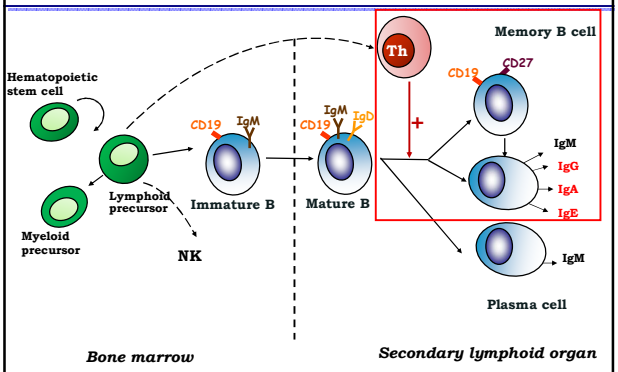
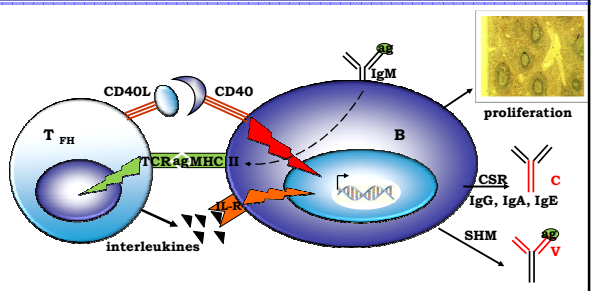
Hyper IgM Syndromes

ANN DURANDY

B lymphocyte differentiation

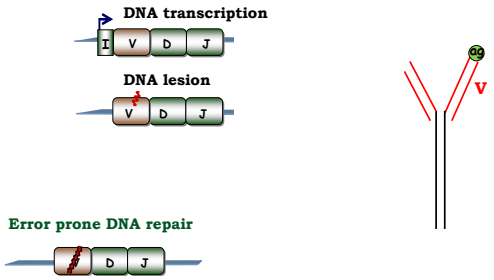


T:B cell cooperation in germinal centres



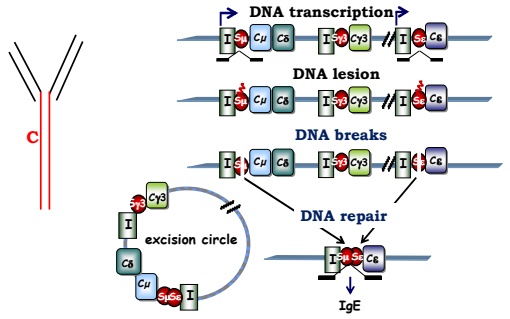
T_{FH}: T follicular helper, TCR: T cell receptor, MHC II: major histocompatibility complex class II, CD40L: CD40 Ligand, IL-R: interleukine receptor, CSR: Ig class switch recombination, SHM: Somatic hypermutation

Schematic representation of antibody maturation: Somatic hypermutation



Somatic hypermutation

Schematic representation of antibody maturation: Class switch recombination



Class switch recombination

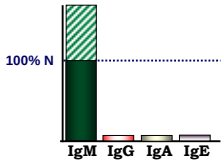
Antibody maturation: class switch recombination and somatic hypermutation

1. Class switch recombination (CSR) ⇨ diverse antibodies
   IgM ⇨ IgG, IgA, IgE
   IgG: longer half-life, binding to Fcγ receptors, complement activation
   IgA: mucosae localization
   IgE: anti-parasite infection

2. Somatic hypermutation (SHM) ⇨ efficient antibodies
   Mutations in V regions
   ⇨ selection of B cells expressing a BCR with high affinity for antigen (role of follicular dendritic cells)

Ig class switch recombination deficiencies

- Rare primary immunodeficiency (1:500,000 births)
- Serum Ig levels:



- Defective or normal somatic hypermutation generation
- Defective T/B cooperation (50%)
- Intrinsic B cell defect (50%)

Ig class switch recombination deficiencies

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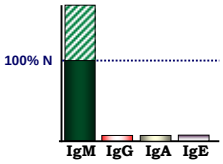
- Serum Ig levels:



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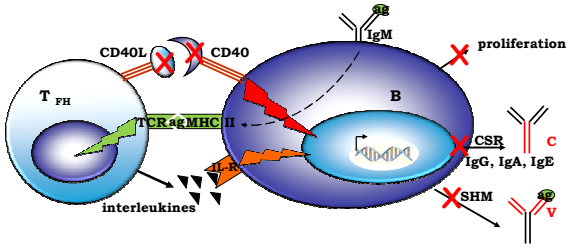
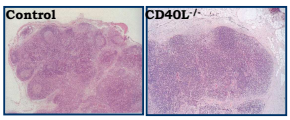
T/B cooperation deficiencies



