X-linked Severe Combined Immunodeficiency

FIFTH EDITION

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X-linked Severe Combined Immunodeficiency

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The science of immunology started as a case study. On May 15, 1796 Edward Jenner inoculated a neighbor’s son, James Phipps, with vaccinia (cowpox) virus. Six weeks later, on July 1, 1796, Jenner challenged the boy with live smallpox and found that he was protected against this infection. During its 208 year history the basic science of immunology has been closely related to clinical observations and has shed light on the pathogenesis of disease.

The study of immunology provides a rare opportunity in medicine to relate the findings of basic scientific investigations to clinical problems. The case histories in this book are chosen for two purposes: to illustrate in a clinical context essential points about the mechanisms of immunity; and to describe and explain some of the immunological problems often seen in the clinic. For this fifth edition, we have added five completely new cases that illustrate both recently discovered genetic immunodeficiencies and some more familiar and common diseases with interesting immunology. We have revised other cases to add newly acquired information about these diseases. Fundamental mechanisms of immunity are illustrated by cases of genetic defects in the immune system, immune complex diseases, immune mediated hypersensitivity reactions and autoimmune and alloimmune diseases. These cases describe real events from case histories, largely but not solely drawn from the records of the Boston Children’s Hospital and the Brigham and Women’s Hospital. Names, places, and time have been altered to obscure the identity of the patients described; all other details are faithfully reproduced. The cases are intended to help medical students and pre-medical students to learn and understand the importance of basic immunological mechanisms, and particularly to serve as a review aid; but we hope and believe they will be useful and interesting to any student of immunology.

Each case is presented in the same format. The case history is preceded by basic scientific facts that are needed to understand the case history. The case history is followed by a brief summary of the disease under study. Finally there are several questions and discussion points that highlight the lessons learned from the case. These are not intended to be a quiz but rather to shed further light on the details of the case.

The Garland Science website (www.garlandscience.com) now provides instructors who adopt Case Studies with a link to Garland Science Classwire, where the textbook art can be found in a downloadable, web-ready format, as well as in PowerPoint-ready format.

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Levin of St. Mary’s Hospital, London for supplying case materials. Our colleagues in the Immunology Division of the Children’s Hospital have provided invaluable service by extracting summaries of long and complicated case histories; we are particularly indebted to Drs. Lynda Schneider, Leonard Bacharier, Francisco Antonio Bonilla, Hans Oettgen, Jonathan Spergel, Rima Rachid, Scott Turvey, Jordan Orange, Emanuela Castigli, Andrew McGinnitie, Marybeth Son, Melissa Hazen, Douglas McDonald and John Lee, and to Lilit Garibyan, third year medical student at Harvard Medical School, in constructing several case histories. In the course of developing these cases, we have been indebted for expert and pedagogic advice to Fred Alt, Mark Anderson, John Atkinson, Hugh Auchincloss, Stephen Baird, Zuhair K. Ballas, Leslie Berg, Corrado Betterle, Kurt Bloch, Jean-Laurent Casanova, John J. Cohen, Michael I. Colston, Anthony DeFranco, Peter Densen, Ten Feizi, Alain Fischer, Christopher Goodnow, Edward Kaplan, George Miller, Luigi Notarangelo, Peter Parham, Jaakko Perheentupa, Jennifer Puck, Westley Reeves, Patrick Revy, Peter Schur, Anthony Segal, Lisa Steiner, Stuart Tangye, Cox Terhorst, Emil Unanue, André Veillette, Jan Vilcek, Mark Walport, Fenella Woznarowska, and John Zabriskie.

Eleanor Lawrence has spent many hours honing the prose as well as the content of the cases and we are grateful to her for this. We would also like to acknowledge the Garland Science team for their work on the fifth edition.

