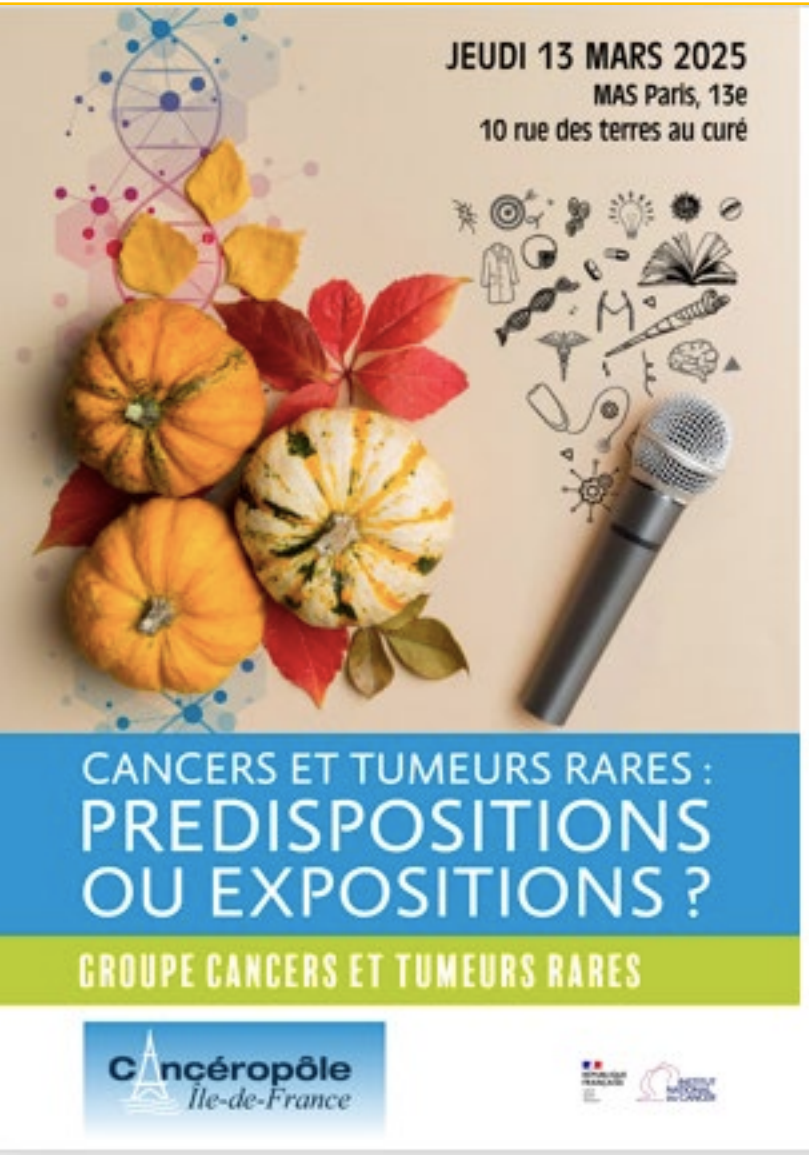

Séminaire

« Cancers et tumeurs rares : prédispositions ou expositions ? »

Lymphomes EBV induits : rôle des prédispositions immunitaires

Jeudi 13 Mars 2025

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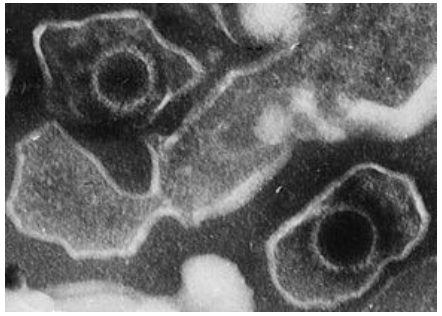
Epstein Barr virus

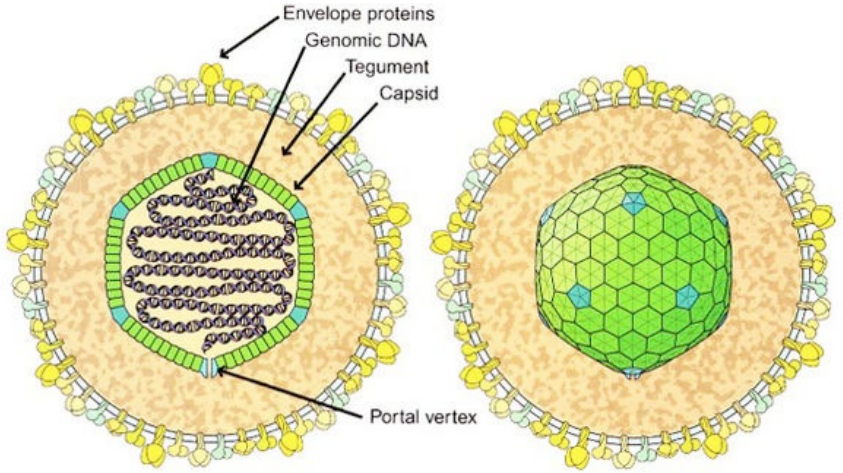
-EBV is a gamma herpes virus (HHV-4) (herpes simplex, VZV (Varicella), CMV, Kaposi…)

-discovered in 1964 by Dr. M. Epstein and Y. Barr in Burkitt lymphoma cells from Ugandan patient

-encapsided DNA virus, 172 kpb, > 100 genes/ORFs



Liza Gross — (2005). PLoS Biol 3(12): e430 DOI:



-persists in infected cells as an episome

-only found in humans and widespread in all human populations

-over 90% of individuals have been infected at the age of 20 and are asymptomatic carriers

