Introduction: Tumor-Immune Interactions *

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INTRODUCTION: TUMOR-IMMUNE INTERACTIONS

Overview

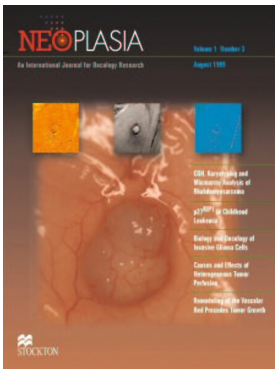
1. Mysteries of the Immune System: Dormancy and Chemotherapy response.
2. Importance of the Immune System for Cancer Treatment.
3. Overview of the Human Immune Response.
   - Immune system targets cancer
   - Activation of B-cells and Helper T-cells
   - Natural Killer Cells
   - Activation of Killer T-Cells
   - Flow Chart

Introduction: Tumor-Immune Interactions

Mystery of the Immune System: Dormancy

Mystery 1: Why is it that one patient's cancer returns after some time, while another patient can remain cancer free? This phenomenon is known as:

- **Tumor** _____(1). Disappearance and reappearance of tumors. Mathematically possible with immune system component.



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Notes for Mathematical Importance of Immune System slide:

Answers:

(1) Dormancy

Mathematical models without an immune system and without angiogenesis do not exhibit this behavior. The simple inclusion in a model of an immune response (even in the absence of angiogenesis) will allow for the emulation of a dormant state.

The image is one of a tumor that has just been "awakened" from its dormant state. It was on the cover of Neoplasia, Volume 1, Number 3, August 1999. The image on the slide is borrowed from http://www.neoplasia.org/images/v01i03big.jpg. The point of the article associated with this image was to explore the connection between angiogenesis and tumor dormacy. Our focus, however, will not be on angiogenesis, but instead on the immune system response to the presence of tumor.

The comment with the image is "Tumor dormancy is characterized by vascular instability rather than lack of angiogenesis. Using MRI, Gilead and Neeman followed angiogenesis and growth of MLS human ovarian carcinoma spheroids implanted in nude mice. The cover background shows one tumor after exit from dormancy. The

top images acquired before exit from dormancy show mature and functional vessels surrounding the tumor. ”

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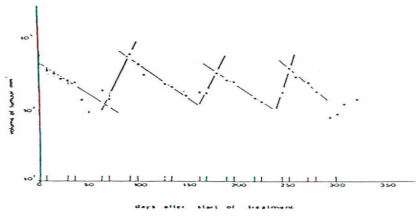
Mystery of the Immune System: Chemotherapy Response

Mystery 2: Why would a tumor treated with chemotherapy first grow, and then shrink?

- **Asynchronous tumor response to** _____(2) (Thomlinson 1982). Also mathematically achievable with immune system interaction.



Note: The tickmarks on the horizontal axis represent administration of chemotherapy, the dots represent measured volume of tumor. Horizontal axis represents days of treatment, vertical axis represents volume of tumor.

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Notes for Mathematical Importance of Immune System slide:

Answers:

(2) chemotherapy

Question: You may want to ask the students: If there were no immune response, what would we expect this plot to look like?

Answer: We would expect tumor volume to diminish as soon as the patient is treated with chemotherapy, and grow between treatments. But the tumor response to the chemotherapy appears to be asynchronous. For example, during the treatment between days 50 and 100, the tumor appears to grow instead of shrink. This could be explained if the drug also attacks beneficial immune cells.

Note: The other possible explanation is that the patient is not responding at all the chemotherapy, and the tumor is going through a natural cycling in size. However, the authors of this study addressed that question, and in this particular case (for a breast cancer patient), the patient was treated with multiple drugs (including 5-FU and cyclosplatin), against which the clinicians were positive the patient had not developed a resistance [Tho82].

The point of the two previous slides is that when developing a mathematical model, one concrete way of mathematically emulating these clinical phenomena is to include an immune system component in the model. This does not guarantee that this, then, is the mechanism by which these phenomena occur, but it does suggest that it is one possible mechanism.

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Problem Statement

We will develop a mathematical model of tumor-immune interactions which will exhibit

- Tumor dormancy
- Asynchronous response to chemotherapy

This mathematical model will focus on two populations of cells. We present the background and justification for our model assumptions in the slides that follow.

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Importance of the Immune System

Two clinical approaches to fighting cancer:

- **Immunotherapy**: Enlisting the body's own defenses, also known as the _____(1), to join the fight against cancer.
- **Vaccine**: A compound or group of compounds designed to produce a _____(2) immune response to a tumor.

