Update on the hyper immunoglobulin M syndromes

E. Graham Davies and Adrian J. Thrasher

Centre for Immunodeficiency, Institute of Child Health, London, UK

Summary

The Hyper-immunoglobulin M syndromes (HIGM) are a heterogeneous group of genetic disorders resulting in defects of immunoglobulin class switch recombination (CSR), with or without defects of somatic hypermutation (SHM). They can be classified as defects of signalling through CD40 causing both a humoral immunodeficiency and a susceptibility to opportunistic infections, or intrinsic defects in B cells of the mechanism of CSR resulting in a pure humoral immunodeficiency. A HIGM picture can also be seen as part of generalized defects of DNA repair and in antibody deficiency syndromes, such as common variable immunodeficiency. CD40 signalling defects may require corrective therapy with bone marrow transplantation. Gene therapy, a potential curative approach in the future, currently remains a distant prospect. Those with a defective CSR mechanism generally do well on immunoglobulin replacement therapy. Complications may include autoimmunity, lymphoid hyperplasia and, in some cases, a predisposition to lymphoid malignancy.

Keywords: immunodeficiency, hyper immunoglobulin M syndromes (HIGM), class switch recombination defect, CD40 ligand deficiency, activation induced cytidine deaminase (AID).

The Hyper-immunoglobulin M (HIGM) syndromes are a group of primary immunodeficiency disorders in which defective immunoglobulin (Ig) class switch recombination (CSR) leads to deficiency of IgG, IgA and IgE with preserved or elevated levels of IgM. A number of different gene products are involved in this process and defects of a number of these have now been described (Lee et al., 2005). Studies of patients affected by these conditions have helped elucidate the process of CSR and the related process of somatic hypermutation (SHM). Most, but not all, patients with CSR defects also show defective SHM. The genetic disorders can be broadly classified into defects restricted to B cells and defects that additionally affect the functions of other cells, including monocytes, macrophages and dendritic cells, whose function requires signalling through the CD40 receptor. The former cause a pure humoral immunodeficiency while the latter are associated with an additional defect of cell-mediated immunity and a consequent susceptibility to opportunistic infections.

In addition to the classical forms of HIGM, other more complex defects of the DNA repair mechanism can also lead to a HIGM-like immunological pattern as part of a more generalized disorder. Additionally, other antibody deficiency disorders, such as common variable immunodeficiency (CVID) or occasionally X-linked agammaglobulinaemia, can present with a picture of low IgG and IgA with preserved IgM thus mimicking HIGM.

A secondary HIGM pattern of immunodeficiency can be seen with congenital rubella infection, malignancy or in patients on antiepileptic medication. This review will not address these forms of the disorder.

An understanding of the details of B cell development and the generation of diverse antibodies of different isotypes is helpful in explaining the different causes of HIGM and will be described here.

B cell development

Maturation from the common lymphoid precursor to a class-switched immunoglobulin-producing B cell or a terminally differentiated plasma cell involves antigen-independent and -dependent phases (Fig 1). This has been described in previous reviews (Ghia et al., 1998; LeBien, 1998). The antigen-independent phase occurs in the liver during fetal life and thereafter in the bone marrow. Ig gene rearrangement of the germline DNA to produce unique antibody specificities commences at the pro (precursor)- B cell stage and is completed in the pre- B cell stage. The process of Ig gene rearrangement is initiated by the recombination activating genes (RAG1 and RAG2), which bind to specific recombination signal sequences to initiate double stranded (ds) DNA breaks. There is excision of intervening DNA to bring the required genes into juxtaposition followed by dsDNA repair using the non homologous end-joining (NHEJ) apparatus. Genetic defects in RAG genes or in the genes encoding proteins...
involved in the NHEJ dsDNA repair process (for example Artemis or Ligase IV) result in a failure to generate T and B cell receptors and a clinical picture of severe combined immunodeficiency rather than HIGM (de Villartay, 2009). Exceptions to this are Ataxia–telangiectasia and Nijmegen breakage syndrome, both affecting NHEJ, and sometimes resulting in a HIGM picture (see below).

Immunoglobulin heavy chain gene (IGH) rearrangement always results initially in the association of VDJ sequences with the \( \mu \) chain constant region gene, IGHM. Mature naïve B cells express surface IgM and IgD.

### Class switch recombination

The second antigen-dependent stage of B cell development occurs in the periphery and is continued in the germinal centres of lymphoid tissue (MacLennan, 1994; Rajewsky, 1996). This stage is dependent on a number of signals including antigen engagement of the B cell receptor and co-stimulatory signals through the effects of cytokines and direct interaction with T cells. B cells may progress to become plasma cells or follow a route of germinal centre maturation (including CSR) to become memory B cells which express CD27. CD40Ligand/CD40 interaction promotes germinal centre development of B cells and is an absolute requirement for the initiation of CSR and SHM. This process is illustrated in Fig 2. CD40 is a member of the tumour necrosis factor (TNF) receptor family expressed constitutively on the B cell surface while CD40 ligand (or CD154) is a member of the TNF family, which is transiently expressed on activated CD4-positive T lymphocytes during the immune response. Signalling through CD40 occurs through activation of a family of TNF receptor associated factors (TRAFs) and thence via nuclear factor kappa B (NFκB) signalling to the nucleus.

CSR involves relocating the previously constructed unique \( V(D)J \) combination from its association with the constant region gene \( IGHM \) of IgM to an alternative constant region gene, one of the \( IGHG \) genes for IgG, \( IGHGA \) gene for IgA or \( IGHE \) for IgE (Coffman et al, 1993). The process, illustrated in Figs 3 and 4, involves the creation of dsDNA breaks, excision of the intervening sequences and then dsDNA repair. This process is distinct from that involved in immunoglobulin gene (VDJ) rearrangement. Recombination occurs between switch (S) regions that are found flanking each constant region gene at the 5′ end and in the intron between the VDJ and IGHM sequences. The process is initiated by DNA transcription at a point upstream from the S regions. This creates single strand DNA substrates for the enzyme activation induced cytidine deaminase (AID). Through a process of deamination, AID is able to convert cytidine into uracil residues (Branstetter et al, 2003). The enzyme uracil N glycosylase (UNG) excises the uracil residues facilitating the production of a single-stranded break in the DNA strand by an endonuclease (Rada et al, 2002). The mismatch repair (MMR) complex of proteins, including the PMS2 (postmeiotic segregation increased 2) protein, has a probable role in converting single stranded into double strand DNA breaks (Schrader et al, 2007; Stavnezer et al, 2008) as does the MRE11-RAD50-NBS1 (MRN) complex (Larson et al, 2005). Following excision of the intervening DNA, repair of the dsDNA is initiated. Ataxia-telangiectasia mutated (ATM) protein kinase is involved in this process (Reina-San-Martin et al, 2004) and DNA repair employs the NHEJ machinery (Kotnis et al, 2009).
Somatic hypermutation

The process of SHM is also initiated by the action of AID (Fig 3). SHM results in the generation of very frequent mutations in the IGHV genes. B cells expressing those mutated IGHV genes that have higher antibody affinity are preferentially selected to proliferate in germinal centres in the presence of antigen loaded follicular dendritic cells and follicular B helper T cells thus achieving affinity maturation of the antibody response (Vinuesa et al, 2005). The process of SHM is less well understood than CSR. AID function is critical and dsDNA breaks occur as in CSR. The mismatched repair enzymes and error – prone DNA polymerases are employed to achieve repair with a high rate of base substitutions but the NHEJ machinery is not involved (Schrader et al, 1999; Poltoratsky et al, 2000).

Table I lists the primary genetic disorders causing HIGM syndrome. Although others have classified Hyper IgM syndromes into Types 1–6, this is not helpful in terms of functional consequences and, though defined in Table I, the classification will not be used in this review.

The relative frequencies of the different causes of HIGM have been reported in a group of 140 patients (130 males) with a susceptibility to infections associated with deficiency of IgG and IgA in combination with normal or elevated circulating
levels of IgM (Lee et al., 2005). These patients underwent extensive genetic testing. By far the commonest defect found, accounting for 98 (70%) of cases, was X-linked HIGM caused by mutations in the gene encoding CD40 ligand (CD40LG). Other identified defects affected AID in 4 (3%) cases, UNG and NFκB in one case each and Bruton tyrosine kinase (the cause of X-linked agammaglobulinaemia) in 3 (2%) cases. No mutations were identified in the CD40 gene, in SH2D1A (a gene associated with X linked lymphoproliferative disease) or in ICOS (a gene associated with a rare form of CVID). The thirty-three (24%) patients who did not have identified mutations were thought to include molecularly undefined cases of CVID. Other genes now known to be associated with CVID (see below) were not examined in this study.

