

Omenn syndrome does not live by V(D)J recombination alone

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Purpose of review

During the past decade, easy access to sequence analyses has allowed us to increase our understanding of the pathogenesis of severe combined immunodeficiencies. Here, we describe the expanding clinical and immunological spectrum associated with Omenn syndrome phenotype. In particular, we review the cellular and molecular mechanisms involved in the pathophysiology of ‘classical’ Omenn syndrome due to the recombination activating gene (RAG) defects and of a new subgroup of Omenn-like disorders.

Recent findings

Different types of mutations are associated with the Omenn phenotype characterized by skin erythroderma, oligoclonal-activated T cells and elevated IgE in the absence of circulating B cells. Extensive studies conducted over the last few years have allowed the definition of the ‘classical form’ of Omenn syndrome due to hypomorphic defects in genes involved in V(D)J recombination, mainly RAG genes, and ‘Omenn-like’ features associated with mutations in genes involved in the maturation steps of lymphoid cells other than V(D)J recombination. Moreover, an increasing number of diseases other than those due to V(D)J recombination defects develop Omenn signs.

Summary

Impaired but not abolished V(D)J recombination process leads to the generation of a few T cells which expand in the periphery, infiltrate target organs such as skin and gut, resulting in severe erythroderma and colitis, both typical signs of Omenn syndrome. Extensive molecular studies now demonstrate that genes other than V(D)J molecules have a role in the pathogenesis of this disease, supporting the evidence that ‘Omenn’ defines an inflammatory condition associated with various genetic defects.

Keywords

inflammation, Omenn syndrome, severe combined immunodeficiency, V(D)J recombination

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Introduction

Omenn syndrome [Mendelian Inheritance (OMIM 603554)] is an autosomal recessive form characterized by the presence of fatal generalized severe erythroderma, lymphadenopathy, eosinophilia and profound immunodeficiency. It was first described by Omenn in 1965 [1] in a patient with a pedigree of familial reticuloendotheliosis with eosinophilia. Because of the coexistence of severe immunodeficiency with important allergic inflammation, Omenn syndrome was considered for a long time an enigmatic disease whose molecular bases have only been revealed in the last decade. Genetic studies have demonstrated that the Omenn phenotype, although usually dependent on mutations in recombination activating gene (RAG) genes, can also be caused by different genotypes [2–7]; however, despite extensive molecular analyses, some Omenn syndrome cases still remain molecularly unsolved [8]. Here, we review recent data that may help explain the molecular heterogeneity of Omenn

syndrome. In particular, we will distinguish the ‘classical’ Omenn form due to defects in molecules involved in the Variable (V) diversity (D) and joining (J) recombination process from ‘Omenn-like’ cases or ‘atypical’ severe combined immunodeficiencies (SCIDs) which associate with Omenn clinical signs.

‘Full blown’ Omenn syndrome: clinical and immunological features

Omenn syndrome is characterized by symptoms of SCID arising during the first years of life with erythroderma, hepatosplenomegaly, lymphadenopathy and alopecia. Generalized oedema and metabolic alterations are frequently observed as a result of a high loss of proteins. Omenn syndrome patients suffer from pneumonitis caused by *Pneumocystis jiroveci* or viruses such as cytomegalovirus or parainfluenza. Laboratory findings of Omenn syndrome display normal or elevated T-cell counts with a restricted, oligoclonal T-cell receptor (TCR) repertoire.

Maternal T-cell engraftment has to be excluded. These T cells are autologous and show an activated phenotype skewing toward Th2 cytokine production [9–11]. B cells are typically largely absent despite low or variable levels of immunoglobulin with the exception of IgE, which are usually markedly elevated [8]. Of note, plasma cells can be detected in lymphoid organs along with the presence of autoantibodies and elevated B cell-activating factor (BAFF) levels [12*,13*]. Autoimmune or dysreactive manifestations are common with infiltrations of activated T cells and result in profound tissue damage [9,14,15]. Absence of corticomedullary demarcation, lack of Hassall bodies along with dramatic reduction in the autoimmune regulator (AIRE) and tissue-restricted antigens (TRAs) have been reported [16–18]. On the basis of these findings, it has been hypothesized that alteration in central tolerance contributes to Omenn syndrome immunopathology. In parallel, we have recently demonstrated the impaired development and function of CD4⁺ CD25⁺ Foxp3⁺, T regulatory cells (Tregs) implying that both central and peripheral tolerance are compromised [19]. Finally, absence of invariant natural killer T (iNKT) cells (V α 24⁺ V β 11⁺) described by Notarangelo's group makes the pathogenesis more complex, suggesting altered lymphocyte homeostasis [20].