A note to the reader

The cases presented in this book have been ordered so that the main topics addressed in each case follow as far as possible the order in which these topics are presented in the seventh edition of Janeway's Immunobiology by Kenneth Murphy, Paul Travers, and Mark Walport. However, inevitably many of the early cases raise important issues that are not addressed until the later chapters of Immunobiology. To indicate which sections of Immunobiology contain material relevant to each case, we have listed on the first page of each case the topics covered in it. The color code follows the code used for the five main sections of Immunobiology: yellow for the introductory chapter and innate immunity, blue for the section on recognition of antigen, red for the development of lymphocytes, green for the adaptive immune response, purple for the response to infection and clinical topics, and orange for methods.

Dedication

This fifth edition is dedicated to Fred Rosen (1935-2005). Fred dedicated his career of more than 50 years to the investigation and care of patients with primary immunodeficiency disease. Above all, he loved to teach and he did so superbly, aided by an encyclopedic knowledge of immunology, an incisive intelligence, an incredible memory, and charisma combined with an aura of authority. Fred had an enormous influence on many generations of both basic and clinical immunologists. This book is his brainchild and his contribution to it will be sorely missed.
Case 1 Congenital Asplenia
Case 2 Chronic Granulomatous Disease
Case 3 Leukocyte Adhesion Deficiency
Case 4 Hereditary Angioneurotic Edema
Case 5 Factor I Deficiency
Case 6 Deficiency of the C8 Complement Component
Case 7 Hereditary Periodic Fever Syndromes
Case 8 Interleukin 1 Receptor-associated Kinase 4 Deficiency
Case 9 X-linked Hypohydrotic Ectodermal Dysplasia and Immunodeficiency
Case 10 X-linked Agammaglobulinemia
Case 11 X-linked Hyper IgM Syndrome
Case 12 Activation-induced Cytidine Deaminase (AID) Deficiency
Case 13 Common Variable Immunodeficiency
Case 14 X-linked Severe Combined Immunodeficiency
Case 15 Adenosine Deaminase Deficiency
Case 16 Omenn Syndrome
Case 17 MHC Class I Deficiency
Case 18 MHC Class II Deficiency
Case 19 Multiple Myeloma
Case 20 T-Cell Lymphoma
Case 21 Interferon-γ Receptor Deficiency
Case 22 Wiskott-Aldrich Syndrome
Case 23 X-linked Lymphoproliferative Syndrome
Case 24 Autoimmune Lymphoproliferative Syndrome (ALPS)
Case 25 Immune Dysregulation, Polyendocrinopathy, Enteropathy X-linked Disease
Case 26 Toxic Shock Syndrome
Case 27 Acute Infectious Mononucleosis
Case 28 Mixed Essential Cryoglobulinemia
Case 29 Rheumatic Fever
Case 30 Lepromatous Leprosy
Case 31 Acquired Immune Deficiency Syndrome (AIDS)
Case 32  Acute Systemic Anaphylaxis
Case 33  Allergic Asthma
Case 34  Atopic Dermatitis
Case 35  Drug-Induced Serum Sickness
Case 36  Celiac Disease
Case 37  Contact Sensitivity to Poison Ivy
Case 38  Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy
Case 39  Autoimmune Hemolytic Anemia
Case 40  Myasthenia Gravis
Case 41  Pemphigus Vulgaris
Case 42  Rheumatoid Arthritis
Case 43  Systemic Lupus Erythematosus
Case 44  Multiple Sclerosis
Case 45  Hemolytic Disease of the Newborn
Case 46  A Kidney Graft for Complications of Autoimmune Insulin-Dependent Diabetes Mellitus
Case 47  Graft-Versus-Host Disease
Without T cells, life cannot be sustained. In Case 10 we learned that an absence of B cells was compatible with a normal life as long as infusions of immunoglobulin G were maintained. When children are born without T cells, they appear normal for the first few weeks or months. Then they begin to acquire opportunistic infections and die while still in infancy. An absence of functional T cells causes severe combined immunodeficiency (SCID). It is called severe because it is fatal, and called combined because, in humans, B cells cannot function without help from T cells, so that even if the B cells are not directly affected by the defect, both humoral and cell-mediated immunity are lost. Unlike X-linked agammaglobulinemia, which results from a monogenic defect, SCID is a phenotype that can result from any one of several different genetic defects. The incidence of SCID is three times greater in males than in females and this male:female ratio of 3:1 is due to the fact that the most common form of SCID is X-linked. Approximately 55% of individuals with SCID have the X-linked form of the disease.