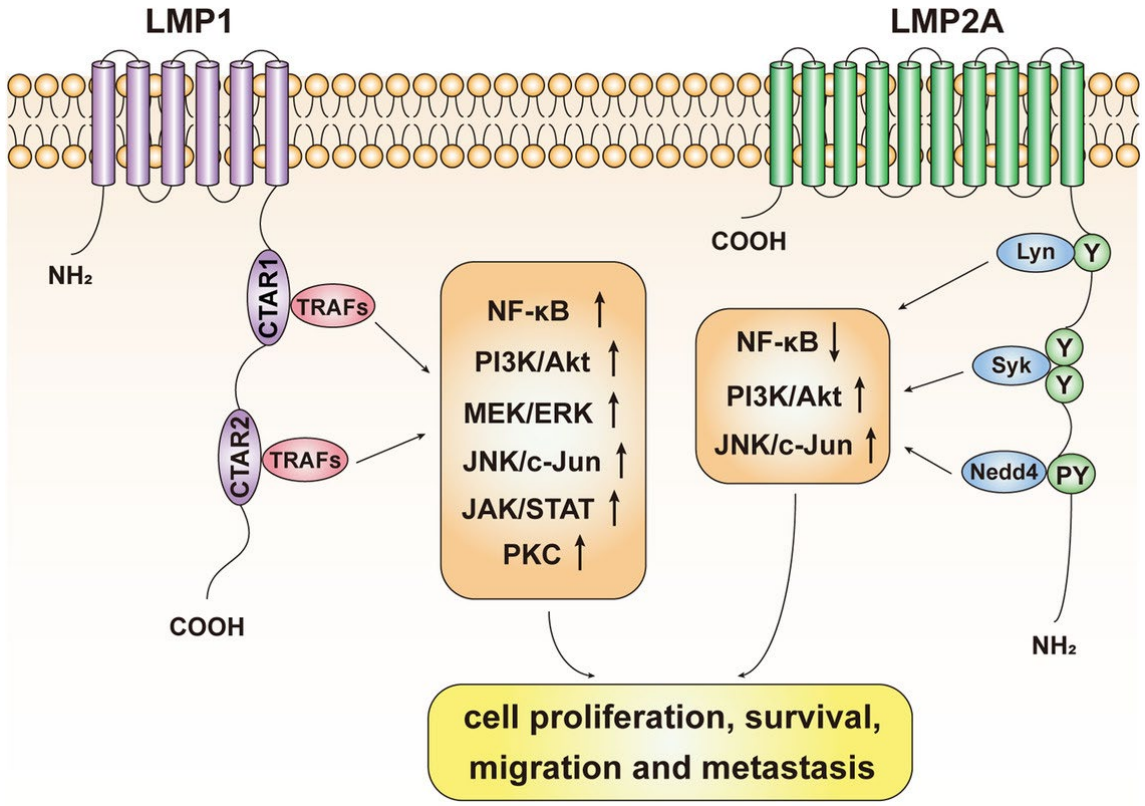
Epstein Barr virus and cancer

-EBV is oncogenic (first identified oncogenic virus)

-110,000 to 200,000 cancer cases (lymphoma and carcinoma) per year ; 1-2% of cancer-related deaths attributable to EBV worldwide (*Cancer Research UK; IARC-Lyon*)

-EBV is the first cause of cancer-associated mortality in emerging countries

-EBV transforming genes LMP1 and LMP-2A



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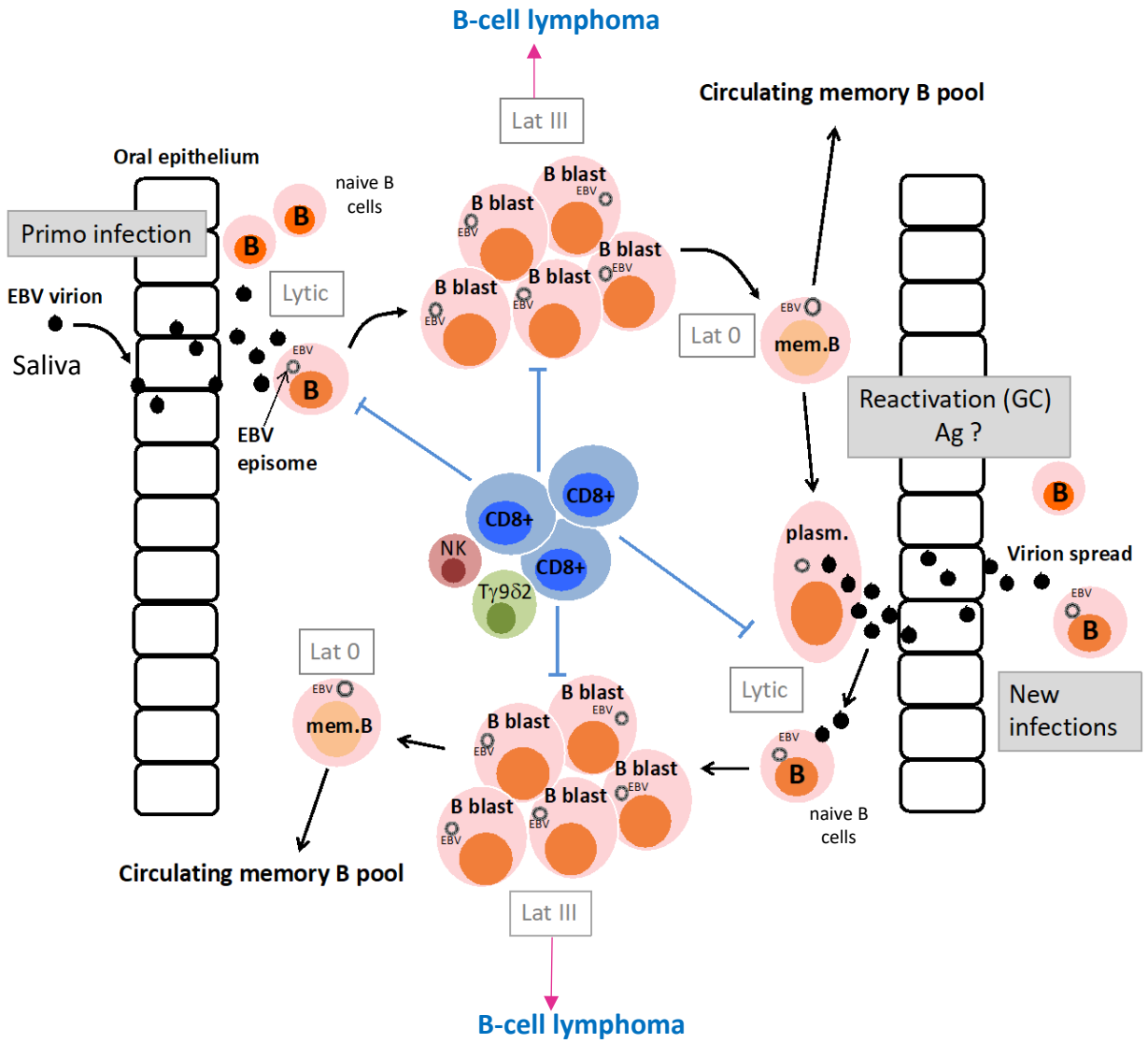
Epstein Barr virus infection and immune response

