REVIEW ARTICLE

The Hyper IgM Syndrome—An Evolving Story

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ABSTRACT

The hyper IgM syndromes (HIGM) are a group of primary immune deficiency disorders characterized by defective CD40 signaling by B cells affecting class switch recombination and somatic hypermutation. As a consequence, patients with HIGM have decreased concentrations of serum IgG and IgA and normal or elevated IgM, leading to increased susceptibility to infections. The most common HIGM syndrome is X-linked and due to mutations of *CD40 ligand* (*CD40L*) expressed by activated CD4$^+$ T lymphocytes. Four other genes, expressed by B cells, have been associated with the HIGM phenotype. Mutations of *CD40*, the receptor for CD40L, cause a rare autosomal form of HIGM with a clinical phenotype similar to CD40L deficiency. Mutations of *Activation-Induced Cytidine Deaminase* (*AICDA*) and *Uracil (DNA) Glycosylase* (*UNG*), both expressed by follicular B lymphocytes, lead to defective class switch recombination and somatic hypermutation. Mutations of *Nuclear Factor κB Essential Modulator* (*NEMO*), an X-chromosome associated gene, result in hypohidrotic ectodermal dysplasia and immune deficiency. Thus, the molecular definition of these rare primary immune deficiency disorders has shed light on the complex events leading to the production of high-affinity, antigen-specific antibodies of different isotypes. (***Pediatr Res* 56: 519–525, 2004**)

Abbreviations

AICDA (AID), activation-induced cytidine deaminase
BMT, bone marrow transplantation
CD40L, CD40 ligand
CSR, class switch recombination
EDA, ectodermal dysplasia
EDA-ID, ectodermal dysplasia with immunodeficiency
HIGM, hyper IgM syndrome
IKK, Ikappa B kinase
IVIG, intravenous Ig
NEMO, nuclear factor κB essential modulator
PCP, *Pneumocystis carinii* pneumonia
SHM, somatic hypermutation
UNG, uracil DNA glycosylase
XHIGM, X-linked hyper IgM syndrome

In 1961, Rosen *et al.* (1) described two brothers with recurrent infections, and Burtin (2) reported a similar patient who had low levels of 7S gamma-globulin (IgG) and elevated 19S gamma-globulin (IgM). In view of the dissociation between normal or elevated IgM and low-to-undetectable IgG and IgA, this syndrome was originally termed "dysgammaglobulinemia." A World Health Organization working party, in 1974, named the syndrome immunodeficiency with hyper IgM (HIGM) (3). The nature of the immune defect(s) in HIGM remained elusive. For more than 20 y it was hypothesized that B-lymphocytes from HIGM patients had an intrinsic inability to undergo Ig isotype switching (4). The observation that many patients, especially those with the X-linked form, were also susceptible to opportunistic infections should have pointed to a possible T-cell defect. The important role of defective T helper cells was recognized in 1986, when the observation was made that B cells from male HIGM patients differentiated into IgG secreting cells if co-cultured *in vitro* with T lymphoblasts from a patient with a Sézary-like syndrome (5). Recently, as more genes were found to be mutated in the syndrome with different clinical presentations, it was suggested to change the name to "defective Ig class switch recombination."

The gene responsible for the X-linked form of HIGM (XHIGM) was mapped to the long arm of the X-chromosome (Xq26–27) and subsequently identified as CD40ligand (CD40L), expressed by activated CD4$^+$ T cells. CD40L is crucial for T-B cell interaction by its binding to CD40, constitutively expressed by B cells. In 1993, five groups independently and simultaneously showed that mutation in the *CD40L* gene is the molecular defect responsible for XHIGM (6–10). Subsequent sequence analysis of CD40L revealed that, al-

though most patients with HIGM had mutations in this gene, there was a subgroup of HIGM patients with normal CD40L, including families in which autosomal recessive inheritance was evident. To date, five different genetic defects leading to HIGM have been identified, providing new insight into the complicated process of generating high-affinity antibodies of various Ig isotypes.

