



Leucopenia & Immunodeficiency Cancers

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Case Report

- A 4-year-old boy is referred due to severe anemia. the hemolytic anemia was diagnosed,(DAT positive +++) which is treated with corticosteroids & IVIG .After 6 months complete response to treatment
- A year later, the child presented with seizures, in the examinations, vasculitis and thrombosis of cerebral vessels were diagnosed, and she was treated with high dose corticosteroid and LMWH.

Case Report

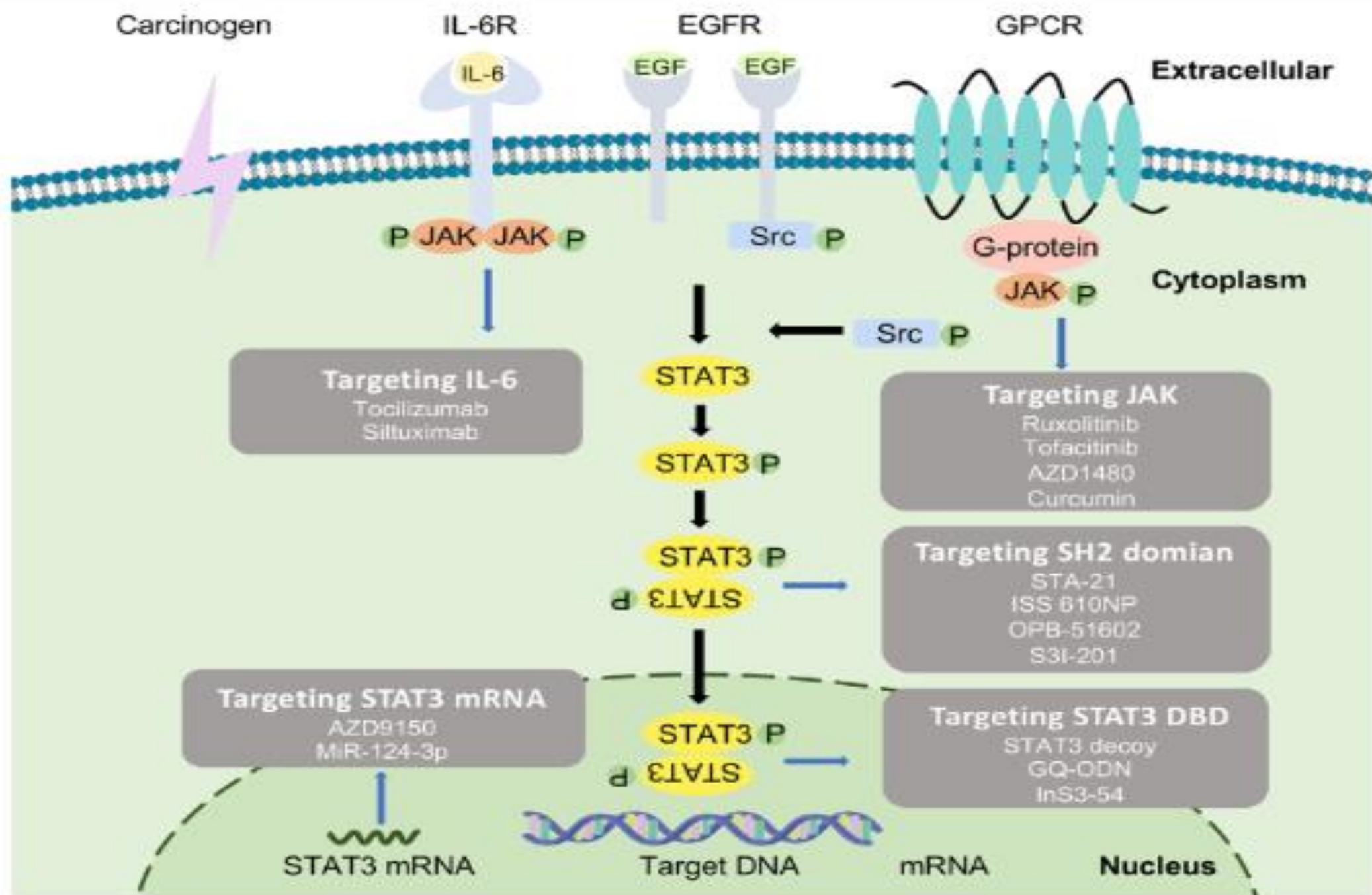
- After few month Patient admitted with prolonged fever. continues and further studies demonstrated CMV positive
- The patient had clinical presentation of respiratory distress in admission CXR : Bat wings pattern (possible PCP)
- Workup for Immune deficiencies cause of several infections , Uncommon infections & atypical germs
- In further evaluations by gene analysis: **STAT 3 mutation** considered for patient