HIGM as part of a combined immunodeficiency

Defects of signalling through the CD40 receptor affect more than just B cell function, because CD40 is also expressed on macrophages/monocytes and dendritic cells and lack of signalling to such cells results in impaired handling of opportunistic pathogens. CD40 is also expressed on platelets and, in the presence of inflammation, on endothelial and epithelial cells. The pathway is involved in platelet activation (Inwald et al., 2003) and there is increasing evidence for its role in the generation of atheroclerosis (Engel et al., 2009). Clinical problems related to defective signalling in non-immunological cells have not been described.

CD40 ligand deficiency

The first recognized and by far the commonest form of HIGM Syndrome, accounting for at least 70% of patients with CSR

Table I. Genetically defined types of HIGM syndrome.

| Defect                        | Inheritance | Infection susceptibility | Lymphoid Hypertrophy | Autoimmunity | Lymphoma | CSR defect | SHM defect | DNA Repair defect |
|-------------------------------|-------------|--------------------------|----------------------|--------------|----------|------------|------------|------------------|
| XHIM-CD40 L deficiency        | XL          | Bacterial, opportunistic | –                    | Yes          | No       | Yes        | Yes        | No               |
| (Type 1 HIGM)                 |             |                          |                      |              |          |            |            |                  |
| CD40 defect (Type 3 HIGM)     | AR          | Bacterial, opportunistic | –                    | Yes          | No       | Yes        | Yes        | No               |
| NFκB signalling defects       | XL/AD       | Bacterial, opportunistic | –                    | Yes          | No       | Yes        | Yes        | No               |
| (Type 6 HIGM)                 |             |                          |                      |              |          |            |            |                  |
| AID deficiency (Type 2 HIGM)  | AR          | Bacterial                | ++                   | Yes          | No       | Yes        | Yes        | No               |
| AID C terminal defect         | AD          | Bacterial                | +                    | ?            | No       | Yes        | No         | No               |
| UNG deficiency (Type 5 HIGM)  | AR          | Bacterial                | +                    | ?            | Probable | Yes        | No         | No               |
| PMS2 deficiency               | AR          | Bacterial                | ?                    | ?            | Yes      | Yes        | No         | No               |
| Complex disorders affecting NHEJ DNA repair (Ataxia-Telangiectasia, Nijmegen breakage syndrome) | AR | Mainly bacterial some opportunistic | – | Yes | Yes | Yes | No | Yes |

XL, X linked; AR, autosomal recessive; AD, autosomal dominant. AID, activation-induced cytidine deaminase; UNG, uracil N glycosylase; PMS2, postmeiotic segregation increased 2; NHEJ, non-homologous end joining. Type 4 HIGM refers to a genetically undefined type.
Defects is caused by mutations in the gene encoding CD40 ligand (CD40LG) (Korthauer et al, 1993). CD40 ligand is a 39 kDa glycoprotein that is a member of the TNF family. The gene, at chromosome Xq26, encodes the molecule expressed in trimeric form on the cell surface and comprises a CD40 binding domain on the cell surface, a short transmembrane domain and a cytoplasmic tail. Occasional symptomatic female carriers with skewed lyonization have been reported (de Saint Basile et al, 1999; Imai et al, 2006). Expression of the molecule is very tightly regulated occurring only transiently upon activation of CD4+ve T lymphocytes. Testing for expression of the molecule involves overnight activation of T-cells, typically with phytohaemagglutinin and phorbol myristate acetate followed by flow cytometric analysis. It is important to look for other markers of T-cell activation, such as CD25 or CD69 expression, as controls for the activation process (Gilmour et al, 2003). This will confirm the diagnosis in the majority of cases in whom mutations result in a lack of protein expression on the cell surface. In a minority of cases with splice site (Seyama et al, 1998a) or cytoplasmic tail mutations (Yong et al, 2008a) some, or even normal, surface expression is seen making the diagnosis more difficult to confirm. In the neonatal period immaturity in T-cell responses results in failure of expression of this molecule using standard T-cell activation stimuli. Except in rare cases with some protein expression, there is severely impaired production of IgG and IgA. Around half of the patients have elevated levels of IgM at presentation, the remainder having levels within the normal range (Levy et al, 1997). The humoral immunodeficiency results in susceptibility to bacterial infections particularly affecting the respiratory tract. There is no response to protein antigens, though some IgM anti-polysaccharide antibodies, including isohemagglutinins, can be produced. Memory (CD27+ve) B-cells are either absent or present in only very reduced numbers (Agematsu et al, 1998).

A second consequence of a lack of CD40 ligand expression involves T-cell interaction with macrophages/monocytes. Expression of CD40 on activated monocytes normally results in interaction with activated CD4 cells expressing CD40 ligand to facilitate the production of T-helper cell type 1 (TH1) cytokines (DeKruyff et al, 1997), including interleukin-12 and interferon-gamma, which are important in the normal handling of opportunistic intracellular pathogens including *Pneumocystis jiroveci* (Levy et al, 1997; Winkelstein et al, 2003), *Cryptosporidium* species (Hayward et al, 1997), *Toxoplasma gondii* (Subauste et al, 1999) and *Mycobacteria* species (Hayashi et al, 1999). In the case of *Cryptosporidium* species it has been shown that ligation of CD40 expressed on inflamed biliary epithelium, using soluble CD40L, has a direct effect in killing the organism even in the absence of effector T-cells (Hayward et al, 1997).

**CD40 deficiency**

This syndrome, a rare cause of HIGM, has been described in patients presenting a very similar clinical picture to boys with X-linked HIGM Syndrome caused by CD40 Ligand deficiency (Ferrari et al, 2001; Lougaris et al, 2005). Flow cytometric analysis of CD40 expression on B cells and mutation analysis can be used to confirm the diagnosis.

**HIGM syndrome associated with ectodermal dysplasia and immunodeficiency**

Signalling through CD40 on B-cells involves NFκB. Boys with X-linked anhidrotic ectodermal dysplasia and immunodeficiency have hypomorphic mutations in the *IKBKG* gene, coding for a protein IKK – gamma part of a kinase complex involved in releasing NFκB from its association with the inhibitory complex IκB allowing translocation to the nucleus. (Zonana et al, 2000; Doffinger et al, 2001). An overlapping clinical syndrome with autosomal dominant inheritance causing ectodermal dysplasia and immunodeficiency is caused by mutations in *NFKBIA* encoding IκBz, part of the inhibitory complex (Courtois et al, 2003). Both these syndromes are very variable both in immunological and non-immunological features. A HIGM pattern of immunodeficiency can be seen with some mutations (Jain et al, 2001; Orange et al, 2003). Given that NFκB is involved in a number of T-cell and Toll receptor signalling pathways the immunodeficiency is more extensive than simply a class switch defect. Patients are therefore prone to a variety of bacterial and opportunistic infections. The non-haemopoietic features of the syndrome reflect the usage of NFκB signalling by other cell lineages.

**Clinical complications**

Most of the experience with these disorders is from CD40 Ligand deficiency (Levy et al, 1997; Winkelstein et al, 2003) as the number of reported cases with the other two disorders is too small to allow firm conclusions. Clinical problems occur early in life with a median age at diagnosis of <12 months.

**Bacterial infections**. Recurrent sinopulmonary infections are a consequence of the humoral immunodeficiency in this syndrome. The picture is similar to that seen in other forms of humoral immunodeficiency with recurrent respiratory tract infections potentially leading to bronchiectasis, sinus infections and ear infections. Treatment with immunoglobulin replacement in adequate doses will largely prevent these complications provided the treatment is started before significant damage to the lungs has been sustained.

**Opportunistic infections**. Pneumonia due to *Pneumocystis jiroveci* (PCP) is a presenting feature of this syndrome in around 40% of cases (Levy et al, 1997; Winkelstein et al, 2003). In the presence of normal T lymphocyte counts and a negative human immunodeficiency virus test, this will be the most likely underlying diagnosis in male infants presenting with PCP. Chronic cryptosporidial infection is another common infection in these patients. Symptomatic chronic intestinal...
cryptosporidiosis may occur, leading to failure to thrive and weight loss with persistent diarrhoea. Molecular studies for cryptosporidium infection, involving polymerase chain reaction amplification of parasite DNA in patients with CD40 ligand deficiency suggest that subclinical infection is common and in many cases the organism is not detectable by stool microscopy, but only by molecular testing (McLauchlin et al., 2003).