- transmission by saliva containing lytic particules/EBV virions
- EBV infects **epithelial cells** (via neuropillin-1) and **naïve B cells** (via CD21/MHC II) in the oropharynx
- rarely infection of T and NK cells (mechanism ?)
- EBV persists in B cells establishing a chronic latent infection for all the life (leading to EBV reactivations-B-cell transformation sometimes)
- EBV induces a strong proliferation of naïve B cells
- **sustained expansion EBV-specific T cells (CD8+)** is required to eliminate EBV-infected B cells
- up to 40% of circulating T cells can be specific to EBV during primary infection



EBV infection and associated pathologies

- **Infectious Mononucleosis** (IM) : self-limiting proliferation of activated CD8+ T cells and infected B-cells (primo infection)

- **Virus-associated hemophagocytic syndrome (VAHS) or Hemophagocytic LymphoHistiocytosis (HLH)** : uncontrolled (non-resolutive) proliferation of activated CD8+ T cells (IFN-γ ↑) and EBV-infected B cells leading to secondary macrophage activation →severe inflammatory disorder

- **Lymphoproliferative disorders :**
  - **B-cell lymphoproliferative disorders (B-LPD)** : -non malignant lymphoproliferations
    - **B lymphomas** : • **Hodgskin's lymphoma**
      • **non-Hodgskin's types : Burkitt, DLBCL**
  - -T/NK-cell lymphoproliferative disorders (chronic EBV infections) : **T/NK cell lymphoma**
    Initially identified in Asia, South-North Native American populations ; recently reported in Caucasian/European populations (Fournier et al. 2020)

- **Non lymphoid tumors :**
  - -Epstein-Barr virus-associated smooth muscle tumors (EBV-SMT)
  - -Nasopharyngeal carcinoma (*Asia, Africa*)
  - -Gastric carcinoma

EBV-driven B cell lymphoproliferations in immunocompromised individuals

Acquired immunodeficiencies :

- Post-transplanted individuals with immunosuppressive treatments who can develop post-transplant lymphoproliferative disorders (PTLD)

- HIV-infected individuals with acquired immunodeficiency syndrome-AIDS

Primary immunodeficiencies (PIDs) (inherited mutations/inborn errors) **:**

These rare diseases are mostly **pediatric** :

- PIDs with low penetrance of EBV-LPD (no particular susceptibility)
  -gene defects globally impairing T-cell functions
  (*ZAP-70, STIM1, DOCK8, WASP….)*

- PIDs with strong penetrance of EBV-LPD (high susceptibility)
  -with >30-100% of patients having developed one episode of EBV-driven lymphoproliferation
  -high risk to develop an EBV+ B LPD/lymphoma (30-70%), EBV+ SMT and EBV+ T/NK LPD/

PIDs with high susceptibility to EBV and EBV+ B-cell lymphomas

- XL-LP1 (XLP1): SAP deficiency: ***SH2D1A*** (Coffey, et al. Nature Genet. 1998)
- XL-Magnesium defect, EBV, Neoplasia (XMEN): ***MAGT1*** (Li F-Y, et al. Nature 2011)
- AR-IL-2 inducible T-cell kinase (ITK) deficiency: ***ITK*** (Huck, et al. J. Clin. Inv. 2009)
- AR-CD27 (TNFRSF7) deficiency: ***CD27*** (van Montfrans et al. JACI 2012)
- AR-CD70 (TNFSF7) deficiency: ***CD70*** (Abolhassani, et al. JEM 2017 ; Izawa, et al. JEM 2017)
- AR-Cytidine 5' Triphosphate Synthetase 1 (CTPS1) deficiency: ***CTPS1*** (Martin, et al Nature 2014)
- AR-Ras Guanyl Nucleotide-Releasing Protein 1 (RASGRP1) deficiency: ***RASGRP1***