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Notes for Importance of Immune System slide:

Answers:

(1) immune system

(2) specific

Note:

Here we introduce the students to the fundamental concept that the immune system has a key role to play in the dynamics of tumor progression. Although to many this may seem obvious, it has not always been accepted in the medical community that a strong immune system can significantly hinder tumor growth. However, there is now an overwhelming body of evidence that shows the immune system is of central importance. This is why in the tumor growth model we will develop in this module, we include immune system dynamics.

We note that although we refer to immunotherapy and vaccine therapy separately, vaccine therapy can be considered a type of immunotherapy that is very specific to targeting particular cancer cells.

For example, this is a quote from the Cancer Research Institute at

http://www.cancerresearch.org/immintro.html:

"For over 30 years, the Cancer Research Institute (CRI) has been providing support to research programs and scientists whose field of endeavor is cancer immunology. During this time, we have seen remarkable advances in our field. By gaining an understanding of the immune system and finding ways to strengthen its natural ability to fight disease, immunologists have been able to develop a new approach to treating cancer – immunotherapy. Several forms of immunotherapy are being rigorously explored in laboratories and tested in clinical trials, where they are showing promise as effective treatments for cancer. Today, we are more committed than ever to our long-term goal of fostering cancer immunology."

Comments on vaccines

(paraphrased from the Duke University web site http://cancer.duke.edu/vaccine/vaccines.asp)

The students will likely know that vaccines have virtually eliminated many once common diseases such as polio, measles, mumps, small-pox and others. These vaccines all teach the body to recognize the causes of these diseases and to fight off infections before they result in the actual diseases. Right now, however, cancer vaccines have a different goal. Instead of preventing the initial disease, physicians are looking at cancer vaccines both as therapeutic agents and as a way to prevent a

second episode of cancer. By teaching the body to watch out for certain characteristics of cancer cells, the vaccine jump-starts the immune system. The idea is that the immune system will then kill any remaining cancer cell before it can start forming a tumor. Some cancer vaccines are already being tested in human trials, for example at UCLA (http://cancer.mednet.ucla.edu/), at the University of Michigan (http://www.cancer.med.umich.edu/learn/cancervaccines.htm) and at Duke University (http://cancer.duke.edu/Vaccine/trials/), just to name a few. It will be some years, however, before cancer vaccines can be created and tested for true disease prevention.

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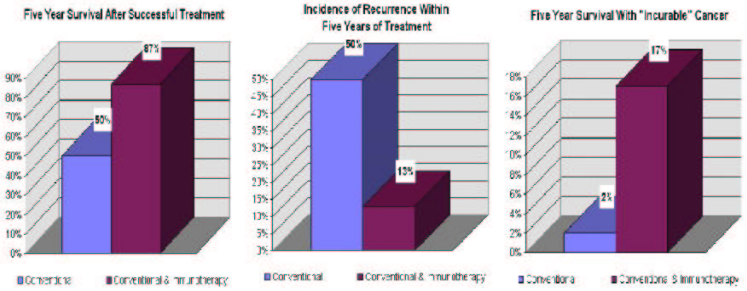
Importance of the Immune System: Clinical Evidence

From the ISSELS FOUNDATION: A restoration of the immune functions can reduce the incidence of relapse from about 50% (World Statistic) to 13% by combined conventional treatments and comprehensive immunotherapy.



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Notes for Importance of Immune System: Clincal Evidence slide:

These graphs borrowed from http://www.issels.com/statistics.asp?pg=3 show increased survival and reduced recurrence rates of cancer when treated with immunotherapy in conjunction with traditional chemotherapy. These graphs do not necessarily represent the state of the art in immunotherapy. They are only meant to illustrate the importance of immunotherapy.

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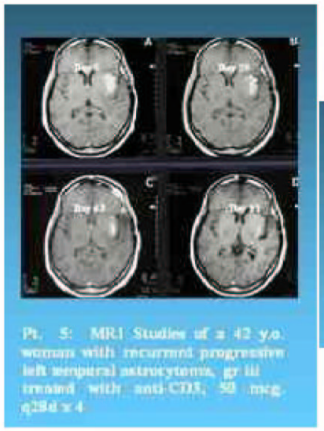
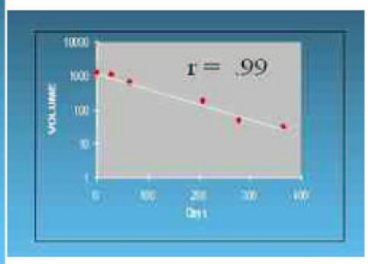
Importance of the Immune System: Clinical Evidence