Antibody-mediated immune responses play a critical role in the defense against extracellular pathogens and many viruses. The primary antibody repertoire, generated in the bone marrow B cells by means of V(D)J recombination, allows genomic rearrangement between variable (V), diversity (D), and joining (J) gene elements of the Ig heavy and light chain genes. As a result of this process, IgM and IgD antibodies of low avidity are generated, largely in an antigen-independent way. Once IgM-expressing B cells engage antigen, two additional genetic alterations occur to improve specificity and avidity of the antibody to specific microorganisms. This secondary antibody repertoire is generated in the peripheral lymphoid organs and is antigen and T-cell dependent, mainly through the interaction between CD40L (CD154) expressed by activated T cell and CD40 expressed by B cells.

The first modification of the primary IgM antibody response involves CSR. In this process, the constant region of the μ heavy chain is replaced by a downstream heavy chain, *e.g.* Cγ, Cα, or Cϵ, leading to the generation of IgG, IgA, or IgE, respectively, with a corresponding change in antibody effector function. This is accomplished through recombination between the switch element upstream of Cγ and that located 5' to the downstream heavy chain to which rearrangement is targeted (11). The intervening sequences between these two switch regions are deleted.

A second antigen-dependent B-cell alteration, SHM, involves the introduction of point mutations at a high rate in the V regions of the Ig genes, resulting in an expansion of the antibody repertoire by allowing the selection of high-affinity antigen-specific antibodies (12). Both CSR and SHM require transcription through target S and V regions on V(D)J exons and DNA editing, which requires two crucial enzymes expressed by germinal center B cells, AID and UNG. Although representing unique modification processes, CSR and SHM are interdependent and nonredundant (13). Defects in any of these events result in antibody deficiency affecting CSR and SHM, collectively referred to as hyper IgM (HIGM) syndromes (14). The characterization of the molecular defects (Table 1, Fig. 1) has been instrumental in unraveling the molecular events leading to antibody diversity and the generation of high-affinity antibodies (15,16).
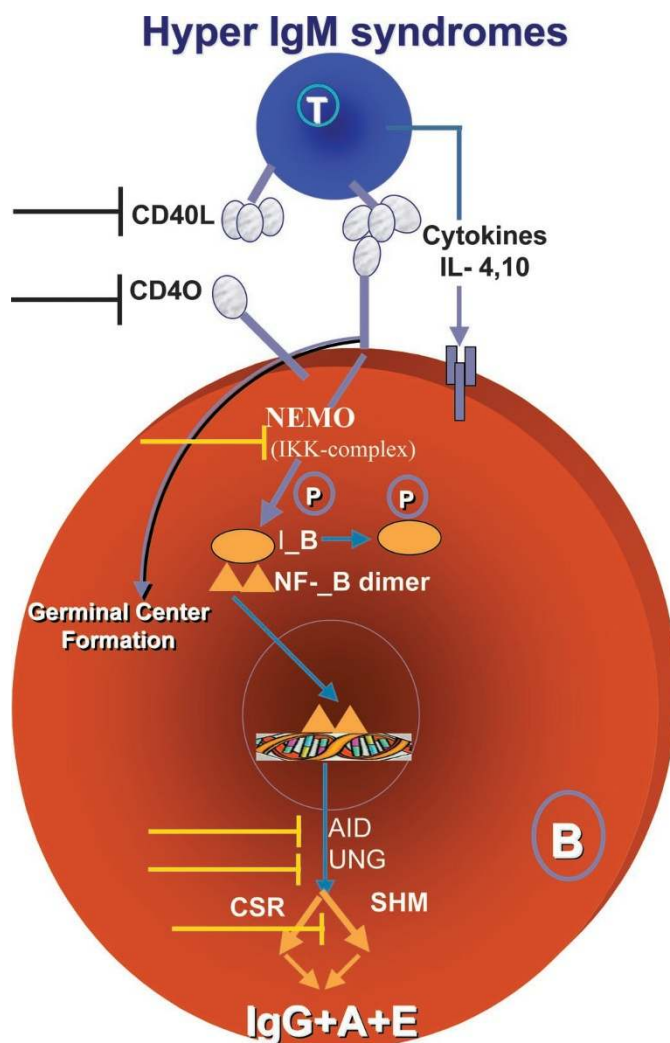

Figure 1. Schematic representation of the various known molecular defects leading to hyper IgM syndromes.

