

Activated phosphokinase- δ -syndrome (APDS) masquerading as growth retardation and oligoarthritis

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Background

APDS is a primary immunodeficiency often presenting as growth failure, pronounced fatigue, infection susceptibility, lymphoproliferation/lymphoma, gut inflammation and other signs of immune dysregulation such as autoimmune cytopenias, arthritis, thyroiditis.

Diagnosing APDS is challenging due to its symptom variability. Diagnostic delay – often of several years – may be avoided through interdisciplinary team communication. Targeted treatments are helpful to avoid accumulation of organ damage and unnecessary side effects from consecutive courses of non-targeted immunosuppressants.

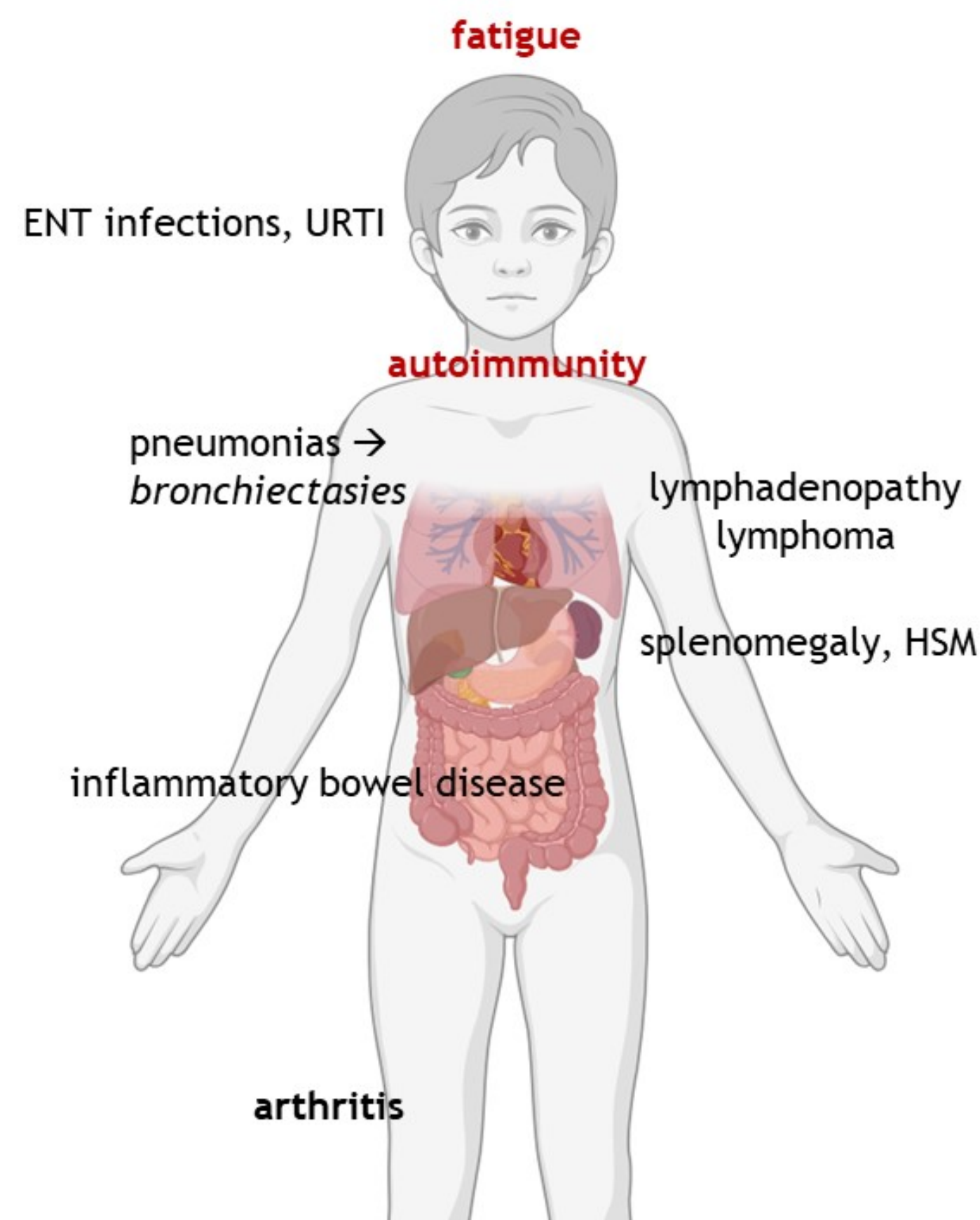


Figure 1 Frequent signs and symptoms in APDS (biorender)

Immunological and genetic work-up

- ❖ Hypogammaglobulinemia, insufficient vaccine titres
 - IgG 3.8 (5-11.7) g/L, IgM 1.7 g/L (0-15-1.6), IgA 0.64 g/L
 - non-protective vaccine titres for TT, DT, pneumococcus
 - EBV VCA IgG and IgM positive (EBV DNA 38 IE/ml)
- ❖ T-cell activation, inverse CD4/CD8 ratio
- ❖ **increased transitional B cells** and poor class-switch
- ❖ PI3KCD-GOF variant: Glu1021Lys