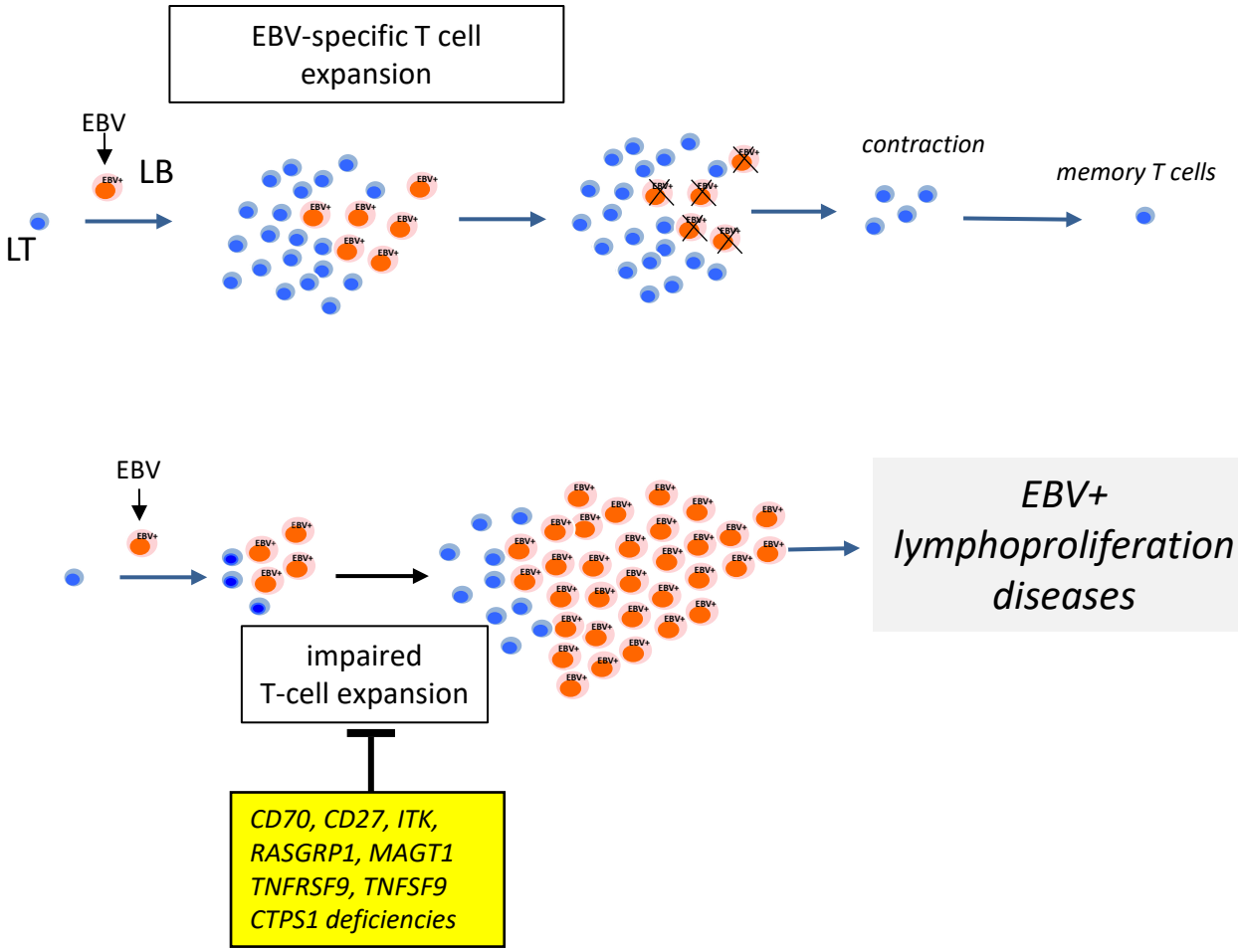
  (Salzer, et al. Nature Immun. 2016, Winter et al. EMBO Mol Med, 2018)
- AR-CD137 (4-1BB) deficiency: ***TNFRSF9***

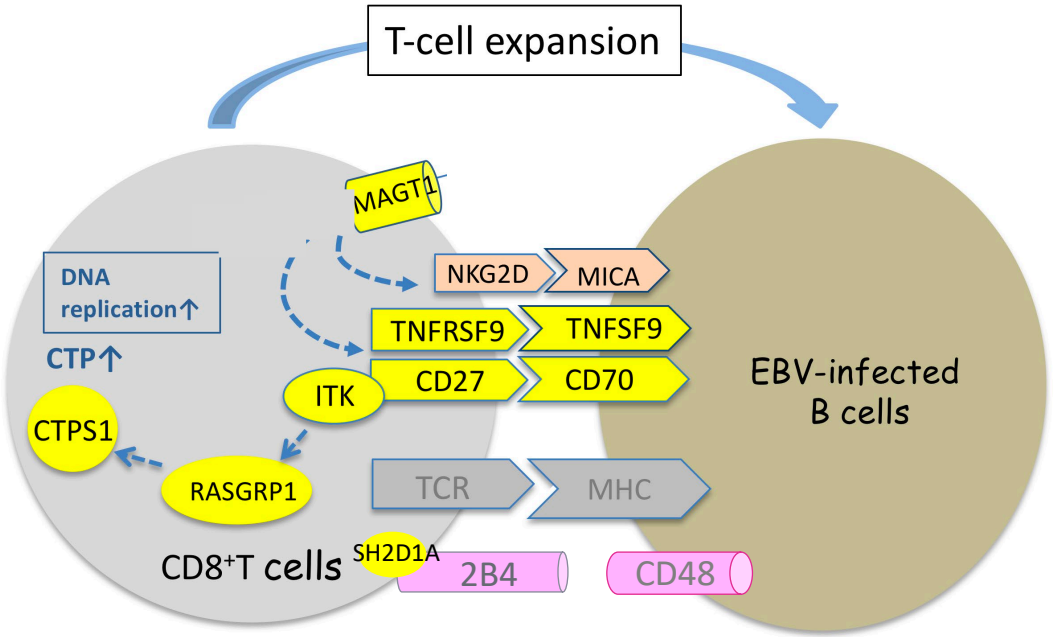
  (Somekh et al., Blood 2019; Alosaimi et al., JACI 2019; Rodriguez et al. JEM 2019)
- AR-CD137L (4-1BBL) deficiency: ***TNFSF9***

