Pathogenesis of cSLE & aSLE

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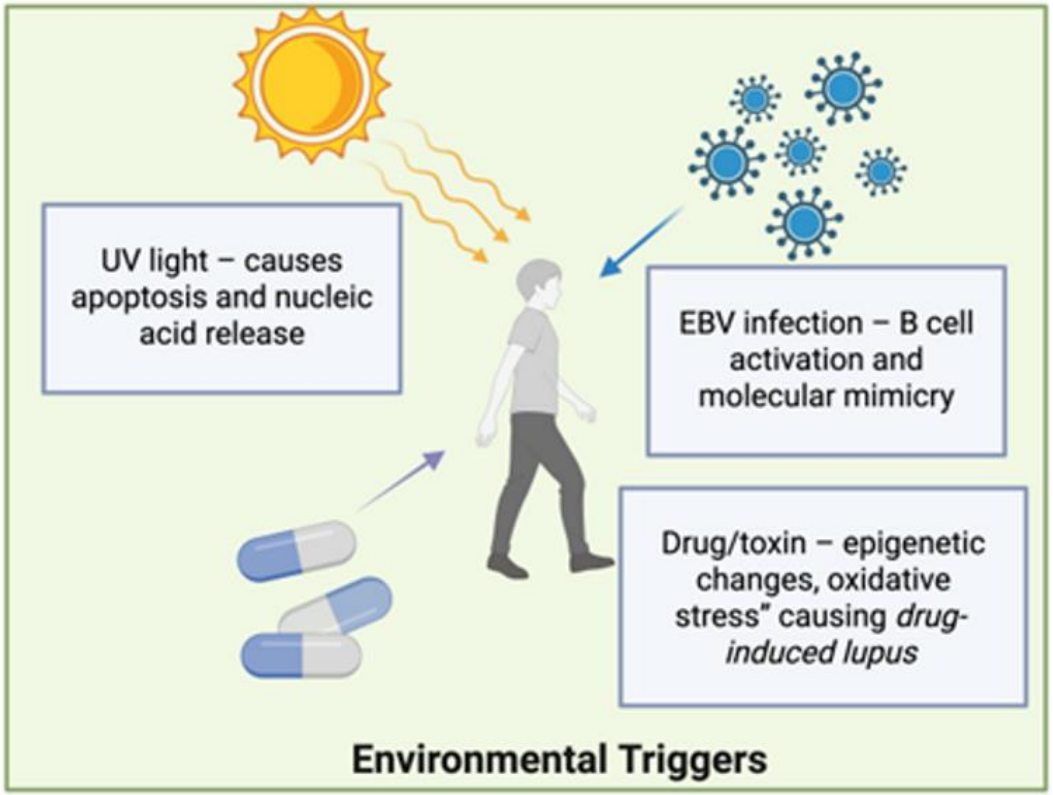
