

Omenn syndrome: a lack of tolerance on the background of deficient lymphocyte development and maturation

Manfred Hönig^{a,b} and Klaus Schwarz^a

Purpose of review

Omenn syndrome is a rare inherited primary immunodeficiency characterized by severe combined immunodeficiency in combination with autoimmune features leading to squamous erythrodermia, alopecia, lymphadenopathy, hepatosplenomegaly, and intractable diarrhea. Recent advances include characterizing the genetic basis of the syndrome and integrating the genetic defects into knowledge of tolerance induction.

Recent findings

Molecular studies have shown that besides the well-known hypomorphic recombination activating gene defects, mutations in the nonhomologous end-joining factor Artemis and in the interleukin-7 receptor α chain can contribute to the development of Omenn syndrome. These investigations established that Omenn syndrome is a genetically heterogeneous condition. Whereas the majority of patients with Omenn syndrome bear hypomorphic gene alterations, some exhibit somatic mosaicism due to second-site reversions of null alleles. A lack of central tolerance contributes to the autoimmune pathology of the disease.

Summary

Research has begun to clarify the genetic defects and the conditions underlying the lack of tolerance enforcement that predispose to Omenn syndrome. Clinical applications of this research include the identification of the causative genetic defect in the majority of Omenn syndrome cases and the use of this genetic knowledge in family and prenatal analyses and in difficult differential autoimmune diagnoses.

Keywords

immunodeficiency, lymphocyte development, Omenn syndrome, tolerance, V(D)J recombination

Abbreviations

AIRE	autoimmune regulator element
DNA-PKcs	DNA-dependent protein kinase catalytic subunit
Foxp3	forkhead box P3 transcriptional regulator
IL7RA	interleukin-7 receptor α chain
NHEJ	nonhomologous end joining
RAG	recombination activating gene
SCID	severe combined immunodeficiency
TCR	T cell receptor
Treg	regulatory T cell
TSLP	thymic stromal lymphopoietin
V(D)J	variable, (diversity), joining elements

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Introduction: clinical features and therapy

More than 40 years ago Gilbert Omenn [1] described a rare clinical entity that he called reticuloendotheliosis with eosinophilia characterizing the microscopic lymph node morphology of the disease. Originating from this report the term 'Omenn syndrome' was coined in the medical literature for the clinical description of infants with severe combined immunodeficiency (SCID) in combination with failure to thrive, squamous erythrodermia, alopecia, lymphadenopathy, hepatosplenomegaly, and intractable diarrhea. The presentation is reminiscent of, but must be clearly distinguished from, the clinical picture resulting from maternofetal transfusion in newborn infants with SCID and from graft-versus-host reactions in patients who have undergone allogeneic stem cell transplantation.

Even though the laboratory and molecular basis for Omenn syndrome has become much clearer in recent years, the diagnosis is still made on a clinical basis. Typical Omenn syndrome laboratory findings are high T cell counts, low or absent B cells (in the majority of patients), eosinophilia, and hypogammaglobulinemia, but elevated serum levels for IgE [2]. Many reports attributed the pathology of Omenn syndrome to autoregulatory T cells, which are abnormal in several respects: the T cells are predominantly activated (CD25⁺, HLA-DR⁺) memory (CD45RO⁺) cells; their response to mitogens is reduced [2,3]; and importantly, their T cell receptor (TCR) repertoire is skewed with oligoclonal expansions [4–6]. These T cells are found in infiltrations of skin, gut, and other organs [7]. The thymus is absent or dysmorphic as expected in patients with SCID. The microscopic lymph node architecture is altered with interdigitating reticular cells in the paracortical region, scattered

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^aInstitute for Clinical Transfusion Medicine and Immunogenetics, Department of Transfusion Medicine, Germany and ^bChildren's Hospital, The University Hospital Ulm, Ulm, Germany

Correspondence to Klaus Schwarz, MD, Institute for Clinical Transfusion Medicine and Immunogenetics, Ulm, Department of Transfusion Medicine, The University Hospital Ulm, Helmholtzstraße 10, D-89081 Ulm, Germany
Tel: +49 731 150 642; fax: +49 731 150 575; e-mail: klaus.schwarz@uni-ulm.de

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lymphocytes, large numbers of eosinophils, and absent follicles and germinal centers [7–9].

