

The Case of Baby Joe: Chronic Infections in an Infant

by

Kristen L.W. Walton

SPIRE Postdoctoral Fellowship Program
University of North Carolina—Chapel Hill



Part I—Background

At birth, Baby Joe appeared to be a normal, healthy baby boy. Both of his parents were in their late twenties and were healthy as well. At four weeks of age, Joe developed a middle-ear infection (called otitis media). He suffered from recurrent ear infections over the next three months, which required antibiotic treatment. Joe's pediatrician recommended placing tubes in Joe's ears to provide drainage of the fluid resulting from the infections. Cultures of the drainage fluid showed the presence of *Haemophilus influenzae*, a pathogen commonly found in ear infections in infants.

Starting at three months of age, Joe had four bouts of diarrhea which persisted for 3–5 days each time. Joe also was not gaining weight as rapidly as was expected during this time. This reduced weight gain and growth is referred to as “failure to thrive.”

When Joe was four months old, he developed another ear infection, this one more severe than the previous infections. Joe's parents took him to see his pediatrician, Dr. Smith. During the visit, Joe's mother mentioned that when changing the baby's diapers she had noticed an unusual, unpleasant odor to his urine. Dr. Smith ordered a culture of the fluid draining from Joe's ears. This time, the ear drainage fluid cultures revealed the presence of *Pseudomonas aeruginosa*, a bacterium which is not typically present in infant ear infections. In addition, Dr. Smith determined that Joe was also suffering from a bladder infection, which caused an unpleasant odor in his urine.

Questions

1. Given the information presented above, what do you suspect is the underlying cause or causes of Joe's health problems? Do you think the cause is genetic, environmental, or both?
2. How might these health problems cause Joe's slow weight gain (also called “failure to thrive”)?



Part II—Further Medical Testing

No lymph nodes could be palpated in Joe’s neck or armpits. His heart, lungs, liver, and spleen were of normal size. Suspecting a problem with Joe’s immune system, his physicians took a blood sample for a complete blood count (CBC). The CBC revealed the following results:

Cell Type	Joe’s Blood Count	Normal Range
Red blood cells	3.1×10^6 /microliter	2.7×10^6 – 4.9×10^6 /microliter
Platelets	180,000/microliter	150,000–440,000/microliter
Total white blood cells	3500/microliter	6000–17500/microliter
Neutrophils	2600/microliter	2000–7500/microliter
Eosinophils	170/microliter	0–400/microliter
Monocytes	300/microliter	200–800/microliter
Basophils	10/microliter	0–100/microliter
Lymphocytes	350/microliter	1000–4000/microliter
T cells	2% of total lymphocytes	60–80% of total lymphocytes
B cells	< 1% of total lymphocytes	15–25% of total lymphocytes
NK cells	90% of total lymphocytes	10–20% of total lymphocytes

Questions

1. Which types of cells are the most affected? Provide evidence to support your answer.
2. Based on this information, identify the stage in immune cell development (also called hematopoiesis) that appears to be defective in Baby Joe’s immune system.
3. Do you think that Joe will have normal levels of antibodies present in his blood? Why or why not?
4. How do these data help explain Baby Joe’s symptoms?
5. List molecular defects that could result in the immune system phenotype observed in Baby Joe. Be ready to explain your answers.

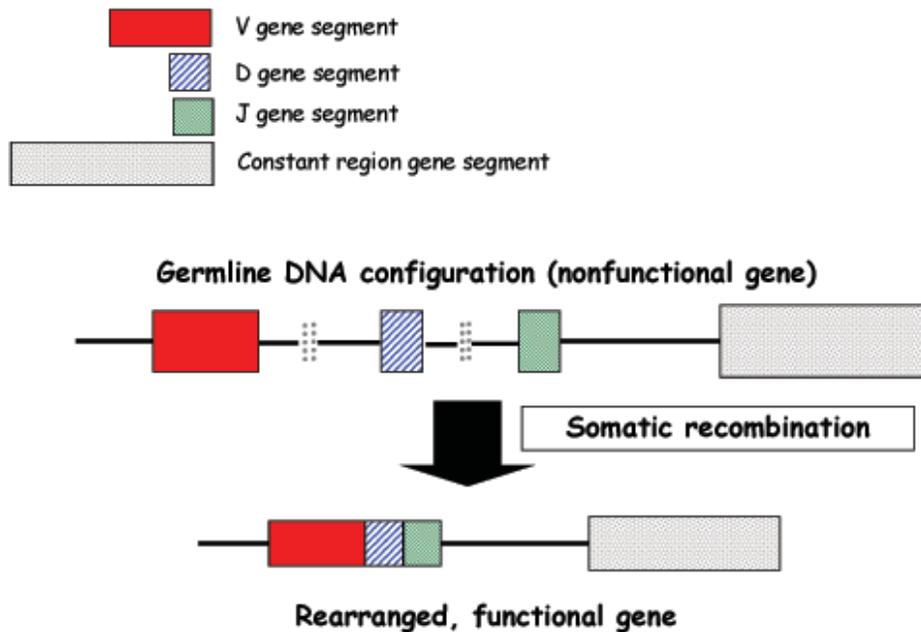
Part III—Immunoglobulin and τ Cell Receptor Genetics

Baby Joe's doctors diagnosed his condition as severe combined immunodeficiency (SCID). This disease is life-threatening; without treatment, it is usually fatal in childhood. SCID can be caused by several genetic mutations. Many of these mutations are in genes involved in somatic recombination.