Cholangiopathy, with the organism found in the biliary tree, is a common complication of both clinical and subclinical infection. It can result in disturbed liver function tests typically with raised gamma glutamyl transferase levels and, over a period of time, the development of sclerosing cholangitis potentially leading to cirrhosis with a risk of cholangiocarcinoma (Hayward et al., 1997; Rodrigues et al., 2004). In early series not treated with bone marrow transplantation, chronic liver disease was a feature in 50% of affected individuals and was responsible for early death in many cases (Levy et al., 1997). Liver transplantation has been attempted, but with poor results and recurrence of the disease in the transplanted liver. A single successful case of combined liver and bone marrow transplant action has been reported (Hadzic et al., 2000). The handling of certain other pathogens requires similar mechanisms to that for cryptosporidium (Subauste et al., 1999). Cerebral toxoplasmosis (Leiva et al., 1998; Yong et al., 2008a) and cryptococcosis (Simon et al., 2005) have been described. Cotrimoxazole has been shown to have some beneficial effect in the prevention of toxoplasma infection in immunocompromised individuals but is not completely efficacious (Bucher et al., 1997; Weigel et al., 1997; de Medeiros et al., 2001).

Though CD40/CD40 ligand interaction is thought to be important in the handling of mycobacteria, in practice, tuberculosis is relatively uncommon, being reported in only one case in the two large series (Levy et al., 1997; Winkelstein et al., 2003) and in occasional other case reports (Shah, 2005). Histoplasmosis was reported in one case in the North American series (Winkelstein et al., 2003). Disseminated atypical mycobacterial or Bacillus Calmette-Guérin (BCG) infection has not been reported in patients with CD40 ligand deficiency. However, atypical mycobacterial disease is a relatively common manifestation in defects of NFκB signalling (Dai et al., 2004). This may reflect deficiencies of signalling pathways other than through CD40.

Handling of cytomegalovirus (CMV) infection can be problematic in these patients (Levy et al., 1997; Winkelstein et al., 2003) and disseminated infection can be seen as an initial presenting illness (Benesch et al., 2000). CMV has also been implicated in some cases of chronic sclerosing cholangitis (Hayward et al., 1997). Human Parvovirus infection was described in three cases with leaky splice mutations resulting in partial molecular expression and therefore late presentation of the disorder. In all cases there was a chronic anaemia, which resolved upon commencement of immunoglobulin therapy (Seyama et al., 1998b).

Neutropenia. Neutropenia is a common complication in boys with CD40 Ligand deficiency. In one series it was reported as occurring at some stage in 50% of cases (Levy et al., 1997). The clinical course of the neutropenia may be transient or it may be prolonged and persistent. The precise mechanism by which this occurs is not well understood. Anti-neutrophil antibodies cannot be detected. Early myeloid progenitors express CD40 and ligation has been shown to stimulate myelopoiesis, suggesting that lack of a CD40-mediated stimulation of precursors may play a role (Atkinson et al., 1998; Brown et al., 1998; Solanilla et al., 2000).

Early reports suggested that treatment with high doses of immunoglobulin helped resolve the neutropenia (Banatvala et al., 1994) but in the wider European experience the problem only responded to this treatment in around half the cases (Levy et al., 1997). The neutropenia is usually responsive to granulocyte colony-stimulating factor.

Autoimmunity. Autoimmune complications are relatively common in patients with defects of CD40 signalling. Mature naïve B-cells from CD40 ligand-deficient patients were shown to express a high proportion of auto-reactive antibodies suggesting a role for CD40 ligand/CD40 interaction in mediating peripheral B-cell tolerance (Herve et al., 2007). In the Levy study, seronegative arthritis affected 11% and inflammatory bowel disease affected 6% of cases while there were three patients with thrombocytopenia and one with autoimmune haemolytic anaemia. A small number of cases were also shown to have a variety of autoantibodies though not associated with disease at the time (Levy et al., 1997). In the North American series, 12 of 79 (15%) of patients had anaemia. Three of these were due to parvovirus infection. Some of the remainder may have been autoimmune in nature though insufficient detail was reported to be sure (Winkelstein et al., 2003). Other occasional cases of autoimmune disease have been reported in CD40 ligand deficiency (Schuster et al., 2005).

Autoimmune/inflammatory disease is also a feature in those patients with defective NFκB signalling presenting with a Crohns-like inflammatory colitis (Orange et al., 2005).

Malignancy. Boys with CD40 ligand deficiency suffer an excess risk of malignant disease affecting the biliary tree (Hayward et al., 1997; Levy et al., 1997) and intestine, including neuroendocrine tumours (Zirkin et al., 1996; Malhotra & Li, 2008). An excess risk of lymphoid malignancy has not been reported.

Management

Immunoglobulin replacement therapy should be initiated on diagnosis and will largely correct the clinical consequences of humoral immunodeficiency. The susceptibility to opportunistic infections is more problematic. Prophylaxis against pneumocystis should be commenced and consideration given to approaches to correct the underlying disorder.
Administration of recombinant soluble CD40L (Mazzei et al, 1995) is a theoretical possibility for corrective therapy but the potential clinical problems associated with unregulated ligation of CD40, not only on immunological cells but also on other cell lineages, mitigates strongly against this approach.

The mainstay of corrective therapy is bone marrow transplantation and this has been successfully employed to treat all three of these conditions. The largest reported series of bone marrow transplantation for CD40 ligand deficiency (Gennery et al, 2004) looked at 38 patients from eight European countries. These included a mixture of patients with and without organ damaging complications including liver disease and bronchiectasis. Twenty-six (68%) of the patients survived but four (10%) had autologous reconstitution, one of whom achieved full engraftment after a second procedure. Two of the four with autologous reconstitution had received full and two reduced intensity conditioning (RIC). One patient had extremely poor immunological reconstitution despite achieving full donor engraftment. Overall, a cure was achieved in 22 (58%). Though the cure rate was better in those without liver disease (72%), absence of pre-existing liver disease was not a significant predictor of survival. The presence of lung disease and the use of a mismatched unrelated donor did correlate with a poorer chance of survival. Fully matched unrelated donors did as well as matched sibling donors. RIC regimens were used in too few patients in the survey to draw any conclusions about its usefulness. Other studies have used RIC to good effect but only in small numbers (Kikuta et al, 2006). RIC may improve the outcome but carries the risk of rejection, which was not insignificant in the larger survey. Infection was a major factor in all 12 fatal cases (32%). In 6 this was caused by cryptosporidium. There was no association between transplant variables, such as donor type or conditioning used, and the occurrence of cryptosporidial infection. Another report indicates that cryptosporidial infection can reactivate after BMT even when apparently subclinical and with negative stools on conventional testing (McLauchlin et al, 2003). In the same report it was shown that, despite the fact that antimicrobial treatment for cryptosporidium is poorly efficacious, some patients with cryptosporidial reactivation after transplantation can control the infection and survive. In survivors who had pre-existing liver disease, there is resolution of symptoms and normalization of abnormal liver function tests (authors’ unpublished observations and Dimicoli et al, 2003).

Given the potential problems with stem cell transplantation, an alternative approach for boys with CD40 ligand deficiency is to adopt a waiting brief; treating with immunoglobulin and cotrimoxazole and monitoring closely for complications such as liver disease and neutropenia. In this approach, transplantation is only performed at the first sign of problems. This is particularly relevant if a fully matched donor cannot be found or if the patient has a hypomorphic mutation. Some boys with the condition will remain well and thrive for a number of years on this regimen (authors’ unpublished observations) Careful attention to avoidance of cryptosporidium exposure is important. The advice given to patients is shown in Table II.

The numbers of patients transplanted for CD40 deficiency and NF kB signalling defects are too small to derive firm conclusions about this approach in these disorders. Case reports describing successful outcomes are described for both (Dupuis-Girod et al, 2006; Mazzolari et al, 2007; Tono et al, 2007). A recent review suggested that in transplantation for NFkB signalling defects, achieving good levels of engraftment may be difficult (Fish et al, 2009) while in another report transplantation corrected the immunodeficiency but failed to correct the colitis (Pai et al, 2008).

Gene therapy for CD40 ligand deficiency is under development. However, experiments on CD40 ligand knockout mice show that introduction of CD40LG, resulting in constitutive expression of this molecule, caused lymphoproliferative disease in the majority of mice treated that was unrelated to potential insertional mutagenesis (Brown et al, 1998; Sacco et al, 2000). This indicates that tight control of the expression of this molecule is essential. As a result strategies for developing gene therapy for this condition will need to employ transduction not only of the structural gene but also the elements for regulating its expression, or possibly use methods utilizing DNA or RNA repair (Tahara et al, 2004).