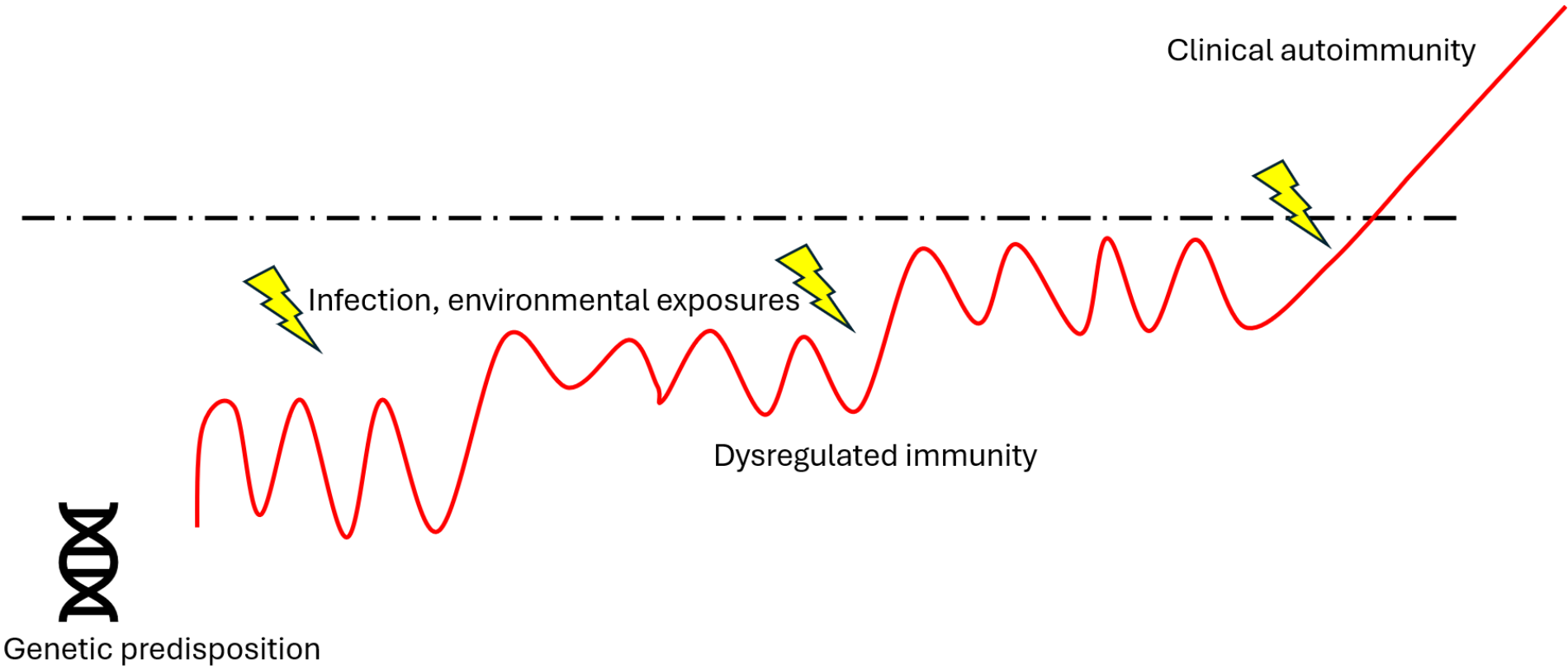
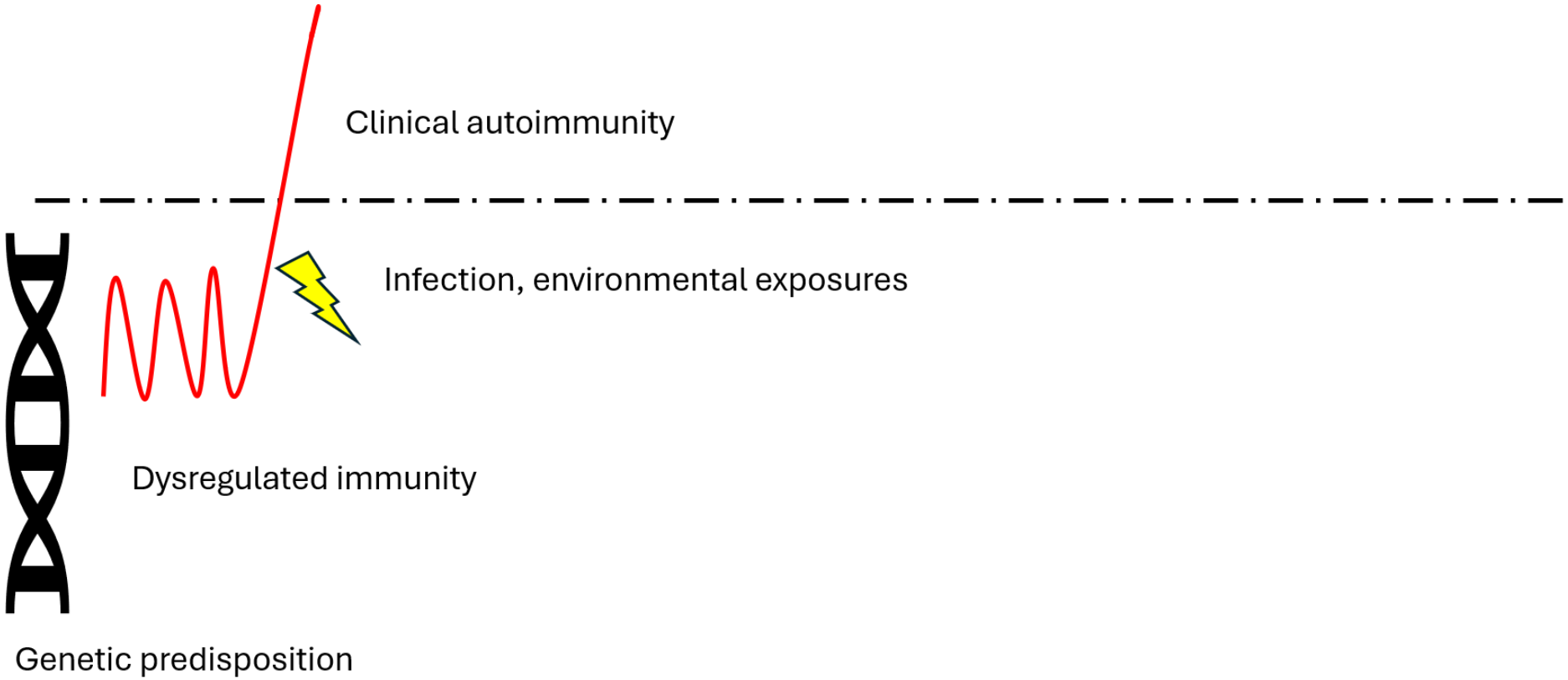
Genetics