Example: Clinical Response to Anti-CD3



Pt. S: MRI Studies of a 42 y.o. woman with recurrent progressive left temporal astrocytoma, gr iii treated with anti-CD3, 50 mcg. q28d x 4



Treatment: Day 0 - Anti CD-3 10-75 mcg iv/60 min
Day 1 - Cyclophosphamide 300 mg/m^2
Day 28 - Re-evaluate, MRI, re-treat

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Notes for Importance of Immune System: Clinical Evidence slide:

Note: This is a photograph from one of the patients in a clinical trial run by Dr. Charles Wiseman at the Los Angeles Oncologic Institute of St. Vincent's Medical Hospital. The treatment was meant to target GR II-IV glioma and other primary brain tumors. This patient was treated with low-dose anti-CD3 monoclonal antibody (which has a well-known effect on T-cell function, as well as up-regulation of IL-6). The patient in these pictures had evidence of tumor progression on MRI, despite previous therapies. Cyclophosphamide was also administered to down-regulate suppressor-cell activity, thereby allowing immune system cells to flourish. This patient experienced complete remission! As a group, there were higher survival and remission rates than expected for this poor-prognosis group.

There are many other sources of evidence that cancer immunotherapy and cancer vaccines are very promising therapeutic tools. New trials are being conducted and new research is being published every day. There are even some commercial companies already marketing medicine (see, for example, http://www.anticancer.net/ where the medicine Resan is discussed.) You may wish to do a quick web search and supplement these slides with additional slides of your own that refer to current research. Alternately, this can be made into an assignment for the students. Have the students search the web for information about cancer and the immune system, and have them present their results in class.

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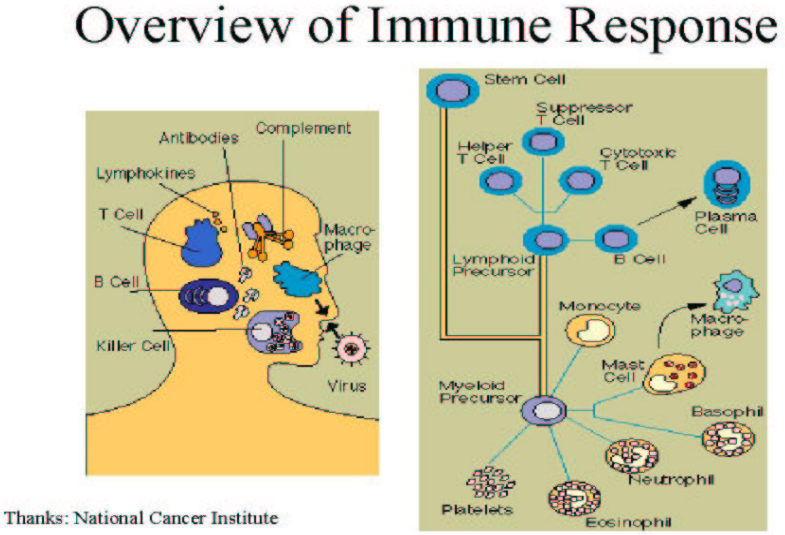

Thanks: National Cancer Institute

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Notes for Overview of Immune Response slide:

The next few slides are intended to give the students a very brief overview of the human immune system. We are also providing more detailed background reading for them, so it is not necessary to spend too much time on these slides. The pictures and comments on the following slides are borrowed from the National Cancer Institute's website at http://newscenter.cancer.gov/sciencebehind/immune.

The immune system is an extremely complicated network of interconnected functional components. It is a bodywide network of cells and organs that has evolved to defend the body against attacks by "foreign" invaders.

Mounting an Immune Response: Microbes attempting to get into the body must first get past the skin and mucous membranes, which not only pose a physical barrier but are rich in scavenger cells and IgA antibodies. Next, they must elude a series of nonspecific defenses-cells and substances that attack all invaders regardless of the epitopes they carry. These include patrolling scavenger cells, complement, and various other enzymes and chemicals. Infectious agents that get past the nonspecific barriers must confront specific weapons tailored just for them. These include both antibodies and cells. Almost all antigens trigger both nonspecific and specific responses.

Cells of the Immune System: Cells destined to become immune cells, like all blood cells, arise in the bone marrow from so-called stem cells. Some develop into myeloid cells, a group typified by the large, cell- and particle-devouring white blood cells known as phagocytes; phagocytes include monocytes, macrophages, and neutrophils. Other myeloid descendants become granule-containing inflammatory cells such as eosinophils and basophils. Lymphoid precursors develop into the small white blood cells called lymphocytes. The two major classes of lymphocytes are B cells and T cells.