**Forms of HIGM syndrome associated with a pure humoral immune defect**

Intrinsic B cell defects in the mechanism of CSR result in HIGM syndrome with a pure humoral immunodeficiency without susceptibility to opportunistic infections.

**Activation induce cytidine deaminase (AID) deficiency HIGM**

This was the second recognized genetic cause of HIGM syndrome and the first autosomal recessive variety (Revy et al, 2000). It is much rarer than CD40 ligand deficiency. AID is expressed transiently and selectively in germinal centre B-cells following stimulation through CD40 and cytokines. It is responsible for deaminating cytidine into uracil residues in the early phase of CSR and SHM. In most cases mutations in the AID gene (AICDA) cause HIGM syndrome in an autosomal recessive manner. In the largest reported study, 15 different mutations were reported in 29 patients with no evidence of a
genotype-phenotype correlation in that study (Quartier et al., 2004). Other reports suggest there may be some genotype/phenotype correlation in that patients with mutations in the C terminal part of the gene have impaired CSR but not SHM (Ta et al., 2003) and patients with a specific heterozygous mutation in the C terminal end of the molecule exhibit a similar phenotype with autosomal dominant inheritance – see below. In other studies a few commonly occurring mutations were found (Minegishi et al., 2000; Zhu et al., 2003). In typical AID defects, both CSR and SHM are defective. IgM levels are normal or high while absent or very low levels of IgG, IgA and IgE are seen. Memory B cells expressing CD27 are present in normal numbers.

AID C terminal defect

An autosomal dominant form of AID deficiency has been described as caused by a missense mutation in the C terminal domain of the molecule, which is the domain involved in nuclear egress. Studies on these patients showed that there was defective CSR but not SHM, suggesting that the C terminal part of the molecule is involved with the enzyme complexes involved in DNA repair in CSR but not repair after SHM which uses different mechanisms (Imai et al., 2005).

Uracil N glycosylase (UNG) deficiency

Deficiency of this enzyme has been described as another cause of HIGM syndrome in a small number of patients (Imai et al., 2003a). Patients suffer a similar clinical picture to AID deficiency. CSR but not SHM is impaired in this disorder although there is marked skewing of the bases involved in SHM towards G–C rather than A-T. Numbers of cases reported are too small to draw firm conclusions about the clinical phenotype but frequent bacterial infections and lymphoid hypertrophy seem to occur.

PMS2 deficiency

PMS2 (postmeiotic segregation increased 2) is one of the proteins involved in the complex mediating mismatch repair of DNA. Along with other members of the mismatch repair enzyme complex, mutations in PMS2 have been identified as being associated with gastrointestinal adenocarcinomas (Gologan & Sepulveda, 2005). A recent report described the presence of mutations in PMS2 in three patients with a defect in DNA cleavage as part of a CSR defect (Peron et al., 2008). There was a partial immunological phenotype of HIGM with low (but not absent) IgG associated with complete IgA deficiency in one patient and a low IgA in one other which corrected over time. CSR was markedly abnormal in vitro. There was either no defect or only a mild defect of SHM. The patient with the most severe immunophenotype was reported as having severe bacterial infections prior to diagnosis and subsequently developed colonic adenocarcinoma.

Other undefined forms of HIGM syndrome due to defects of CSR mechanism

Not all cases of HIGM syndrome can be ascribed to known genetic defects. The characteristics of two defects of CSR both inherited in an autosomal recessive fashion but for which no genetic cause has yet been identified have been reported. In the first (Imai et al., 2003b) a B cell defect affecting CSR downstream of DNA transcription step was found without radiosensitivity. SHM was not affected. A possible cofactor for AID function has been postulated. A second form of CSR abnormality reported in 16 patients was associated with radiosensitivity implying a defect in dsDNA repair mechanisms (Peron et al., 2007). Durandy (2009) recently reported an update on these defects.

Clinical complications

Other than AID deficiency, very small numbers of cases have been reported on which to base a description of clinical features. Some of the defects, such as PMS2, may result in a partial phenotype as far as immunological findings are concerned though clinical features are not fully described. The main potential clinical complications are described below.

Infections. In AID deficiency, two case series have been reported (Minegishi et al., 2000; Quartier et al., 2004). Prior to commencing treatment with immunoglobulin, recurrent severe infections mainly bacterial and most often causing pneumonia were seen. Other sites of infection were the skin, lymph nodes, gastrointestinal tract and central nervous system, the last including bacterial meningitis and one case of Herpes simplex encephalitis. The onset of infections was early, usually before 2 years of age, but in the study reported by Minegishi et al (2000) a considerable delay often occurred before a diagnosis of immunodeficiency was made. Opportunistic infections were not described. The numbers of cases reported with disorders other than AID deficiency is too small to draw firm conclusions but the clinical susceptibility to bacterial infections seems to be similar.

Lymphoid hypertrophy. Marked lymphoid hypertrophy is a clinical feature of AID deficiency that is reported in one half to two-thirds of cases (Minegishi et al., 2000; Quartier et al., 2004). It has also been described in the other forms of CSR defect (Durandy et al., 2006). It can affect all lymphoid tissues but peripheral lymphadenopathy and tonsillar hypertrophy were most commonly reported. Splenomegaly was relatively uncommon, being reported in 2 of 29 in one series (Quartier et al., 2004). Lymph node and tonsillar histology characteristically shows giant germinal centres (Revy et al., 2000). The driver for such germinal centre hypertrophy is not clear. Interestingly, treatment with immunoglobulin seems to reduce the likelihood of developing this complication with only two of 29 patients developing this complication after
commencement of treatment (Quartier et al., 2004). In AID knock out mice, Peyer’s patch hypertrophy has been shown to be driven by intestinal bacterial overgrowth (Fagarasan et al., 2002).

Autoimmunity. In both reported series of AID-deficient HIGM syndrome, autoimmune complications were described with an incidence of around 20% and included immune cytopenias, arthritis and hepatitis (Minegishi et al., 2000; Quartier et al., 2004). Potential mechanisms for the autoimmune process have been reviewed (Jesus et al., 2008). It has also been postulated that the B cell lymphoproliferation characteristic of the condition leads to the development of ectopic lymphoid tissue in non lymphoid organs, predisposing to organ specific autoimmunity (Hase et al., 2008). Autoimmune complications would also be expected to occur in UNG-deficient forms of the disorder.

Malignancy. To date, despite the tendency to lymphoid hyperplasia in AID deficient patients, malignant lymphoproliferation has not been described. There is a probable predisposition to B cell malignancy in UNG deficiency although this has not been reported in the few cases described (Durandy et al., 2006). UNG knock out mice are prone to B cell lymphomas consistent with a role for the base excision function of this enzyme in correcting mutagenic influences (Nilsen et al., 2003).

Management

The mainstay of treatment for these forms of HIGM syndrome is immunoglobulin replacement therapy. This is reported as reducing markedly the incidence of bacterial infections and also reducing the likelihood of developing lymphoid hypertrophy (Quartier et al., 2004). Early diagnosis and initiation of treatment is important in reducing the likelihood of the patient developing bronchiectasis and/or chronic sinusitis. Studies of immunoglobulin-deficient patients generally have found that these complications are usually established before initiation of replacement therapy and may then progress despite treatment (Wood et al., 2007). Subcutaneous treatment with immunoglobulin has been shown to be both efficacious and acceptable to antibody-deficient patients (Chapel et al., 2000).

Autoimmune complications are generally managed along the lines used in non-immunodeficient patients. The authors are not aware of any reports of usage of anti CD20 monoclonal antibody (rituximab) in these disorders.

Corrective therapy, such as bone marrow transplantation, cannot generally be justified given the fact that these are pure humoral deficiencies showing good response to immunoglobulin therapy. Theoretically, such an approach might be justified in patients with uncontrollable autoimmune manifestations or in those who have developed lymphoid malignancies.