  (Fournier et al. JEM 2022)
- AR-IL-27 receptor α chain deficiency: ***IL27RA***, AA anti-IL-27 phenocopy (Martin et al; Nature 2024)

XL: X-linked
AR: Autosomal recessive

IEIs with EBV-susceptibility are mostly characterized by impaired T-cell expansion





High risk to B-cell lymphomas in immunodeficient patients with EBV susceptibility

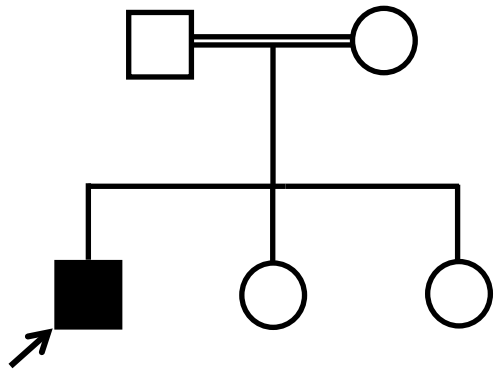
Gene defects	Patients N=	B Lymphoma	Hodgkin lymphoma	DLBCL	Burkitt	Others/not specified
SH2D1A	>100	30%	no	30%	50%	20%
ITK	22	**70%**	80%	10%	10%	
MAGT1	22	**70%**	40%	20%	20%	20%
CD27	33	36%	75%	25%	no	
CD70	16	**56%**	78%		11%	11%
TNFRSF9	8	**62.5 %**	40%	20%	no	40%
RASGRP1	9	**70%**	70%			30%
CTPS1	19	20%				20%

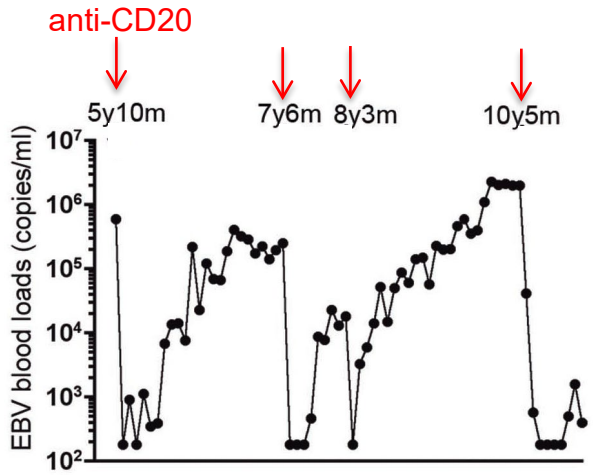
Patients can present additionnal signs of immunodeficiency including persistent EBV viremia, auto-immunity, inflammation, other viral/bacterial infections, hypogammaglobunemia….

Tangye and Latour, Blood, 2020
Latour and Winter,, Frontiers in Immunology, 2018
Ghosh et al., Blood 2020

Early-onset Hodgkin lymphoma can be the initial presentation without obvious immunodeficiency signs in CD70, CD27, ITK and RASGRP1 deficiencies

Genetics :
CD70 deficiency (hmz)
p.R179X





Clinical features :

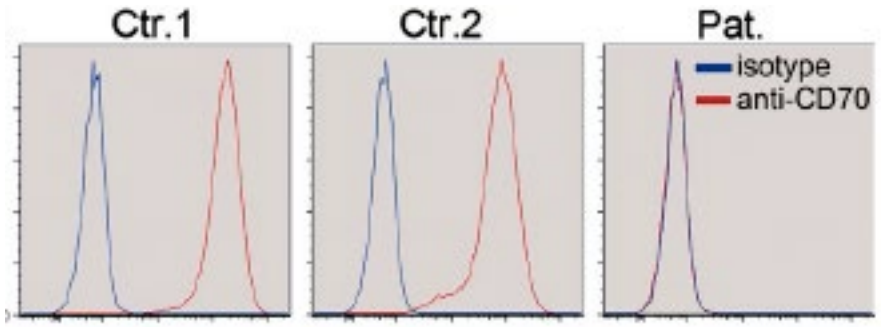
-EBV-positive Hodgkin's lymphoma at 3y. (successfully treated)

-no other clinical signs

-normal immunological parameters

-at the age of 4 y., relapse with recurrent EBV-driven LPD associated with high EBV loads (transiently relieved with anti-CD20 treatments)

-HSCT at 11 y., well since



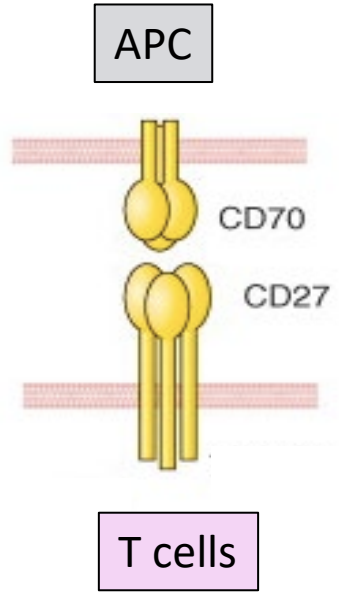
Izawa et al., 2017

CD70

- CD70 (TNFSF7) belongs to the TNF superfamily and binds the TNF receptor CD27 (TNFSFR7)

