Omenn syndrome: Inflammation in leaky severe combined immunodeficiency

Anna Villa, MD,[a] Luigi D. Notarangelo, MD,[b] and Chaim M. Roifman, MD, FRCPC,[c] *Milan, Italy, Boston, Mass, and Toronto, Ontario, Canada*

Omenn syndrome (OS) was reported until recently as a distinct form (phenotype and genotype) of severe combined immunodeficiency (SCID). Similar to other patients with SCID, patients with OS present early in infancy with viral or fungal pneumonitis, chronic diarrhea, and failure to thrive. Unlike typical SCID, patients with OS have enlarged lymphoid tissue, severe erythroderma, increased IgE levels, and eosinophilia. The inflammation observed in these patients is believed to be triggered by clonally expanded T cells, which are predominantly of the T_H2 type. These abnormal T cells, in the absence of proper regulation by other components of the immune system, secrete a host of cytokines that promote autoimmune as well as allergic inflammation. The emergence of these T-cell clones occurs in patients with hypomorphic mutations in recombination activating gene 1 or 2, but not in patients with deleterious mutations in these enzymes which render them inactive. Recently, OS was also identified in a growing list of other leaky SCIDs with mutations in *RNA component of mitochondrial RNA processing endoribonuclease*, *adenosine deaminase*, *IL-2 receptor* γ, *IL-7 receptor* α, *ARTEMIS*, and *DNA ligase 4*. This new information revealed OS is a distinct inflammatory process that can be associated with genetically diverse leaky SCIDS. (J Allergy Clin Immunol 2008;122: 1082-6.)

Key words: *Immunodeficiency, Omenn syndrome, mutation, SCID*

Abbreviations used

ADA:	Adenosine deaminase
AIRE:	AutoImmune REgulator
CHARGE:	Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth and/or development, Genital and/or urinary abnormalities, and Ear abnormalities and deafness
CHD7:	Chromodomain helicase DNA binding protein 7
CHH:	Cartilage hair hypoplasia
DCLRE1C:	DNA cross-link repair 1C protein
LIG4:	DNA ligase 4
OS:	Omenn syndrome
RAG:	Recombination activating gene
RMRP:	RNA component of mitochondrial RNA processing endoribonuclease
SCID:	Severe combined immunodeficiency
Treg:	Regulatory T

The combination of clinical and laboratory features in infants who present with fatal generalized severe erythroderma, lymphadenopathy, eosinophilia, and profound immunodeficiency was first described by Gilbert Omenn in 1965.[1]

The peculiar coexistence of severe immunodeficiency with allergic inflammation intrigued many investigators and stimulated research aimed at understanding the molecular basis of this immunodeficiency. The poor outcome of these patients in the early days invited creative modalities of treatment that dramatically improved survival.[2,3] Genetic studies have revealed that the Omenn phenotype can be associated with many different genotypes[4-9]; however, the gene mutations causing Omenn syndrome (OS) remain elusive in nearly half of affected patients. These discoveries forced a shift in the manner by which we define, evaluate, study, and treat patients with this syndrome.

We attempt here to amass the current knowledge concerning the diagnosis, pathogenesis, and treatment of these patients.

CLINICAL PRESENTATION

Similar to severe combined immunodeficiency (SCID), patients with OS frequently present during the first year of life with chronic diarrhea, pneumonitis, and failure to thrive. Pneumonitis is typically caused by *Pneumocystis jiroveci* or viruses such as cytomegalovirus or parainfluenza.

Whereas typical patients with SCID present with paucity or absence of lymph nodes, patients with OS invariably have enlarged lymph nodes and frequently hepatosplenomegaly. In addition, they have generalized erythroderma, which may often cause alopecia and loss of eyebrows and eyelashes. Significant protein loss through the skin and the gut frequently leads to generalized edema and metabolic disturbances. Importantly, signs and symptoms of OS can evolve with time and may not appear simultaneously. Moreover, some patients present with some but not all signs consistent with OS. These patients are commonly referred to as affected with atypical Omenn syndrome.