Forms of HIGM syndromes associated with syndromes affecting DNA repair

Ataxia-telangiectasia (A-T) and Nijmegen Breakage syndrome involving defects in ATM and NBS1, respectively, are both conditions in which immunodeficiency can be a prominent feature (Taalman et al., 1989; Staples et al., 2008). These enzymes are closely involved in CSR (Reina-San-Martin et al., 2004; Kracker et al., 2005). ATM deficiency does not affect SHM while NBS1 does (Pan-Hammarsstrom et al., 2003). Clinically, a number of A-T patients have been described as presenting with a classical HIGM pattern of immunoglobulin deficiency (Etzioni et al., 2007; Sorensina et al., 2008; Noordzij et al., 2009). More commonly there is IgA and/or IgG2 deficiency. Since the IGH heavy chain genes for these two isotypes are amongst the furthest downstream from the VDJ genes it has been postulated that the defective CSR function in A-T is more marked for rearrangements involving longer intervening DNA sequences (Giovannetti et al., 2002). In both conditions chromosomal translocations, particularly affecting the immunoglobulin and T cell receptor genes on chromosomes 7 and 14, are commonly found. Lymphomas are common in both conditions. In A-T these are more often of T rather than B cell origin. Ataxia-telangiectasia-like disorder (ATLD) is caused by mutations in the MRE11A gene, also involved in CSR and SHM. Though defective CSR has been shown, clinical or laboratory evidence for immunodeficiency is usually not present (Delia et al., 2004; Taylor et al., 2004; Fernet et al., 2005).

HIGM as part of other primary antibody deficiency disorders

Preserved levels of IgM may be found at presentation in patients presenting with antibody deficiency syndromes not due to any of the classical HIGM disorders. This includes X-linked agammaglobulinaemia caused by mutations in Bruton tyrosine kinase (BTK). In a series including 140 patients with a HIGM picture, BTK mutations were found in three patients (Lee et al., 2005). In the same study, 33 patients without an identifiable genetic defect were thought to include patients with CVID. This disorder is often part of the differential diagnosis in patients with a HIGM as preservation of IgM production is not unusual, at least in the early stages of CVID. Sometimes a frank HIGM picture is seen. Causes of CVID have recently been reviewed (Yong et al., 2008b). A number of genetic defects have been described, which may account for around 10% of cases, with genetic lesions still to be identified in the remainder. Mutations in genes encoding TACI (TNFRSF13B), ICOS (ICOS), CD19 (CD19), and, most recently, B cell activating factor receptor (BAFF-R; TNFRSF13C) (Warnatz et al., 2009) all involved in the process of B cell activation, have been described in CVID. It can be postulated that failure of signals through these receptors could affect the antigen-dependent
pathway of B cell maturation during which CSR and SHM take place. Recently, variant sequences in MSH5, one of the complex of mismatch repair enzymes involved in CSR and SHM have been shown to be associated with some cases of CVID and IgA deficiency (Sekine et al., 2007). This finding suggests that defects in the mechanisms of CSR (and thus true HIGM disorders) may account for a proportion of genetically undefined cases labelled as having CVID.

Conclusion

Studies on patients with HIGM syndrome can now identify the genetic cause in around 75–80% of cases. The remainder is currently undiagnosed at the genetic level. Treatment options depend on the type of defect with those involving defective CD40 signalling requiring consideration of corrective therapy whilst those with intrinsic B cell defects mostly require immunoglobulin replacement therapy alone.

References

Agematsu, K., Nagumo, H., Shinozaki, K., Hokiibara, S., Yasui, K., Terada, K., Kawamura, N., Toba, T., Nonoyama, S., Ochs, H.D. & Komiyama, A. (1998) Absence of IgD-CD27(+) memory B cell population in X-linked hyper-IgM syndrome. The Journal of Clinical Investigation, 102, 853–860.

Atkinson, T.P., Smith, C.A., Hsu, Y.M., Garber, E., Su, L., Howard, T.H., Prchal, J.T., Eversion, M.P. & Cooper, M.D. (1998) Leukocyte transfusion-associated granulocyte responses in a patient with X-linked hyper-IgM syndrome. Journal of Clinical Immunology, 18, 430–439.

Banatvala, N., Davies, J., Kanariou, M., Strobel, S., Levinsky, R. & Morgan, G. (1994) Hypogammaglobulinaemia associated with normal or increased IgM (the hyper IgM syndrome): a case series review. Archives of Disease in Childhood, 71, 150–152.

Benesch, M., Pfleger, A., Eber, E., Orth, U. & Zach, M.S. (2000) Disseminated cytomegalovirus infection as initial manifestation of hyper-IgM syndrome in a 15-month-old boy. European Journal of Pediatrics, 159, 453–455.

Branstetter, R., Pham, P., Scharff, M.D. & Goodman, M.F. (2003) Activation-induced cytidine deaminase deaminates deoxycytidine on single-stranded DNA but requires the action of RNase. Proceedings of the National Academy of Sciences of the United States of America, 100, 4102–4107.

Brown, M.P., Topham, D.J., Sangster, M.Y., Zhao, J., Flynn, K.J., Surman, S.L., Woodland, D.L., Doherty, P.C., Farr, A.G., Pattengale, P.K. & Brenner, M.K. (1998) Thymic lymphoproliferative disease after successful correction of CD40 ligand deficiency by gene transfer in mice. Nature Medicine, 4, 1253–1260.

Bucher, H.C., Griffith, L., Guyatt, G.H. & Opravil, M. (1997) Meta-analysis of prophylactic treatments against Pneumocystis carinii pneumonia and toxoplasma encephalitis in HIV-infected patients. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 15, 104–114.

Chaple, H.M., Spickett, G.P., Ericson, D., Engl, W., Eibl, M.M. & Bjorkander, J. (2000) The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. Journal of Clinical Immunology, 20, 94–100.

Coffman, R.L., Lebman, D.A. & Rothman, P. (1993) Mechanism and regulation of immunoglobulin isotype switching. Advances in Immunology, 54, 229–270.

Courtou, G., Smahi, A., Reichenbach, J., Doffinger, R., Cancrini, C., Bonnet, M., Puel, A., Chable-Bessia, C., Yamaoka, S., Feinberg, J., Dupuis-Girod, S., Bodemer, C., Livadiotti, S., Novelli, F., Rossi, P., Fischer, A., Israel, A., Munnich, A., Le Diest, F. & Casanova, J.L. (2003) A hypermorphic I kappa B alpha mutation is associated with autosomal dominant anhidrotic ectodermal dysplasia and T cell immunodeficiency. The Journal of Clinical Investigation, 112, 1108–1115.

Dai, Y.S., Liang, M.G., Gellis, S.E., Bonilla, F.A., Schneider, L.C., Geha, R.S. & Orange, J.S. (2004) Characteristics of mycobacterial infection in patients with immunodeficiency and nuclear factor-kappaB essential modulator mutation, with or without ectodermal dysplasia. Journal of the American Academy of Dermatology, 51, 718–722.

DeKruyff, R.H., Gieni, R.S. & Umetsu, D.T. (1997) Antigen-driven but not lipopolysaccharide-driven IL-12 production in macrophages requires triggering of CD40. Journal of Immunology, 158, 359–366.

Dela, D., Piane, M., Buscemi, G., Savio, C., Palmeri, S., Lulli, P., Carlessi, L., Fontanella, E. & Chessa, L. (2004) MRE11 mutations and impaired ATM-dependent responses in an Italian family with ataxia-telangiectasia-like disorder. Human Molecular Genetics, 13, 2155–2163.

Dimicoli, S., Bensousan, D., Latger-Cannard, V., Straczek, J., Antunes, L., Mainard, L., Dao, A., Barbe, F., Auarco, J., Clement, L., Feugier, P., Lecompte, T., Stoltz, I.F. & Bordigoni, P. (2003) Complete recovery from Cryptosporidium parvum infection with gastroenteritis and sclerosing cholangitis after successful bone marrow transplantation in two brothers with X-linked hyper-IgM syndrome. Bone Marrow Transplantation, 32, 733–737.

Doffinger, R., Smahi, A., Bessa, C., Geissmann, F., Feinberg, J., Durandy, A., Bodemer, C., Kenrick, S., Dupuis-Girod, S., Blanche, S., Wood, P., Rabia, S.H., Headon, D.J., Overbeek, P.A., Le, D.F., Holland, S.M., Belani, K., Kumararatne, D.S., Fischer, A., Shapiro, R., Conley, M.E., Reimund, E., Kalhoff, H., Abinun, M., Munnich, A., Israel, A., Courtois, G. & Casanova, J.L. (2001) X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF-kappaB signaling. Nature Genetics, 27, 277–285.

Dupuis-Girod, S., Cancrini, C., Le, D.F., Palma, P., Bodemer, C., Puel, A., Livadiotti, S., Picard, C., Bossuyt, X., Rossi, P., Fischer, A. & Casanova, J.L. (2006) Successful allogeneic hemopoietic stem cell transplantation in a child who had anhidrotic ectodermal dysplasia with immunodeficiency. Pediatrics, 118, e205–e211.