- ~50 genes have been implicated in monogenic lupus (AR, AD, x-linked)
- Genome-wide association studies (GWAS) have identified over 300 susceptibility loci (genetic predisposition)
- Identical twin concordance ~25-55%



https://doi.org/10.1007/s12016-025-09119-1


Clinical autoimmunity
Infection, environmental exposures
Dysregulated immunity
Genetic predisposition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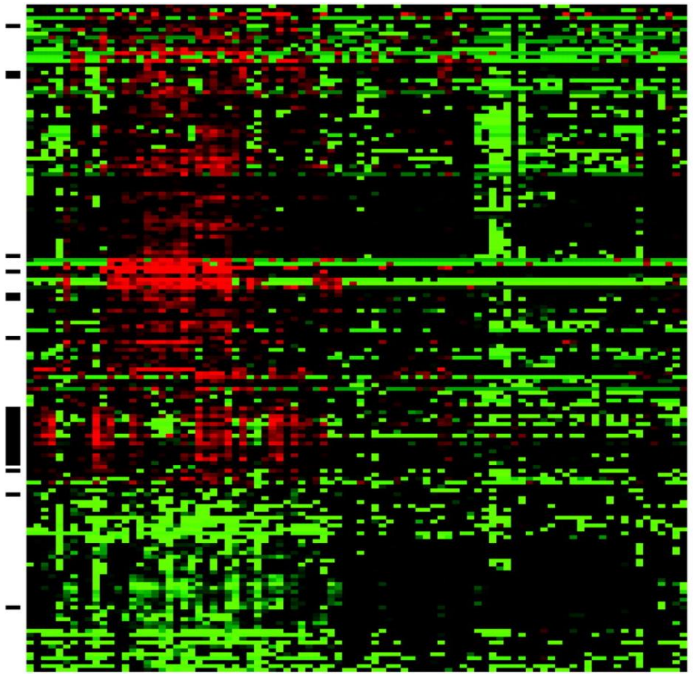
Dysfunction of Innate Immunity (all ages)

