

Autoimmune Lymphoproliferative Syndrome (ALPS)

Case Study

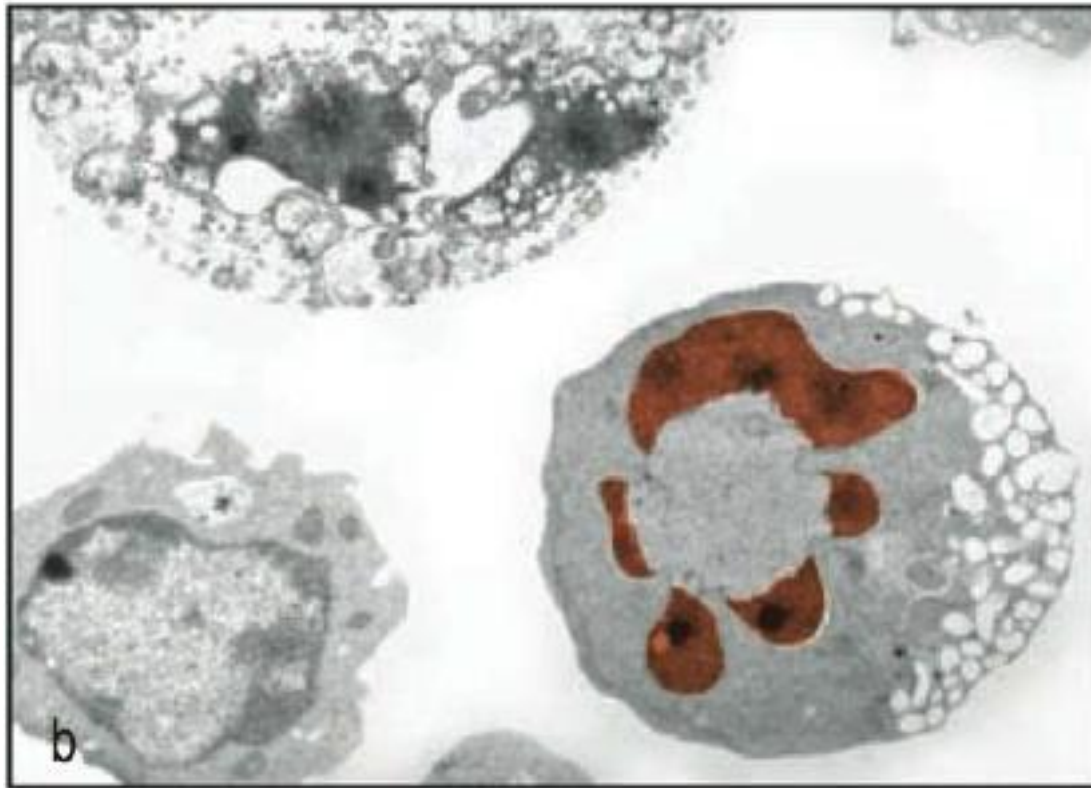
ALPS

Most cases are heterozygous for a dominant mutation in the Fas gene.