'Classical' Omenn syndrome is due to defects in V(D)J recombination

So far, four genes involved in V(D)J recombination have been found mutated in Omenn syndrome. The pathogenesis of this complex immunophenotype can easily be explained by a partial defect in the implementation of this process which is fundamental for a correct maturation of both B and T lymphocytes. In fact, the vast majority of Omenn syndrome are caused by mutations in genes which typically associate with SCID when their function is completely abolished, but allowing the generation of a residual number of T cells when their activity is partially maintained; this in turn results in the egression from the thymus of potentially autoreactive lymphoid clones.

In particular, hypomorphic mutations of the RAG1 and RAG2 account for more than 90% of Omenn syndrome cases [17,21–23]. Extensive biochemical and molecular studies have revealed that most RAG1 hypomorphic mutations map to domains involved in DNA binding, particularly in the region of recognition of recombination signal sequences (RSSs) flanking the coding regions of T and B cells rearranging genes, whereas others are located in the region interacting with RAG2 protein. Most of the mutations are amino acid changes, although also small in-frame deletions have been reported [22]. The presence of a single partially functioning allele is sufficient for an Omenn syndrome phenotype. This is shown by the coexistence of a null and a hypomorphic mutation in

Key points

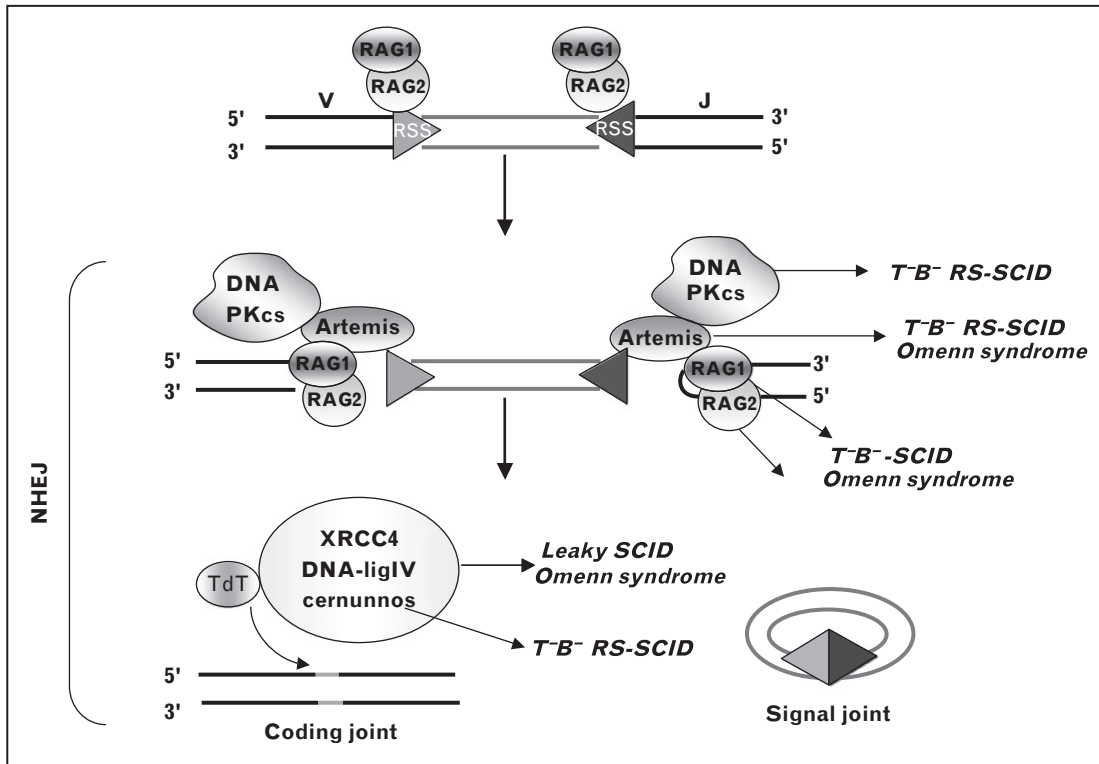
- 'Classical' Omenn syndrome, characterized by severe erythroderma, colitis, oligoclonal-activated T cells, hyperIgE and autoantibodies in the absence of circulating B cells, is mainly due to hypomorphic mutations in genes involved in the V(D)J recombination process.
- Omenn-like features can be observed in severe combined immunodeficiencies (SCIDs) occurring in genes involved in T-cell generation and in other diseases not related to SCID, such as cartilage hair hypoplasia (CHH) and CHARGE syndrome.
- Omenn syndrome could be considered a 'continuous' entity whose common feature is the presence of inflammatory conditions associated with severe infections.

several patients and is clearly demonstrated by a compound heterozygote patient with 'full-blown' Omenn syndrome associated with aniridia. In this patient, a maternal allele with two missense mutations in RAG1 gene (M453V; M1006V) and another, M502V, in RAG2 gene coexisted with a paternally derived allele, showing a deletion encompassing the region including the RAG1/RAG2/PAX6 genes [24].