At presentation patients are often seriously sick and threatened not only by infections due to the immunodeficiency but also by organ damage due to autoimmune reactions. Therefore, rapid diagnosis and therapy are crucial.

Therapy for Omenn syndrome follows two intentions: immunosuppression to stop autoaggressive organ damage and establishment of long-term immunologic recovery to avoid serious infections. Hematopoietic stem cell transplantation is the only curative therapy currently available. Mortality, however, is higher than in other SCID variants [2,10,11] and can often be directly or indirectly attributed to problems associated with pretransplant or posttransplant autoimmunity. To eliminate autoaggressive T cells and to allow engraftment, conditioning chemotherapy and specific anti-T cell agents are considered necessary before and after stem cell transplantation [11,12]. Nevertheless, graft failure coincides with recurrence of erythema and autoimmune symptoms in some patients [12].

V(D)J recombination and lymphocyte development

Variable, (diversity), joining elements [V(D)J] recombination is the somatic recombination in precursor lymphocytes by which the highly diverse immunoglobulin and TCR genes are generated from subgenic V(D)J [13–15]. This process is initiated by the recombination activating complex (composed of the RAG-1, RAG-2, and HMG1 proteins). The heteromultimeric, nucleolytic RAG complex cleaves the DNA at the border between signal sequences and their adjacent coding segments and seals the coding ends by hairpin structures. Subsequently, the factors of the general DNA repair nonhomologous end-joining (NHEJ) pathway reopen the hairpins and join the coding and signal ends [16,17]. NHEJ components involved are the DNA-binding Ku proteins (Ku70 and Ku86), the DNA-dependent protein kinase catalytic subunit (DNA-PKcs), the structure-specific nuclease Artemis, and the ligase complex XRCC4/ligase IV. The role of the recently identified NHEJ factor Cernunnos/XLF (XRCC4-like factor) in this process remains to be clarified [18,19].

In humans a severe/null defect in either RAG-1/RAG-2, Artemis, or ligase IV leads to the SCID phenotype [20–24] due to impaired V(D)J recombination activity, the lack of the generation of immunoglobulin and TCR genes, and a block of development of lymphocyte precursors [25,26]. Except for RAG deficiencies, cells of these patients also display an increased radiosensitivity, due to a general deficiency in NHEJ.

Genetic basis

Recent research has begun to clarify the variable genetic defects that predispose to Omenn syndrome.

Recombination activating gene-associated mutations

At first glance, the clinical and laboratory features of Omenn syndrome with the presence of lymphocytes do not qualify the RAG proteins as first choice for a putative defect in Omenn syndrome. The observation that the T⁺B⁺SCID and the Omenn syndrome phenotype coexist in patients in the same family, however, was an important hint that paved the way for RAG analyses [27]. By sequencing the coding regions of RAG-1/RAG-2 in patients with Omenn syndrome, Villa and coworkers [28] identified germline mutations in these genes. Large surveys of RAG deficiencies firmly established that, in contrast to SCID patients bearing RAG null alleles, every patient with Omenn syndrome carries at least one RAG allele that potentially codes for a hypomorphic RAG mutant, the majority of those being missense mutations [29,30]. Functional and biochemical analyses of these mutants [28] revealed that the proteins resulting from missense mutations had reduced but measurable V(D)J recombination capacity. This allowed for the conclusion that in patients with Omenn syndrome, limited V(D)J recombination events occur and support the development of a highly restricted oligoclonal TCR repertoire, with the restriction already being detectable in the thymus [6]. A similar mechanism may also be true for B-lymphocyte development, because patients with Omenn syndrome produce immunoglobulin E (hyper IgE), although in the majority of cases in the absence of detectable peripheral B lymphocytes.