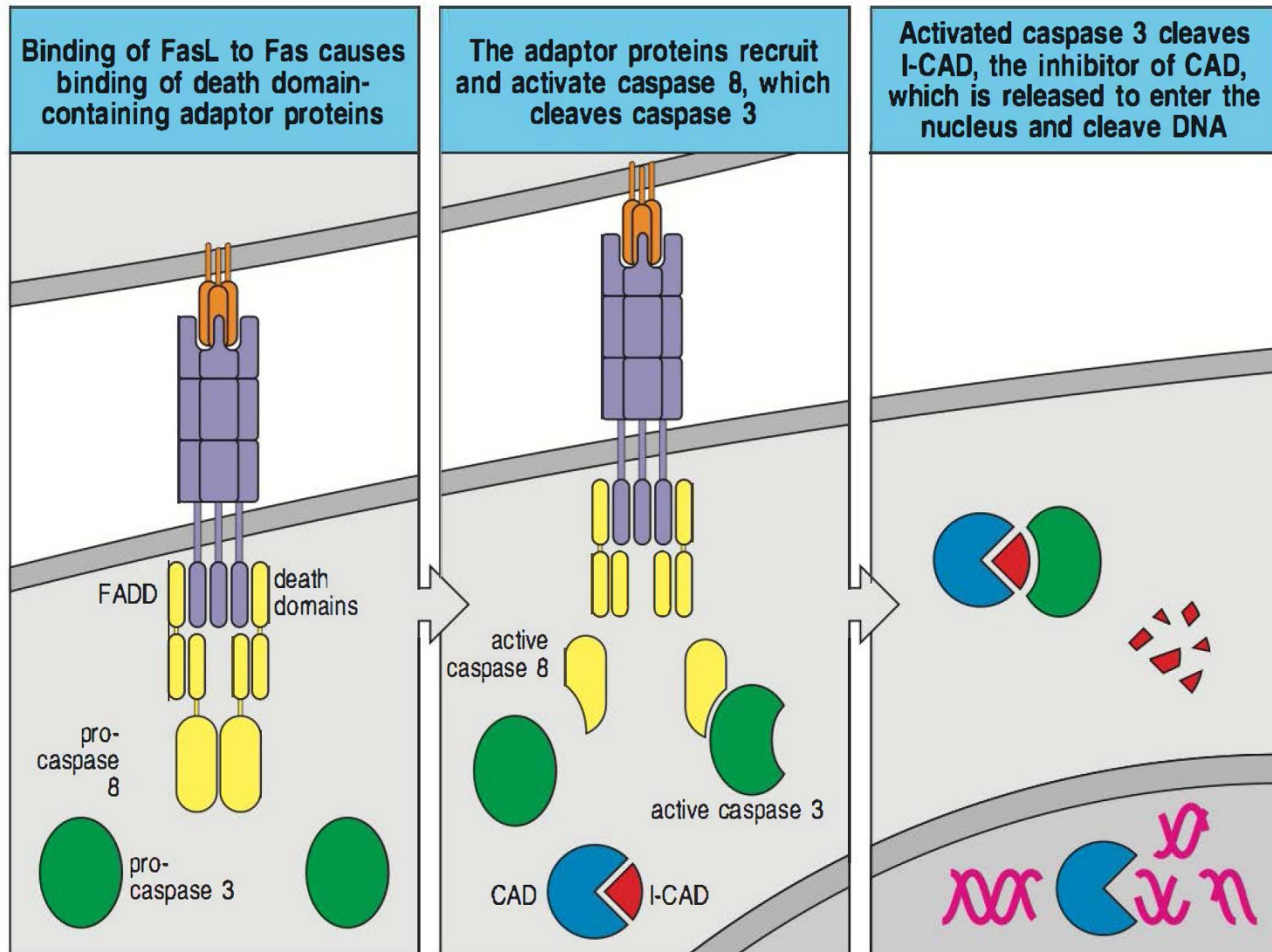
Other ALPS patients have mutations in FASL or caspase genes.

