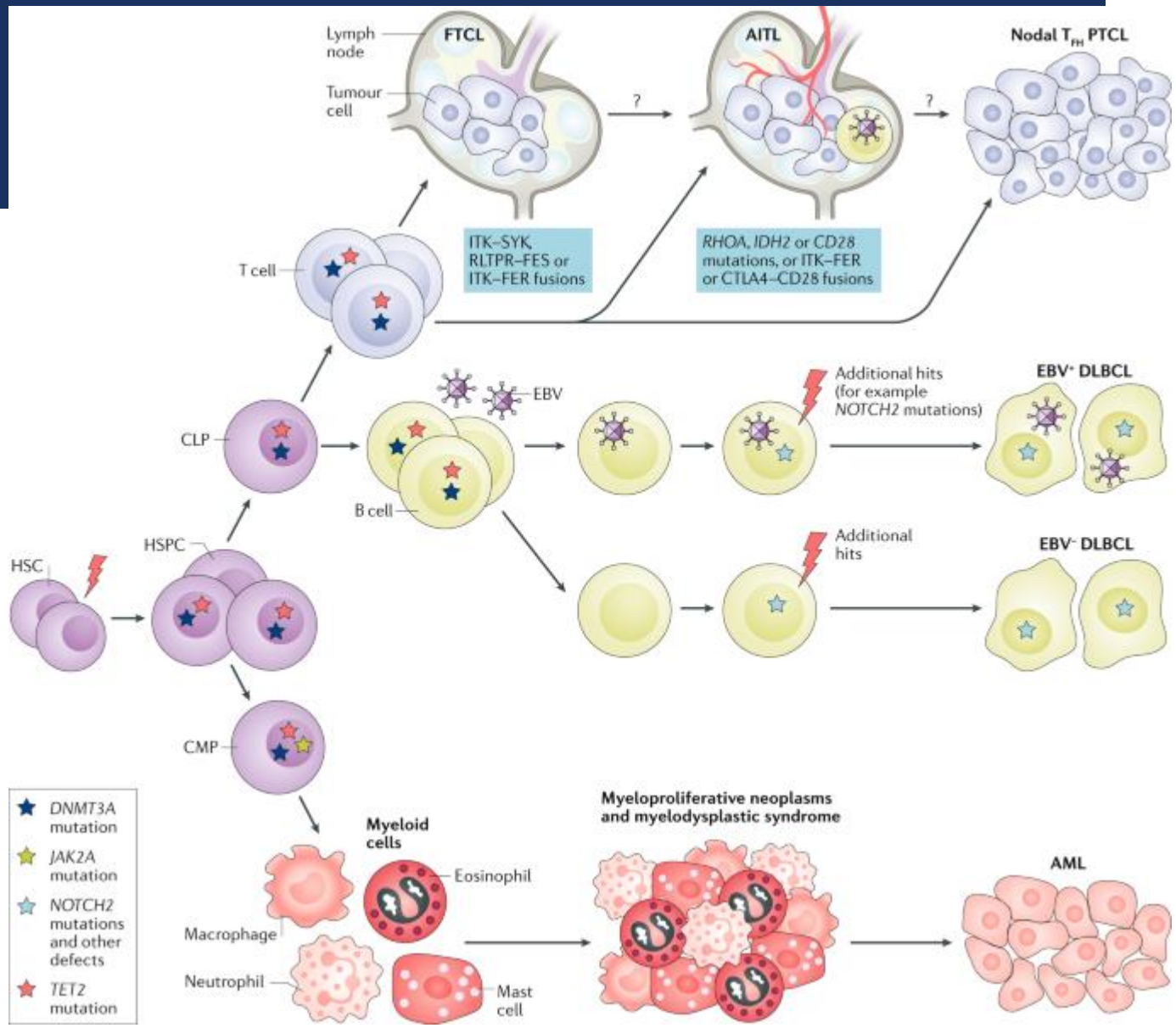
NON-HODGKIN LYMPHOMAS



https://media.springernature.com/lw685/springer-static/image/art%3A10.1038%2Fs41568-020-0247-0/MediaObjects/41568_2020_247_Fig3_HTML.png?as=webp