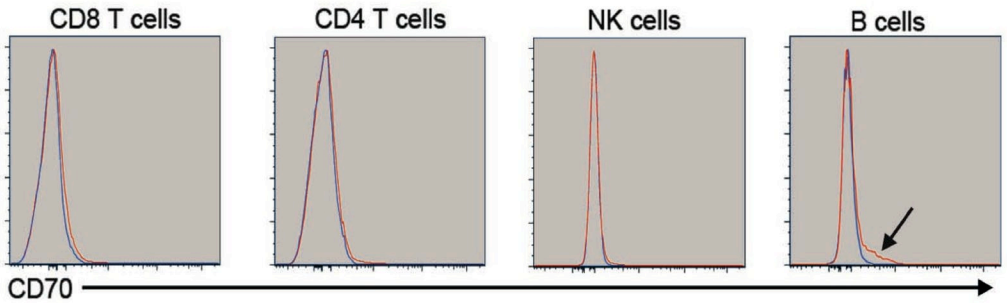
- CD70 is expressed B-cell lymphomas and DCs subpopulations
- CD27 is expressed on resting and activated T cells and is a well-known co stimulatory molecule in T cells

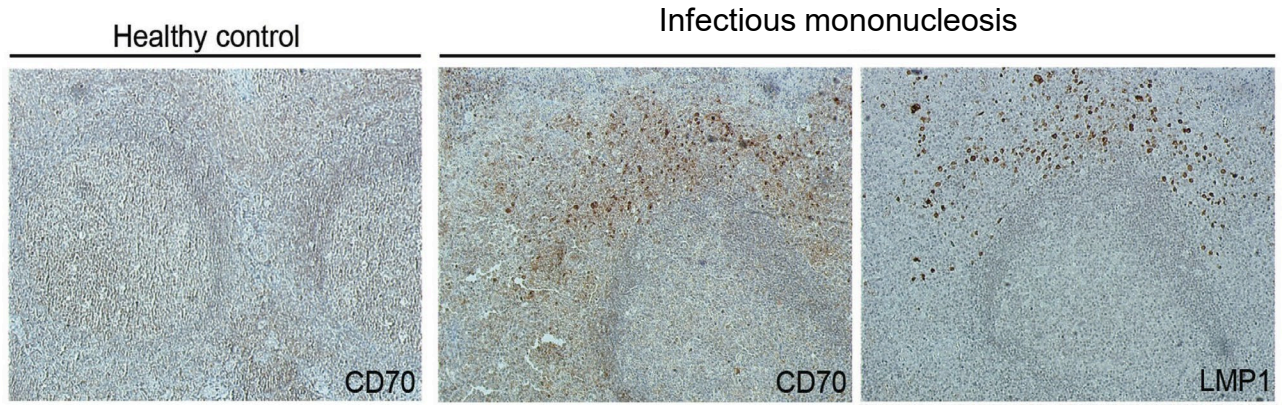
- CD27-CD70 interactions have been shown to enhance T-cell survival and effector functions (in mice)



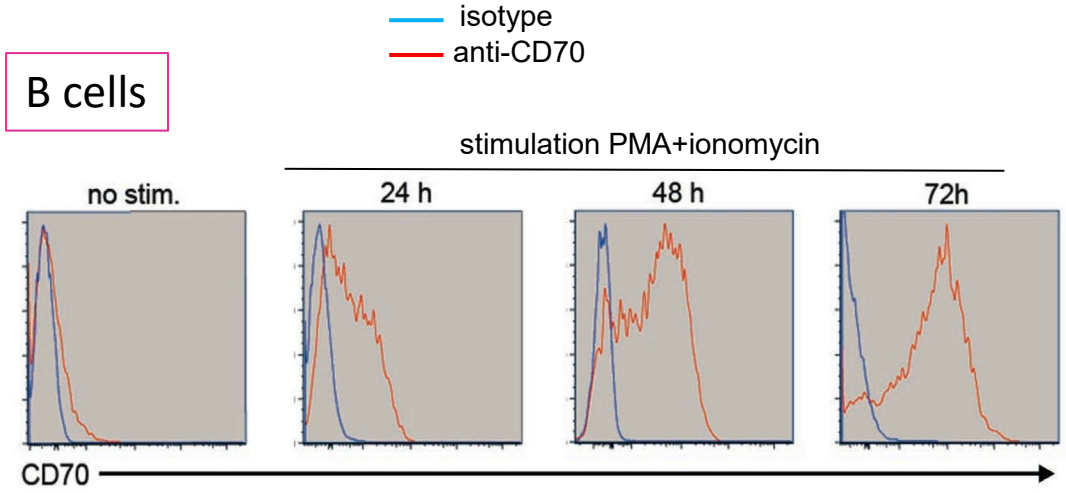
Expression of CD70 is up-regulated on EBV-infected B cells

