Dear Dr. Greenberg,

As I read more and more about NF2, and Rac, Ras and Cdc42, it would seem CAPRI would have some role in NF2. What are your thoughts about that? Could I email me your article on CAPRI? I was only able to access the abstract.

My son has NF2. He is half blind and half deaf and is fighting many more brain and spinal tumors, which are progressing.

I've been following Pak inhibitors for NF2.

Please help me save my son.

Dianne

NF2: Neurofibromatosis 2, an inherited autosomal dominant disease characterized by multiple CNS tumors (schwannomas, meningiomas, and ependymomas) resulting from mutations in merlin

Merlin: An actin binding protein that inhibits Ras-induced foci-formation and associated AP-1 activity. Merlin blocks Ras-induced Rb phosphorylation, and inhibits the increase in cyclin D1 levels.

Rac, Ras, Cdc42: GTPases involved in cell signaling. Ras activates the MAP kinase pathway. Rac and Cdc42 activate cytoskeletal alterations and activation of the protein kinase, PAK

PAK: A protein serine/threonine kinase

CAPRI: An adaptor protein for Rac
The Problem of Biological Complexity and “Information Overload”

Analogy: Structural Programming


In it he criticized programming constructs that allowed undisciplined jumps in flow of control leading to so-called ‘spaghetti code,’ which made larger programs unwieldy.

Courtesy: David Searls, Glaxo-Smith-Kline
Analogy: Structural Programming

He helped to launch the **structured programming** movement, which enforced a strictly nested modularity for more manageable growth, debugging, modification, etc.

Analogy: Modular Design of Integrated Circuits

LM555 Timer

Pinout & functional block diagram
The “Circuitry” of the Primary Immune Response

The “electronic lymph node”

Immunology--The Whirlwind Tour
Ontogeny of the Acquired Immune System

Step 1. Lymphocytes develop in the bone marrow and thymus

Step 2. Naive lymphocytes circulate in the blood and lymph

Step 3. The primary immune response occurs in the lymph nodes and spleen

Step 4. Lymphocytes exit the lymph nodes and spleen and become effector lymphocytes--they produce antibody (B cell-derived plasma cells) and become competent to produce cytokines, particularly CD4+ T cells, and kill (CD8+ T cells)

Stages in the Development of a Primary Immune Response

Step 1. Lymphocytes develop in the bone marrow and thymus

The immune repertoire develops

Lymphocytes develop early in life in the 1st lymphoid organs (bone marrow and thymus). They are competent to respond to a broad array of antigens. Diversity in antigen recognition is accomplished by random rearrangements of the immunoglobulin (Ig) gene in B cells and the antigen receptor gene in T cells (TCR).

Those lymphocytes that survive do so through positive selection. Unproductive or inefficient interactions between lymphocyte and antigen results in death by negative selection.
Antibody (Ig) and TCR are the Only Genes that Undergo Somatic Cell Recombination

How is Diversity in Antigen Recognition Achieved?
Ig Maturation

Ordered TCR gene rearrangement and TCR expression

Ordered expression of surface molecules, including the TCR, CD4 and CD8

Thymocyte Education: Selection of the T cell repertoire through negative selection and positive selection

What Happens in the Thymus?
The Primary Immune Response

Input: Ag-loaded APCs and naïve lymphocytes
Output: Effector and memory lymphocytes

Phases of the Primary Immune Response
How Do the Relevant Lymphocytes “Know” to be Activated?

The Clonal Selection Theory

- Naïve state
- Ag encounter
- Clonal expansion
Three Types of APCs

The Itinerant Dendritic Cell
Functional Anatomy of a Lymph Node

The Antigen “Vetting” Process: Who Decides Which Antigens are Presented
Structure of Peptide-binding Class I MHC Domains

Contact Between the TCR and MHC/peptide: Not All MHC Molecules are Created Equal
The “Fit” Between MHC Molecules and Peptide Defines MHC Restriction

Polymorphisms (allelic differences within a population) of the MHC loci account for the variability of the immune response between individuals.

Functions of MHC I and II

<table>
<thead>
<tr>
<th>Degraded in</th>
<th>Peptides bind to</th>
<th>Presented to</th>
<th>Effect on presenting cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytosol</td>
<td>MHC class I</td>
<td>CD8 T cells</td>
<td>Cell death</td>
</tr>
<tr>
<td>Endocytic vesicles (low pH)</td>
<td>MHC class II</td>
<td>CD4 T cells</td>
<td>Activation to kill intravascular bacteria and parasites</td>
</tr>
<tr>
<td>Endocytic vesicles (low pH)</td>
<td>MHC class II</td>
<td>CD4 T cells</td>
<td>Activation of B cells to secrete Ig to eliminate extracellular bacteria/toxins</td>
</tr>
</tbody>
</table>
Antigen Presentation at the Cellular Level

The “Immuneologic Synapse”
The Two-Signal Theory of T-cell Activation

APC = Antigen-presenting cells
TCR = T cell receptor for antigen
DC = Dendritic cell
CD80 = Co-stimulatory receptor

CD4+ T Cells Activate Macrophages and B cells

T_{H}1 cell recognizes complex of bacterial peptide with MHC class II and activates macrophage

Helper T cell recognizes complex of antigenic peptide with MHC class II and activates B cell

Figure 1-31: Immunobiology, 6/e, (c) Garland Science 2005)
CD8+ CTLs Kill Viral-infected Cells

Regulation of the Immune Response: a Conceptual View

- Immunity
- Activation
- Suppression
- Tolerance
Systemic Lupus Erythematosus (SLE): An Autoimmune Disease

Clinical Manifestations of Rheumatoid Arthritis
Summary

1. The immune system is complex. Try to understand it in terms of specific functional modules.

2. Diversity in antigen recognition is accomplished, in part, by rearrangements in the Ig and TCR loci. This occurs in the bone marrow and thymus, respectively.

3. The T and B cell repertoire determines the spectrum of antigens that can be recognized in an individual's lifetime. The nature of this repertoire is determined by the Major Histocompatibility Complex (MHC), which binds peptide antigen.

4. In a primary immune response, antigen presenting cells (APCs) present antigen bound to MHC molecules to T cells in the lymph nodes and spleen. T cells “help” B cells to develop further and clonally expand in germinal centers of these organs.

5. Lymphocytes exit these organs to become effector or memory cells. Effector cells secrete Ab (plasma cells) or cytokines (CD4+ T cells) and kill virally-infected cells (CD8+ T cells). Memory cells re-circulate until they encounter Ag again.

6. The immune system is tightly regulated. It exists in a delicate balance of immunity and tolerance. A lack of tolerance to self antigen coupled to excessive immune activation (or inadequate immune suppression) can lead to autoimmunity.