Mutations in the RAG2 gene, although less frequent, have been reported in parallel [2,22,25]. Biochemical analysis of these mutations supports the structural model of a six-bladed β propeller with a C terminus containing a noncanonical plant homeodomain (PHD) finger. This region directly interacts with histones [26] and in particular with hypermethylated histone H3 at lysine 4, which is crucial for efficient V(D)J recombination [27*]. Point mutations in the PHD affect the subcellular localization and stability of Rag2, rendering them unable to reach their DNA target [25]. Furthermore, it is important to note that the mutation of a single critical residue within the RAG2-PHD finger, tryptophan 453, is associated with Omenn syndrome.

Initial analysis of a large cohort of SCID patients with 'classical' Omenn features allowed us to understand that Omenn syndrome is a heterogeneous disease as a small number of patients without mutations in RAG genes were reported by many authors [28,29]. It has been speculated that these patients might harbour defects in other molecules involved in the V(D)J recombination or nonhomologous end joining (NHEJ) pathway. This observation led to the identification of novel 'pieces' in the Omenn puzzle (Fig. 1).

Ege *et al.* [7] described, in a compound heterozygous patient with clinical and immunological features of Omenn syndrome, mutations in the DCLRE1C gene

Figure 1 Schematic representation of the main steps of the V(D)J recombination process

Rag proteins recognize recombination signal sequences (RSS), represented as triangles. Upon introduction of double strand breaks, recombination intermediates are further processed by Artemis in association with DNA-PK. Finally, upon the addition of nucleotides by TdT, coding and signal joints are formed by the cooperation of several proteins involved in the NHEJ pathway (Ligase IV, XRCC4 and Cernunnos). The arrows near the molecules indicate the disease caused when the genes are mutated. Modified with permission from [8].

encoding ARTEMIS, a nuclease, essential factor of V(D)J recombination and important component of the NHEJ–double-strand breaks (DSBs) pathway [30,31]. Interestingly, the paternal mutation consisted of an amino acid change (M1T) at the site of the protein translation initiation codon, resulting in a dramatic decrease of recombination efficiency, whereas the maternal allele carried a null mutation mapping within the active core. In agreement with the role of ARTEMIS in the NHEJ–DSB pathway, fibroblasts derived from this ARTEMIS-dependent Omenn syndrome case showed increased sensitivity to ionizing radiation (radiosensitive, RS-SCID) compared with fibroblasts derived from Omenn RAG-dependent. To our knowledge, M1T is so far the only mutation described in ARTEMIS associated with Omenn syndrome, with the exception of c.512C>G polymorphism generating an amino acid substitution P171R [32,33].

Subsequently to the identification of a hypomorphic mutation in the ARTEMIS gene in Omenn syndrome, a Ligase IV defect was described in a girl of 3 weeks of age with erythroderma, hepatosplenomegaly, generalized lymphadenopathy and diarrhoea [34]. This child carried

three heterozygous mutations: a C26T polymorphism and two changes (A845T and H282L) in amino acids located near the adenosine triphosphate (ATP)-binding site. It is important to consider that a variety of clinical presentations including leukaemia/lymphoma, bone marrow failure or developmental delay can also result from mutations in this gene [35]. Although not described yet, it could be possible that other players of the V(D)J and/or NHEJ pathways could have a role in the pathogenesis of Omenn syndrome by allowing the generation of residual T cells which reach the periphery and result in tissue infiltration.

Omenn-like features in severe combined immunodeficiency due to genes involved in the maturation steps of lymphoid cells other than V(D)J recombination

In our series, in about 10% of Omenn syndrome the responsible gene remains unknown. If the hypothesis that the unifying factor in the pathogenesis of ‘classical’ Omenn syndrome is the ability to perform a few V(D)J recombination events giving rise to autoreactive clones, then the possibility exists that other known severe

immunodeficiencies might show Omenn-like features. Generally speaking, most SCID show a complete differentiation block, but the possibility of the existence of partially functioning molecules cannot be a priori excluded. In addition, we have previously described patients with incomplete Omenn features due to RAG mutations [36]. This suggests that Omenn syndrome could be considered a 'continuous' entity whose common feature is the presence of inflammatory conditions associated with severe infections [8].