T-cell precursors migrate to the thymus to mature, at first from the yolk sac of the embryo, and subsequently from the fetal liver and bone marrow (Fig. 14.1). The rudimentary thymus is an epithelial anlage derived from the third and fourth pharyngeal pouches. By 6 weeks of human gestation, the invasion of precursor T cells, and of dendritic cells and macrophages, has transformed the gland into a central lymphoid organ (Fig. 14.2). T-cell precursors undergo rapid maturation in the thymus gland (Fig. 14.3), which becomes the site of the greatest mitotic activity in the developing fetus. By 20 weeks of gestation, mature T cells start to emigrate from the thymus to the peripheral lymphoid organs. In all common forms of SCID the thymus fails to become a central lymphoid organ. A small and dysplastic thymus, as revealed by biopsy, used to be the confirming diagnostic indicator of SCID. Now that the various gene defects that underlie SCID are better understood, confirmation usually involves a screen for the mutations in the genes likely to be involved.
Defects that result in SCID are classified into three general categories. One comprises those defects that impair lymphocyte survival; the prototype of this class is adenosine deaminase (ADA) deficiency (see Case 15), in which adenosine metabolites that are toxic to T cells and B cells accumulate.

Fig. 14.1  T-cell precursors migrate to the thymus to mature. T cells derive from bone marrow stem cells, whose progeny migrate from the bone marrow to the thymus (left panel), where the development of the T cell takes place. Mature T cells leave the thymus and recirculate from the bloodstream through peripheral lymphoid tissues (right panel) such as lymph nodes, spleen or Peyer’s patches, where they may encounter antigen.

Fig. 14.2  The cellular organization of the thymus. The thymus, which lies in the midline of the body above the heart, is made up from several lobules, each of which contains discrete cortical (outer) and medullary (central) regions. The cortex consists of immature thymocytes (dark blue), branched cortical epithelial cells (pale blue), with which the immature cortical thymocytes are closely associated, and scattered macrophages (yellow) involved in clearing apoptotic thymocytes. The medulla consists of mature thymocytes (dark blue), and medullary epithelial cells (orange), along with macrophages (yellow) and dendritic cells (yellow) of bone marrow origin. Hassall’s corpuscles found in the human thymus are probably also sites of cell destruction. The thymocytes in the outer cortical cell layer are proliferating immature cells, while the deeper cortical thymocytes are mainly cells undergoing thymic selection. The upper photograph shows the equivalent section of a human thymus, stained with hematoxylin and eosin. The lower photograph shows a SCID thymus. There is no corticomedullary differentiation, very low thymocytes and no Hassall’s corpuscles. Photographs courtesy of C.J. Howe (upper) and A. Perez-Atayde (lower).
A second category consists of defects in the machinery for somatic gene rearrangement that assembles the immunoglobulin and T-cell receptor genes during lymphocyte development. This category can be divided into lymphocyte-specific defects, namely defects in the RAG genes that encode the lymphocyte-specific recombinase (see Case 16), and defects in ubiquitously expressed DNA repair genes that are also involved in this recombination.

The third category consists of defects in cytokine-mediated signals for lymphocyte maturation and proliferation, and includes the X-linked form of SCID that is the subject of this case. The genetic defect responsible for the X-linked form of SCID has been mapped to the long arm of the X chromosome at Xq11. From this region the gene encoding the γ chain (CD132) of the interleukin-2 receptor (IL-2R) (Fig. 14.4) was cloned and was found to be mutated in X-linked SCID.

The case of Martin Causubon: without T cells life cannot be sustained.