Given this knowledge we are still left with the conundrum that members of the same family may present with either SCID or Omenn syndrome. Corneo *et al.* [30] hypothesized that an additional factor such as a particular antigen (autoantigen or exoantigen) that presents in some patients with Omenn syndrome but not in those with SCID is required for the switch from T⁺B⁺SCID to Omenn syndrome. Alternatively, the influence of modifier genes may be blamed for the different phenotypes.

Two recent reports may shed light on this puzzle [31,32^{••}]. Dalal and colleagues [31] followed an Arabian pedigree with three patients bearing a homozygous RAG-2 missense mutation (Gly35Val) [14]. The mutation had been observed earlier in another patient and had been scored a bona-fide null mutant on an in-vitro fibroblast-based functional assay [33]. One of the patients who all exhibited initially a T⁺B⁺SCID phenotype developed typical Omenn syndrome subsequent to infection with parainfluenza 3 virus. An analysis of the V γ -TCR repertoire of the patient with

Omenn syndrome showed oligoclonality not only during the Omenn syndrome phase of the disease but previously when the patient presented with T⁻B⁻SCID. (Of note, the other T⁻B⁻SCID pedigree members also had an oligoclonal V γ -TCR repertoire at presentation.) In light of the functional assay mentioned above, we might speculate that either the fibroblast-based assay was not sensitive enough to pick up low-level V(D)J recombination activity of the RAG-2 Gly35Val mutant, or under appropriate stimulation(s) this mutant may work albeit very inefficiently in lymphocyte precursors. The study of Dalal *et al.* [31] did not clarify whether T-cell expansion in the Omenn syndrome phase was due to parainfluenza 3 virus-driven proliferation of virus-specific but potentially cross-reactive T cells or to expanding autoreactive T cells as a bystander effect. In addition, the authors did not exclude somatic reversions in the generated T cells. Nevertheless, the study underscores that under the influence of an exoantigen, T⁻B⁻SCID may evolve into Omenn syndrome in a single patient, thus at least in this case excluding modifier gene influence on the phenotype.

In another report Wada *et al.* [32^{••}] described a patient with Omenn syndrome with an unusual RAG-1 deficiency. In DNA from his granulocytes, the child was homozygous for a single base C deletion (delC) after nucleotide 2113 of the RAG-1 gene, which results in a frameshift and presumably codes for a nonfunctional protein. His healthy, consanguineous parents were both heterozygous for this mutation. In contrast, the child's lymphocyte fraction harbored in addition to the delC mutation at least six different second-site mutations. All of them exhibit mismatch mutations, restore the RAG-1 reading frame, and (although not tested *in vitro*) may exhibit residual V(D)J recombination activity. Given that the second-site mutations were detected only in T cells but not in granulocytes, monocytes, or natural killer cells, this suggests that the reversion events occurred in committed T cell progenitors. So far reported with single-event reversions, somatic revertant mosaicism is a rare phenomenon that may play a more important role in the phenotypic variance of primary immunodeficiencies [34,35]. Due to the demonstration of somatic mosaicism with multiple reversion events, the study of Wada *et al.* provides significant implications not only for the pathogenesis of Omenn syndrome.

Defects in nonhomologous end-joining factors

During V(D)J recombination, NHEJ factors execute the downstream processing of RAG-generated DNA double-strand breaks. A complete deficiency of one of these factors leads to radiosensitivity in human and murine (knockout) models. Given that in 1993 Cavazzana-Calvo and coworkers [27] had already described a patient with Omenn syndrome with radiosensitivity, it is surprising

that so far only two patients with Omenn syndrome in one family with a defect in a NHEJ factor, i.e. Artemis, have been characterized at the molecular level [36^{••}]. Artemis associated with and phosphorylated by the DNA-PKcs possesses overhang endonucleolytic and DNA hairpin-opening activities *in vitro*. Without the activation by DNA-PKcs, Artemis only exhibits its intrinsic DNA single-strand specific 5' to 3' exonuclease activity *in vitro* [37].