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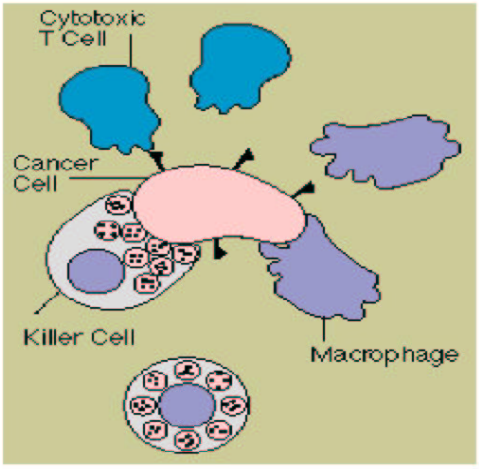
Immune System Targets Cancer



Thanks: National Cancer Institute

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Notes for Cancer and the Immune System slide:

Caner and Immune Response: When normal cells turn into cancer cells, some of the antigens on their surface change. These new or altered antigens flag immune defenders, including cytotoxic T cells, natural killer cells, and macrophages. According to one theory, patrolling cells of the immune system provide continuing bodywide surveillance, spying out and eliminating cells that undergo malignant transformation. Tumors develop when the surveillance system breaks down or is overwhelmed.

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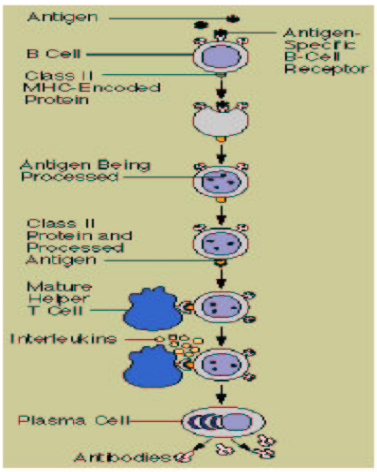
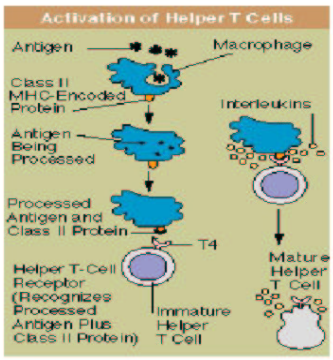
Activation of B and Helper T





Thanks: National Cancer Institute

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Notes for B and Helper T Cells slide:

Activation of B Cells: The B cell uses its receptor to bind a matching antigen, which it proceeds to engulf and process. Then it combines a fragment of antigen with its special marker, the class II protein. Th is combination of antigen and marker is recognized and bound by a T cell carrying a matching receptor. The binding activates the T cell, which then releases lymphokines-interleukins-that transform the B cell into an antibody-secreting plasma cell.

Helper T Cells: After an antigen-presenting cell such as a macrophage has ingested and processed an antigen, it presents the antigen fragment, along with a class II marker protein, to a matching helper T cell with a T4 receptor. The binding prompts the macrophage to release interleukins that allow the T cell to mature.

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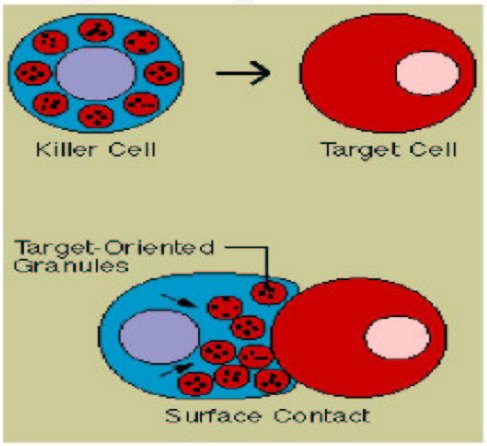
Natural Killer Cells (do not need to recognize specific antigen)



Thanks: National Cancer Institute

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Notes for Natural Killer Cells slide:

Natural Killer Cells: At least two types of lymphocytes are killer cells-cytotoxic T cells and natural killer cells. To attack, cytotoxic T cells need to recognize a specific antigen, whereas natural killer or NK cells do not. Both types contain granules filled with potent chemicals, and both types kill on contact. The killer binds to its target, aims its weapons, and delivers a burst of lethal chemicals.