Mr and Mrs Causubon had a normal daughter 3 years after they were married. Two years later they had a son and named him Martin. He weighed 3.5 kg at birth and seemed to be perfectly normal. At 3 months of age, Martin developed a runny nose and a persistent dry cough. One month later he had a middle ear infection (otitis media) and his pediatrician treated him with amoxicillin. At 5 months of age Martin had a recurrence of otitis media. His cough persisted and a radiological examination of his chest revealed the presence of pneumonia in both lungs. He was treated with another antibiotic, clarithromycin. Mrs Causubon noticed that Martin had thrush (Candida spp.) in his mouth (Fig. 14.5) and an angry red rash in the diaper area. He was not gaining weight; he had been in the 50th percentile for growth and development.

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weight at age 4 months but by 6 months he had fallen to the 15th percentile. His pediatrician had given him oral polio vaccine at ages 4 and 5 months and, at the same time, diphtheria–pertussis–tetanus (DPT) immunizations.

Martin’s pediatrician referred him to the Children’s Hospital for further studies. On admission to the hospital, he was fretful and had tachypnea (fast breathing). A red rash was noted in the diaper area as well as white flecks of thrush on his tongue and buccal mucosa. His tonsils were very small. He had a clear discharge from his nose, and cultures of his nasal fluid grew *Pseudomonas aeruginosa*. Coarse, harsh breath sounds were heard in both lungs. His liver was slightly enlarged.

Martin’s white blood count was 4800 cells \( \mu l^{-1} \) (normal 5000–10,000 cells \( \mu l^{-1} \)) and his absolute lymphocyte count was 760 cells \( \mu l^{-1} \) (normal 3000 lymphocytes \( \mu l^{-1} \)). None of his lymphocytes reacted with anti-CD3 and it was concluded that he had no T cells. Ninety-nine percent of his lymphocytes bound antibody against the B-cell molecule CD20 and 1% were natural killer (NK) cells reacting with anti-CD16. His serum contained IgG at a concentration of 30 mg dl–1, IgA at 27 mg dl–1, and IgM at 42 mg dl–1 (IgG levels are normally 400 mg dl–1; the IgA and IgM levels were at the low end of the normal range for Martin’s age). His blood mononuclear cells were completely unresponsive to phytohemagglutinin (PHA), concanavalin A (ConA), and pokeweed mitogen (PWM) (Fig. 14.6), as well as to specific antigens to which he had been previously exposed by immunization or infection—tetanus and diphtheria toxoids, and *Candida* antigen. His red cells contained normal amounts of adenosine deaminase and purine nucleoside phosphorylase. His B lymphocytes did not react with an antibody against the \( \gamma \) chain of the interleukin-2 receptor (IL-2R\( \gamma \)). Cultures of sputum for bacteria and viruses revealed the abundant presence of respiratory syncytial virus (RSV).

At this point a blood sample was obtained from Martin’s mother to examine her T cells for random inactivation of the X chromosome (a diagnostic test explained in Case 10). It was found that her T cells exhibited complete nonrandom X-chromosome inactivation. HLA typing showed that Martin’s sister had no matching HLA alleles. His parents, as expected, each shared one HLA haplotype with Martin.

Martin was treated with intravenous gamma globulin at a dose of 2 g kg–1 body weight and his serum IgG level was maintained at 600 mg dl–1 by subsequent IgG infusions. He was given aerosolized ribavirin to control his RSV infection and trimethoprim-sulfamethoxazole intravenously for prophylaxis against *Pneumocystis carinii*. Without any further preparation, Martin was given \( 500 \times 10^6 \) bone marrow cells from his mother. The bone marrow donation from his mother was depleted of mature T cells by treatment with a monoclonal antibody against T cells together with complement. After the transplant of the maternal bone marrow cells, Martin was given cyclosporin and prednisone to suppress any graft-versus-host disease. Sixty days after receiving the maternal bone marrow, Martin’s blood

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**Fig. 14.5** An infant with SCID suffering from *Candida albicans* in the mouth.

