Maturation of the antibody repertoire (class switch recombination (CSR) and somatic hypermutation generation (SHM)) is required for the production of efficient antibodies of diverse isotypes. The recent elucidation of the molecular basis of inherited immunodeficiencies, the hyper-IgM syndromes (HIGM), has made it possible to delineate some of the molecular events involved in both processes of antibody maturation.

HIGM are characterized by normal or elevated serum concentrations of IgM, with the dramatically decrease or absence of other isotypes, strongly suggesting a CSR defect. Most of them are associated with defective SHM.

Two syndromes, caused by mutations in CD40L or CD40 genes, are characterized by a defect in CSR and SHM, giving evidence for the essential role of B cell-CD40 activation pathway for both events of B cell maturation. Since CD40/CD40L interaction is also required for T cell immune function, this HIGM condition is associated to a T cell defect which strongly worsens the prognosis (1-2).

 Activation–Induced Cytidine Deaminase (AID) DEFICIENCY

AID is a B cell specific molecule induced by CD40-activation and is essential for both CSR and SHM, as shown by the immune phenotype of AID-deficient patients (3). AID acts by deamination of cytosine into uracil residues. Although its mode of action has been debated for a long time, several pieces of evidence strongly argue in favor of a direct AID activity on DNA.

Mutations in the C terminal part of AID lead to a pure B cell defect without affecting SHM (4). Moreover, mutations affecting the Nuclear Export Signal of AID (also located in the C ter part) are responsible for an autosomal dominant HIGM with variable clinical phenotype (dominant negative effect) (5). Both observations suggest that AID, as a multimeric complex, binds a CSR specific co-factor by its C terminal part.

Uracil-N Glycosylase (UNG) DEFICIENCY

The description of an HIGM caused by mutations in UNG gene and characterized by a defective CSR and normal frequency of SHM, however exhibiting a skewed pattern, is a strong argument for a direct role of AID on DNA (6). UNG recognizes the uracil residues misintegrated onto DNA by AID. After uracil residue deglycosylation and removal, the eventual abasic site is attacked by an endonuclease that leads to the DNA double stranded breaks necessary for CSR.

Two other HIGM are not yet molecularly defined: «HIGM4m» is characterized by a defective CSR but normal SHM, a phenotype similar to that of HIGM due to mutations located in the C ter part of AID. «HIGM4» could thus be due to a defect in the CSR-specific AID cofactor. «HIGM4n» is characterized by a defective CSR but normal generation of SHM. However, the «memory» B cell compartment which exhibits the CD27 marker is strongly reduced. We postulated a defect in the survival of switching B cells. We therefore studied the irradiation-induced DNA damage in fibroblasts and EBV B cell lines and found an increased radiosensitivity, suggesting that «HIGM4n» is truly due to DNA repair defect (7).

HIGM due to an intrinsic B cell defect are of good prognosis since bacterial infections are easily controlled by Immunoglobulin substitution. However, 2 major complications can occur:

1. Auto-immunity in all HIGM conditions (AIHA, IPT, auto-immune hepatitis, etc.).
2. Occurrence of lymphomas: indeed, UNG, as a base excision repair enzyme, plays a major role against spontaneous mutagenesis, and «HIGM4n», a DNA repair
defect, is reported as associated to Non Hodgkin B cell lymphoma.

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