Patient report

- ❖ 3 9/12 year-old boy presenting with **pneumonia** and oedema of both feet
- ❖ On clinical examination he had **lymphadenopathy**, hepatosplenomegaly, signs of ascites and arthritis
- ❖ Laboratory results showed hypalbuminemia and **hypogammaglobulinemia** and elevated stool calprotectin (>2100 µg/g)
- ❖ abdominal ultrasound revealed lymphadenitis mesenterialis and ileitis terminalis as well as pronounced splenomegaly
- ❖ Chest X-ray showed reticular markings/bronchopneumonic infiltrate
- ❖ The boy was positive for rhinovirus, parainfluenza virus and EBV, he also had enteritis due to clostridia
- ❖ **growth** and developmental/speech **delay**, **fatigue** +++ percentiles P4-7 (Weight and height) – P10-20 for head circumference
- ❖ Infectious history
 - recurrent bronchitis, otitis and one previous pneumonia
 - 3 x placement of tympanostomy tubes
 - treatment with fluticason p.inh.
- ❖ early-onset **oligoarthritis**

Therapeutic management and patient benefit

- ❖ antibiotics
- ❖ immunoglobulin replacement therapy (IgRT)
- ❖ mTor inhibition
- ❖ haematopoietic stem cell transplantation?
- ❖ leniolisib: *compassionate-use* 2x 20 mg bid (Pharming), since 2023 approval by FDA for »12 y/o patients with APDS
- ❖ 4 months since initiation of IgRT and Joenja® (leniolisib) the patient is in excellent clinical condition off any additional immunosuppression and is followed as an outpatient

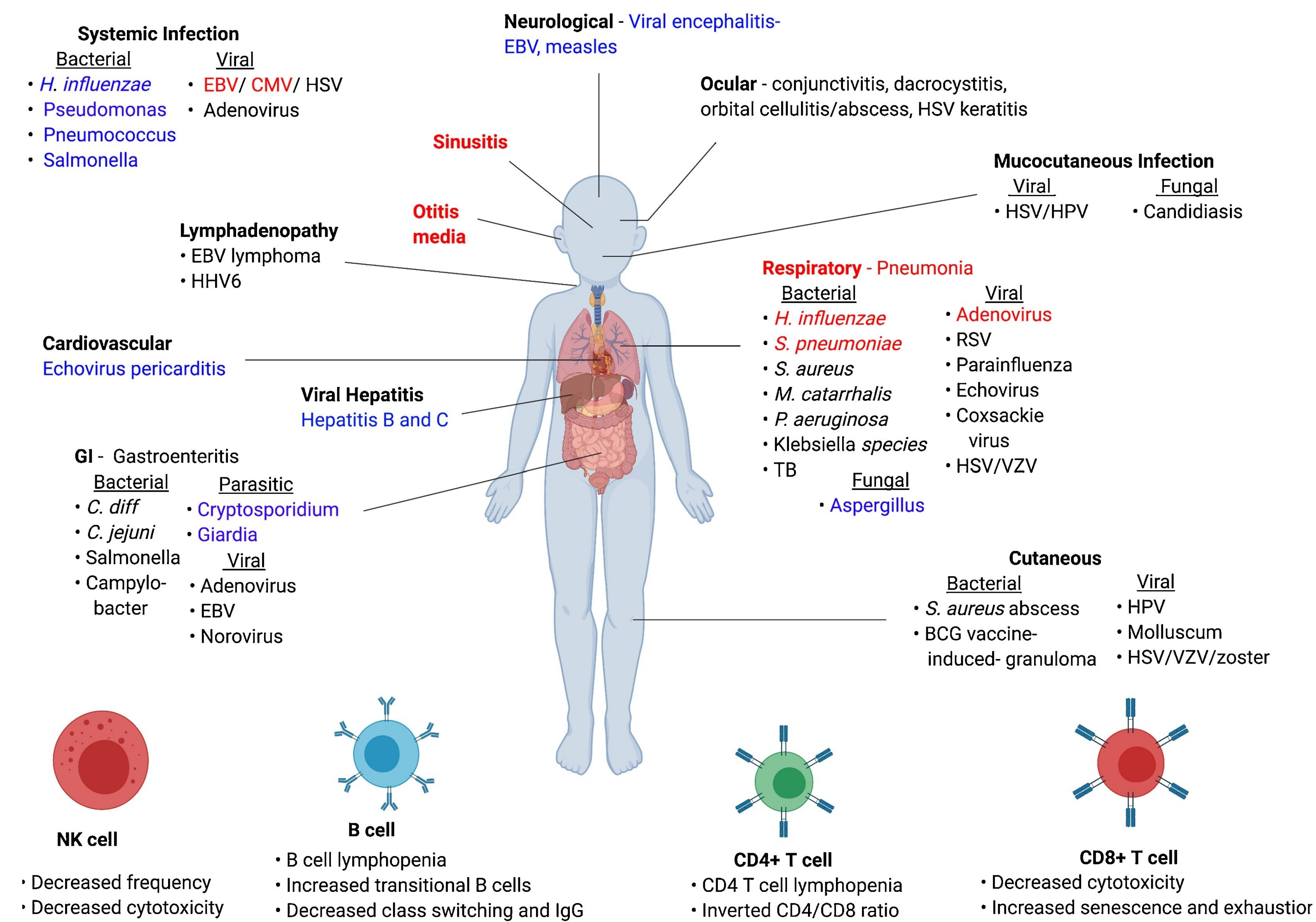


Figure 2 Infections in APDS. Brodksy and Lucas. *Curr Opin Immunol* 2021. doi: 10.1016/j.coi.2021.04.010.