=Unrestricted Lymphoproliferation

Apoptosis is Essential in Getting Rid of Activated Immune Cells



Fas-FasL Interaction and Apoptosis



Case of Ellen O'Hara

At 18 months, splenomegaly and lymphadenopathy, Family history on father's side

High lymphocyte count

IgM, IgG, IgA all elevated

Presence of many CD4⁺CD8⁺ DN cells by FACS

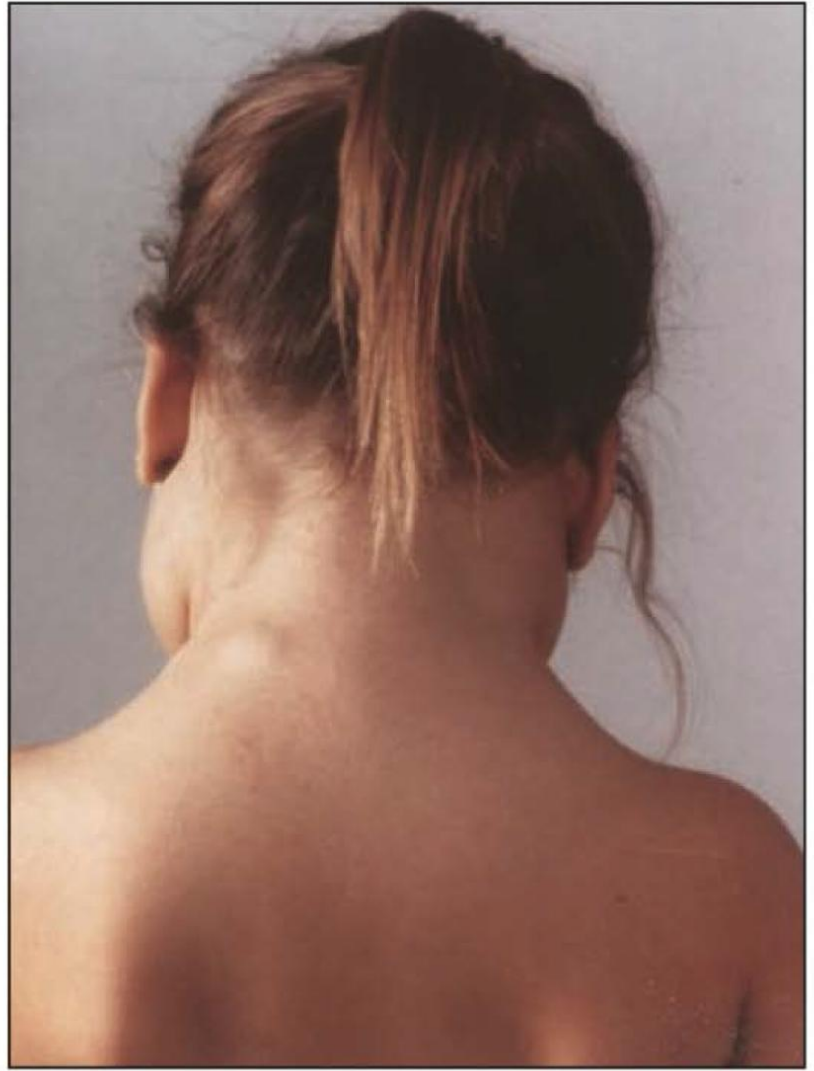
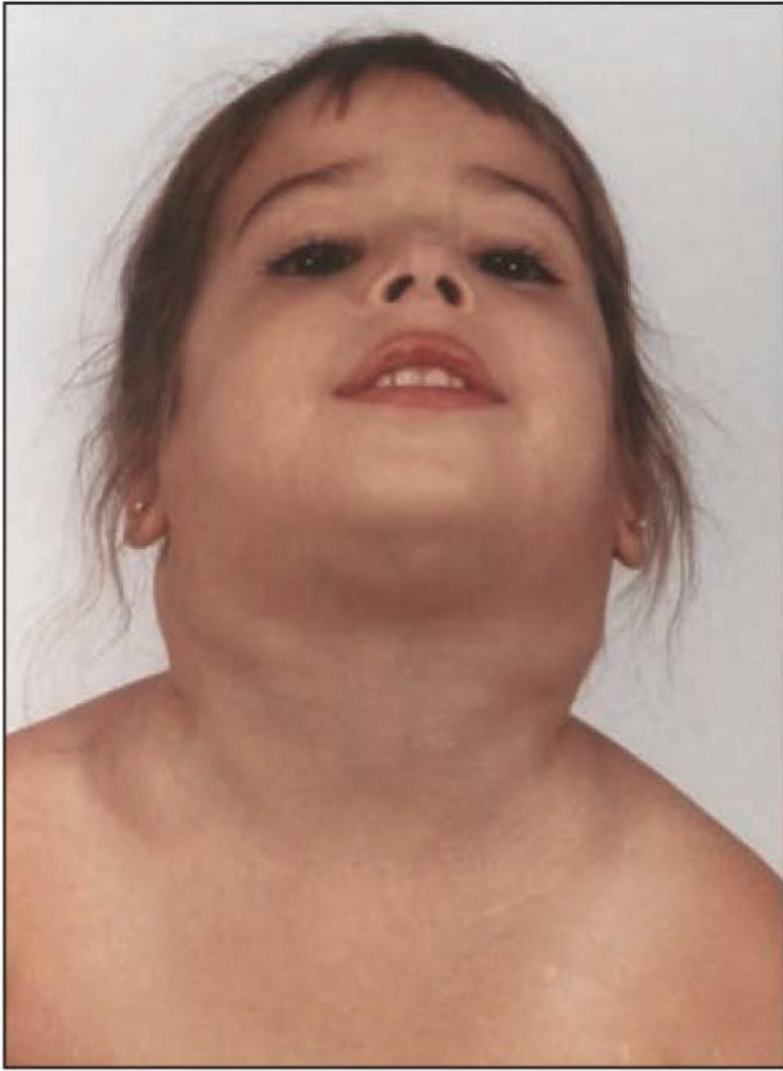
No infectious agents seen in lymph node biopsy