Somatic recombination occurs in the immunoglobulin (Ig) genes in B cells and in the T cell receptor (TCR) genes in τ cells. In each individual developing B or τ cell, the DNA composing the Ig or TCR gene is physically cut and spliced to yield functional genes. Recombination does not occur in other types of somatic cells; this is a process unique to lymphocytes.

The Ig and TCR genes are actually composed of many gene segments which cannot be transcribed into a functional gene product. In B cells, the Ig gene segments are cut and spliced back together to make a functional Ig gene. This rearranged gene can then be transcribed and translated to result in a normal protein. In τ cells, the same process occurs in the TCR gene locus (and not in the Ig locus). Figure 1 illustrates the process of somatic recombination in an Ig heavy chain gene locus.

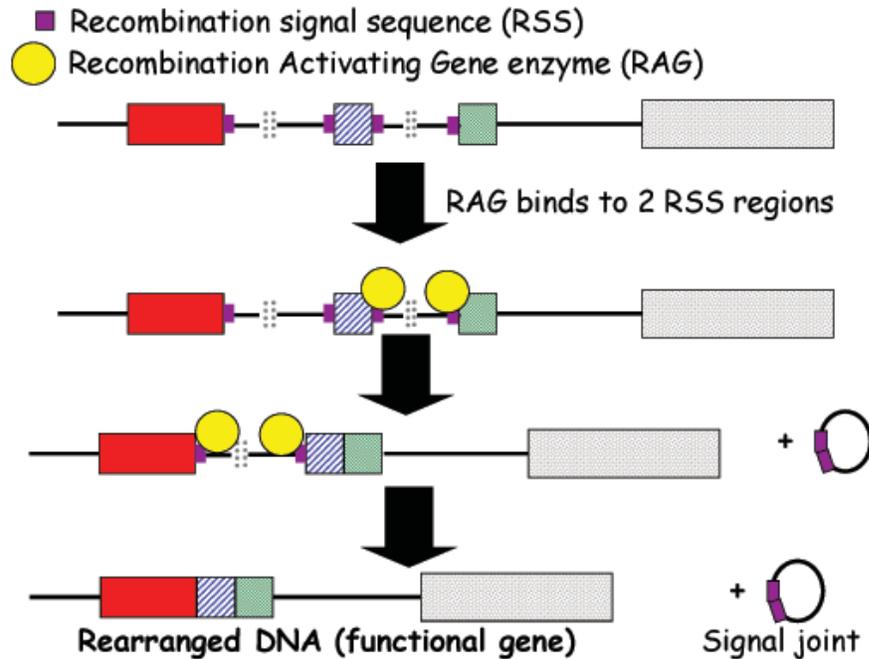
Figure 1



*Note: For simplicity, only one I segment, one D segment, and one J segment are shown. See Figure 3 for a more detailed view of the structure of the Ig heavy chain gene locus.

Somatic recombination depends on the expression of several enzymes involved in DNA splicing. One of these enzymes is called RAG (Recombination Activating Gene). The function of RAG is shown in Figure 2.

Figure 2

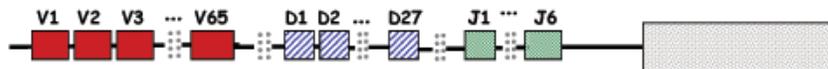


Figures 1 and 2 showed only one each of the V, D, and J segments for simplicity. Figure 3 below gives a more accurate representation of the Ig heavy chain gene locus:

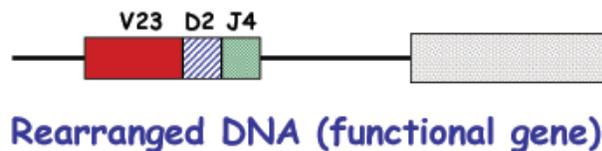
Figure 3

Somatic recombination

- There are multiple V, D, and J segments



- One of each type is randomly selected during somatic recombination



(To go through the somatic recombination process yourself, check out the following interactive animation by Dr. Malcolm Campbell at Davidson College:

<http://www.bio.davidson.edu/courses/immunology/Flash/somaticrecomb.html>)

A sample of Baby Joe's DNA was sent for sequence analysis, which revealed mutations in both copies of his RAG gene. The mutations in both genes were frameshift mutations, which resulted in a complete lack of expression of functional RAG protein.