In analogy to patients with Omenn syndrome who have RAG mutations, the Artemis-deficient patients with Omenn syndrome were compound heterozygotes with one null and one hypomorphic allele. The null mutation disables the catalytic site of Artemis, whereas the hypomorphic allele bears a translation initiation codon substitution (AUG to ACG), lowering the efficiency of Artemis protein synthesis and in the end V(D)J recombination efficiency [36^{••}]. Except for the radiosensitivity of dermal fibroblasts, the Artemis-deficient patients with Omenn syndrome were phenotypically and in clinical and laboratory features indistinguishable from patients with Omenn syndrome with affected RAG genes.

Whether mutations in the NHEJ factors ligase IV and Cernunnos/XLF can cause Omenn syndrome remains to be elucidated.

Omenn syndrome with defects of non-V(D)J recombination factors

Several investigators [38[•]] have identified 50–80% of patients with Omenn syndrome either without RAG [39] or without RAG and Artemis mutations. In some of these patients with clinically defined, typical Omenn syndrome, oligoclonal B cells were present in peripheral blood [38[•]].

Investigating a patient with Omenn syndrome with B cells and memory CD45R0⁺ T cells but low numbers of recent thymic emigrants, a mutation in the gene (*IL7RA*) coding for the interleukin-7R α chain was discovered [40[•]]. The *IL7RA* mutation (Cys118Tyr) is permissive for protein expression, as was shown on lymphoblastoid cell lines of T⁻B⁺ natural killer-positive SCID patients [40[•]]. In analogy to findings in RAG-deficient Omenn syndrome, these discrepant immunophenotypes may be accounted for by epigenetic or background genetic factors. The low number of recent thymic emigrants in the *IL7RA*-defective patient with Omenn syndrome suggested that the circulating T cells most likely were generated by peripheral expansion, reflecting the patient's general mycobacteriosis.

Some B-cell-positive patients with complete DiGeorge syndrome have oligoclonal T cells, which may generate an autoimmune response similar to Omenn syndrome,

including rash, lymphadenopathy with B-cell clustering, but no normal follicles [41].

Taken together, these investigations established that Omenn syndrome is a genetically heterogeneous condition, possibly with unidentified gene defects in patients with similar clinical signs and immunophenotypes.

Tolerance enforcement in Omenn syndrome

Central self-tolerance is enforced in the thymus by an active elimination of high-avidity self-reactive T-cell clones, a process called negative selection. How does this deletion happen? Recent animal research [42] has identified expression of nonthymic, nonlymphoid proteins within the thymus under the control of a single protein: AIRE (autoimmune regulator element). By allowing autoreactive thymocytes to encounter a broad spectrum of proteins from extrathymic organs, AIRE allows deletion of these cells and the maintenance of tolerance. The absence of AIRE leads to autoimmune polyendocrinopathy [43,44], proving that AIRE is the center of a 'filtering' system.

In a seminal paper, Cavadini *et al.* [45**] showed that in thymi of RAG-defective patients with T⁻B⁻SCID and Omenn syndrome, AIRE mRNA and protein levels were profoundly reduced. In consequence, a lack of expression of nonthymic, nonlymphoid proteins was observed. The few T-cell clones that develop in Omenn syndrome may thus escape negative selection, and autoreactive T cells are released into the periphery.

In animal models, AIRE expression in the thymus requires a cross-talk between the developing thymocytes and stromal cells. This process depends on a highly organized thymic microenvironment with an appropriate corticomedullary differentiation and normal representation of medullary epithelium [46]. In patients with SCID and Omenn syndrome, the typical compartmentalization of the thymus was missing, suggesting that defective thymocyte development due to the underlying genetic defect may interrupt the bilateral interaction between thymocytes and epithelial cells with the concomitant loss of AIRE expression [45**].