Case Report

- 3 years later patient admitted with clinical presentation of respiratory distress .CXR : White lung of left hemi thorax
- Chest CT scan : Large mediastinal mass in left side especially in posterior mediastinum that cause mass effect on main bronchus & pulmonary veins & severe pleural effusion.
- Pathology of mediastinal mass : **Large B cell lymphoma**
- WBC & Hb were decreased but BMA is normal
- EBV positive in biopsy

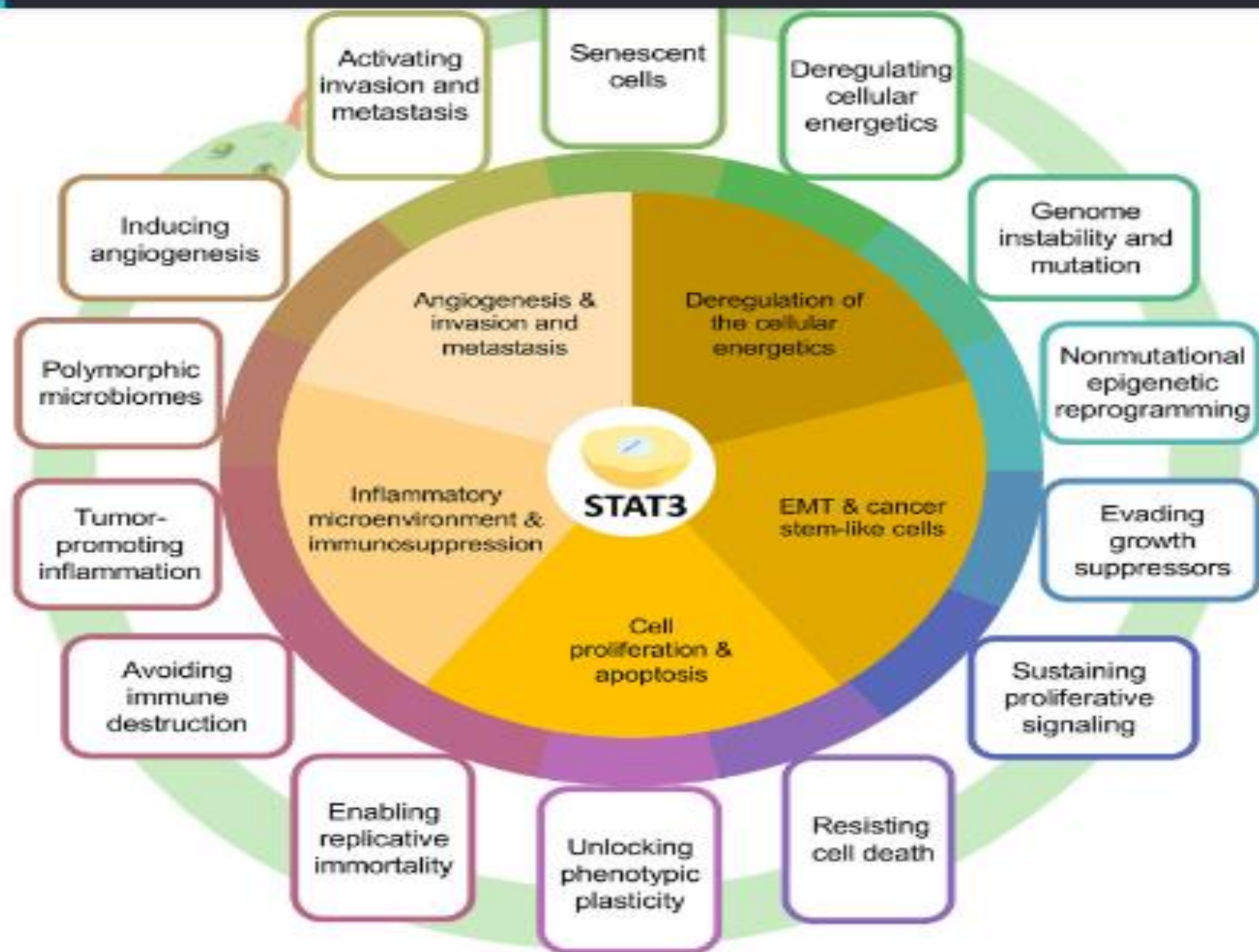
Signal transducer and activator of transcription 3 (STAT3)