**Fig. 14.6** Polyclonal mitogens, many of plant origin, stimulate lymphocyte proliferation in tissue culture. Many of these mitogens are used to test the ability of lymphocytes in human peripheral blood to proliferate.

<table>
<thead>
<tr>
<th>Mitogen</th>
<th>Abbreviation</th>
<th>Source</th>
<th>Responding cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phytohemagglutinin</td>
<td>PHA</td>
<td><em>Phaseolus vulgaris</em> (Red kidney beans)</td>
<td>T cells (human)</td>
</tr>
<tr>
<td>Concanavalin A</td>
<td>ConA</td>
<td><em>Canavalia ensiformis</em> (Jack bean)</td>
<td>T cells</td>
</tr>
<tr>
<td>Pokeweed mitogen</td>
<td>PWM</td>
<td><em>Phytolacca americana</em> (pokeweed)</td>
<td>T and B cells</td>
</tr>
<tr>
<td>Lipopolysaccharide</td>
<td>LPS</td>
<td><em>Escherichia coli</em></td>
<td>B cells (mouse)</td>
</tr>
</tbody>
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contained 1000 maternal CD3+ T cellsμl–1, which responded to PHA. His immune system was slowly reconstituted over the ensuing 3 months.

Severe combined immunodeficiency, or SCID, presents the physician with a medical emergency. Unless there is a known family history, which provides the opportunity to take corrective therapeutic measures before the onset of infections, children with SCID come to medical attention only after they have been infected with a serious opportunistic infection. Because these infants die rapidly from such infections, even when treated adequately with antibiotics or antiviral agents, measures must be taken quickly to reconstitute their immune system. In most cases of SCID, the first symptoms are those of thrush in the mouth and diaper area. A persistent cough usually betrays infection with *Pneumocystis carinii*. The third most common symptom of SCID is intractable diarrhea, usually due to enteropathic coliform bacilli.

As previously noted, SCID has many known genetic causes. The autosomal recessive form of SCID is most commonly caused by mutations in the purine degradation enzyme adenosine deaminase (ADA) (see Case 15), and, more rarely, by mutations in another such enzyme, purine nucleoside phosphorylase (PNP). Defects in these enzymes lead to an accumulation of their nucleotide substrates that are highly toxic to developing T cells, and to a lesser extent to developing B cells. The X-linked form of SCID differs from these autosomal recessive forms in that males with this form of the disease have normal numbers of B cells, but they fail to function in the absence of T cells.

Other cases of autosomal recessive SCID resemble the phenotype of X-linked SCID and have been ascribed to defects in the protein Jak-3, which transduces the signal from many different interleukin receptors, and to defects in the α chain of the IL-7 receptor. SCID can also be caused by defects in the γ and ε components of the T-cell receptor or in other proteins that transduce signals from the T-cell receptor, such as the tyrosine kinase ZAP-70 and the calcium channel protein ORAI1, a CRAC channel (calcium-release activated calcium channel) protein (Fig. 14.7). In these cases B cells are normal and at least some T cells are present, but they fail to activate in an adaptive immune response, so that a combined immunodeficiency is seen.

Mice lacking IL-2 do not develop SCID, which argues against an important function for IL-2 signaling in thymocyte development. The discovery that mutations in the IL-2 receptor γ chain (IL-2Rγ) caused X-linked SCID in humans seemed inconsistent with this finding in mice. This led to a search for the γ chain in other interleukin receptors that might be more important for lymphocyte development. It was found that this chain also forms part of the receptors for IL-4, IL-7, IL-9, IL-15, and IL-21, and it was renamed the common gamma (γc) chain. Jak-3 transduces the signal from all these receptors by binding the γc chain. IL-7 is known to be involved in T-cell development because mutations in the IL-7Rα chain result in SCID.