- Defective clearance of apoptotic debris (nuclear contents)
- Activated plasmacytoid dendritic cells (pDCs)
- Leads to excessive IFN-α production



https://doi.org/10.1073/pnas.0337679100

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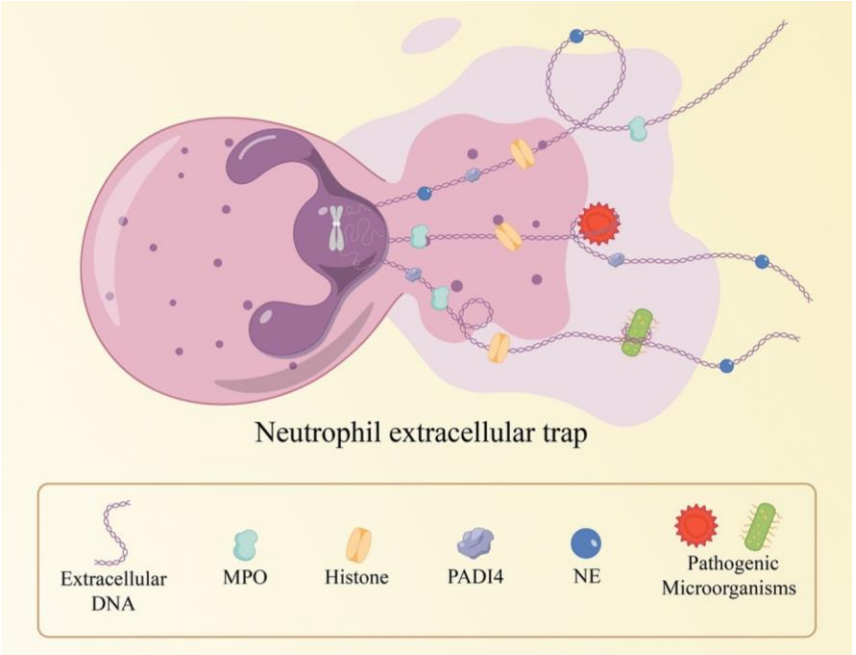
- ↑ ↑ ↑ in pDC production of IFN-α
- Nuclear contents also stimulate toll-like receptors (TLRs), esp TLR7
- Maturation of myeloid DCs (mDCs)
- ↑ antigen presentation to lymphocytes & ↑ BAFF



https://doi.org/10.1186/s40001-025-03408-3

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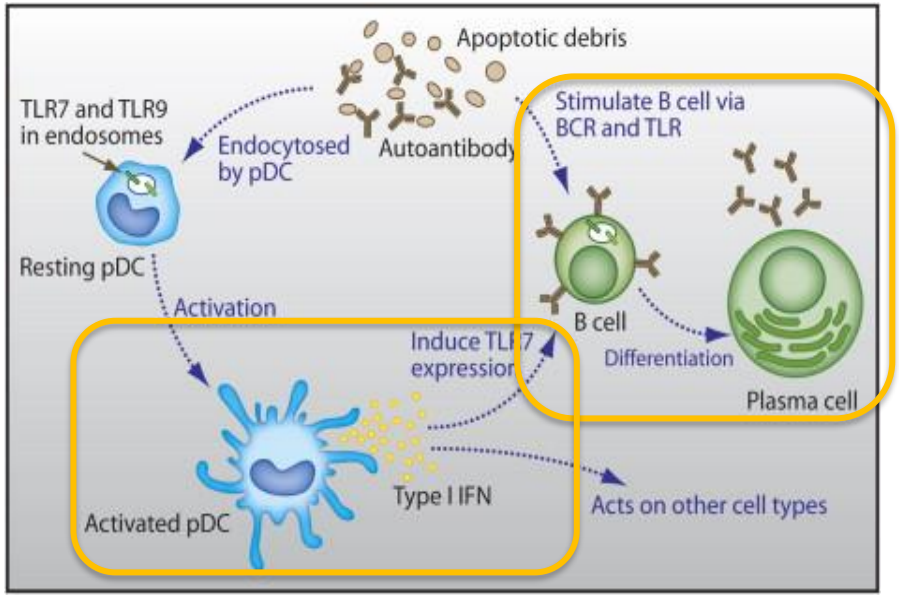
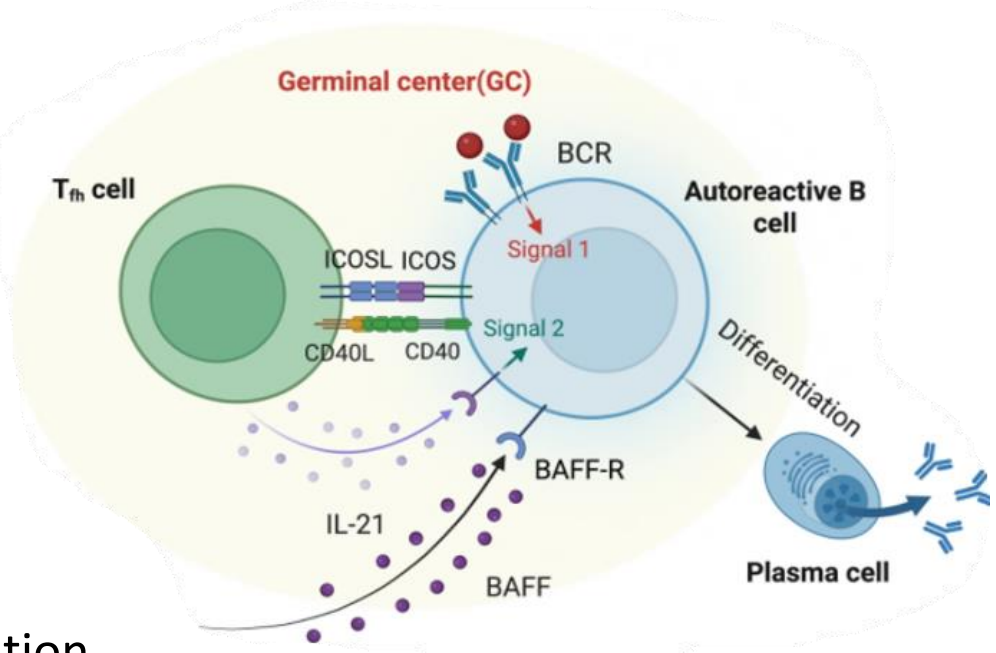