- STAT3 a member of the STAT family, discovered in the cytoplasm of almost all types of mammalian cells, plays a significant role in biological functions. **STAT3 is a transcription factor which in humans is encoded by the STAT3 gene.**
- In response to cytokines and growth factors, STAT3 is phosphorylated by receptor-associated (JAK), and translocates to the cell nucleus where it acts as a **transcription activator**.
- STAT3 mediates the expression of a **variety of** genes in response to **cell stimuli**, and thus **plays a key role in many cellular processes such as cell growth and apoptosis.**



STAT3 & Cancer

- There is strong evidence to suggest that aberrant STAT3 signaling promotes initiation and **progression of human cancers** by either **inhibiting apoptosis** or **inducing cell proliferation, angiogenesis**, invasion, and metastasis.
- Activation of STAT3 in a wide variety of human tumors, including hematological malignancies (leukemias, lymphomas, and multiple myeloma) as well as diverse solid tumors (such as head and neck, breast, lung, gastric, hepatocellular, colorectal and prostate cancers



Introduction

The increased incidence of cancer in patients of Primary Immunodeficiency (PID) is seen

- 1. Development of Malignancies**
- 2. Relationship Cancer & Primary Immunodeficiency**
- 3. Susceptibility to malignancy in infection**
- 4. Epstein–Barr virus (EBV) & Malignancies**
- 5. Immunodeficiency and lymphoma**
- 6. Conclusion**