NON-HODGKIN LYMPHOMAS





https://media.springernature.com/lw685/springer-static/image/art%3A10.1038%2Fs41568-020-0247-0/MediaObjects/41568_2020_247_Fig5_HTML.png?as=webp
https://www.researchgate.net/publication/303388820/figure/fig2/AS:651522887143450@1532346569265/The-role-of-T-and-B-cell-interaction-in-the-development-of-MALT-lymphoma-FH-Follicular.png

LYMPHOMA MANIFESTATION

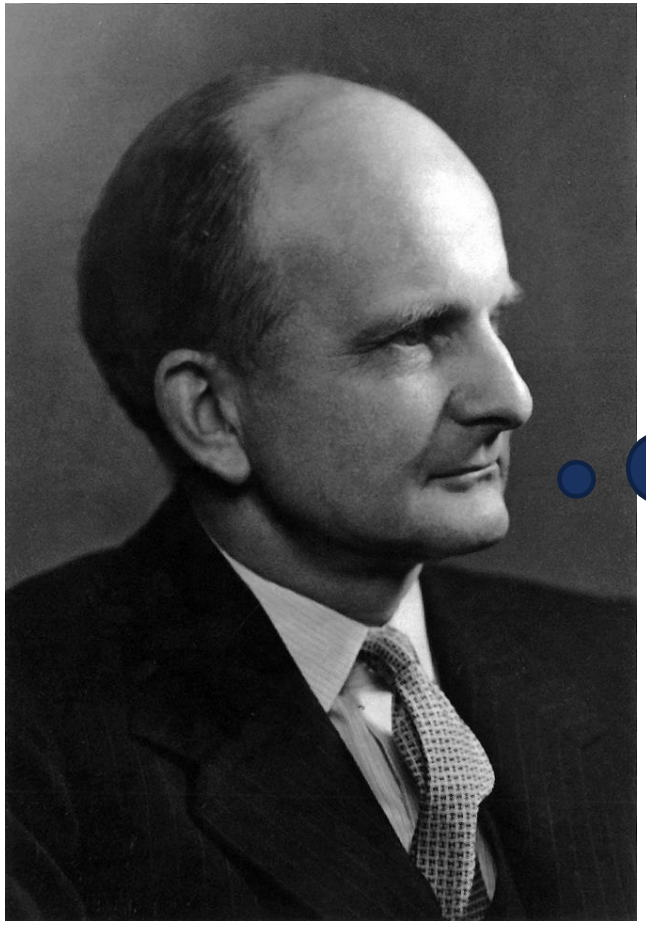
Hodgkin lymphoma

- Lymphadenopathy
  - Sole lymphatic nodes group, upper body, painless
- Systemic signs
  - Pruritus, night sweats, weight loss, mild fever, fatigue
  - Hepato- and/or splenomegaly
  - Pulmonar, cardiovascular, bone marrow invasion
- Pel-Ebstein fever?

Non-Hodgkin lymphoma

- Lymphadenopatia
  - Multiple groups – skin, neck, armpit
- Systemic signs
  - Fever and chills
  - Fatigue, abdominal „mass“ perception
  - Chest pain, chest pressure

DOES PEL-EBSTEIN FEVER EXIST? (A PHENOMENON THAT SOMEBODY NAME)



"Every student and every doctor knows that cases of Hodgkin's disease may show a fever that is high for one week and low for the next week and so on. Does this phenomenon really exist at all?..."

Richard Asher (GBR, endocrinologist and hematologist, 1912-1969)