X-Linked Hyper IgM Due to CD40L Deficiency

The X-linked form of HIGM (XHIGM, HIGM-1) is most common and accounts for about 65–70% of all cases with the HIGM phenotype. Sequence analysis of CD40L and the development of specific disease registries (17–19) have helped in delineating the clinical features of XHIGM. Most, but not all, affected males present in infancy with upper and lower respiratory tract infections. In contrast to most other forms of hypogammaglobulinemia, patients with X-linked HIGM are susceptible to interstitial pneumonia caused by PCP, which can

Table 1. *Hyper IgM Syndrome (HIGM)*

Defective Gene Product	CD40L	CD40	AID	UNG	Unknown (HIGM with CSR-Def	NEMO	Unknown (unclassified HIGM)
Prevalence (%)	70	10	<1	5	<1	1-2	15
Inheritance	X-linked	AR	AR	AR(?)	(?)	X-linked	–
CSR defect	Yes	Yes	Yes	Yes	Yes	Yes	Variable
SHM defect	Yes	Yes	Yes	No	Yes	Yes	Yes
Onset of symptoms (years)	0-5-1	2-10	0.5-1	0.3-20	3-5	0.5-1	–
Opportunistic infection	Yes	No	Yes	No	No	No	Unknown
Lymphoid hyperplasia	No	Yes	No	Yes	Yes	No	Unknown

be the presenting symptom (18,19). PCP has been reported in up to 40% of all patients with mutations of CD40L. Diarrhea, present in 50% of the patients, can be acute or chronic and is often associated with cryptosporidium infection that may contribute to the high frequency of sclerosing cholangitis, a severe and often fatal complication. An unusual susceptibility to liver and biliary tract tumors has also been reported (20). Lymph nodes of patients with CD40L deficiency lack germinal centers, attributed to ineffective CD40L/CD40 interaction in the extrafollicular areas, resulting in poor recruitment of germinal center precursors (21).

Autoimmune manifestations are quite common and include thrombocytopenia, seronegative arthritis, and inflammatory bowel disease (18). Neutropenia, which is present in two out of three patients (18) does not seem to be associated with auto-antibodies. It can be found in patients who have also chronic parvovirus B19 infection (22). Like all forms of HIGM, patients with mutations of CD40L have markedly reduced levels of serum IgG, IgA, and IgE with normal to elevated IgM and a normal number of circulating B cells, although the proportion of IgD$^-$, CD27$^+$ isotype switched memory B cells is markedly decreased. CD40 signaling is normal as demonstrated by the *in vitro* production of IgG and IgE when peripheral blood lymphocytes are incubated with antiCD40 or soluble CD40L in the presence of lymphokines (6,7,9). It appears that serum IgM levels increase with age, particularly if initiation of IVIG substitution therapy is delayed (18), indicating that an increase in IgM reflects chronic antigen stimulation rather than a direct effect of the molecular defect.

Whereas the antibody deficiency is considered to be a direct consequence of defective CD40 cross-linking by CD40L, resulting in abnormal CD40 signaling in B cells, the opportunistic infections and increased risk of autoimmune diseases and malignancies are the consequence of the defective T-cell/antigen-presenting cell interaction due to absence of CD40L/CD40 binding. In normal subjects, but not XHIGM patients, activation of T cells is further enhanced by the expression of B7 on the surface of stimulated antigen-presenting cells, a molecule that can deliver a co-stimulatory signal back to T cells *via* CD28, resulting in optimal T-cell function (23). A direct signal for T cells, *via* the CD40L intracellular tail, initiated by the engagement of CD40L/CD40 has been postulated by Brenner and coworkers (24) (see below).

The gene responsible for XHIGM, *CD40L*, was discovered more than 10 y ago (6–10) and belongs to the superfamily of tumor necrosis factor (also known as TNFSFS). The human CD40L protein is 261 amino acid long with a short intracytoplasmic tail (amino acid 1–22), a transmembrane region (amino acid 23–46), and an extracellular domain that shares homology to tumor necrosis factor-α. Crystal structure analysis of the extracellular region shows that both hydrophobic and hydrophilic regions are involved in CD40 binding (25).