Durandy, A. (2009) Immunoglobulin class switch recombination: study through human natural mutants. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 364, 577–582.

Durandy, A., Peron, S. & Fischer, A. (2006) Hyper-IgM syndromes. Current Opinion in Rheumatology, 18, 369–376.

Engel, D., Seijkens, T., Poggi, M., Sanati, M., Thevissen, L., Beckers, L., Wijnands, E., Lievegoed, D. & Lutgens, E. (2009) The immunobiology of CD154-CD40-TRAF interactions in atherosclerosis. Seminars in Immunology, 21, 308–312.

Etzioni, A., Ben-Barak, A., Peron, S. & Durandy, A. (2007) Ataxia-telangiectasia in twins presenting as autosomal recessive hyper-immunoglobulin M syndrome. The Israel Medical Association Journal, 9, 406–407.

Fagarasan, S., Muramatsu, M., Suzuki, K., Nagaoka, H., Hiai, H. & Honjo, T. (2002) Critical roles of activation-induced cytidine deaminase of B cells in the regulation of antibody diversity. Nature, 415, 88–92.
deaminase in the homeostasis of gut flora. Science, 298, 1424–1427.

Fernet, M., Gribaa, M., Salih, M.A., Seidahmed, M.Z., Hall, J. & Koenig, M. (2005) Identification and functional consequences of a novel MRE11 mutation affecting 10 Saudi Arabian patients with the ataxia telangiectasia-like disorder. Human Molecular Genetics, 14, 307–318.

Ferrari, S., Giliani, S., Insalaco, A., Al-Ghonaium, A., Soresina, A.R., Loubser, M., Avanzini, M.A., Marconi, M., Badolato, R., Ugazio, A.G., Levy, Y., Catalan, N., Durandy, A., Tbakhi, A., Notarangelo, L.D. & Plebani, A. (2001) Mutations of CD40 gene cause an autosomal recessive form of immunodeficiency with hyper IgM. Proceedings of the National Academy of Sciences of the United States of America, 98, 12614–12619.

Fish, J.D., Duerst, R.E., Gelfand, E.W., Orange, J.S. & Bunin, N. (2009) Challenges in the use of allogeneic hematopoietic SCT for ectodermal dysplasia with immune deficiency. Bone Marrow Transplantation, 43, 217–221.

Gennery, A.R., Khwaja, K., Veys, P., Bredius, R.G., Notarangelo, L.D., Mazzolari, E., Fischer, A., Landais, P., Cavazzana-Calvo, M., Friedrich, W., Fasth, A., Wulffraat, N.M., Matthes-Martin, S., Bensussan, D., Bordignon, P., Lange, A., Pagliuca, A., Andolina, M., Cant, A.J. & Davies, E.G. (2004) Treatment of CD40 ligand deficiency by hematopoietic stem cell transplantation: a survey of the European experience, 1993–2002. Blood, 103, 1152–1157.

Ghia, P., ten, B.E., Rolink, A.G. & Melchers, F. (1998) B-cell development: a comparison between mouse and man. Immunology Today, 19, 480–485.

Gilmour, K.C., Walshe, D., Heath, S., Monaghan, G., Loughlin, S., Gologan, A. & Sepulveda, A.R. (2005) Microsatellite instability and autosomal recessive form of immunodeficiency with hyper IgM. Journal of Clinical Immunology, 25, 179–190.

Hayashi, T., Rao, S.P., Meylan, P.R., Kornbluth, R.S. & Catanzaro, A. (2004) CD40LG. Biochimica et Biophysica Acta, 1682, 335–340.

Heaton, N.D., Mufti, G.J. & Mieli-Vergani, G. (2000) Correction of CD40 ligand deficiency by hematopoietic stem cell transplantation: a survey of the European experience, 1993–2002. Blood, 103, 1152–1157.

Herve, M., Isnardi, I., Ng, Y.S., Bussel, J.B., Ochs, H.D., Cunningham-Rundles, C. & Meffre, E. (2007) CD40 ligand and MHC class II expression are essential for human peripheral B cell tolerance. The Journal of Experimental Medicine, 204, 1583–1593.

Ikei, K., Slupphaug, G., Lee, W.I., Revy, P., Nonoyama, S., Catalan, N., Yel, L., Forveille, M., Kavli, B., Krokan, H.E., Ochs, H.D., Fischer, A. & Durandy, A. (2003a) Human uracil-DNA glycosylase deficiency associated with profoundly impaired immunoglobulin class-switch recombination. Nature Immunology, 4, 1023–1028.

Ikei, K., Catalan, N., Plebani, A., Marodi, L., Sanal, O., Kumaki, S., Nagendra, V., Wood, P., Glastre, C., Sarrot- Reynaud, F., Hermine, O., Forveille, M., Revy, P., Fischer, A. & Durandy, A. (2003b) Hyper-IgM syndrome type 4 with a B lymphocyte-intrinsic selective deficiency in Ig class-switch recombination. The Journal of Clinical Investigation, 112, 136–142.

Ikei, K., Zhu, Y., Revy, P., Morio, T., Mirzutani, S., Fischer, A., Nonoyama, S. & Durandy, A. (2005) Analysis of class switch recombination and somatic hypermutation in patients affected with autosomal dominant hyper-IgM syndrome type 2. Clinical Immunology, 115, 277–285.

Ikei, K., Shimadzu, M., Kubota, M., Morio, T., Matsunaga, T., Park, Y.D., Yoshioka, A. & Nonoyama, S. (2006) Female hyper IgM syndrome type 1 with a chromosomal translocation disrupting CD40LG. Bone Marrow Transplantation, 37, 12614–12619.

Inwald, D.P., McDowall, A., Peters, M.J., Callard, R.E. & Klein, N.J. (2003) CD40 is constitutively expressed on platelets and provides a novel mechanism for platelet activation. Circulation Research, 92, 1041–1048.

Jain, A., Ma, C.A., Liu, S., Brown, M., Cohen, J. & Strober, W. (2001) Specific missense mutations in NEMO result in hyper-IgM syndrome with hypohydrotic ectodermal dysplasia. Nature Immunology, 2, 223–228.

Jesus, A.A., Duarte, A.J. & Oliveira, J.B. (2008) Autoimmunity in hyper-IgM syndrome. Journal of Clinical Immunology, 28 Suppl. 1, S62–S66.

Kikut, A., Ito, M., Mochizuki, K., Akahata, M., Nemoto, K., Sano, H. & Ohto, H. (2006) Nonmyeloablative stem cell transplantation for nonmalignant diseases in children with severe organ dysfunction. Bone Marrow Transplantation, 38, 665–669.

Korthauer, U., Graf, D., Mages, H.W., Briere, F., Padayachee, M., Malcolm, S., Ugazio, A.G., Notarangelo, L.D., Levinsky, R.J. & Kroczek, R.A. (1993) Defective expression of T-cell CD40 ligand causes X-linked immunodeficiency with hyper-IgM. Nature, 361, 539–541.

Kotnis, A., Du, L., Liu, C., Popov, S.W. & Pan-Hammarstrom, Q. (2009) Non-homologous end joining in class switch recombination: the beginning of the end. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 364, 653–665.

Kracker, S., Bergmann, Y., Demuth, L., Frappart, P.O., Hildebrand, G., Christine, R., Wang, Z.Q., Sterling, K., Digweed, M. & Radbruch, A. (2005) Nibrin functions in Ig class-switch recombination. Proceedings of the National Academy of Sciences of the United States of America, 102, 1584–1589.

Larson, E.D., Cummings, W.J., Bednarski, D.W. & Maizels, N. (2005) MRE11/RAD50 cleaves DNA in the AID/UNG-dependent pathway of immunoglobulin gene diversification. Molecular Cell, 20, 367–375.

LeBien, T.W. (1998) B-cell lymphopenia in mouse and man. Current Opinion in Immunology, 10, 188–195.

Lee, W.I., Torgerson, T.R., Schumacher, M.J., Yel, L., Zhu, Q. & Ochs, H.D. (2005) Molecular analysis of a large cohort of patients with the hyper immunoglobulin M (IgM) syndrome. Blood, 105, 1881–1890.
Leiva, L.E., Junprasert, J., Hollenbaugh, D. & Sorensen, R.U. (1998) Central nervous system toxoplasmosis with an increased proportion of circulating gamma delta T cells in a patient with hyper-IgM syndrome. *Journal of Clinical Immunology*, 18, 283–290.