From [a]the Istituto Tecnologie Biomediche, Consiglio Nazionale delle Ricerche, San Raffaele Telethon Institute for Gene Therapy, Milan; [b]the Division of Immunology, Children's Hospital Boston, Harvard Medical School; and [c]the Division of Immunology and Allergy, Hospital for Sick Children and the University of Toronto.

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

Received for publication September 3, 2008; accepted for publication September 10, 2008.

Available online November 7, 2008.

Reprint requests: Chaim M. Roifman MD, FRCPC, Division of Immunology/Allergy, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada. E-mail: chaim.roifman@sickkids.ca.

0091-6749/$34.00

doi:10.1016/j.jaci.2008.09.037

It has been recently recognized that OS may associate with syndromic disorders, in particular cartilage hair hypoplasia (CHH),[5] adenosine deaminase (ADA) deficiency,[9] DiGeorge syndrome,[10] Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth and/or development, Genital and/or urinary abnormalities, and Ear abnormalities and deafness (CHARGE) syndrome,[11] and ligase 4 deficiency[12] (see letter by Grunebaum et al[12]). It is therefore prudent to investigate patients with OS for these possibilities.

Patients with CHH typically have a very short stature (<3rd percentile) and short limbs. Other common manifestations that can aid in the diagnosis include hair abnormalities, anemia, and Hirschsprung disease. Metaphyseal dysplasia can be recognized by skeletal radiographs and may be present in infancy or become more obvious after the first years of life. However, growth retardation maybe variable with some individuals maintaining a normal growth pattern (see article by Kavadas et al[13]). Further, typical metaphyseal changes as originally described by McKusick[14] may be delayed or absent in rare cases.

The association of OS with hypocalcemia, congenital heart diseases, and micrognathia or neurologic manifestations should raise the suspicion of DiGeorge syndrome and ADA deficiency, respectively. Finally, the association of OS with microcephaly should alert to investigate defects of *DNA ligase 4*.

EVALUATION OF THYMUS, LYMPH NODES, AND SKIN OF OMENN SYNDROME

In patients with OS, the thymus is dysplastic with few remnant lymphoid cells.[5,10] Hematoxylin and eosin staining shows a marked depletion of thymocytes and a complete loss of corticomedullary architecture, with absence of Hassall corpuscles.[5,15] The thymic epithelium is arranged in small nests of cohesive spindle shaped cells, separated by fibrovascular septae. Immunohistochemical analysis consistently shows presence of residual $CD3^+$ thymocytes that express either CD4 or CD8 and are frequently located in the vestigial medullary areas.

Skin biopsies may be helpful in guiding to the diagnosis of OS. Typically, staining with hematoxylin and eosin shows acanthosis and parakeratosis. Dyskeratosis and spongiosis are seen in the Malpighian layer, and vacuolation is often observed in the basal layer. Inflammatory cells can be present in the epidermis but are typically more prominent in the dermis[16] and to a lesser degree at the dermal/epidermal junction.[5,17,18] Inflammatory infiltrates consist predominately of mononuclear cells and eosinophils that are identified by immunohistochemistry to contain $CD3^+$ T cells (mostly of the $CD4^+$ subset) and a small number of macrophages.

IMMUNOGIC EVALUATION

Unlike typical cases of SCID, patients with OS may pose a diagnostic challenge because they may have normal or high lymphocyte count. Even the assessment of lymphocyte markers by flow cytometry may be misleading, because the proportion and number of circulating $CD3^+$ T cells is frequently normal.[19,20] The number of $CD4^+$ and $CD8^+$ cells may vary and may occasionally be normal.[17] However, a low number of $CD8^+$ cells has been recently reported in patients with OS and associated CHH.[5,13] Importantly, and at variance with observations in healthy infants, T lymphocytes from patients with OS coexpress activation markers (CD45R0, HLA-DR). A similar pattern is also observed in SCID with maternal T-cell engraftment, whose clinical features may overlap with OS, and that represents an important differential diagnosis. Despite the presence of normal or increased number of circulating T cells, *in vitro* proliferative response to antigens is severely depressed.[13,19] Although *in vitro* proliferation to mitogens and anti-CD3 is variable, it is often reduced.[17,19]

A low to absent number of $CD19^+$ B cells is characteristic of OS associated with mutations in *recombination activating gene (RAG)–1*, *RAG2*, *DNA cross-link repair 1C protein (DCLRE1C)* (Artemis), or *DNA ligase 4*. However, B cells are normally present in other forms of OS.[4,6,20] Nevertheless, humoral immunity is invariably depressed, similar to most other types of SCID. However, IgE levels are frequently elevated.[21] $CD56^+$/$CD516^+$ natural killer cells are typically normal or even increased. Their absence should lead to investigate a possible association of OS with X-linked SCID[7] or with Janus kinase 3 deficiency.