PBMCs

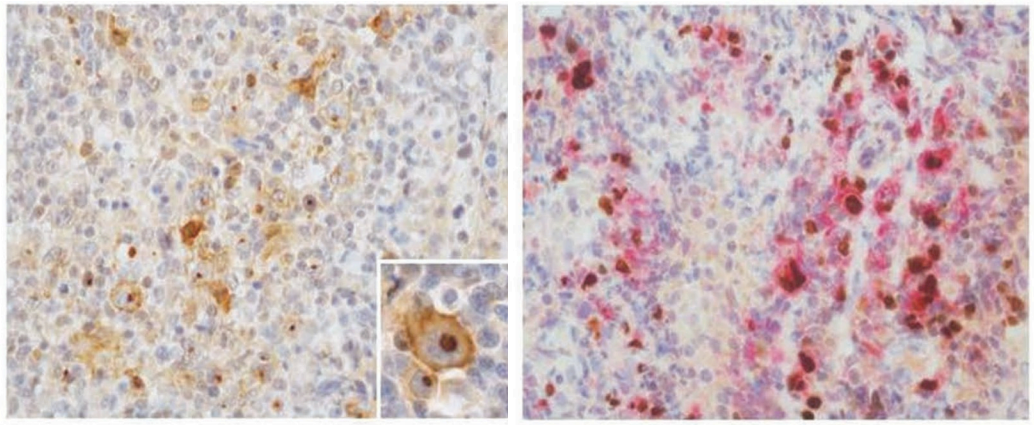




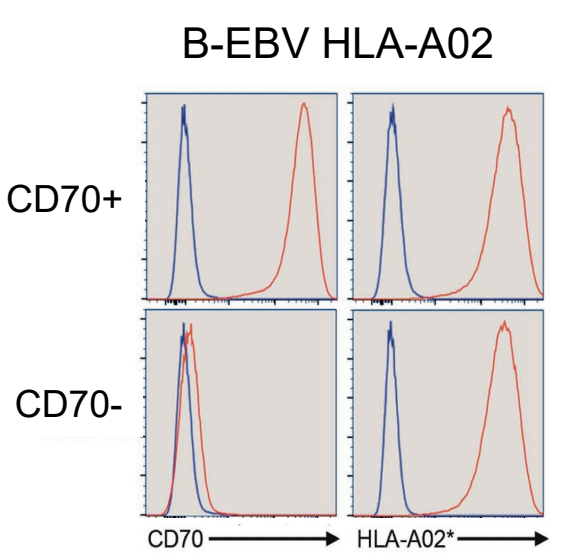
B cells



Tonsils

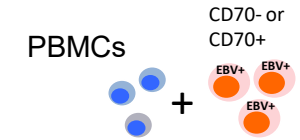


CD70 on EBV+ B lymphoma cells is required for the expansion of EBV-specific T cells



B-EBV LCL deficient for CD70 (patient) or obtained by CRISPR-cas9 editing

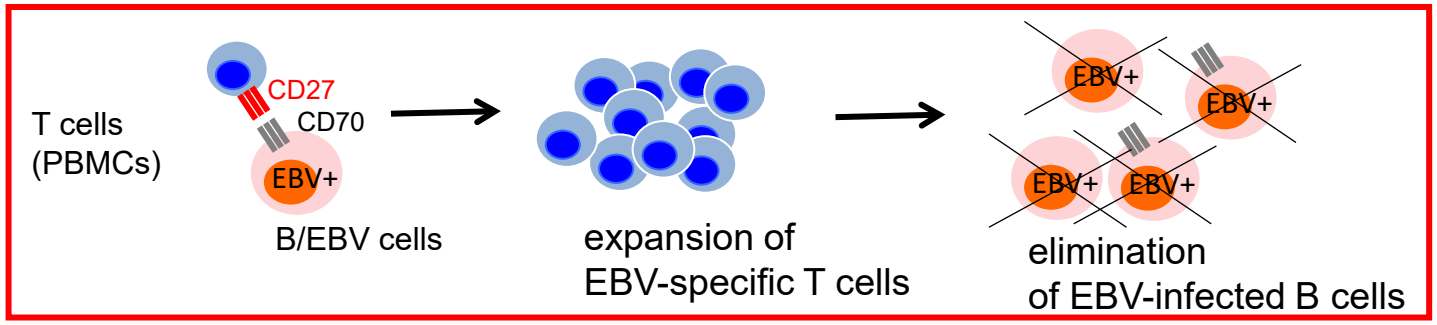
Coculture of PBMCs
with irradiated B-EBV LCL HLA-A02
expressing CD70+ or not CD70-

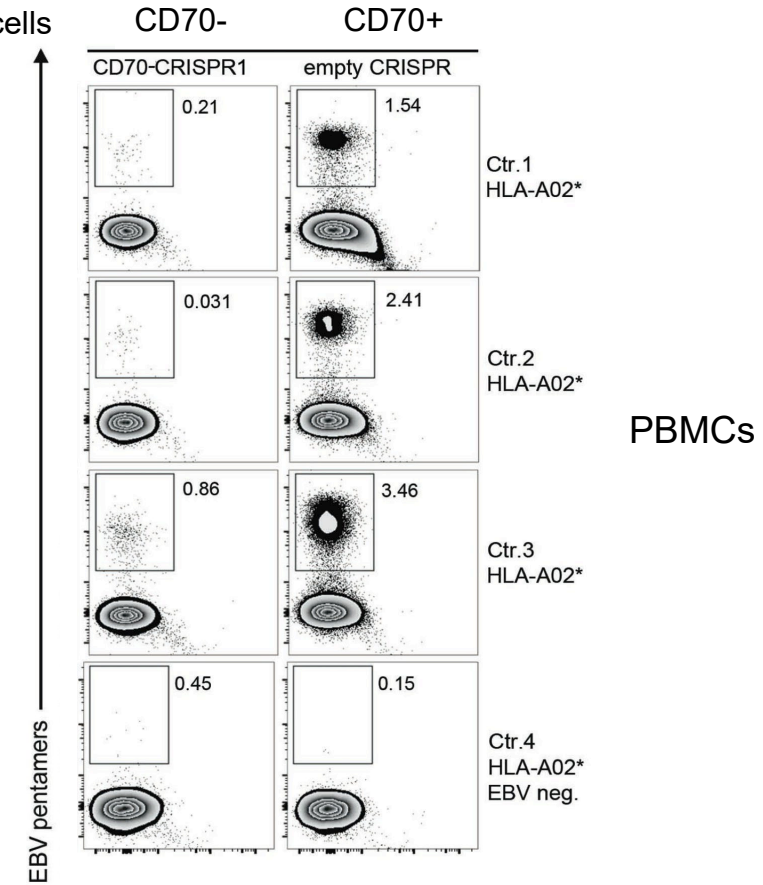


Staining
Cell Trace violet

8-10 days

Detection of the expansion of EBV-specific T cells
with HLA-A2-EBV pentamers





Somatic mutations in *CD70* in lymphoma (DLBCL)

-Six cohorts of DLBCL analyzed *(Giefing et al. Br. J. Haematol. 2008 ; Morin et al. Nature, 2011 ; Scholtysik et al., Int. J. Cancer, 2012 ; Lohr et al., PNAS, 2012 ; Bertrand et al. Genes, Chromosomes & Cancer, 2013 ; Miranda et al., Blood, 2014)*

-4% to 22% (total 79/853 ; 9.2%) of DLBCL samples were found to be mutated in CD70 including htz, hmz, stop codon mutations, deletions….