The more than 100 unique mutations of CD40L reported (16,26,27; HDO, unpublished data) are scattered throughout the entire gene and may affect the intracellular tail, the transmembrane region, or, most often, the extracellular domain containing the CD40 binding region. The mutations most frequently observed are those resulting in frameshift and early

termination (41%) followed by nonsense mutations (26%) and missense mutations (20%). In a few families, mutations involving splice sites may result in the generation of small amounts of wild-type CD40L, associated with a milder clinical phenotype (26).

The clinical diagnosis has to be confirmed by demonstrating a defect in the expression of CD40L by activated peripheral blood CD4$^+$ lymphocytes using anti-CD40L MAb or a soluble CD40-Ig fusion protein and flow cytometry. However, because most mutations result in nonfunctional/truncated protein expression, activated CD4$^+$ lymphocytes from approximately 20% of XHIGM patients can bind anti-CD40L MAb and therefore have to be identified by binding CD40-Ig fusion protein or by sequence analysis. In some instances, when small amounts of wild-type CD40L are expressed by activated CD4$^+$ cells, the CD40-Ig fusion protein may be bound, although at low intensity. Therefore, the final molecular diagnosis depends on sequence analysis using cDNA or genomic DNA (26).

There is no strong genotype/phenotype correlation in XHIGM, however, several mutations have been reported to be associated with a mild phenotype, late onset, and prolonged survival (21).

Conservative treatment consists of prophylactic IVIG at doses of 400–600 mg/kg per month. Infants with XHIGM are particularly susceptible to PCP and should receive prophylaxis with trimethoprim-sulfamethoxazole. Patients with persistent severe neutropenia are candidates for treatment with granulocyte colony-stimulating factor (G-CSF) (28). Prevention of liver disease is of prime concern and necessitates careful monitoring of liver and biliary tract function, which may require ultrasound examinations and biopsies. Because cryptosporidium infection has been associated with chronic cholangitis, avoiding this parasite is important, *e.g.* use of boiled or filtered water is recommended.

Nevertheless, the long-term prognosis of XHIGM is guarded. A multicenter European study suggests that only 20% of the patients survive beyond 25 y of age (17). The causes of death included infections during early life, liver disease, and malignancies. For these reasons, stem cell transplantation has been advocated (30), using HLA-identical siblings, matched unrelated donors, or partially matched umbilical cord blood. Although preliminary reports were encouraging (29,30), a recent study of 38 patients with XHIGM who underwent BMT in Europe showed only 68% survival rate (31). If the patient is relatively young (≤8 y of age) and without serious infection and if an optimal donor (*e.g.* matched sibling) is available, stem cell transplantation should be seriously considered. Gene therapy will be more complicated than that of X-linked severe combined immunodeficiency. Because the expression of the *CD40L* gene is highly regulated, a dominant negative situation may occur and overexpression may be detrimental (32).

Autosomal Recessive HIGM Due to CD40 Deficiency

This rare form of HIGM (HIGM-3), recognized to-date in only four patients from three unrelated families (33,34), with autosomal recessive mode of inheritance is due to mutations in CD40, a member of the tumor necrosis factor receptor super-

family. CD40 is expressed constitutively on the surface of B-lymphocytes, mononuclear phagocytes, dendritic cells, and activated epithelial cells (33). Activated T cells that express CD40L will engage and cross-link CD40 on resting B cells and provide key signals for B cells to generate a set of proteins/enzymes required for CSR and SHM (35).

Similar to CD40L deficiency, patients with CD40 mutations present during infancy with severe clinical symptoms, including opportunistic infections and failure to thrive, suggestive of combined immunodeficiency. The lack of activation of monocytes and dendritic cells in the absence of CD40 may account for opportunistic infections in both CD40L and CD40 deficiencies. Cross-linking of CD40 is required for the initiation of CD40 signaling, which results in increased expression of B7 by B cells (23,35). The interaction of B7 with the T-cell surface molecules CD28 and CTLA-4 results in additional T-cell activation. Finally, although the signaling within the T cell mediated by CD40L is still controversial, there is experimental evidence that co-stimulation of T cells *via* CD40L following CD40L–CD40 interaction is required to initiate direct activation of T lymphocytes by tyrosine phosphorylation of cellular proteins including PLCγ; however, no binding partner for CD40L has been identified in CD4$^+$ T cells (24).