Development of Malignancies

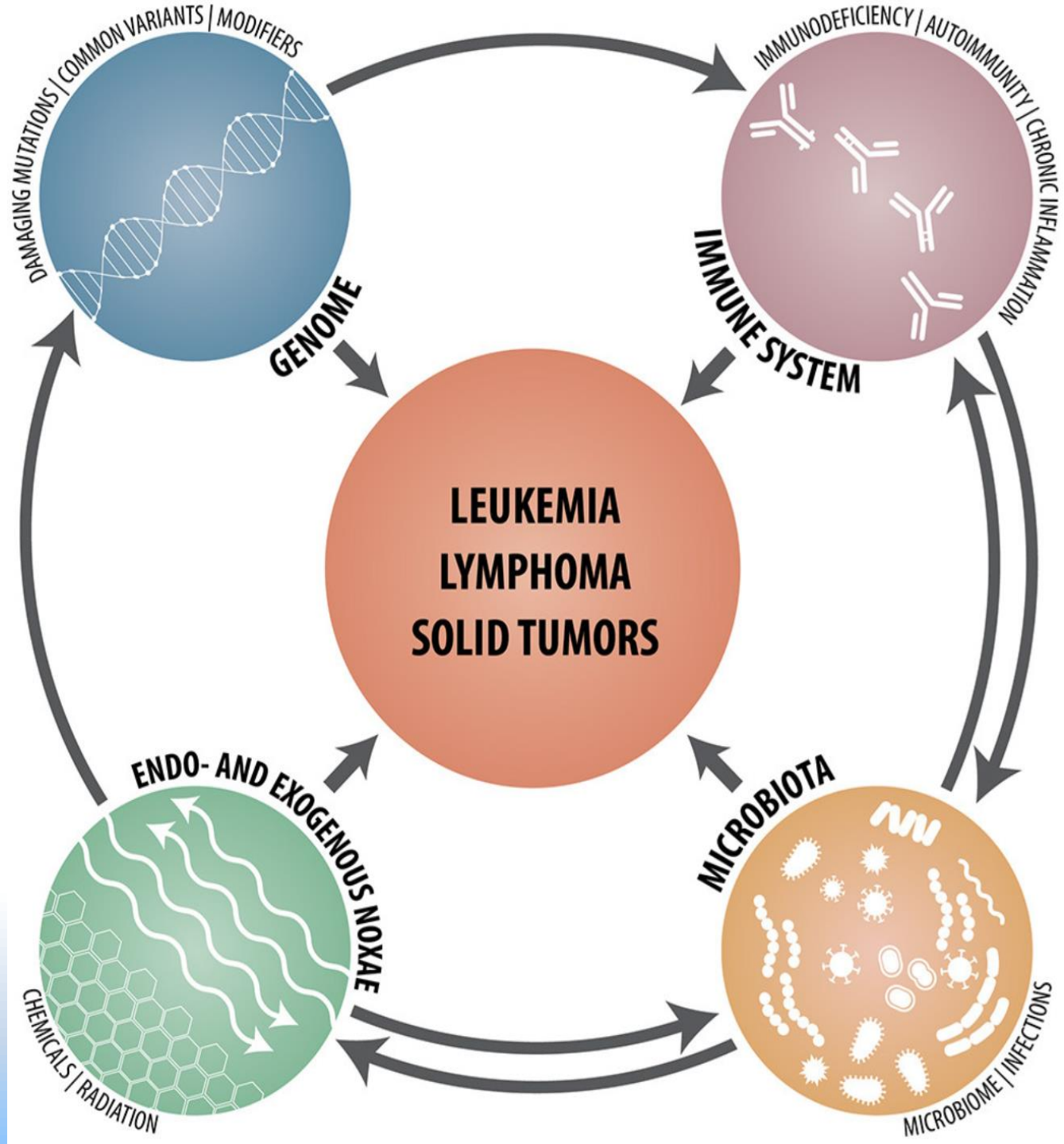
➤ Development of Malignancies strongly predisposing genetic component

The development of malignancies is always a multifactorial process that not only requires a liable genetic architecture but also some probabilistic elements as well as the participation and interaction of a multitude of other intrinsic and extrinsic factors and mechanisms.

Malignancies

Cell-extrinsic factors & cell-intrinsic defects and abnormalities

- I. stem cell development, differentiation and apoptosis
- II. cytoskeleton, cytotoxicity and metabolism
- III. chromosome stability as well as DNA repair.
- IV. Cell-extrinsic factors,, comprise chronic inflammation ,autoimmune- and autoinflammatory diseases, chronic (viral) infections



Relationship Cancer & Primary Immunodeficiency

- ❑ The **risk of malignancies is higher** in patients with genetically determined Primary immunodeficiencies than in **the general population**.
- ❑ Malignancy may occur in **parallel to or even precede** immune deficiency.
- ❑ Causal **germ line mutations** were identified in $\approx 8\%$ of malignancies in children and was created **to increase relationships** with immunodeficiencies
- ❑ PID disorders like **DNA repair defects** may be perceived tumor predisposition,
- ❑ **factors in treatment** such as alterations of the **microbiome** can contribute to tumor predisposition.
- ❑ Chronic **inflammation or infections**, predispose to tumorigenesis



Malignancy & Infection

10 microbial agents (7 viruses, 2 parasites, and 1 bacterium) as group 1 human carcinogens.

Microbe-induced human malignancies for this way:

- All human oncogenic viruses **encode at least one oncogene** and may therefore **directly induce neoplastic transformation**.
- Is defined as involving **immunologic tissues**(infection-associated inflammation)
- Requires **direct microbial interactions with parenchymal cells**
- Involves distant effects **from local interactions**



Susceptibility to malignancy in infection

- Chronic inflammatory gastric mucosa-associated lymphoid tissue lymphomas. (MALT) associations of *Helicobacter pylori*
- Chronic infections with *Epstein-Barr virus* (EBV) usually predispose to **Burkitt- & Hodgkin lymphomas**.
- *Hepatitis C virus* (HCV) to marginal zone lymphomas
- Hepatitis B virus (HBV) to **hepatocellular carcinoma**
- The role of chronic inflammation remains in case of **human papillomavirus**, **herpes simplex virus 2**, **Human herpesvirus 8**
- **Cytomegalovirus-triggered malignancies & HIV**