One of the hallmarks of OS is the abnormal expansion of 1 or more T-cell clones in peripheral blood and in tissues.[3,13,17,18,22] Hypomorphic mutations in *RAG1*, *RAG2*, *DCLRE1C*, *LIG4, RNA component of mitochondrial RNA processing endoribonuclease (RMRP)*, and *ADA* genes hamper but do not completely abolish the function of the respective enzymes, resulting in a leaky defect[4,6,12,13,20] that allows for maturation of a very limited number of T cells in the thymus. Regardless of the methods used (spectratyping, quantitative PCR, or flow cytometry), assessment of the expression of various Vβ families reveals overrepresentation of a few T-cell clones and underrepresentation or complete absence of most other Vβ families,[4,6,18-20] but the underlying mechanisms of this phenomenon remain undefined. Interestingly, although there is extensive variability in the representation of T-cell clonotypes among patients with OS, a few Vβ families (Vβ 17, Vβ 14, Vβ 13, and Vβ 3) appear more frequently overexpanded than others even across different genotypes,[5,10,17,19] suggesting a common (auto)antigen-driven mechanism of T-cell expansion.

INFLAMMATION IN OMENN SYNDROME

Inflammation evolved as an adaptive response to restore homeostasis. If the acute inflammatory response fails to eliminate pathogens, the inflammation persists, and neutrophils are replaced with macrophages and T cells in the target tissue. Cytokines and vasoactive molecules secreted by these cells cause tissue damage by inducing cell apoptosis and necrosis. This process seems to be exaggerated in cases of OS, in part because elements and molecules responsible to keep inflammation in check, like regulatory T (Treg) cells[23-25] or IL-10, are missing.

The thymus of patients with Omenn syndrome is dysplastic, but it retains residual, albeit aberrant, thymus function, which allows for maturation and escape of some T-cell clones to the periphery. Clonally expanded T cells infiltrate tissues such as skin and lymph nodes, causing damage. It remains unclear whether these clones are driven and attracted by an antigenic load or superantigen stimulation, or propagated as a result of homeostatic proliferation in a lymphopenic environment. It is also possible that some of these mechanisms combine to trigger and maintain this unusual inflammatory process of OS.[26] It has been recently demonstrated that the expression of the transcription factor *AIRE* (AutoImmune REgulator) by medullary thymic epithelial cells is reduced in thymuses of patients with Omenn syndrome. *AIRE* regulates the

TABLE I. Conditions associated with OS

Genotype	Immunotype	Phenotype
RAG1/RAG2	$T^+ B^- NK^+$	SCID
Artemis	$T^+ B^- NK^+$	SCID
ADA	$T^+ B^- NK^+$	SCID, multisystem involvement
DNA ligase 4	$T^+ B^- NK^+$	SCID, microcephaly
RMRP	$T^+ B^+ NK^+$	CHH, SCID
IL-2 receptor γ	$T^+ B^+ NK^-$	SCID
IL-7 receptor α	$T^+ B^+ NK^+$	SCID
22q11	$T^+ B^+ NK^+$	DiGeorge syndrome
CHD7	$T^- B^+ NK^+$	CHARGE syndrome

NK, Natural killer.

transcription of a set of tissue-restricted antigens,[27] thus mediating negative selection of autoreactive T cells in the thymus.