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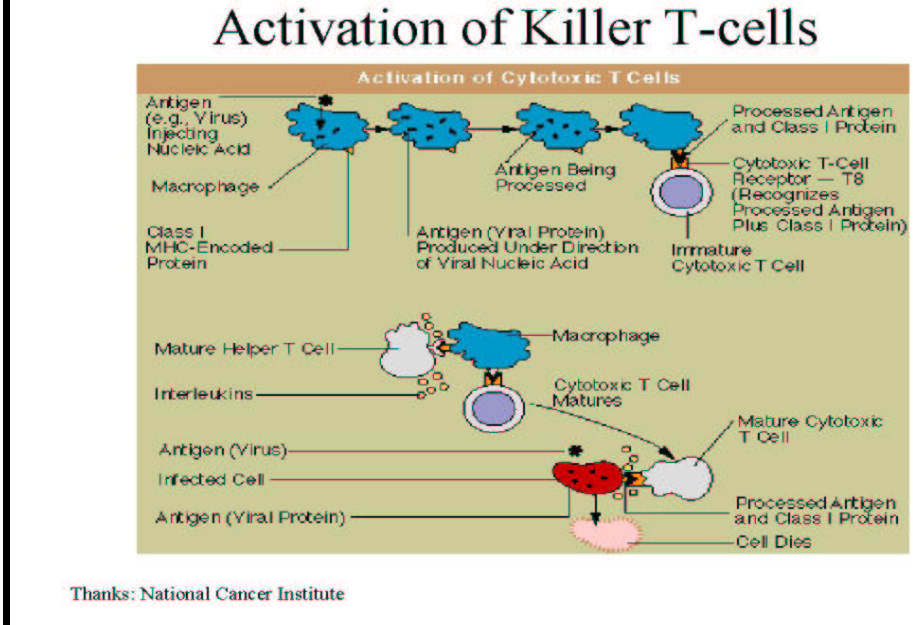

Thanks: National Cancer Institute

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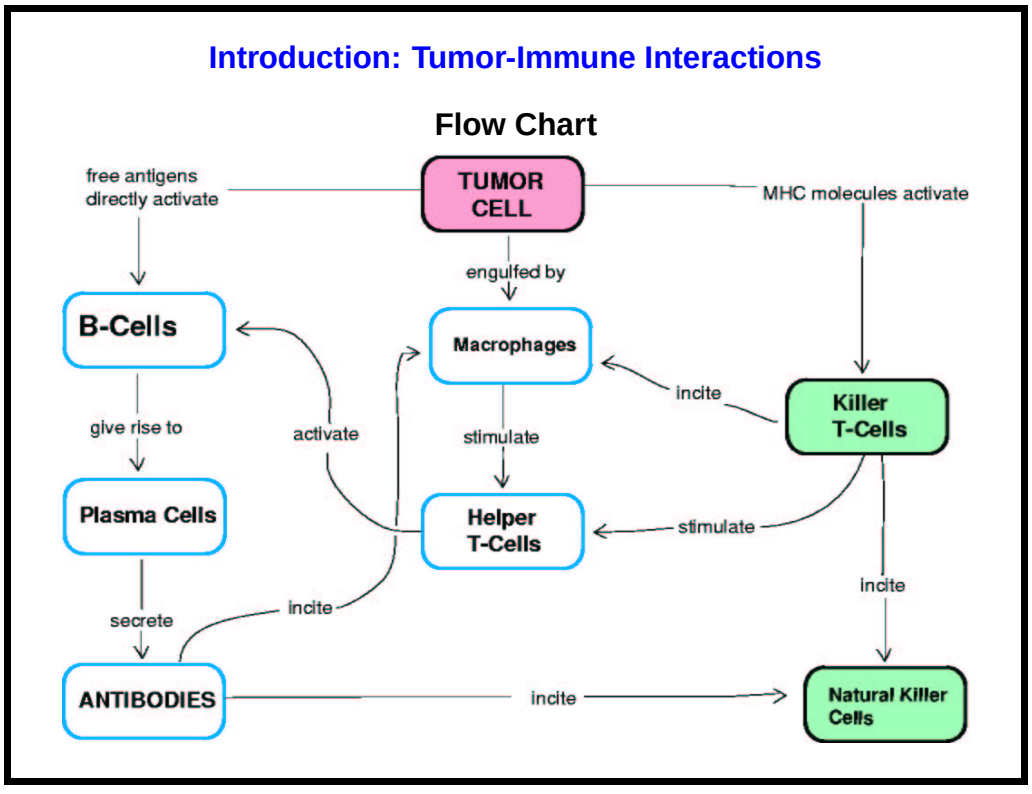
Notes for Killer T Cells slide:

Killer T Cells: A cytotoxic T cell recognizes antigens such as virus proteins,which are produced within a cell, in combination with a class I self-marker protein. With the cooperation of a helper T cell, the cytotoxic T cell matures. Then, when the mature cytotoxic T cell encounters its specific target antigen combined with a class I marker protein-for instance, on a body cell that has been infected with a virus-it is ready to attack and kill the target cell.



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