The CD40-deficient patients identified to date were found to have a complete lack of CD40 expression on the surface of B lymphocytes and monocytes. B-cell stimulation *in vitro* with anti CD40 and IL-10 failed to induce IgA or IgG production (33) in contrast to B cells from XHIGM patients who do (6,7,9). Similar to XHIGM patients, CD40 deficient infants have decreased numbers of IgD$^-$, CD27$^+$ memory B cells.

Treatments include IVIG infusions every 3–4 wk, PCP prophylaxis, and attention to nutrition. Stem cell transplantation is expected to be less successful (36), since it restores CD40 expression only for hematopoietic stem cell–derived cell lineages and not for other CD40-expressing cell types.

Autosomal-Recessive Hyper-IgM Syndrome Due to AID Deficiency

Following the discovery of the molecular basis of XHIGM, a number of investigators identified male and female patients with HIGM, normal CD40L, increased susceptibility to bacterial, but not opportunistic infections, and in some families an autosomal-recessive pattern of inheritance (37–39). In 2000, Revy *et al.* (40) studied such a group of HIGM patients and found mutations within *Activation-Induced Cytidine Deaminase (AICDA)*, the gene encoding AID.

AID-deficient (HIGM-2) patients present during early childhood with recurrent bacterial sinorespiratory and gastrointestinal tract infections. However, because of the milder disease and lack of opportunistic infections, many patients with mutations of AID are not recognized as having immunodeficiency until the second or third decade of life (41) (Table 1). Similar to patients with CD40L mutations, AID-deficient patients present with markedly diminished levels of IgG and IgA, and with normal or elevated IgM. Specific antibodies of the IgG class to T-cell-dependent protein antigens are absent, whereas IgM isohemagglutinins are present. The numbers of CD19$^+$ B cells and CD27$^+$ memory B cells are normal, and T-cell immunity is universally intact (40). A characteristic clinical finding, present in half of the patients with AID deficiency, is lymphoid hyperplasia due to the presence of giant germinal centers filled with proliferating B-lymphocytes co-expressing IgM, IgD, and CD38 (42).

The *AICDA* gene was cloned by subtractive hybridization between murine lymphoma B cells that had or had not been induced to undergo CSR *in vitro*. AID expression is restricted to LPS-activated B cells undergoing *in vitro* Ig CSR and to germinal center B cells (43). The gene encoding human AID is located on chromosome 12p13, includes 5 exons, and generates a 198 amino acid protein. Mutations of *AID*, most often homozygous, rarely compound heterozygous, have been found throughout the gene, predominantly in exon 3. They include amino acid substitutions, premature stop codons, and deletions (40,41). AID contains an active site for cytidine deamination that is conserved in members of the large cytidine deaminase family.

Originally, AID was considered to be an RNA-editing enzyme involved in one or several target mRNA (42–44). However, recent data have provided strong evidence that AID acts directly on DNA (45). In this model, AID is expected to convert deoxycytidine (dC) into deoxyuridine (dU) in one strand of DNA (46). The strongest evidence that AID acts directly on DNA has been provided by the recent description of a partial impairment in CSR associated with a normal frequency but skewed pattern of SHM in mice deficient of uracil *N*-glycosylase (UNG) (47) and of a new HIGM condition characterized by a profound defect in CSR at a DNA precleavage step and a partial disturbance of the SHM pattern caused by mutations of the human *UNG* gene (48) (see below). Deamination of cytidine represents a physiologic trigger for base excision repair, which is a crucial step in DNA cleavage. Thus, a single protein, AID, differentially regulates V-region point mutation and S-region recombination. It was recently reported that AID requires interaction with specific co-factor(s) to induce CSR (49). It was also shown that the block of CSR caused by AID deficiency occurs before the generation of DNA double-strand breaks in the switch μ-region (50). Thus, although the precise mechanism by which AID exerts its function is still not completely understood, its essential role in CSR and SHM has been demonstrated convincingly. A positive *in vitro* class switching with anti-CD40 and cytokines essentially rules out the diagnosis of AID deficiency

The diagnosis of AID deficiency should be considered in patients with abnormal serum Ig levels, suggesting the HIGM phenotype in the presence of normal CD40L expression and/or sequence and the inability of peripheral blood lymphocytes to generate *in vitro* Ig other than IgM if stimulated with antiCD40 and lymphokines. To confirm the molecular diagnosis, it is necessary to demonstrate mutations within the AID gene.