Levy, J., Espanol-Boren, T., Thomas, C., Fischer, A., Tovo, P., Bordigoni, P., Resnick, I., Fasth, A., Baer, M., Gomez, L., Sanders, E.A., Tabone, M.D., Plantaz, D., Etizioni, A., Monofo, V., Abinun, M., Hammarstrom, L., Abrahamsen, T., Jones, A., Finn, A., Klemola, T., Devries, E., Sanal, O., Peitsch, M.C. & Notarangelo, L.D. (1997) Clinical spectrum of X-linked hyper-IgM syndrome. *The Journal of Pediatrics*, 131, 47–54.

Lougaris, V., Badalato, R., Ferrari, S. & Plebani, A. (2005) Hyper immunoglobulin M syndrome due to CD40 deficiency: clinical, molecular, and immunological features. *Immunological Reviews*, 203, 48–66.

MacLennan, I.C. (1994) Germinal centers. Annual Review of Immunology, 12, 117–139.

Malhotra, R.K. & Li, W. (2008) Poorly differentiated gastroenteropancreatic neuroendocrine carcinoma associated with X-linked hyperimmunoglobulin M syndrome. *Archives of Pathology and Laboratory Medicine*, 132, 847–850.

Mazzolari, E., Lanzi, G., Forino, C., Lanfranchi, A., Aksu, G., Ozturk, C., Giliani, S., Notarangelo, L.D. & Kutzkuculer, N. (2007) First report of successful stem cell transplantation in a child with CD40 deficiency. *Bone Marrow Transplantation*, 40, 279–281.

McLauchlin, J., Amar, C.F., Pedraza-Diaz, S., Mieli-Vergani, G., Hadzic, N. & Davies, E.G. (2003) Polymerase chain reaction-based diagnosis of infection with Cryptosporidium in children with primary immunodeficiencies. *The Pediatric Infectious Disease Journal*, 22, 329–335.

de Medeiros, B.C., de Medeiros, C.R., Werner, B., Loddo, G., Pasquini, R. & Bleggi-Torres, L.F. (2001) Disseminated toxoplasmosis after bone marrow transplantation: report of 9 cases. *Transplant Infectious Disease*, 3, 24–28.

Minegishi, Y., Lavoie, A., Cunningham-Rundles, C., Bedard, P.M., Hebert, J., Cote, L., Dan, K., Sedlak, D., Buckley, R.H., Fischer, A., Durandy, A. & Conley, M.E. (2000) Mutations in activation-induced cytidine deaminase in patients with hyper IgM syndrome. *Clinical Immunology*, 97, 203–210.

Nilsen, H., Stamp, G., Andersen, S., Hrivnak, G., Krokan, H.E., Lindahl, T. & Barnes, D.E. (2003) Gene-targeted mice lacking the Ung uracil-DNA glycosylase develop B-cell lymphomas. *Oncogene*, 22, 5381–5386.

Noordzij, J.G., Wulffraat, N., Haraldsson, A., Meyts, I., van’t Veer, L., Warris, A., Hogervorst, F. & Weemaes, C. (2009) Ataxia-telangiectasia patients presenting with hyper-IgM syndrome. *Archives of Disease in Childhood*, 94, 448–449.

Orange, I.S., Levy, O. & Geha, R.S. (2005) Human disease resulting from gene mutations that interfere with appropriate nuclear factor-kappaB activation. *Immunological Reviews*, 203, 21–37.

Pai, S.Y., Levy, O., Jabara, H.H., Glickman, J.N., Stoler-Barak, L., Sachs, J., Nurko, S., Orange, I.S. & Geha, R.S. (2008) Allogeneic transplantation successfully corrects immune defects, but not susceptibility to colitis, in a patient with nuclear factor-kappaB essential modulator deficiency. *The Journal of Allergy and Clinical Immunology*, 122, 1113–1118.

Pan-Hammarstrom, Q., Dai, S., Zhao, Y., van Dijk-Hard, I.F., Gatti, R.A., Borresen-Dale, A.L. & Hammarstrom, L. (2003) ATM is not required in somatic hypermutation of VH, but is involved in the introduction of mutations in the switch mu region. *Journal of Immunology*, 170, 3707–3716.

Peron, S., Pan-Hammarstrom, Q., Imai, K., Du, L., Taubenheim, N., Sanal, O., Marodi, L., Bergelin-Besancon, A., Benkerroum, M., de Villartay, J.P., Fischer, A., Revy, P. & Durandy, A. (2007) A primary immunodeficiency characterized by defective immunoglobulin class switch recombination and impaired DNA repair. *The Journal of Experimental Medicine*, 204, 1207–1216.

Peron, S., Metin, A., Gardes, P., Alynakian, M.A., Sheridan, E., Katz, C.P., Fischer, A. & Durandy, A. (2008) Human PMS2 deficiency is associated with impaired immunoglobulin class switch recombination. *The Journal of Experimental Medicine*, 205, 2465–2472.

Poltoratsky, V., Goodman, M.F. & Scharff, M.D. (2000) Error-prone candidates vie for somatic mutation. *The Journal of Experimental Medicine*, 192, F27–F30.

Quartier, P., Bustamante, J., Sanal, O., Plebani, A., Debre, M., Deville, A., Litzman, J., Levy, J., Femand, J.P., Lane, P., Horneff, G., Aksu, G., Yalcin, I., Davies, G., Tezcan, I., Ersoy, F., Catalan, N., Imai, K., Fischer, A. & Durandy, A. (2004) Clinical, immunological and genetic analysis of 29 patients with autosomal recessive hyper-IgM syndrome due to Activation-Induced Cytidine Deaminase deficiency. *Clinical Immunology*, 110, 22–29.

Rada, C., Williams, G.T., Nilsen, H., Barnes, D.E., Lindahl, T. & Neuberger, M.S. (2002) Immunoglobulin isotype switching is inhibited and somatic hypermutation perturbed in UNG-deficient mice. *Current Biology*, 12, 1748–1755.

Rajewsky, K. (1996) Clonal selection and learning in the antibody system. *Nature*, 381, 751–758.

Reina-San-Martin, B., Chen, H.T., Nussenzeig, A. & Nussenzeig, M.C. (2004) ATM is required for efficient recombination between immunoglobulin switch regions. *The Journal of Experimental Medicine*, 200, 1103–1110.

Revy, P., Muto, T., Levy, Y., Geissmann, F., Plebani, A., Sanal, O., Catalan, N., Forveille, M., Dufourcq-Labelouse, R., Gennery, A., Tezcan, I., Ersoy, F., Kayserili, H., Ugazio, A.G., Brousse, N., Muramatsu, M., Notarangelo, L.D., Kinoshta, K., Honjo, T., Fischer, A. & Durandy, A. (2000) Activation-induced cytide deaminase (AID) deficiency causes the autosomal recessive form of the Hyper-IgM syndrome (HIGM2). *Cell*, 102, 565–575.

Rodrigues, F., Davies, E.G., Harrison, P., McLauchlin, J., Karani, J., Portmann, B., Jones, A., Veys, P., Mieli-Vergani, G. & Hadzic, N. (2004) Liver disease in children with primary immunodeficiencies. *The Journal of Pediatrics*, 145, 333–339.

Sacco, M.G., Ungari, M., Cato, E.M., Villa, A., Strina, D., Notarangelo, L.D., Jonkers, J., Zecca, L., Facchetti, F. & Vezzoni, P. (2000) Lymphoid abnormalities in CD40 ligand transgenic mice suggest the need for tight regulation in gene therapy approaches to hyper immunoglobulin M (IgM) syndrome. *Cancer Gene Therapy*, 7, 1299–1306.

de Saint Basile, G., Tabone, M.D., Durandy, A., Phan, F., Fischer, A. & Le Diest, F. (1999) CD40 ligand expression deficiency in a female carrier of the X-linked hyper-IgM syndrome as a result of X chromosome lyonization. *European Journal of Immunology*, 29, 367–373.
Schrader, C.E., Edelmann, W., Kucherlapati, R. & Stavnezer, J. (1999) Reduced isotype switching in splenic B cells from mice deficient in mismatch repair enzymes. *The Journal of Experimental Medicine*, 190, 323–330.

Schrader, C.E., Guilkema, J.E., Linehan, E.K., Selsing, E. & Stavnezer, J. (2007) Activation-induced cytidine deaminase-dependent DNA breaks in class switch recombination occur during G1 phase of the cell cycle and depend upon mismatch repair. *Journal of Immunology*, 179, 6064–6071.

Schuster, A., pfelstedt-Sylla, E., Pusch, C.M., Zrenner, E. & Thirkill, C.E. (2005) Autoimmune retinopathy with RPE hypersensitivity and ‘negative ERG’ in X-linked hyper-IgM syndrome. *Ocular Immunology and Inflammation*, 13, 235–243.