The first evidence that molecules other than those involved in V(D)J process might cause Omenn syndrome came from the observation of a missense (C118Y) mutation in the gene encoding the α chain of the interleukin 7 receptor (IL7R α) [6] (Table 1) [3–6,37,38]. Null mutations in IL7R α gene cause a severe block in T-cell development resulting in a T⁺B⁺NK⁺ form of SCID [39,40]. In the reported Omenn syndrome-like patient, hypomorphic mutations in this molecule allowed the survival of oligoclonal T cells. Interestingly, IL7R α Omenn form is characterized by the presence of circulating B cells, usually absent in the 'classical' Omenn syndrome due to RAG defects.

Later on, a novel missense mutation (R226H) in the gene coding the γ -common chain, a component shared by the receptors of IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21, whose null mutations cause the X-linked T⁺B⁺NK⁺ SCID, was reported in an X-SCID patient with Omenn-like manifestations [3]. However, this case of Omenn syndrome was different from the Rag-dependent Omenn syndrome form, as the generalized erythroderma-like lesion reflected the skin infiltration by CD56^{bright} CD16⁺ NK⁺ cells highly expressing inflammatory cytokines. A second case of amino acid change (Y125N) in the extracellular domain of the γ -common chain was reported in an infant with Omenn-like manifestations with elevated circulating B cells, erythematous scaly rash, mild hepatomegaly, eosinophilia and restricted T-cell repertoire [37].

The last variant of SCID associated with features of Omenn syndrome was reported by Roifman's group in

two unrelated patients with adenosine deaminase (ADA) deficiency presenting erythroderma, protracted diarrhoea and pneumonitis [4]. Both cases showed a low number of B cells and a very limited number of T cells. Because of the decreased activity of ADA (2 and 1% of controls for patients 1 and 2, respectively), the ADA gene was sequenced revealing two missense mutations (S291L and R156H) in patient 1 associated with residual ADA activity, while in the second case a stop mutation (R142X) and a four base deletion in exon 10 (955–959).

These observations further extend the molecular bases of Omenn syndrome and indicate that the Omenn phenotype can also reflect the impaired activity of some cytokines involved in the proliferation and survival of T cells.

Not only leaky severe combined immunodeficiency develops Omenn syndrome

Cartilage hair hypoplasia (CHH; OMIM 250250) is an autosomal recessive disorder caused by mutations in the ribonuclease mitochondrial RNA-processing (RMRP) gene encoding for the RNA component of the mitochondrial RNA-processing endonuclease [41]. Mutations in this gene lead to a spectrum of clinical manifestations in the skeletal system, hair, immune system, hematopoiesis and gut. The most common feature is short stature caused by metaphyseal chondrodysplasia, which in a minority of cases can be associated with a variable degree of immunodeficiency and occasionally to humoral defects [42,43]. Sequence analysis of the RMRP RNA gene revealed mutations in two patients showing skeletal changes typical of CHH associated with some Omenn-like clinical signs, such as infections, erythroderma, lymphadenopathy and hepato-splenomegaly [5]. Interestingly, both patients were lymphopenic with a restricted T-cell repertoire. The CD20⁺ B cell number was normal, although the serum level of immunoglobulins was low (IgG) or undetectable (IgA and IgM) in the first patient. These findings represent the first observation that the lack of normal RMRP RNA levels permits the expansion of a low number of T-cell clones which infiltrate the skin and

Table 1 Genes associated with Omenn-like manifestations

Gene	Function	Mutation	Clinical phenotype
IL7R α	Lymphocyte development	C118Y [6]	Omenn syndrome with presence of B cells
IL2R γ	Lymphocyte development	R226H [3] Y125N [37]	Omenn syndrome with NK ⁺ infiltrating skin Omenn syndrome with presence of B cells
CHD7	Chromatin remodelling	S230X R2098X [38]	Omenn syndrome with normal number of B cells and absence of erythroderma
ADA	Involved in purine metabolism needed for the turnover of nucleic acids in tissues	S291L and R156H R142X [4]	Omenn syndrome with limited number of T cells
RMRP	RNA primer formation Progression of the cell cycle at the end of mitosis	28-bp insertion between TATA box and transcription site/C4T 28-bp insertion between TATA box and transcription site/A240C [5]	Omenn syndrome with normal number of B cells

lymphoid organs. Consistently, Poliani *et al.* [18] have reported a lack of medullary differentiation in the thymus obtained from a CHH patient showing Omenn phenotype and carrying mutations in RMRP gene, a markedly reduced lymphoid cell component and a severe depletion of mature medullar thymic epithelial cells expressing autoimmune regulator element (AIRE), a key factor driving the expression of tissue restricted antigens. As a consequence of such a defect, a reduced number of recent thymic emigrants, in-vitro T-lymphocyte proliferation and enhanced apoptosis have been described in 18 patients with typical features of CHH and a variable degree of immunodeficiency [44].

