A Brief Background on the Immune System *

E. Buchla and L.G. de Pillis and A.E. Radunskaya

August 31, 2002

1 Introduction

This document is intended to provide some background on the basic functions of the human immune system. Please note that this information is by no means comprehensive, and that many of these terms are defined only in their broadest and least technical sense. Terms in *italics* are important to understanding the structure of the immune system, and those interested should take the time to look them up in a dictionary of medicine or immunology. (See for example, [CL95].)

The main function of the immune system is to deal with foreign invaders, whether these are particles or living organisms. Hence the key to the immune system's successful functioning is its ability to distinguish between "self" and "non-self." Once a foreign agent is identified, the body is then able to mount a response to it.

An *antigen* is, generally speaking, any foreign agent that the can be recognized by the body's immune system. If the immune system is then able to mount an active response to it, the agent is also said to be *immunogenic*. Bear in mind that antigens are not necessarily immunogenic, and antigens need not necessarily originate from outside the body. Discrepancies like these lie at the root of many immune system diseases. With large tumors, for example, the immune system is frequently ineffective in keeping the disease in check, possibly because the tumor cells are not properly recognized as antigens. To consider issues like this it is first necessary to understand some of the basic mechanisms of the immune system.

There are essentially two different ways that the immune system responds to infection, though as we will see they are closely related. Both response systems involve the use of specialized cells called lymphocytes that are mostly found in the blood. The first type of response is known as humoral immunity and is effected by means of factors called antibodies which are secreted into the body's fluids (or "humors.") Antibodies are produced by a class of lymphocytes called B lymphocytes or B-cells because they develop in the bone marrow, or bursa. The second type of immune system response is called cellular immunity.

*This work was supported in part by a grant from the W.M. Keck Foundation

This type of response is facilitated by T lymphocytes, or more simply T-cells, so called because they develop in the thymus gland. In addition to the highly specialized B and T cells, there is also a set of lymphoctyes whose functions are sometimes collectively referred to as "natural immunity" although they in fact operate integrally with the other lymphocytes. These cells include macrophages, which are large "scavenger" cells, and natural killer cells, which target tumor cells and infectious microbes.

2 Markers of Self

All body cells carry molecular markers on their surface that enable them to be identified as "self" by immune system cells. The most important self marking molecules are encoded by a group of genes contained in a section of a specific chromosome known as the *major histocompatibility complex*, or MHC. There is one group of proteins in the MHC which are carried by almost all body cells, called *class I MHC antigens*, that are altered when the cell is infected by a virus or cancer. These molecules serve to alert killer T-cells to the presence of malignant body cells. A second group of MHC proteins, *class II antigens*, are found only on B cells, macrophages, and other cells responsible for presenting foreign antigen to helper T-cells. Class II MHC proteins combine with particles of foreign antigen and, by the resulting shape, directs the actions of the T-cells.

3 Humoral Immunity: B Lymphocytes

Each B lymphocyte is genetically "programmed" to produce a single specific antibody with a particular molecular shape. The shape of an antibody allows it to bind with a specific antigen when a B-cell encounters that antigen in the bloodstream. For this purpose, each B-cell carries a "prototype" of its antibody embedded in its surface. When the matching antigen is encountered, the B-cell proliferates and differentiates, producing *plasma cells* which actively secrete a soluble form of the antibody.

Antibodies can work in several different ways, depending largely on the form of antigen to which they react. Some functions include:

- Interlocking directly with toxic chemicals or toxins produced by an organism to neutralize them
- coating (opsonizing) cells to make them more palatable to scavenger cells or signal their presence to "killer" lymphocytes (this last is a process known as antibody-dependent cell-mediated cytotoxicity or ADCC.)
- binding with antigen to secrete a lethal group of enzymes known as *complement*
- blocking viruses from entering cells

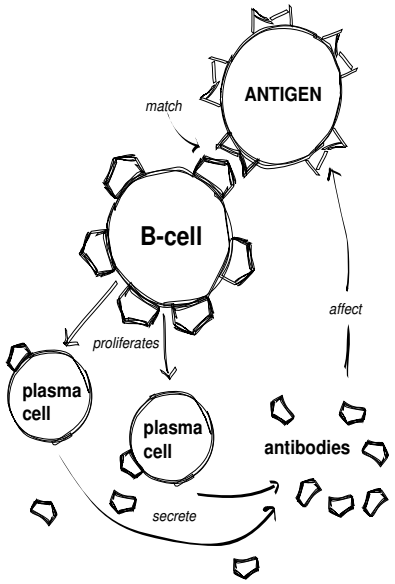

Figure 1: B-Cell Activation

- preventing a cell (usually a virus cell) from reproducing; this function appears to act against tumor cells undergoing metastasis.