No chromosomal abnormalities was found in karyotyping and no oligoclonality of TCR

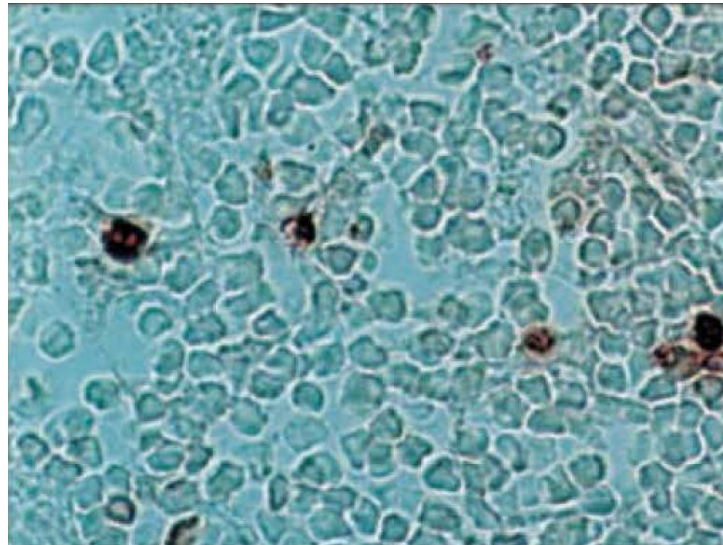
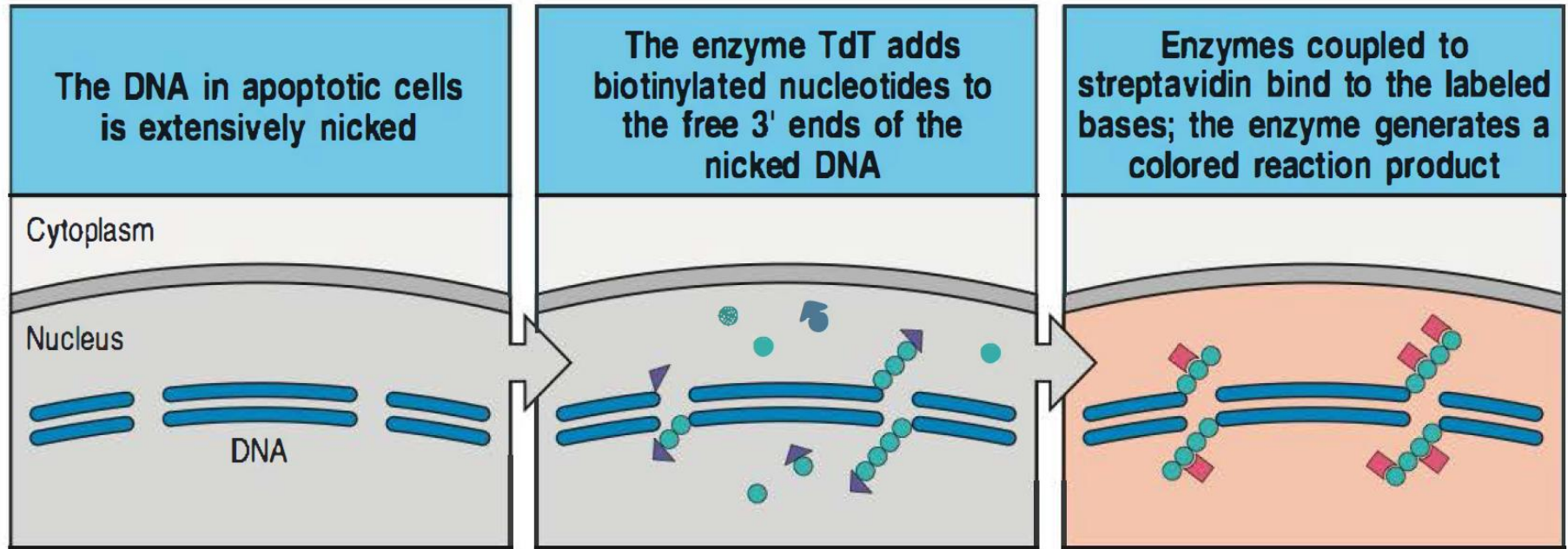
No infection, No malignancy = ALPS

Steroid and Cyclosporin A treatment= Lymph node reduction

In adolescence, autoantibodies developed to platelets (ITP), granulocytes.