Treatment with regular infusions of IVIG (400–600 mg/kg/mo) is effective in reducing infections but does not affect lymphoid hyperplasia.

Autosomal Recessive HIGM Due to UNG Deficiency

In a collaborative study to search for the molecular defect in a group of HIGM patients with normal CD40L, CD40, and AID, three patients, one each from France, Japan, and the United States, were found to have mutations affecting UNG (48). The clinical phenotype of UNG deficiency resembled patients with AID deficiency, including susceptibility to bacterial infections, lymphoid hyperplasia, increased serum IgM concentrations, and profoundly decreased serum IgG and IgA levels. Numbers of B- and T-cell subsets were normal. Memory B cells (CD 27+) were present in normal numbers in two of the three UNG-deficient patients. Their B cells were unable to undergo CSR *in vitro* following CD40 activation with soluble CD40L and lymphokines. RNA transcripts of the *AICDA* gene were present, indicating that the block in CSR was not a consequence of a defect in the signaling events leading to AID expression. However, after activation *via* CD40, B cells from UNG-deficient patients failed to generate double-stranded DNA breaks in S-regions, similar to patients with AID deficiency. When SHM was analyzed in the V_H region of IgM in purified memory B cells, a SHM pattern was found in which mutations at dG and dC residues were biased toward transition, whereas at dA and dT residues, the ratio of transitions to transversions was similar to control values (48). Similar immunologic abnormalities as well as partially defective CSR and a bias pattern of SHM toward transitions at dG-dC nucleotides were reported in UNG-deficient mice (47). As in mice, human UNG has two promoters and two alternative splice products: the mitochondrial isoform, which is ubiquitously expressed, and the nuclear isoform, which is strongly expressed in proliferating cells (51,52). In each of the three patients, mutations were located in the catalytic domain of UNG. One patient was a compound heterozygote for a C deletion in one allele and a TA deletion in the other. The second patient was homozygous for an amino acid substitution (F251S). The third patient was homozygous for an AT deletion in exon 2. UNG, expressed only in activated CD19$^+$ B cells but not in T cells, is also present in EBV-transformed normal B-lymphoblastoid cell lines but was found consistently absent in EBV-transformed B-lymphoblastoid cell lines derived from the three UNG-deficient patients (48).

Although the exact mechanism by which UNG exerts its function is not completely understood (53), analysis of UNG-deficient mice and humans supports the model of CSR in which AID directly deaminases cytidine into uracil residues in the active S-regions, followed by uracil removal mediated by UNG, leading to an abasic site that is essential for SHM as well as for switch recombination.

HIGM with Defective CSR but Normal SHM

Molecular analysis of large cohorts of patients with the HIGM phenotype suggested that 20–30% have normal *CD40L, CD40, AID*, and *UNG* genes. Recently, a subset of these molecularly undefined patients has been identified as having in common a defect of CSR while SHM was intact, accounting for approximately 10% of HIGM patients (54). Most of the cases were sporadic with no family history of immunodefi-

ciency, but in a few an autosomal recessive mode of inheritance was suggested.

Similar to patients with defective AID or UNG, this subgroup of HIGM patients suffers from recurrent bacterial infections, beginning during childhood without particular susceptibility to opportunistic infections (Table 1), suggesting that T-cell immunity is unaffected. In accordance with a clinical course described as "slightly milder" than that of AID deficiency, the mean age of diagnosis was relatively late at 8.8 y. Like subjects with AID and UNG deficiency, this subgroup of HIGM patients often develops lymphoid hyperplasia but without the giant germinal centers typical of AID-deficient patients. The CSR defect is less severe, as suggested by the occasional presence of residual IgG. Numbers of B and T cells, including subsets and T-cell function, are normal. Of note, more than 60% of this cohort of HIGM patients have low numbers of memory B cells (54).