Recently, mouse models that mimic OS have been developed.[28-30] First, a spontaneous mouse mutant (*rag1* R972Q) with partial Rag1 activity was found to have hepatosplenomegaly, eosinophilia, increased levels of IgE, and oligoclonal expansion of $CD4^+$ T cells, reminiscent of OS. Abolishing the IL-4 and IL-6 producing $CD4^+$ T cells prevented the increase in IgE, implicating a dysfunction of these T cells in the pathogenesis of OS-like features in the *rag1* hypomorphic mutant mice.[28] Further, *rag2* mutant mice (R229Q) with OS features lack thymic AIRE expression and show profound reduction in Forkhead box $P3^+$ Treg cells,[29,30] highlighting the critical role of immune dysregulation in OS. Together, these models support the hypothesis that impaired central tolerance, defective generation of Treg cells, and homeostatic proliferation of T lymphocytes may be involved in the pathogenesis of OS.

Allergic inflammation may also be involved in the pathophysiology of OS. Expanded T-cell clones from patients with OS were consistently found to be predominantly of T_H2 type,[14,31] and to secrete IL-4 and IL-13 (which promote immunoglobulin class-switching to IgE[23,24,32-34]) as well as IL-5 (which activates eosinophils) and IL-9 (which activates mast cells). Normally, T_H2 responses promote development of effector mechanisms that help clear parasites[35,36] but also turn on regulatory T cells that secrete IL-10 and thus downregulate inflammation and tissue damage. In OS, these mechanisms of T-cell regulation are lacking, allowing this process to continue in an uncontrolled manner.

In summary, inflammatory changes of OS appear to be sustained by a combination of mechanisms previously described in both autoimmune and allergic disorders. The process in OS appears particularly aggressive because fundamental regulatory elements are severely compromised as a consequence of the severe defects in T-cell development and function.

MOLECULAR BASIS OF OMENN SYNDROME

The vast majority of cases with Omenn syndrome were found so far to have hypomorphic mutations in *RAG1* or *RAG2* genes, which impair but do not abolish V(D)J recombination, the process required for T-cell and B-cell receptor rearrangement and expression[4] (Table I). Biochemical analysis of RAG1 and RAG2 mutants has contributed to further understanding of the role played by different domains of *RAG* genes, which were considered to be dispensable for the catalytic activities of the proteins. Frequently, *RAG1* mutations map to domains involved in the recognition of DNA binding, and in particular, regions that selectively recognize and bind the recombination signal sequences that flank the coding regions of T-cell and B-cell receptor gene elements.[4,37,38] Other mutations map to a domain involved in the recruitment of the RAG2 protein, resulting in a stable complex responsible for DNA bending and cleavage. Most of the mutations found in OS cause amino acid changes that impair RAG activity; however, deletions at the N-terminus of *RAG1* have been also reported. Biochemical analysis of these mutants has demonstrated use of a downstream translation initiation site, leading to a shorter protein that retains recombination activity but is predominantly retained in the cytoplasm.[39] Moreover, a number of *RAG2* gene mutations that cause SCID and OS support the structural model of a 6-bladed β-propeller with a C-terminal noncanonical plant homeodomain domain binding to core histones.[40] It has been recently demonstrated that the recognition of hypermethylated histone H3 at lysine 4 by RAG2 plant homeodomain promotes efficient V(D)J recombination *in vivo*.[41-43] OS was also identified in 1 patient with mutations in the *DLCRE1C* gene, which encodes for Artemis, which mediates hairpin coding end opening during the V(D)J recombination process.[6] The patient was a compound heterozygous, and 1 allele carried a hypomorphic mutation (M1T) that preserved residual V(D)J recombination activity (2.1% to 2.7%).

However, not all cases of Omenn syndrome harbor mutations in *RAG* or *DCLRE1C* genes. In some centers, mutations in these genes have been identified in fewer than 50% of patients with OS, clearly indicating that mutations in other genes can also cause OS. It has been recently discovered that mutations in the *RMRP* gene may cause OS.[5] Mutations in this gene have been previously shown to be associated with CHH.[43-46] CHH was first described by McKusick et al[14] as a metaphyseal chondrodysplasia in the Amish population. This short-limbed dwarfism may associate with cellular immunodeficiency and occasionally with humoral defects.[47,48] Rarely, patients with CHH have profound T-cell deficiency indistinguishable from SCID, leading to fatal varicella and necessitating bone marrow transplantation.[3,49]