The last syndrome associated with Omenn clinical signs is an inherited disease named CHARGE (coloboma, heart defect, atresia choanea, retarded growth, genital hyplasia, ear anomalies/deafness) first described in 1979 and showing some overlapping features with De George Syndrome explained by the deletion of chromosome 22 q11 [45,46]. Haploinsufficiency of the CHD7 gene has been described as a cause of CHARGE [47]. CHD7 is a member of the chromodomain helicase DNA-binding domain family of adenosine-5'-triphosphate-dependent chromatin remodelling enzymes.

The description of CHARGE cases associated with immunodeficiency is anecdotally reported [48,49]; however, no significant distinct correlation between genotype/phenotype has been identified so far [50].

More recently, Gennery *et al.* [38] have described two CHARGE patients presenting with clinical features consistent with Omenn syndrome, although, similarly to Omenn-like patients, B cells were present in normal number and the typical erythroderma caused by T cell and eosinophilic infiltration was absent. These findings highlight the coexistence of immune defects in patients harbouring defects in the CHD7 gene, increasing the spectrum of clinical manifestations.

Hematopoietic stem cell transplantation and innovative therapies in severe combined immunodeficiency

In the majority of SCID cases, the only curative option is hematopoietic stem cell transplantation (HSCT) to cure the immune defect. The outcome of this therapy depends on various factors including donor selection, the age of the recipient, use of conditioning regimen and the presence of preexisting infections [51].

The most controversial aspect of HSCT for SCID is whether myeloablative conditioning is necessary or not. The majority of SCID children should not need conditioning before HSCT to overcome graft resistance,

but it would be preferable in patients with SCID T-B-NK⁺ to facilitate engraftment. Complete ablation is required to eliminate autoreactive T cells in Omenn syndrome; however, the use of an intense conditioning regimen is one of the main causes of transplant-related mortality, particularly in patients suffering from organ damage [52]. For this reason, reduced intensity conditioning may be an alternative for patients with active infections at the time of transplantation [53], although it has been associated with less engraftment, rejection and graft versus host disease (GVHD) [54,55]. With the aim of avoiding adverse events due to the conditioning regimen and HSCT complications, innovative therapeutic approaches have been explored. In-utero bone marrow transplantation has been described in five SCID fetuses, one of which was affected by Omenn syndrome. Good results have been obtained in T-cell reconstitution, although Ig infusion is still needed [56]. Moreover, it has been demonstrated that gammaretroviral gene therapy trials may be a valid treatment option for SCID patients lacking a suitable bone marrow donor [57]. Successful correction of Rag2-deficient SCID has been reported in mice by gene transfer [58]. In parallel, Rag1 knockout mice have been used as a preclinical model for evaluating the efficacy of treating RAG-SCID with lentiviral SIN vector which leads to functional reconstitution T-cell compartment but low number of B cells [59,60]. Further studies are needed to improve the efficacy and safety of gene therapy approach in SCID forms due to RAG defects.

Conclusion

The analysis of rare patients carrying mutations in genes that impair but do not abolish T-cell development has been pivotal in improving our understanding of the wide spectrum of clinical signs associated with Omenn clinical features. The discovery that hypomorphic mutations in RAG genes can sustain the generation and subsequent expansion of a few T-cell clones has paved the way to the analysis of the impact of defects in other molecules involved in the generation and maintenance of T and B lymphocytes. Beyond the 'classical' Omenn syndrome forms mainly due to defects in V(D)J recombination, extensive molecular, biochemical and cellular studies have now provided substantial evidence that Omenn syndrome is more than a distinct form of combined immunodeficiency and is not caused by a defined genetic defect. Because of the presence of activated T cells with an oligoclonal repertoire, Omenn syndrome can be considered an aberrant inflammatory condition that can associate with various genetic disorders that impair but do not abrogate T-cell development. In the near future, the availability of exomes and whole-genome analysis will enable us to unmask the additional other genes involved in the pathogenesis of the complex disorders

associated with the Omenn phenotype, increasing the already large number of genes responsible for the generation of defective T cells.

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Conflicts of interest

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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