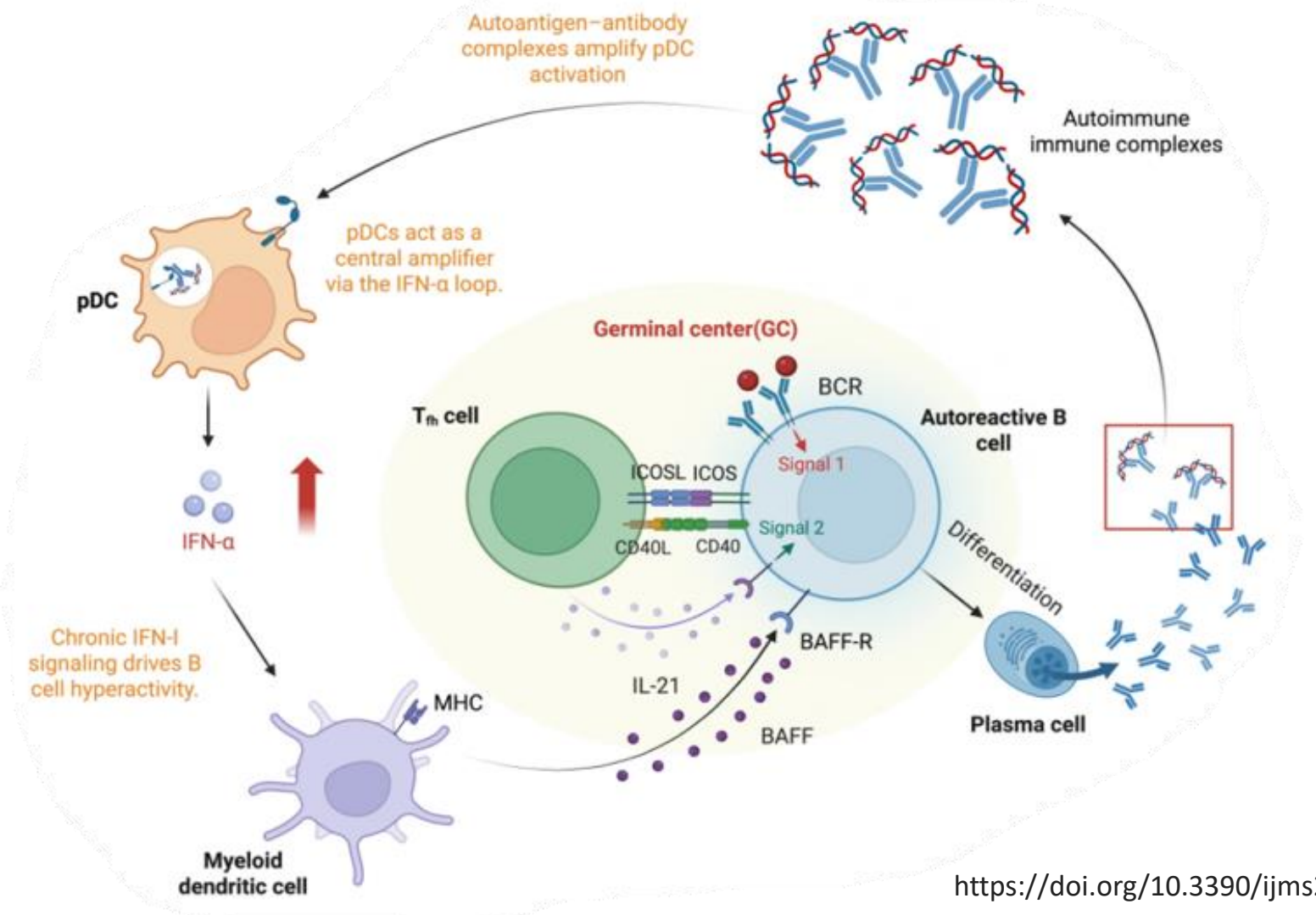
https://doi.org/10.1016/j.immuni.2007.11.001