Questions

1. Explain how a lack of RAG protein results in the phenotype observed in Baby Joe.
2. Some known mutations in RAG genes result in the expression of normal RAG proteins but at reduced levels. Somatic recombination usually occurs in patients with reduced RAG protein expression, but it occurs at a lower frequency than in people with normal RAG protein expression. Do you think that these patients would have B and T cell counts similar to those of Baby Joe? Why or why not?

Part III—Proteins Required for B and T Cell Development

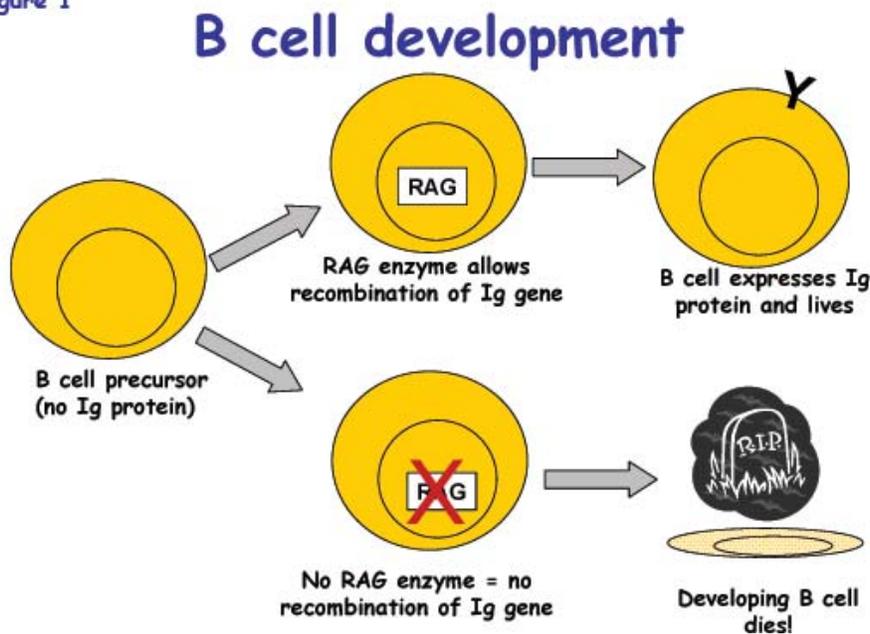
Baby Joe's doctors diagnosed his condition as severe combined immunodeficiency (SCID). This disease is life-threatening; without treatment, it is usually fatal in childhood. SCID can be caused by several genetic mutations. Many of these mutations are in genes involved in the normal development of B and T cells.

B cells begin to express immunoglobulin (Ig) proteins early in their development. If a developing B cell does not express an Ig, it dies. Similarly, developing T cells die if they do not express the required T cell receptor (TCR).

In order for B cells to express Ig proteins and for T cells to express TCR proteins, molecular rearrangements of the DNA encoding these proteins must take place. Before this rearrangement occurs, the genes are not functional; they have early stop codons and do not encode a fully functional protein product. However, in each normally developing B or T cell, the DNA composing the Ig or TCR gene is physically cut and spliced to yield functional genes that encode the full, functional protein. This process is referred to as somatic recombination.

Somatic recombination requires the action of many different enzymes. Some of these enzymes are expressed in all types of cells and are involved in DNA repair. However, some of the enzymes involved are only expressed in B and T cells. One such enzyme is called RAG, or Recombination-Activating Gene. The role of RAG in B cell development is summarized below; it plays a similar role in T cell development.

Figure 1



A sample of Baby Joe's DNA was sent for sequence analysis, which revealed mutations in both copies of his RAG genes. The mutations in both genes were frameshift mutations, resulting in a complete lack of expression of functional RAG protein.

Questions

1. Explain how a lack of RAG protein results in the phenotype observed in Baby Joe.
2. Why doesn't the mutation in RAG affect cell types other than B cells and T cells?



Part IV—Plans for Treatment and Follow-up

Baby Joe was put on intravenous antibiotics to treat the ear and bladder infections. While in the hospital, he developed pneumonia, which was treated with antibiotics and intravenous fluids. He recovered from the infections but remained weak.

For the long term, Baby Joe's prognosis without treatment for SCID is very poor. Most infants with SCID die within the first year of life unless they receive treatment.

Questions

1. What treatment options might help Joe?
2. SCID caused by mutations in RAG genes is an autosomal recessive disease. If you were Joe's physician, what advice would you give to his parents about the chances of the disease occurring in other children they might have? Explain your answer.

Image Credit: Photo © Pavlo E. Perets.

Copyright © 2005 by the National Center for Case Study Teaching in Science.

Originally published 12/13/05 at http://www.sciencecases.org/baby_joe/baby_joe.asp

Please see our [usage guidelines](#), which outline our policy concerning permissible reproduction of this work.