RMRP is the only known nuclear gene that encodes the RNA component of the ribonuclease mitochondrial RNA processing gene.[50] The RNA encoded by this gene is not translated into protein but is associated with multiple proteins to form a complex capable of cleaving the primer RNA needed for mitochondrial DNA replication as well as for processing 5.8S ribosomal RNA,[51,52] and it has a role in regulation of the mitotic cell cycle and cell morphology.[52,53]

Recently, 2 unrelated patients with OS and ADA deficiency have been described.[9] ADA activity was markedly reduced but present (1% to 2% of normal values). Inherited defects in ADA activity result in the accumulation of phosphorylated derivatives of adenosine and 2'-deoxy-adenosine, which are toxic to T and B lymphocytes.[54] In patients with OS associated with ADA deficiency, the levels of deoxyadenosine metabolites in the red blood cells were only moderately increased, in keeping with the milder genetic aberrations.[55] Thus, it can be speculated that the mutations in the *ADA* gene observed in these patients were permissive for residual ADA and for the development of a limited number of T-cell clones that expanded and caused the systemic inflammation typical of OS.

Other patients with DiGeorge syndrome or with leaky SCID caused by hypomorphic mutations in the common γ-chain

(*IL-2 receptor* γ),[7] *IL-7 receptor* α,[8] *chromodomain helicase DNA binding protein 7 (CHD7)*,[11] or *DNA ligase 4*,[12] presented with OS. Overall, these observations support the concept that OS is not a distinct form of combined immunodeficiency and is not caused by a defined genetic defect. Rather, it is an aberrant inflammatory condition that can be associated with multiple genetic abnormalities that significantly reduce, but do not abrogate, T-cell development.

MANAGEMENT AND TREATMENT OF OS

If untreated, patients with OS have a dismal prognosis. Skin inflammation worsens with time, leading to severe barrier problems that facilitate life-threatening and overwhelming bacterial and fungal infections in already severely immunocompromised hosts. Until the late 1980s, OS was considered a fatal condition for a multitude of reasons, of which 2 were most prominent. First, recognition of an underlying severe immunodeficiency in these patients was frequently missed by primary caregivers because of the presence of circulating lymphocytes and the abundance of lymphoid tissues. Many cases were erroneously diagnosed as severe eczema and were treated with topical steroids. Referral to tertiary/quaternary centers was delayed, thus hampering the chances of cure. Second, hematopoietic cell transplantation from HLA-identical family donors, although highly successful in SCID, was challenging in OS. Survival rates in this condition were low mainly because of severe infections and failure to engraft donor cells.

The fate of OS began to turn when treatment with immunosuppressive drugs including prednisone and cyclosporin A was introduced.[3,16,18] This treatment proved effective in suppressing the expansion of T-cell clones and their infiltration in tissues and led to significant improvement of skin changes within 1 to 3 weeks of treatment. In addition, pharmacologic suppression of abnormal and activated autologous T-cell clones appears to facilitate engraftment of bone marrow cells from HLA-identical donors. In the absence of an HLA-identical family donor, T-cell–depleted bone marrow from a relative given with no previous conditioning was considered standard therapy for SCID. However, when applied to OS, this approach yielded poor results (<50% survival rate). In contrast, transplantation from matched unrelated donors after use of myeloablative regimens with busulfan and cyclophosphamide has dramatically improved the outcome of these patients, with reported survival rates >80%.[56-58] Although it is not clear which component of this protocol benefits patients with OS most, it is believed that conditioning combined with rapid engraftment of unmodified bone marrow is key to this success.