Functional *in vitro* studies revealed that B-cell CSR was intrinsically impaired, but SHM assessment in the variable region of the Ig heavy chain gene was completely normal. *In vitro* studies suggested that the molecular defect responsible for this group of patients occurs downstream of AID, as the AID gene was expressed normally and AID-induced DNA double-strand breaks in the switch (S) regions of the Ig heavy chain locus, a requirement for successful CSR, were normally detected. Although this group of CSR-deficient patients has a characteristic phenotype and normal AID and UNG, it is unlikely that they all will have a single gene defect. It remains to be seen whether at least a subset of this group will turn out to have a unique molecular defect involving one or more gene(s) that are directly involved in CSR or in CSR-specific DNA repair, or if these patients have a multifactorial disorder involving multiple predisposition genes.

X-Linked HIGM Due to Mutations of NEMO

Hypohidrotic (anhidrotic) EDA is a rare syndrome associated with abnormal development of hair, teeth, and sweat glands (55). Most patients with EDA are immunologically normal and have mutations caused by the ectodysplasin-A gene, *EDA1*, located on the X chromosome (56), or mutations of the ectodysplasin-A receptor (*EDAR*) an autosomal recessive disorder (57). A subset of the X-linked form of EDA has been found to be associated with immunodeficiency (EDA-ID), characterized by susceptibility to bacterial infections, including atypical mycobacteria (58–60). Many, but not all, of the EDA-ID patients have dysgammaglobulinemia characterized by decreased IgG and decreased or elevated IgM and IgA. The gene responsible for this X-linked form of HIGM has been identified as the *NF κB essential modulator* (*NEMO*), also designated as *IKK-γ* (61–63). Mutations of *NEMO* interfere with NF-κB activation (64). In resting cells, NF-κB activity is inhibited by one of several inhibitors (IκB). The cytoplasmic association of IκB and NF-κB is terminated by the phosphorylation of IκB, which leads to its cytoplasmic degradation. The release of the NF-κB complex from IκB allows NF-κB to translocate to the nucleus and activate transcription. Phosphorylation of IκB is mediated by IκB kinase (IKK), a complex

consisting of IKKα, IKKβ, and IKKγ (the latter also known as NEMO). A variety of cell surface receptors have been identified that can induce signaling pathways that result in the activation of the IKK complex leading to the phosphorylation of IκB. The cell surface receptors involved in this process include TNF superfamily receptors such as EDAR, toll-like receptors, and CD40. Mutation of NEMO is therefore of crucial importance for the clinical phenotypes observed in EDA-ID. For instance, following cell activation by cross-linking CD40, the IKK signalosome is activated, leading to the phosphorylation and degradation of the NF-κB inhibitory protein, IκB, and thus to the translocation of NF-κB to the nucleus. If NF-κB translocation is defective, multiple NF-κB-dependent proteins, including AID and UNG, cannot be expressed.

The *NEMO* gene consists of 10 exons and encodes a protein (IKK-γ) that binds IKK-α and IKK-β, and thus is responsible for maintaining a functional IKK complex. The majority of patients with EDA-ID were found to have a point mutation in the C-terminal portion of the *NEMO* gene that encodes a zinc finger domain believed to be an important modulator for upstream activators (61–63). These hypomorphic NEMO mutations are associated with EDA-ID phenotype and sometimes, in addition, with osteopetrosis and lymphedema (OL-EDA-ID). In contrast, mutations of NEMO that result in "loss of function" are the cause of incontinentia pigmenti in carrier females and lead to embryonic death in males (65). Recently, an autosomal dominant form of EDA-ID has been reported, caused by the mutation of one allele of IκBα, a subunit of the IκB complex (66). Thus, defective NFκB translocation from the cytoplasm to the nucleus can be caused by mutation of more than one gene, and not only interferes with T- and B-cell activation, including CD40 mediated CSR and SHM, but may affect multiple ectoderm-derived structures.

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