T_{FH}: T follicular helper, TCR: T cell receptor, MHC II: major histocompatibility complex class II, CD40L: CD40 Ligand, IL-R: interleukine receptor, CSR: Ig class switch recombination, SHM: Somatic hypermutation

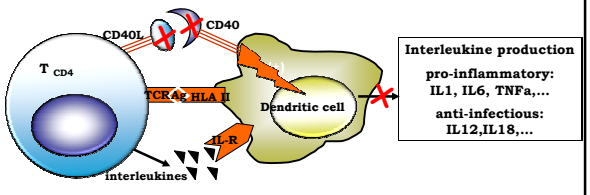
Ig CSR-deficiencies caused by impaired T/B cooperation: X-CD40L or AR CD40-deficiency

- **X-linked CD40L-deficiency** (most frequent of Ig-CSR deficiencies)
- **AR-CD40-deficiency** (very rare cause of Ig-CSR deficiency)
- **Susceptibility to bacterial infections from the first years of age**
- **Lack of germinal centres in secondary lymphoid organs**



- **Defective CSR and SHM**

Associated T cell defect in CD40L or CD40-deficiency



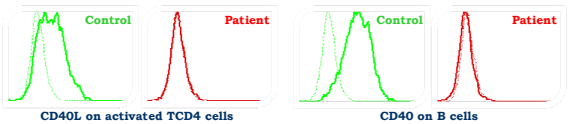
Susceptibility to viral and opportunistic infections
Pneumocystis Jirovici, Giardia Lamblia, Cryptosporidium...

CD40L/CD40 deficiencies combine a B and a T cell defect

- **Impaired B cell immunity:**
  ⇨ **susceptibility to bacterial infections** (100%)
- **Impaired T cell immunity**
  ⇨ **susceptibility to opportunistic infections** (100%)
- **Liver disease: sclerosing cholangitis** (20%)
- **Neutropenia** (68%)
- **Auto-immunity** (5%)
- **Cancers** (3%)

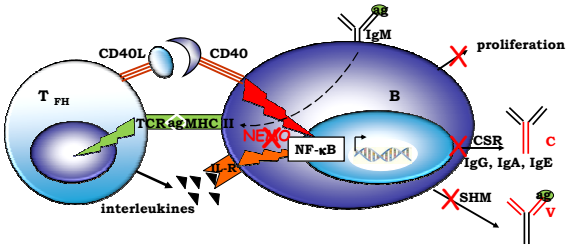
X-CD40L or AR CD40-deficiency: diagnosis and treatment

- Ig levels (Normal or increased IgM, decreased IgG and IgA)
- Neutropenia
- Decrease number of CD27+ memory B cells
- Defective expression of CD40L on activated T cells (X-linked CD40L def.) or of CD40 on B cells (AR CD40 def.)



- Genetic analysis : mutations in *CD40L* or *CD40* genes
- Treatment: Ig, AB, bone-marrow transplantation

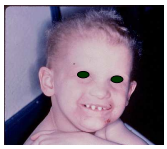
CD40-induced NF-kB activation defect



NF-κB: nuclear factor κB, NEMO: NF-κB essential modulator,
CSR: Ig class switch recombination, SHM: Somatic hypermutation

Ig CSR-deficiency associated to anhydrotic ectodermal dysplasia

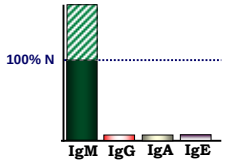
- X-linked anhydrotic ectodermal dysplasia



- Variable defect in CSR and SHM
- Defective response to polysaccharidic antigens
- Hypomorphic mutations in *NEMO* (NF-kB essential modulator)
- Treatment: Ig, AB, bone-marrow transplantation

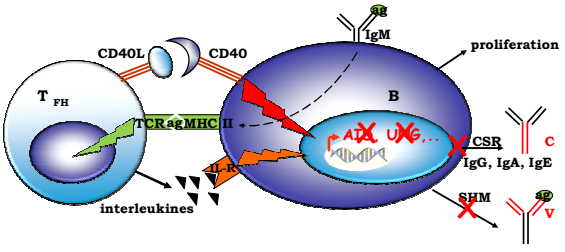
Ig class switch recombination deficiencies

- Rare primary immunodeficiency (1:500,000 births)
- Serum Ig levels:



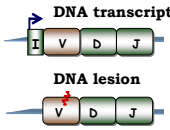
- Defective or normal somatic hypermutation generation
- Defective T/B cooperation (50%)
- Intrinsic B cell defect (50%)

Ig CSR-deficiencies caused by an intrinsic B cell defect



AID: Activation-Induced cytidine Deaminase, UNG: Uracil-N glycosylase
CSR: Ig class switch recombination, SHM: Somatic hypermutation