REFERENCES

1. Omenn GS. Familial reticulonendotheliosis with eosinophilia. N Engl J Med 1965; 273:427-32.
2. Barth RF, Vergara GE, Khurana SK, Lonman JT. Rapidly fatal familial histiocytosis associated with eosinophilia and primary immunological deficiency. Lancet 1972;1:503-6.
3. Wirt DP, Brooks EG, Vaidya S, Klimpel GR, Waldmann TA, Goldblum RM. Novel T-lymphocyte population in combined immunodeficiency with features of graft-versus-host-disease. N Engl J Med 1989;321:370-4.
4. Villa A, Santagata S, Bozzi F, Giliani S, Frattini A, Imberti L, et al. Partial V(D)J recombination activity leads to Omenn syndrome. Cell 1998;93:885-96.
5. Roifman CM, Gu Y, Cohen A. Mutations in the RNA component of RNase mitochondrial RNA processing might cause Omenn syndrome. J Allergy Clin Immunol 2006;117:897-903.
6. Ege M, Ma Y, Manfras B, Kalwak K, Lu H, Lieber MR, et al. Omenn syndrome due to Artemis mutations. Blood 2005;105:4179-86.
7. Shibata F, Toma T, Wada T, Inoue M, Tone Y, Ohta K, et al. Skin infiltration of CD56(bright) CD16(-) natural killer cells in a case of X-SCID with Omenn syndrome-like manifestations. Eur J Haematol 2007;79:81-5.
8. Giliani S, Bonfim C, de Saint Basile G, Lanzi G, Brousse N, Koliski A, et al. Omenn syndrome in an infant with IL7RA gene mutation. J Pediatr 2006;148: 272-4.
9. Roifman CM, Zhang J, Atkinson A, Grunebaum E, Mandel K. Adenosine deaminase deficiency can present with features of Omenn syndrome. J Allergy Clin Immunol 2008;121:1056-8.
10. Pirovano S, Mazzolari E, Pasic S, Albertini A, Notarangelo LD, Imberti L. Impaired thymic output and restricted T cell repertoire in two infants with immunodeficiency and early-onset generalized dermatitis. Immunol Lett 2003;86:93-7.
11. Gennery AR, Slatter MA, Rice J, Hoefsloot LH, Barge D, McLean-Tooke A, et al. Mutations in CHD7 in patients with CHARGE syndrome cause T^-B^+ natural killer cell $^+$ severe combined immune deficiency and may cause Omenn like syndrome. Clin Exp Immunol 2008;153:75-80.
12. Grunebaum E, Bates A, Roifman CM. Omenn syndrome is associated with mutations in DNA ligase IV. J Allergy Clin Immunol 2008; Oct 10 [epub ahead of print].
13. Kavadas FD, Giliani S, Gu Y, Mazzolari E, Bates A, Peoiani E, et al. Variability of clinical and laboratory features among patients with RMRP gene mutations. J Allergy Clin Immunol 2008; Sep 17 [epub ahead of print].
14. McKusick VA, Eldridge R, Hostetler JA, Ruangwit U, Egeland JA. Dwarfism in the Amish, II: cartilage hair hypoplasia. Bull John Hopkins Hosp 1965;116:231-72.
15. Roifman CM. Studies of patients' thymi aid in the discovery and characterization of immunodeficiency in humans. In: Koretzky G, Monroe J, editors. Immunological reviews. Singapore: Blackwell Munksguard; 2005. p. 143-55.
16. Scheimberg I, Hoeger PH, Harper JI, Lake B, Malone M. Omenn's syndrome: differential diagnosis in infants with erythroderma and immunodeficiency. Pediatr Dev Pathol 2001;4:237-45.