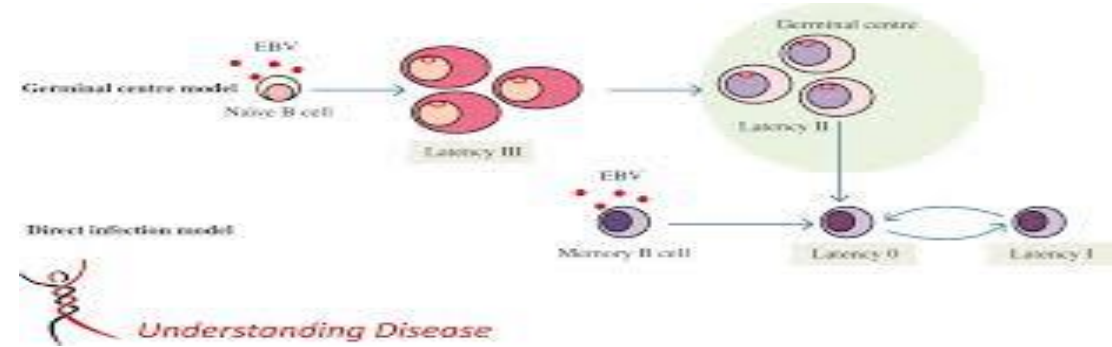
Epstein–Barr virus (EBV)

EBV is a gamma 1 herpes virus that infects human epithelial cells and B cells of the adaptive immune system to establish lifelong latency

- ❑ EBV contributes to about 1.5% of all cases of human cancer worldwide
- ❑ Rarely, EBV can cause ectopic infections and has been found in NK, T, gastric epithelial, and smooth muscle cells
- ❑ EBV infection presents as chronic active infection and is associated with autoimmune disorders, such as multiple sclerosis
- ❑ EBV has an inherent capacity of malignant transformation especially of its B cell target.
- ❑ EBV can lead to post transplant lymphoproliferative disorder (PTLD)
- ❑ EBV can lead to malignant lymphoma, such as Hodgkin's lymphoma, Burkitt's lymphoma, and diffuse large B cell lymphoma

EBV-related disease

EBV-related disease including:



1. Those that are associated with various forms of immunodeficiencies
2. Those that concur with a high propensity to develop diverse hematopoietic, epithelial, and mesenchymal malignancies
3. Reactive EBV-associated lymphoid and histiocytic/dendritic proliferations (including reactive lesions without diverse malignant potential),
4. B /T/NK cell proliferations (including Hodgkin lymphoma and plasma cell neoplasms)

lymphoma & Primary immunodeficiency

- ❑ Non-Hodgkin lymphoma (NHL) is the **most frequent malignancy** associated with primary immune deficiency disease (PID).
- ❑ NHL account for **more than 60%** of the tumors in children with PID
- ❑ PID-associated NHL accounted **for 5.7% of all NHL** and was characterized by younger **median age 10 years**
- ❑ **Each type of immunodeficiency** has its **own risk factors** and is associated with a particular type of lymphoma
- ❑ lymphoma **250-fold risk**, have patients **with chromosomal breakage** syndromes (Nijmegen breakage syndrome, Bloom syndrome, Wiskott-Aldrich syndrome).

lymphoma & Primary immunodeficiency

- ❑ DLBCL **is most common** type(68.8%) of NHL, which was occurred in young children with PID to be frequently associated with EBV
- ❑ All DLBCL **cases were EBV associated** and characterized by rather **massive lung involvement** and having a predilection for **extranodal sites**.
- ❑ Multiple pulmonary lesions may also manifest an extensive fungal infection or tuberculosis. **Lung biopsy early** after the detection of **pulmonary foci in order** not to lose time on preventive antibacterial or antifungal treatment in patients with **combined PID and documented EBV infection**.

A close-up photograph of pink cherry blossoms with yellow stamens, set against a soft, out-of-focus background of more blossoms. The image has a warm, pinkish-orange tint.

Thank you for listening.

Any question?