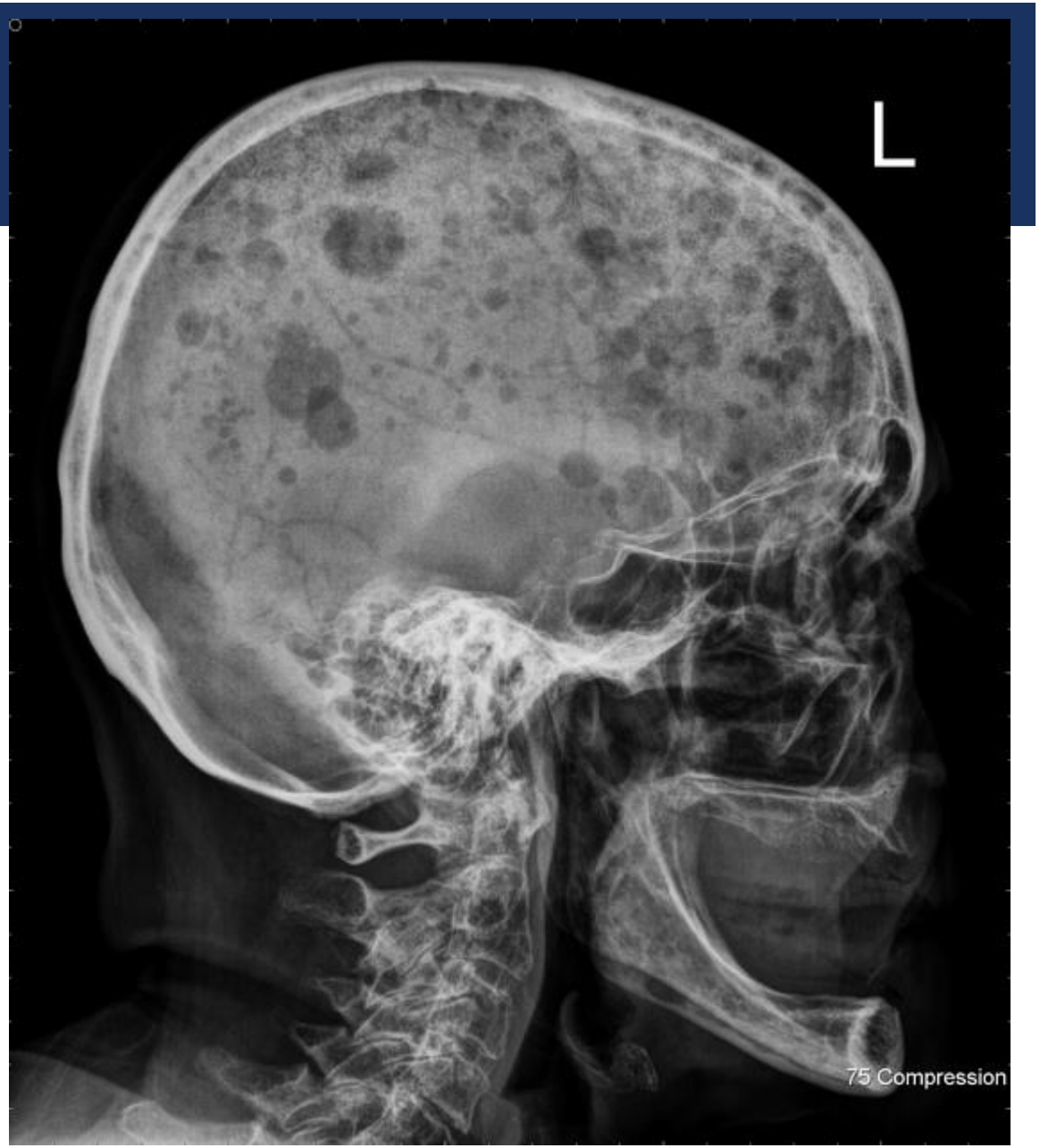
https://en.wikipedia.org/wiki/Richard_Asher#/media/File:Richard_Asher_for_Wikipedia.jpg

MYELOMAS

- Oncohematological disease derived from plasmoblasts (plasmocytes precursors) or activated B-memory cells
- Multiple myeloma (MM)
  - Genetic abnormalities – heavy chain gene (14q32) and oncogene (e.g. 11q13, 4p16.3, 6p21, 16q23 a 20q11) translocation
  - Translocation of Ch14 -> plasmoblasts group emerge -> monoclonal gamapathy of uncertain significance (MGUS) -> „smouldering“ MM -> MM -> plasmoblastic leukemia
  - IL-6 -> decisive factor
  - Manifestations – CRAB (hyperCalcemia, Renal insufficiency , Anemia, Bone lesions -> patolhogic fractures)
  - Bence-Jonesova protein filtrated to urine

MYELOMAS

- Other important myelomas and monoclonal gamapathies
  - Waldenström macroglobulinemia
  - Primary amyloidosis
  - Heavy-chain disease
- Statistics
  - Risk 3–5 % >50 years of age
  - Remissions and relapses according to types
    - MM relapsing in almost all patients after them being „cured“