17. Melamed I, Cohen A, Roifman CM. Expansion of $CD3^+$ $CD4^-$ $CD8^-$ T cell population expressing high levels of IL-5 in Omenn's syndrome. Clin Exp Immunol 1994;95:14-21.
18. de Said-Basile G, Le Deist F, De Villartay J-P, Cerf-Bensussan N, Jounet O, Brousse N, et al. Restricted heterogeneity of T lymphocytes in combined immunodeficiency with hypereosinophilia (Omenn's syndrome). J Clin Invest 1991;87: 1352-9.
19. Zhang J, Quintal L, Atkinson A, Williams B, Grunebaum E, Roifman CM. Novel Rag 1 mutation in a case of severe combined immunodeficiency. Pediatrics 2005; 116:e445-9.
20. Villa A, Sobacchi C, Notarangelo LD, Bozzi F, Abinun M, Abrahamsen TG, et al. V(D)J recombination defects in lymphocytes due to RAG mutations: severe immunodeficiency with a spectrum of clinical presentations. Blood 2001;97:81-8.
21. Businco L, Di Fazio A, Ziruolo MG, Boner AL, Valletta EA, Ruco LP, et al. Clinical and immunological findings in four infants with Omenn's syndrome: a form of severe combined immunodeficiency with phenotypically normal T cells, elevated IgE, and eosinophilia. Clin Immunol Immunopathol 1987;44:123-33.
22. Signorini S, Imberti L, Pirovano S, Villa A, Facchetti F, Ungari M, et al. Intrathymic restriction and peripheral expansion of the T-cell repertoire in Omenn syndrome. Blood 1999;94:3468-78.
23. Larché M, Akdis CA, Valenta R. Immunological mechanisms of allergen-specific immunotherapy. Nat Rev Immunol 2006;6:761-71.
24. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy. J Allergy Clin Immunol 2007;119:780-91.
25. Hawrylowicz CM, O'Garra A. Potential role of interleukin-10 secreting regulatory T cells in allergy and asthma. Nat Rev Immunol 2007;7:220-30.
26. Krupica T Jr, Fry TJ, Mackall CL. Autoimmunity during lymphopenia: a two-hit model. Clin Immunol 2006;120:121-8.
27. Cavadini P, Vermi W, Facchetti F, Fontana S, Nagafuchi S, Mazzolari E, et al. AIRE deficiency in thymus of 2 patients with Omenn syndrome. J Clin Invest 2005;115:728-32.
28. Khiong K, Murakami M, Kitabayashi C, Ueda N, Sawa S, Sakamoto A, et al. Homeostatically proliferating CD4 T cells are involved in the pathogenesis of an Omenn syndrome murine model. J Clin Invest 2007;117:1270-81.
29. Marrella V, Poliani PL, Casati A, Rucci F, Frascoli L, Gougeon ML, et al. A hypomorphic R229Q Rag2 mouse mutant recapitulates human Omenn syndrome. J Clin Invest 2007;117:1260-9.
30. Marrella V, Poliani PL, Sobacchi C, Grassi F, Villa A. Of Omenn and mice. Trends Immunol 2008;29:133-40.
31. Schandene L, Ferster A, Mascart-Lemone F, Crusiaux A, Gerard C, Marchant A, et al. T helper 2 like cells and therapeutic effects of interferon-γ in combine immunodeficiency with hypereosinophilia (Omenn's syndrome. Eur J Immunol 1993;23:56-60.
32. Kay AB. Allergy and allergic diseases: first two parts. N Engl J Med 2001;344: 30-7.