Dysfunction of Adaptive Immunity (all ages)

- **Auto-reactive B cells**
  - Survival of autoreactive B cells
  - Loss of self-tolerance
  - DNB (CD27-IgD-) expansion
  - ABC (T-bet+) expansion for age
- **T cell abnormalities**
  - Treg dysfunction
  - DNT (CD4-/CD8-) expansion
  - Aberrant T helper subset distribution
  - Stimulation of autoreactive B cells
- **Lymphocyte proliferation/activation**



https://doi.org/10.3390/ijms252010905



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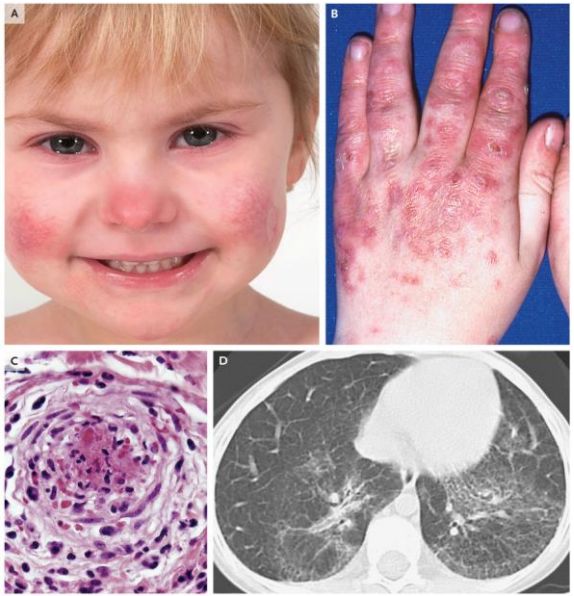
Known Differences btw cSLE and aSLE

	Childhood-Onset Disease	Adult-Onset Disease
Type 1 Interferon signature	60-90% (80%)	50-65% (60%)
Genetic loading	more genes	fewer genes
Monogenic etiology	6-10% (typically ≤ 5 years)	rare