-Accumulation of mutations of *CD70* may represent a mechanism for lymphoma cells to escape to immune surveillance by T cells (CD27+)

PID-L project : Study of genetic susceptibility in paediatric B lymphomas

- Hypothesis :

Gene defects affecting the immune response might be responsible of a part of pediatric forms of B cell lymphomas

- Criteria of recruitment/inclusion :

-B cell lymphoma before the age 8 y.o

-B cell lymphoma after the age 8 y.o with signs of immunodeficiency and/or familial history-consanguinity

-familial forms of adults HL were excluded

- Analysis by Whole Exome Sequencing from DNA of blood or PBMCs

PID-L project : Study of genetic susceptibility in paediatric lymphomas

- 88 patients recruited since 2017 and analyzed by whole exome sequencing
  - Median age : 8 years old
  - Sex ratio : 70,7% males and 29% females

- Lymphoma EBV status
  - EBV pos. (75%)
  - EBV neg. (25%)

- Lymphoma types:
  - **Hodgkin (70%), Burkitt (10%), DLBCL (10%), others (10%)**

- **Proven deleterious bi-allelic variations (hmz or htz cp) in known genes to cause immunodeficiency identified in 15% of patients**

Conclusion

➤Primary immunodeficiencies are conditions that can predispose to EBV-associated lymphoma

Sub group of PIDs with high susceptibiity to EBV infection and EBV+lymphoma (70%)

➤Our current data from WES analysis of pediatric lymphoma suggest that 15% of childhood lymphoma (70% EBV+) could be explained by germinal mutations in known genes causing primary

Lymphomes EBV induits :

Prédisposition (germinal mutations affectant le système immunitaire) **et** exposition (infection virale)

Lymphocyte Activation and Susceptibility to EBV Lab

FONDATION imagine INSTITUT DES MALADIES GÉNÉTIQUES

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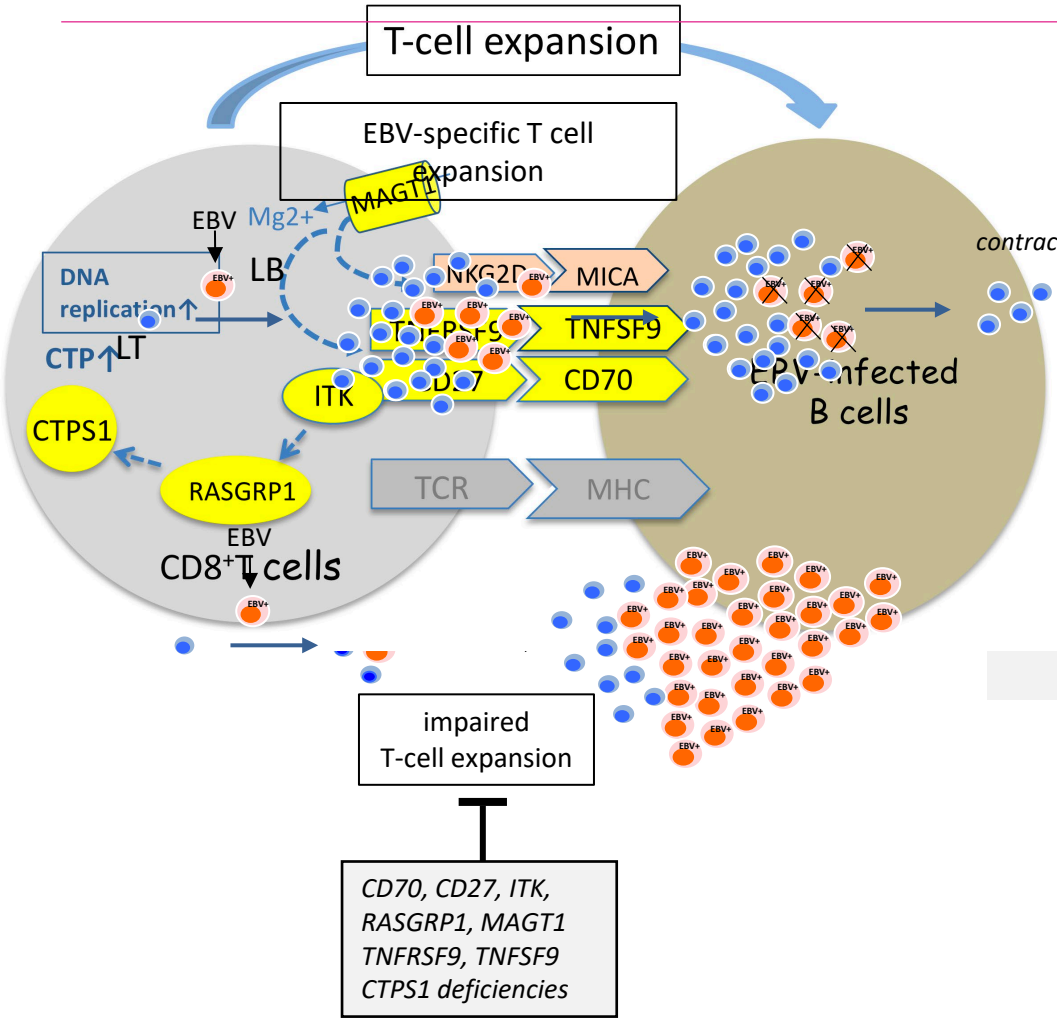
IEIs with EBV-susceptibility are mostly characterized by impaired T-cell expansion



Normal response

EBV+ lymphoproliferation diseases