4 Cellular Immunity: T Lymphocytes

T lymphocytes have several different functions. Currently there are four distinct types of T-cells recognized, divided into two categories: regulatory T-cells, which help orchestrate cell responses; and cytotoxic T-cells which directly attack body cells which are infected (by a virus) or malignant (cancerous.)

T-cells mostly work by secreting enzymes called *cytokines* or, more specifically, *lymphokines* (since they are produced by lymphocytes.) Like antibodies, lymphokines play several different roles; many are toxins that directly attack infected cells. One of these enzymes, called *tumor necrosis factor*, can play an important role in cancer remission. Other lymphokines, including an important one called *interferon*, incite macrophages to engulf tumor and virus cells and to produce cytokines of their own. Still others promote the production or maturation of additional T-cells or direct B-cells to produce antibody.

The most important type of regulatory T-cells are known as *helper/inducer cells*, sometimes abbreviated TH -cells. These are responsible for activating B-cells as well as nearby natural killer cells and macrophages. Helper T-cells carry the T4 molecular marker, which allows the T-cell to identify foreign antigens in the class II MHC molecule carried by macrophages and some B-cells. Once the

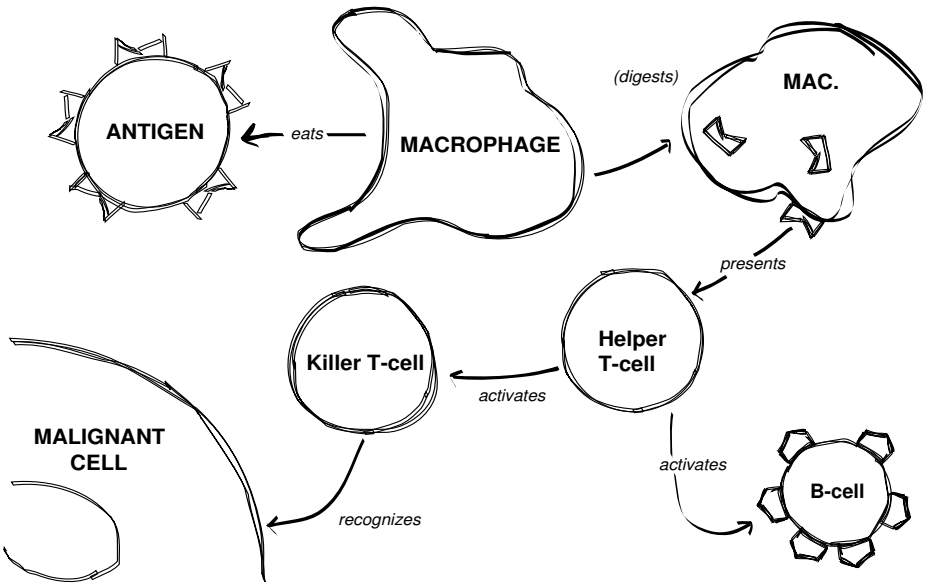

Figure 2: T-Cell Activation

helper T-cell recognizes a specific foreign antigen, it releases lymphokines which activate B-cells to produce the corresponding antibody.

Another type of T-cell is known as a *suppressor cells*. As the name implies, suppressor cells act to turn off or "suppress" the actions of T-cells. Suppressor cells are sometimes abbreviated TS.

Cytotoxic T-cells are a type of "killer cell" which, in addition to attacking malignant cells, are also responsible for rejecting tissue or organ grafts. Because they carry the T8 molecular cell marker, cytotoxic T-cells are sometimes called T8 cells, although the latter term actually defines the cell's recognition mechanism and not its function. T8 molecules "fit" class I MHC molecules that have been altered by infection, enabling killer T-cells to recognize and attack virus and tumor cells. Cytotoxic T-cells can be abbreviated TC.

Like B-cells, T-cells are activated by contact with specific antigens. Unlike B-cells, however, T-cells cannot autonomously respond to foreign agents; they must have the antigen molecules "presented" to them by B-cells or macrophages. On the other hand, killer T-cells are capable of recognizing body cells that have been infected by virus or cancer.

5 Natural Immunity

The so-called "natural immunity" system consists of essentially two types of cells: macrophages and natural killer cells.

Natural killer cells resemble cytotoxic T-cells in that they contain granules filled with toxins that attack foreign or malignant cells. Their name derives from the fact that, unlike T-cells or B-cells, they do not require contact with a specific antigen to be activated. Instead they seem to have a more basic self/non-self distinguishing mechanism that is not clearly understood at this point.

Macrophages are a type of very large phagocyte, or scavenger cell, that engulfs and digests foreign agents. Macrophages carry MHC class II proteins, which combine with fragments of digested antigens and are then recognized by helper T-cells. Macrophages also secrete cytokines including interferon and tumor necrosis factor, which can stimulate more macrophages and NK cells or kill malignant cells.

6 Cell Interactions

As we've already seen, cells within the immune system interact with each other in a variety of ways to handle different kinds of threats. Here's a step-by step summary of what can happen when the immune system encounters an antigen.