33. Geha RS, Jabara HH, Brodeur SR. The regulation of immunoglobulin E class switch recombination. Nat Rev Immunol 2003;3:721-32.
34. Gould HJ, Sutton BJ. IgE in allergy and asthma today. Nat Rev Immunol 2008;8: 205-17.
35. Yazdanbakhsh M, Kremsner PG, van Ree R. Allergy, parasites and the hygiene hypothesis. Science 2002;296:490-4.
36. Fallon PG, Mangan NE. Suppression of TH2 type allergic reactions by helminth infection. Nat Rev Immunol 2007;7:220-30.
37. Corneo B, Moshous D, Güngör T, Wulffraat N, Philippet P, Le Deist FL, et al. Identical mutations in RAG1 or RAG2 genes leading to defective V(D)J recombinase activity can cause either T-B-severe combined immune deficiency or Omenn syndrome. Blood 2001;97:2772-6.
38. Sobacchi C, Marrella V, Rucci F, Vezzoni P, Villa A. RAG-dependent primary immunodeficiencies. Hum Mutat 2006;27:1174-84.
39. Santagata S, Gomez CA, Sobacchi C, Bozzi F, Abinun M, Pasic S, et al. N-terminal RAG1 frameshift mutations in Omenn's syndrome: internal methionine usage leads to partial V(D)J recombination activity and reveals a fundamental role in vivo for the N-terminal domains. Proc Natl Acad Sci U S A 2000;97:14572-7.
40. West KL, Singha NC, De Ioannes P, Lacomis L, Erdjument-Bromage H, Tempst P, et al. A direct interaction between the RAG2 C terminus and the core histones is required for efficient V(D)J recombination. Immunity 2005;23:203-12.
41. Liu Y, Subrahmanyam R, Chakraborty T, Sen R, Desiderio S. A plant homeodomain in RAG-2 that binds hypermethylated lysine 4 of histone H3 is necessary for efficient antigen-receptor-gene rearrangement. Immunity 2007;27:561-71.
42. Matthews AG, Kuo AJ, Ramón-Maiques S, Han S, Champagne KS, Ivanov D, et al. RAG2 PHD finger couples histone H3 lysine 4 trimethylation with V(D)J recombination. Nature 2007;450:1106-10.
43. Ramón-Maiques S, Kuo AJ, Carney D, Matthews AG, Oettinger MA, Gozani O, et al. The plant homeodomain finger of RAG2 recognizes histone H3 methylated at both lysine-4 and arginine-2. Proc Natl Acad Sci U S A 2007;104:18993-8.
44. Ridanpaa M, Sistonen P, Rockas S, Rimoin DL, Kakitie O, Kaitila I. Worldwide mutation spectrum in cartilage hair hypoplasia: ancient founder origin of the major 70A→G mutation of the untranslated. Eur J Hum Genet 2002;10:439-47.
45. Ridanpaa M, Jain P, McKusick VA, Francomano CA, Daitila I. The major mutation in the RMRP gene causing CHH among the Amish is the same as that found in most Finnish cases. Am J Med Genet 2003;121:81-3.
46. Nakashima E, Mabuchi A, Kashimada K, Onishi T, Zhang J, Obashi H, et al. RMRP mutations in Japanese patients with cartilage hair hypoplasia. Am J Med Genet 2003;123:253-6.
47. Makitie O, Kaitila I, Savilahti E. Susceptibility to infections and in vitro immune functions in cartilage hair hypoplasia. Eur J Pediatr 1998;157:816-20.
48. Makitie O, Kaitila I, Savilahti E. Deficiency of humoral immunity in cartilage hair hypoplasia. J Pediatr 2000;137:487-92.
49. Berthet F, Siegrist CA, Ozsahin H, Tuchscmid P, Eich G, Superti-Furga A, et al. Bone marrow transplantation in cartilage hair hypoplasia: correction of the immunodeficiency but not of the chondrodysplasia. Eur J Pediatr 1996;155:286-90.
50. Chang DD, Clayton DA. A mammalian mitochondrial RNA processing activity contains nucleus encoded. Science 1987;235:1178-84.
51. Clayton DA. A nuclear function for RNase MRP. Proc Natl Acad Sci U S A 1994; 91:4615-7.
52. Li X, Zaman S, Langdon Y, Zengel JM, Lindah L. Identification of a functional core in the RNA component of RNase MRP of budding yeasts. Nucleic Acids Res 2004;32:3703-11.
53. Gill T, Cai T, Aulds J, Wierzbicki S, Schmitt ME. RNase MRP cleaves the CLB2 mRNA to promote cell cycle progression: novel method of mRNA degradation. Mol Cell Biol 2004;24:945-53.
54. Cohen A, Hirschhorn R, Horowitz SD, Rubinstein A, Polmar SH, Hong R, et al. Deoxyadenosine triphosphates as a potentially toxic metabolite in adenosine deaminase deficiency. Proc Natl Acad Sci U S A 1978;75:472-6.
55. Santisteban I, Arredondo-Vega FX, Kelly S, Mary A, Fischer A, Hummell DS, et al. Novel splicing, missense and deletion mutation in seven adenosine deaminase deficient patients with late/delayed onset of combined immunodeficiency disease. J Clin Invest 1993;92:2291-302.
56. Mazzolari E, Moshous D, Forino C, De Martiis D, Offer C, Lanfranchi A, et al. Hematopoietic stem cell transplantation in Omenn syndrome: a single-center experience. Bone Marrow Transplant 2005;36:107-14.
57. Roifman CM, Somech R, Grunebaum E. Matched unrelated bone marrow transplant for T+ combined immunodeficiency. Bone Marrow Transplant 2008;41: 947-52.
58. Grunebaum E, Mazzolari E, Porta F, Dallera D, Atkinson A, Reid B, et al. Bone marrow transplantation for Severe combined immune deficiency. JAMA 2006; 295:508-18.