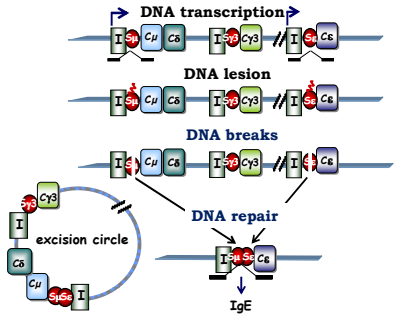
Schematic representation of antibody maturation: Somatic hypermutation



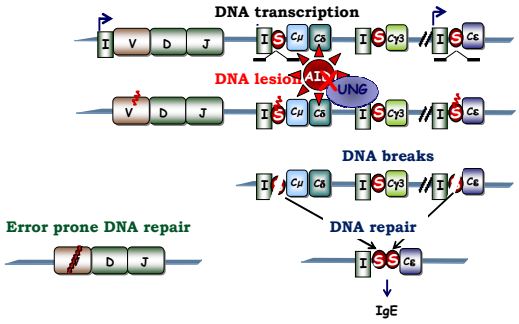
Error prone DNA repair

Somatic hypermutation

Schematic representation of antibody maturation: Class switch recombination



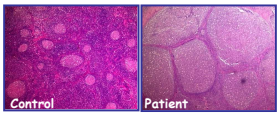
Ig CSR-deficiency caused by defective DNA lesion in V and S regions



AID: Activation-Induced cytidine Deaminase, UNG: Uracil-N glycosylase

Activation-Induced cytidine Deaminase deficiency

- **Autosomal recessive inheritance** (consanguinity: 10-62%)
- **Susceptibility to bacterial infections:** 100%
- **Lymphadenopathies:** 50-72%

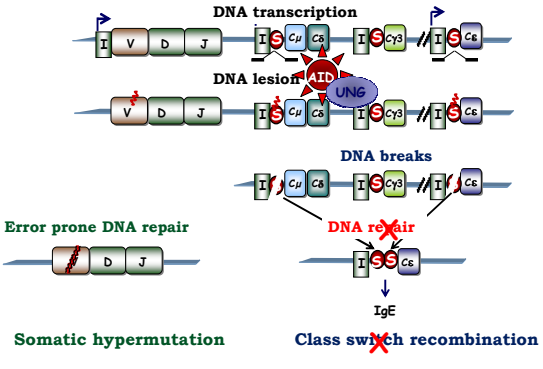


- **Auto-immunity:** 21% **(AHIA, ITP,** AI hepatitis, RA, LED…)
- **Defective CSR and SHM**

Ig CSR-deficiencies caused by defective DNA lesion

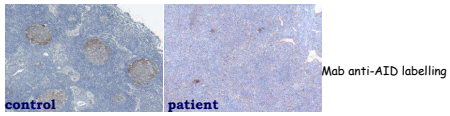
- **Ig levels (Normal or increased IgM, complete lack of IgG and IgA)**
- **Lymphadenopathies**
- **Normal number of CD27+ memory B cells**
- **Genetic analysis:**
  - ***Activation induced cytidine deaminase (AID)*** *40%*
  - ***Uracil-N glycosylase*** *(1%)*
  - **Most are molecularly undefined: AID cofactor?**(60%)
- **Treatment: Ig substitution**

Ig CSR deficiencies caused by defective DNA repair of S regions



An Ig CSR-deficiency associated to a DNA repair defect

- **Autosomal recessive inheritance**
- **Susceptibility to bacterial infections** (100%)
- **Lymphadenopathies** (50%)

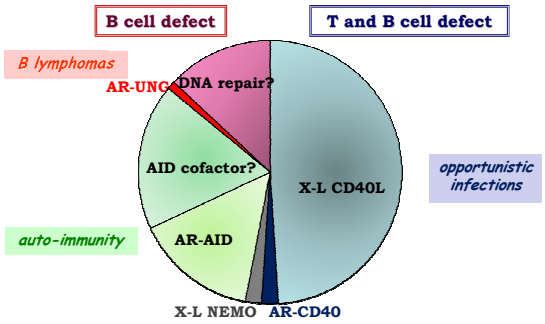


- **Autoimmunity (AIHA, ITP, SLE, uveitis)** (21%)
- **EBV(-) B lymphoproliferative disorder** (11%), **AML** (4%)
- **Defective CSR, normal SHM**

Ig CSR-deficiency associated to a DNA repair defect: diagnosis and treatment

- Ig levels (Normal or increased IgM, decreased IgG and IgA)
- Decrease number of CD27+ B cells
- Molecularly undefined
- Differential diagnosis: Ataxia Telangiectasia++
- Treatment: Ig substitution, follow-up++

Ig CSR-deficiencies



あ AID

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UNG は

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