Discussion

APDS is a rare monogenic disease. While diagnosis is clinically challenging due to the variability in signs and symptoms, interdisciplinary care is crucial to avoid diagnostic delay and unfavorable patient journeys (see *below*). A PI3K-inhibitor (leniolisib) has been approved by the FDA in 2023 and is awaiting approval by EMA. Some patients may benefit from a definite therapy by haematopoietic stem cell transplantation.

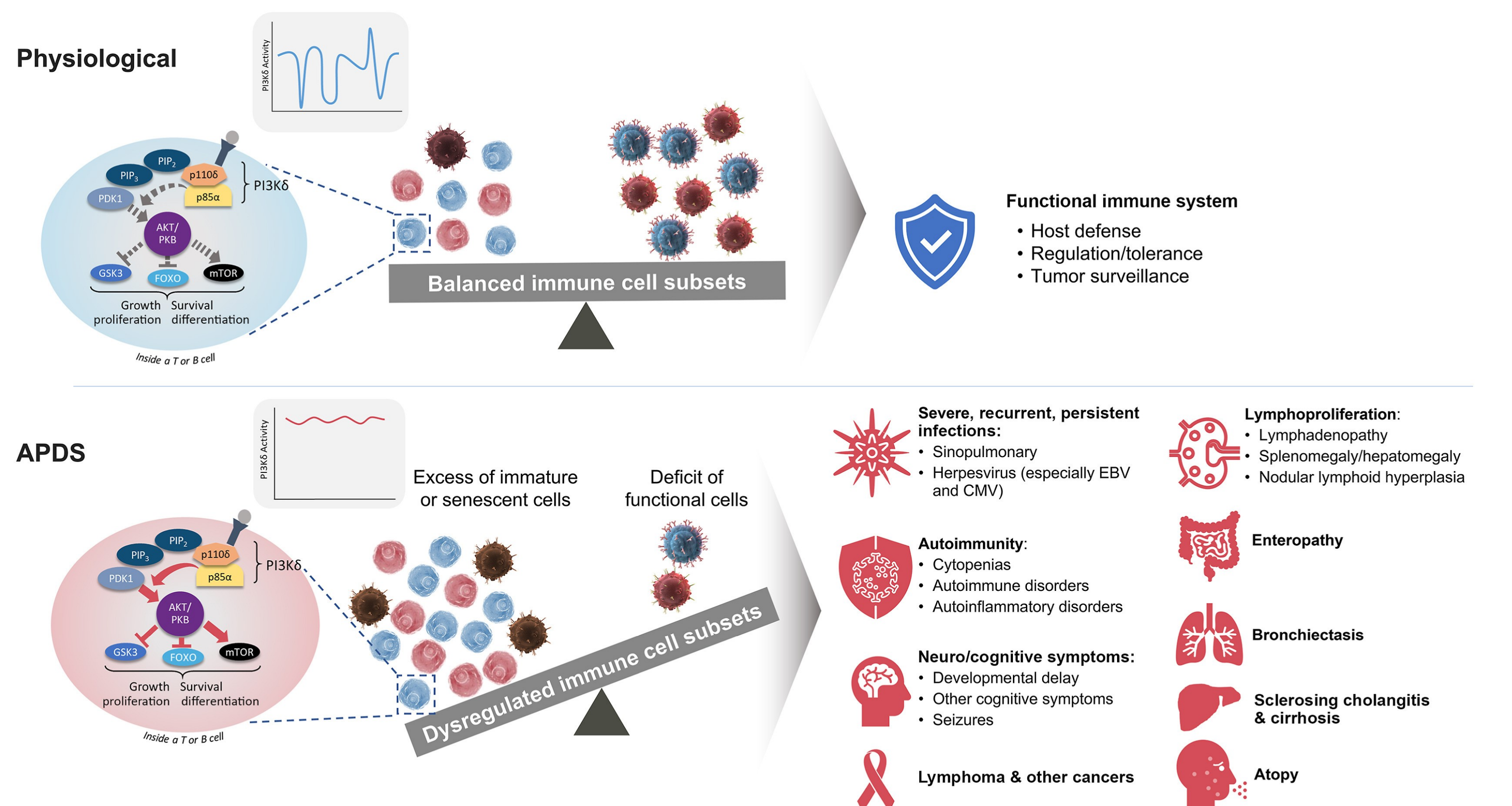


Figure 3 PI3K α pathway dysregulation. Cant et al. *J Allergy Clin Immunol* 2024. doi:10.1016/j.jaip.2023.09.016