Most infants with SCID can be rescued by a successful bone marrow transplant. Continued gamma-globulin therapy is usually necessary, but with this, and with successfully engrafted T cells, SCID infants survive to lead a relatively normal life. Gene therapy has also been tried successfully in some patients with X-linked SCID.
Fig. 14.7 Binding of antigen to the T-cell receptor initiates a series of biochemical changes within the T cell. It is thought that ligand binding to the T-cell receptor and the co-receptor CD4 (in this example) brings together CD4, the T-cell receptor:CD3 complex, and CD45, thus allowing the CD45 tyrosine phosphatase to remove inhibitory phosphate groups and thereby activate the Lck and Fyn tyrosine kinases associated with CD4 and the T-cell receptor:CD3 complex. One effect of tyrosine kinase activation is the activation of the cytosolic tyrosine kinase ZAP-70. Three important signaling pathways result. Two are initiated by the activation of phospholipase C-γ, which cleaves membrane phosphatidylinositol bisphosphate (PIP₂) to yield the second messengers diacylglycerol (DAG) and inositol trisphosphate (IP₃). DAG activates the serine–threonine protein kinase C, which results in the activation of the transcription factor NFkB. Meanwhile, IP₃ acts to release calcium ions (Ca²⁺) from intracellular stores. In addition, a calcium-specific ion channel (the CRAC channel ORAI1) is opened in the T-cell membrane to allow the influx of Ca²⁺ from extracellular sources. The elevated concentration of Ca²⁺ activates a cytoplasmic phosphatase, calcineurin, which activates one part of the transcription factor NFAT. However, full NFAT activity also requires a member of the AP-1 family of transcription factors; these are dimers of members of the Fos and Jun families of transcription regulators. A third signaling pathway involves activation of the G protein Ras, and the subsequent activation of a cascade of protein kinases, culminating in the activation of Fos and hence of the AP-1 transcription factors. The combination of the transcriptional regulators NFkB, NFAT, and AP-1 act on the T-cell chromosomes, initiating new gene transcription that results in the differentiation, proliferation, and effector actions of T cells.
Martin was suspected to have X-linked SCID because he had normal numbers of B cells and a total absence of T cells in his blood. The diagnosis was further confirmed on finding no IL-2R\(\gamma\) on the B cells in his blood. What final confirmation proved that he had X-linked SCID?

What is known about the normal functions of the receptors of which the \(\gamma\) chain forms a part, and how might these account for the phenotype of X-linked SCID?

Martin received a haploidentical transplant from his mother. What was the advantage and the disadvantage of using his mother as a donor as opposed to his father?

Why was it necessary to treat the maternal marrow donation with a monoclonal antibody against mature T cells and complement before the transplant?

Frequently infants with SCID get very ill with Pneumocystis carinii pneumonia after a successful transplant. For this reason they are treated prophylactically with antibiotics to get rid of any P. carinii organisms that may be present in their lungs. Why is this a wise therapeutic maneuver and how do you explain the worsening of pneumonia after a transplant?

We have already discussed the risks associated with giving polio virus vaccine to immunodeficient infants in the case of X-linked agammaglobulinemia (see Case 10). Martin would not have been able to clear the poliovirus he received until he was started on gamma-globulin therapy, but luckily a pathogenic variant did not arise during that time. Fortunately, Martin escaped being given any other live vaccines before he was diagnosed. In many countries (but not the United States) infants are universally given bacille Calmette–Guérin (BCG), an attenuated form of the tuberculosis bacillus, which provides partial protection against tuberculosis infection. BCG incites a cell-mediated immune response and after receiving it infants become tuberculin-positive, which means they show a delayed-type hypersensitivity response to a skin-prick with minute quantities of tuberculin. In the United States, the tuberculin test is considered so diagnostically valuable for the detection of new tuberculosis infections that BCG is not given. What do you think happens to infants with SCID after they are given BCG?

Before smallpox was eradicated in the world, vaccinia virus was routinely administered to all children. What happened to infants with SCID who were vaccinated with vaccinia virus?

What would be another strategy for reconstituting immune function in Martin?