TUNEL Assay to Measure Apoptosis



How do we explain the dominant inheritance of ALPS?

Any mutation of any element of the trimer causes a complete loss of function

Ellen's aunt had same mutations as Ellen but no symptoms, how?

Environmental and/or other genetic factors play a role in phenotype expression (Variable expressivity)

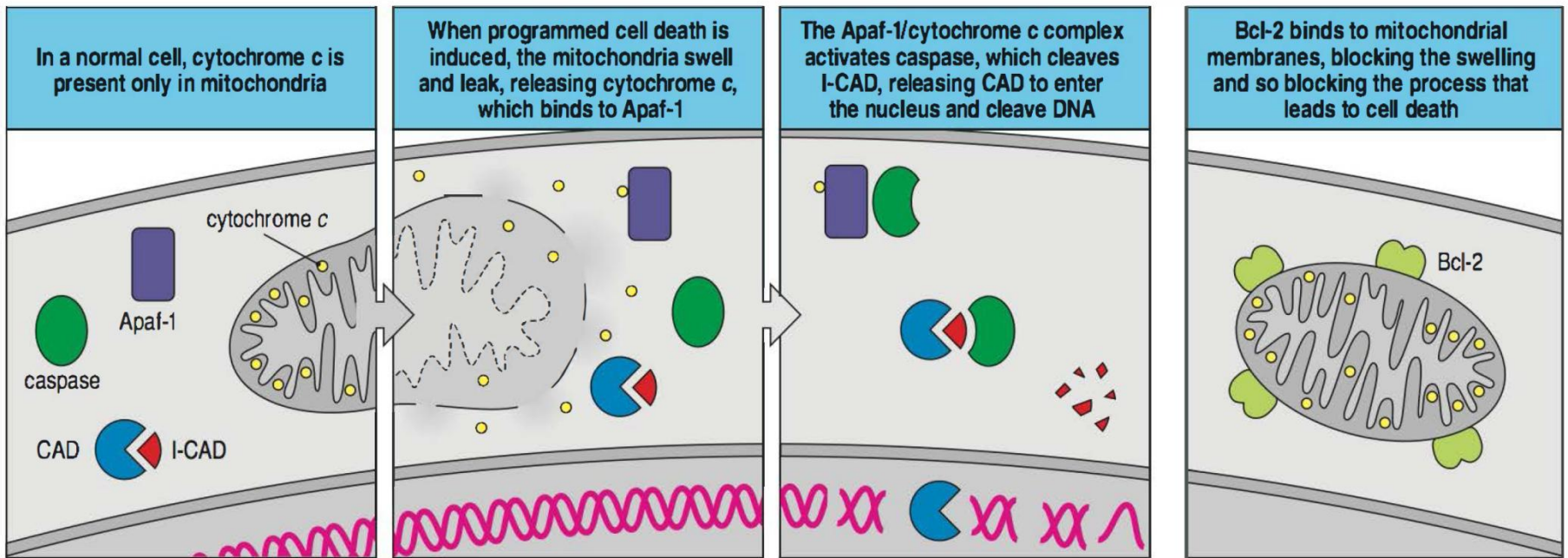
How can a virus benefit from inhibiting apoptosis in host cells?

Block ability of cytotoxic T cells to kill virally infected cells.

How do viruses block apoptosis in host cells?

Vaccinia and HSV produce molecules that block caspases.
EBV produces a Bcl-2-like protein

Bcl-2 Blocks Apoptosis



Caspase 8 gene KO in mice is lethal, is it worth searching for mutations in Caspase 8 in ALPS patients with no mutations in Fas or FasL?

Yes

In mice Caspase 8 is important in fetal tissue remodeling
Interspecies differences??

Point mutation in Caspase 8 can affect its binding to Fas complex...
How about Fas-independent functions?