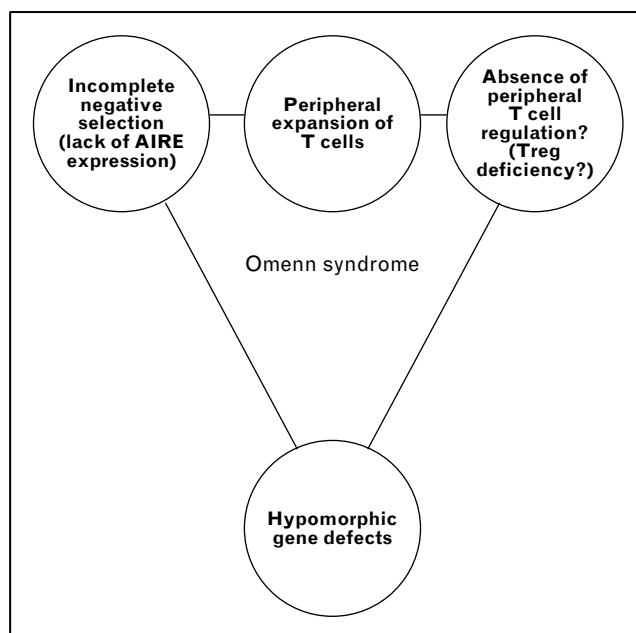
What about peripheral tolerance in Omenn syndrome? In addition to central tolerance, self-tolerance in the periphery is enforced by a CD4⁺CD25⁺ T cell population that expresses the transcriptional regulator forkhead box P3 transcriptional regulator (Foxp3). Upon encounter with self-antigens, these CD4⁺CD25⁺ T-regulatory cells (Tregs) actively suppress autoimmune reactions [47]. Human Hassall's corpuscles express thymic stromal lymphopoietin (TSLP). Human TSLP activates thymic CD11c-positive dendritic cells to express high levels of CD80 and CD86. These TSLP-conditioned dendritic

cells are then able to induce the proliferation and differentiation of CD4⁺CD8⁻CD25⁻ thymic T cells into CD4⁺CD25⁺Foxp3⁺ Treg cells [48]. Given that earlier reports [49,50] claimed the lack of Hassall's corpuscles in Omenn syndrome thymi, CD4⁺CD25⁺Foxp3⁺ Treg cells may well not develop in patients with Omenn syndrome, accounting for the lack of peripheral tolerance.

Conclusion

Genetic factors play a key role in the etiology of Omenn syndrome. Important findings to emerge recently include the observation that defects in different genes are responsible for the Omenn syndrome phenotype. In addition, it was shown that a disorganized thymic architecture, and in consequence a disabled thymic function due to inadequate cross-talk between developing thymocytes and stromal cells, interfere with tolerance induction. From these results, the following pathophysiologic picture of Omenn syndrome emerges (Fig. 1). The genetic defects underlying Omenn syndrome allow for the chance generation of few T cells with a highly restricted repertoire. Due to inadequate negative selection in the thymus, autoreactive T cell clones are released into the

Figure 1 Simplified model for the conditions leading to Omenn syndrome



On the basis of hypomorphic mutations in genes crucial for T cell development and maturation, some T cells develop in the thymus with incomplete negative selection of autoreactive cells. Immunologic triggers in the absence of peripheral regulation can contribute to an expansion of autoreactive T cell clones that lead to the phenotype of Omenn syndrome. AIRE, autoimmune regulator element; Treg, T regulatory cell.

peripheral T cell pool amongst non-self-destructive oligoclonal T cells. Oligoclonal expansion of the self-reactive T cells in the periphery may be due to homeostatic proliferation or supported by antigen (autoantigen, superantigen, or foreign antigen)-driven processes. As a consequence of the postulated lack of Treg cells in the periphery, no peripheral tolerance is enforced on the self-aggressive T cells, which then cause the immunopathology.

Using Omenn syndrome as a model for autoimmune diseases, important directions for future basic research will be to better characterize the genetic background of thus far undefined Omenn syndrome cases. Moreover, the loss of central and peripheral tolerance mechanisms in Omenn syndrome needs to be better understood. Finally, in Omenn syndrome the development of B cells, their tolerization, and their contribution to the immunopathology merit further investigation.

References and recommended reading

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- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 442).

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