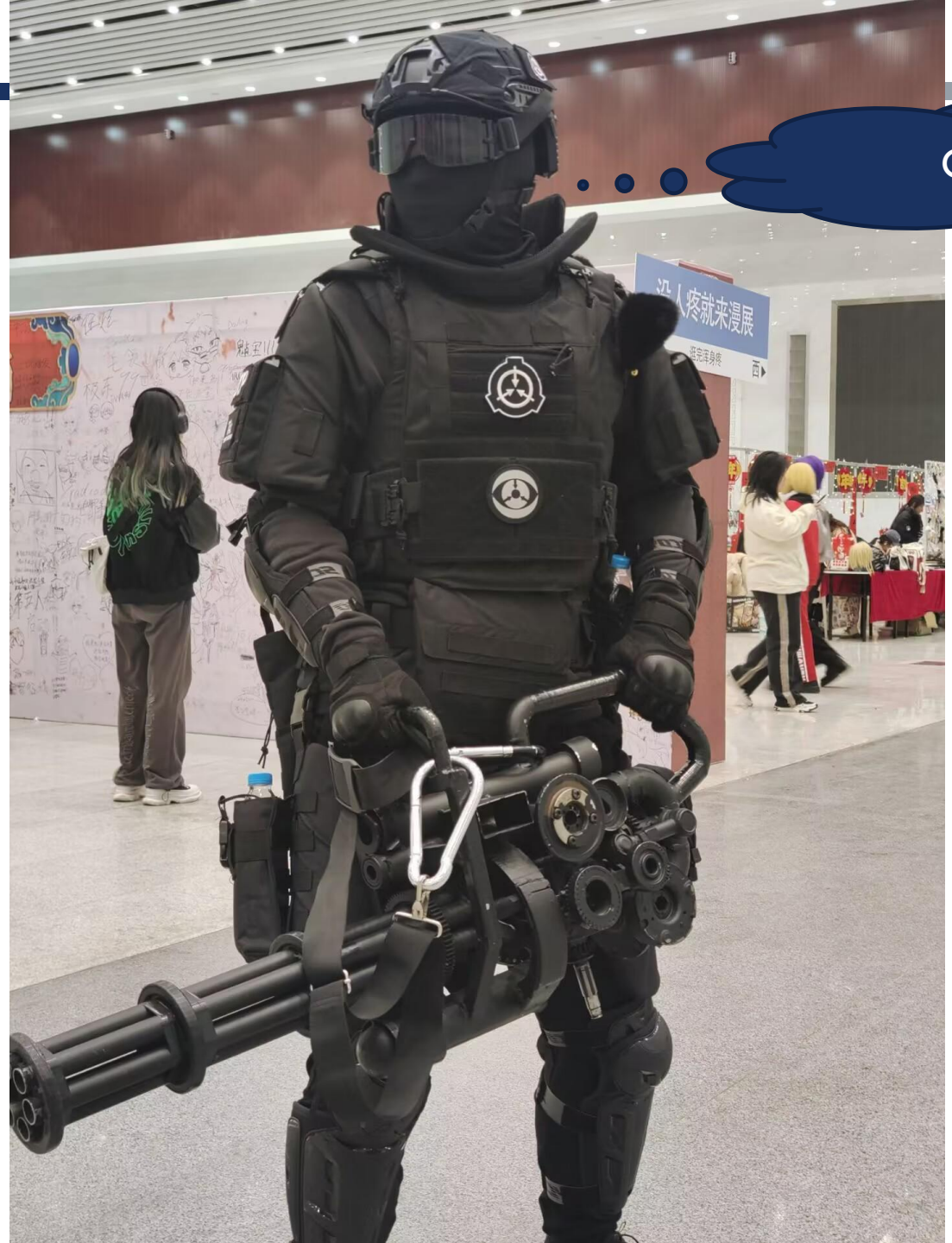


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OTHER IMPORTANT ONCOHEMATOLOGIC DISORDERS AND CONDITIONS – MYELOID PRECURSOR

- Pre-leukemic states or leukemia development risk factors

- Myelodysplastic sy.
- Polycytemia vera rubra
- Essential (primary) thrombocytemia
- Myelofibrosis
- Mastocytosis



Questions?

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