Sekine, H., Ferreira, R.C., Pan-Hammarstrom, Q., Graham, R.R., Seyama, K., Kobayashi, R., Hasle, H., Apter, A.J., Rutledge, J.C., Rosen, I., Shah, I. (2005) Hyper IgM syndrome with tuberculous osteomyelitis.

Simon, G., Simon, G., Erdos, M. & Marodi, L. (2005) Invasive Cryp-

Solanilla, A., Dechanet, J., El, A.A., Dupouy, M., Godard, F., Chabrol, J., Lee, A.T., Zhao, N., Tompkins, J.D., Altshuler, D., Gregersen, W., Iwahori, A., Elliott, M.K., Offer, S., Skon, C., Du, L., Novitzke, M., Darra, F. & Plebani, A. (2008) Different clinical and immuno-

Stavnezer, J., Guikema, J.E. & Schrader, C.E. (2008) Mechanism and regulation of class switch recombination. *Annual Review of Immunology*, 26, 261–292.

Subauste, C.S., Wessendorp, M., Sorensen, R.U. & Leiva, L.E. (1999) CD40-CD40 ligand interaction is central to cell-mediated immu-

Schrader, C.E., Edelmann, W., Kucherlapati, R. & Stavnezer, J. (1999) Reduced isotype switching in splenic B cells from mice deficient in mismatch repair enzymes. *The Journal of Experimental Medicine*, 190, 323–330.

Schrader, C.E., Guilkema, J.E., Linehan, E.K., Selsing, E. & Stavnezer, J. (2007) Activation-induced cytidine deaminase-dependent DNA breaks in class switch recombination occur during G1 phase of the cell cycle and depend upon mismatch repair. *Journal of Immunology*, 179, 6064–6071.

Schuster, A., pfelstedt-Sylla, E., Pusch, C.M., Zrenner, E. & Thirkill, C.E. (2005) Autoimmune retinopathy with RPE hypersensitivity and ‘negative ERG’ in X-linked hyper-IgM syndrome. *Ocular Immunology and Inflammation*, 13, 235–243.

Sekine, H., Ferreira, R.C., Pan-Hammarstrom, Q., Graham, R.R., Seyama, K., Kobayashi, R., Hasle, H., Apter, A.J., Rutledge, J.C., Rosen, I., Shah, I. (2005) Hyper IgM syndrome with tuberculous osteomyelitis.

Simon, G., Simon, G., Erdos, M. & Marodi, L. (2005) Invasive Cryp-

Solanilla, A., Dechanet, J., El, A.A., Dupouy, M., Godard, F., Chabrol, J., Lee, A.T., Zhao, N., Tompkins, J.D., Altshuler, D., Gregersen, W., Iwahori, A., Elliott, M.K., Offer, S., Skon, C., Du, L., Novitzke, M., Darra, F. & Plebani, A. (2008) Different clinical and immuno-

Stavnezer, J., Guikema, J.E. & Schrader, C.E. (2008) Mechanism and regulation of class switch recombination. *Annual Review of Immunology*, 26, 261–292.

Subauste, C.S., Wessendorp, M., Sorensen, R.U. & Leiva, L.E. (1999) CD40-CD40 ligand interaction is central to cell-mediated immu-

Ta, V.T., Nagaoka, H., Catalan, N., Durandy, A., Fischer, A., Imai, K., Nonoyama, S., Tashiro, J., Ikegawa, M., Ito, S., Kinoshiba, K., Muramatsu, M. & Honjo, T. (2003) AID mutant analyses indicate requirement for class-switch-specific cofactors. *Nature Immunology*, 4, 843–848.

Taalman, R.D., Hustinx, T.W., Weemaes, C.M., Seemanova, E., Schmidt, A., Passarge, E. & Scheres, J.M. (1989) Further delineation of the Nijmegen breakage syndrome. *American Journal of Medical Genetics*, 32, 425–431.

Tahara, N., Kai, H., Niyama, H., Mori, T., Sugi, Y., Takayama, N., Yasukawa, H., Numaguchi, Y., Matsui, H., Okumura, K. & Imaizumi, T. (2004) Repeated gene transfer of naked prostacyclin synthase plasmid into skeletal muscles attenuates monocrotaline-induced pulmonary hypertension and prolongs survival in rats. *Human Gene Therapy*, 15, 1270–1278.

Taylor, A.M., Groom, A. & Byrd, P.J. (2004) Ataxia-telangiectasia-like disorder (ATLD)-its clinical presentation and molecular basis. *DNA Repair (Amst)*, 3, 1219–1225.

Tono, C., Takahashi, Y., Terui, K., Sasaki, S., Kamiio, T., Tandai, S., Sato, T., Kudo, K., Toki, T., Tachibana, N., Yoshioka, T., Nakahata, T., Morio, T., Nishikomori, R. & Ito, E. (2007) Correction of immunodeficiency associated with NEMO mutation by umbilical cord blood transplantation using a reduced-intensity conditioning regimen. *Bone Marrow Transplantation*, 39, 801–804.

de Villartay, J.P. (2009) V(D)J recombination deficiencies. *Advances in Experimental Medicine and Biology*, 650, 46–58.

Vinuesa, C.G., Tange, S.G., Moser, B. & Mackay, C.R. (2005) Follicular B helper T cells in antibody responses and autoimmunity. *Nature Reviews. Immunology*, 5, 853–865.

Warnatz, K., Salzer, U., Rizzi, M., Fischer, B., Gutenberger, S., Bohm, J., Kienzler, A.K., Pan-Hammarstrom, Q., Hammarstrom, L., Rakhanov, M., Schlesier, M., Grimbacher, B., Peter, H.H. & Eibel, H. (2009) B-cell activating factor receptor deficiency is associated with an adult-onset antibody deficiency syndrome in humans. *Proceedings of the National Academy of Sciences of the United States of America,*, 137, 81–85.

Weigel, H.M., de, V.E., Regez, R.M., Henrichs, J.H., Ten Velden, J.I., Friesen, P.H. & van der Meer, J.T. (1997) Cotrimoxazole is effective as primary prophylaxis for toxoplasmosic encephalitis in HIV-infected patients: a case control study. *Scandinavian Journal of Infectious Diseases*, 29, 499–502.

Winklstein, J.A., Marino, M.C., Ochs, H., Fuleihan, R., Scholl, P.R., Geha, R., Stiehm, E.R. & Conley, M.E. (2003) The X-linked hyper-IgM syndrome. clinical and immunologic features of 79 patients. *Medicine (Baltimore)*, 82, 373–384.

Wood, P., Stanworth, S., Burton, J., Jones, A., Peckham, D.G., Frissen, P.H. & van der Meer, J.T. (1997) Cotrimoxazole is effective as primary prophylaxis for toxoplasmosic encephalitis in HIV-infected patients: a case control study. *Scandinavian Journal of Infectious Diseases*, 29, 499–502.

Yong, P.F., Post, F.A., Gilmour, K.C., Grosse-Kreul, D., King, A., Easterbrook, P. & Ibrahim, M.A. (2008a) Cerebral toxoplasmosis in a middle-aged man as first presentation of primary immunodeficiency due to a hypomorphic mutation in the CD40 ligand gene. *Journal of Clinical Pathology*, 61, 1220–1222.

Yong, P.F., Tarzi, M., Chua, I., Grimbacher, B. & Chee, R. (2008b) Common variable immunodeficiency: an update on etiology and management. *Immunology and Allergy Clinics of North America*, 28, 367–386.
Zhu, Y., Nonoyama, S., Morio, T., Muramatsu, M., Honjo, T. & Mizutani, S. (2003) Type two hyper-IgM syndrome caused by mutation in activation-induced cytidine deaminase. *Journal of Medical and Dental Sciences*, 50, 41–46.

Zirkin, H.J., Levy, J. & Katchko, L. (1996) Small cell undifferentiated carcinoma of the colon associated with hepatocellular carcinoma in an immunodeficient patient. *Human Pathology*, 27, 992–996.

Zonana, J., Elder, M.E., Schneider, L.C., Orlow, S.J., Moss, C., Golabi, M., Shapira, S.K., Farndon, P.A., Wara, D.W., Emmal, S.A. & Ferguson, B.M. (2000) A novel X-linked disorder of immune deficiency and hypohidrotic ectodermal dysplasia is allelic to incontinentia pigmenti and due to mutations in IKK-gamma (NEMO). *American Journal of Human Genetics*, 67, 1555–1562.