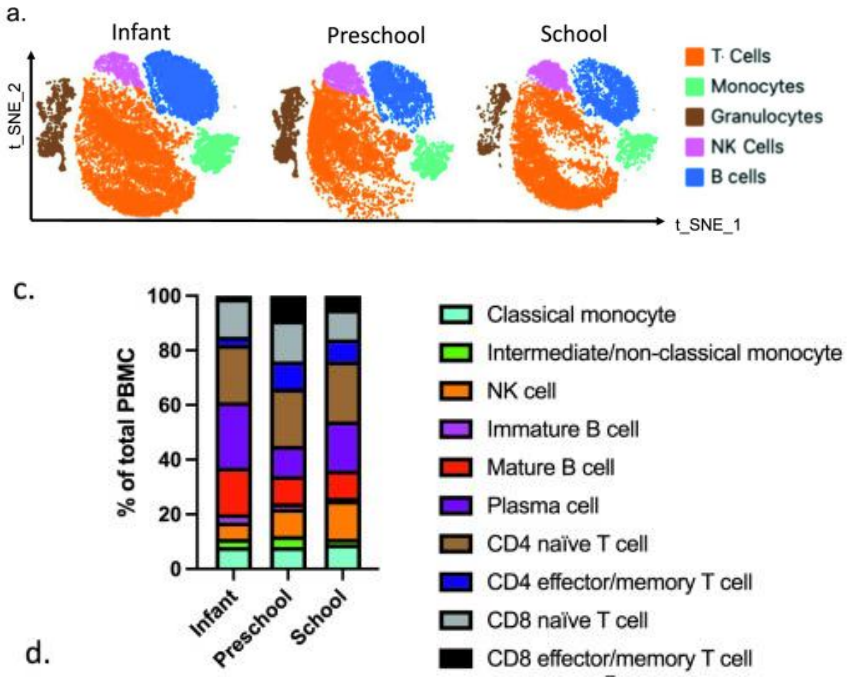


https://doi.org/10.1016/B978-0-443-11980-4.00045-3

SAVI: STING-Associated Vasculopathy w/ onset in Infancy

- GoF mutation in STING1
- Constitutive activation of STING protein (stimulator of interferon genes)
- *Neonatal Onset:* recurrent fevers, cutaneous vasculopathy, ILD (often life threatening)
- *Therapies:* JAK inhibitors (tofacitinib/ruxolitinib) with new evidence for anifrolumab

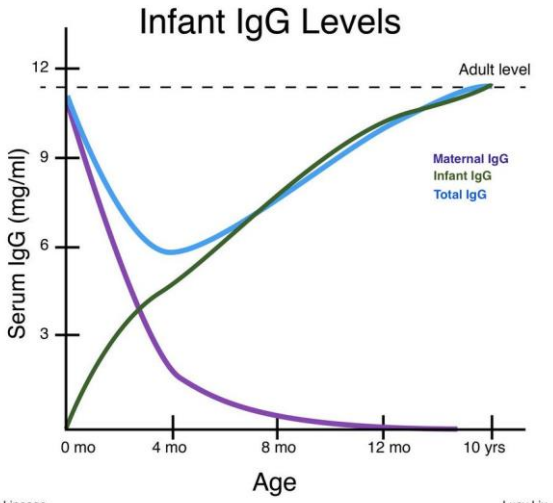
Developing Immune System (infant & child)



Age	IgG (mg/dL)
Newborn	1031 ± 200
1–3 mo	430 ± 119
4–6 mo	427 ± 186
7–12 mo	661 ± 219
13–24 mo	762 ± 209
25–36 mo	892 ± 183
3–5 y	929 ± 228
6–8 y	923 ± 256
9–11 y	1124 ± 235
12–16 y	946 ± 124
Adults	1158 ± 305

Adapted, with permission, from *Disorders of Infants and Children,*

- Thymus grows through 4-6 months of life
- Then “involutes,” losing ~3% per year through mid-adulthood
- Repertoire formed by ~5y



10.1016/j.clim.2023.109728

Key Points

- For non-monogenic lupus:
  - Susceptibility genes are **the same** in cSLE & aSLE
    (children may have *more* susceptibility loci per patient)
  - The pathogenesis & pathophysiology are **the same** in cSLE & aSLE
    (↑ pDC act, ↑ BAFF, ↑ type I IFN, defective NETosis, ↑ DNB/T cells, ↑ ABCs, Treg dysfunction, ↑ autoreactive B cells & autoantibodies)
  - The immune system is considered "**mature**" by age 5
    (the immune systems of a 5-year-old & a 25-year-old are *more similar* than the immune systems of a 25-year-old & a 75-year-old)
  - Pharmacologic targets across the immune system are **the same**