1. Antigen detection:

   - Antigens are either free-floating in the body's fluid or expressed as part of an infected cell. In the first case, the antigen molecules are encountered by B lymphocytes "programmed" for that molecule.
   - Antigens may also be engulfed by wandering macrophages, which digest the antigen and incorporate fragments of it into their MHC Class II markers, to be "presented" to helper T-cells. This task may also be performed by B lymphocytes.
   - Infected or malignant cells are antigenic to cytotoxic T lymphocytes via their MHC Class I marker; these lymphocytes can detect such cells without need of intermediaries.
   - Natural killer cells employ as yet unknown mechanisms to distinguish "good" cells from "bad."

2. Responses:

   - Activated B-cells proliferate and diversify into plasma cells, which secrete antibody. Antibody can either directly affect a foreign agent by poisoning it or inhibiting its growth, or the foreign agent may be coated with antibody (a process known as "opsonization") to make it more palatable to macrophages and other "eaters."
   - Macrophages that have ingested an antigen present fragments of if to helper T-cells. The helper cells then release lymphokines that activate the appropriate B-cells to produce antibody. Other lymphokines activate killer T-cells, natural killer cells, and macrophages.

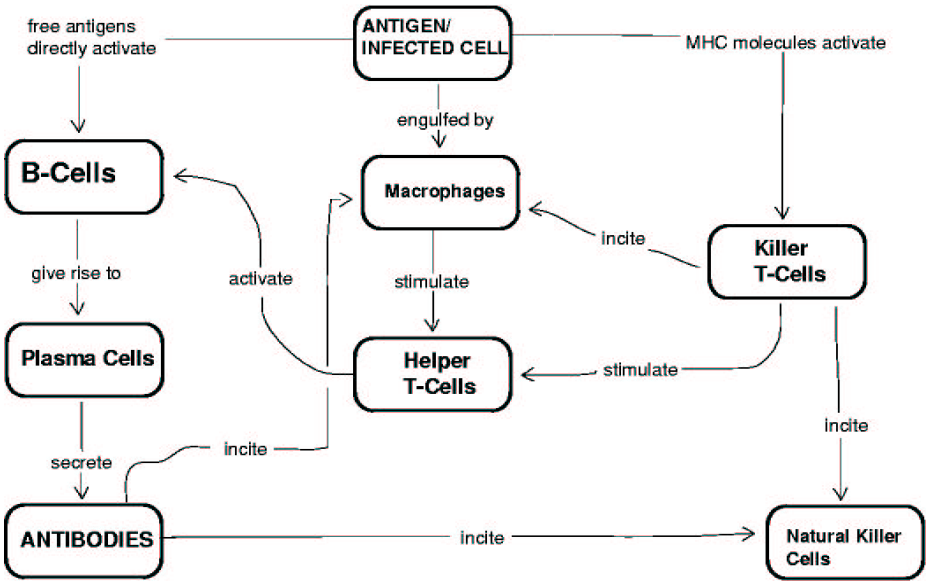

Figure 3: Immune System Respone Flowchart

- Cytotoxic T-cells that have encountered malignant cells release lymphokines that can attack the malignancy directly, activate more T-cells, or incite NK cells and macrophages.
- At some point, suppressor T-cells may activate to "shut down" killer cells and B-cells. Whether this process is continuous and indiscriminate, or stimulated by factors in the blood, or something else, is apparently not agreed on.

7 The Immune System and Cancer

The immune system has several ways of responding to tumors. A malignant cell may be attacked directly by killer T-cells which recognize the altered Class I MHC marker. Macrophages and NK cells may also attack embryonic cells by eating them or releasing cytokines such as tumor necrosis factor. In addition, tumor cells undergoing metastasis may be prevented or killed by antibodies.

However, tumor cells have special characteristics that make them less vulnerable to destruction by the immune system. Some of these characteristics are not clearly understood. Certainly the antigens expressed by tumor cells do not seem to be easily detected by immune sytem cells, for whatever reason. It has been theorized that tumor cells can somehow change or hide their antigenic markers. It has also been theorized that tumor cells are somehow capable of activating suppressor T-cells prematurely or of attracting them to the site of

the tumor. Questions like these may be answered, at least in part, by more extensive modeling.

References

[CL95] Julius M. Cruse and Robert E. Lewis. *Illustrated Dictionary of Immunology*. CRC Press, 1995.

[LS02] Jeanne Kelley Lydia Schindler, Donna Kerrigan. Understanding the immune system. http://newscenter.cancer.gov/sciencebehind/immune/immune01.htm, 2002.

[Pla92] J. H. L. Playfair. *Immunology t a Glance*. Blackwell Scientific, 1992.

[TH92] Ian F. Tannock and Richard P. Hill. *The Basic Science of Oncology*, chapter 14. McGraw-Hill, 1992.