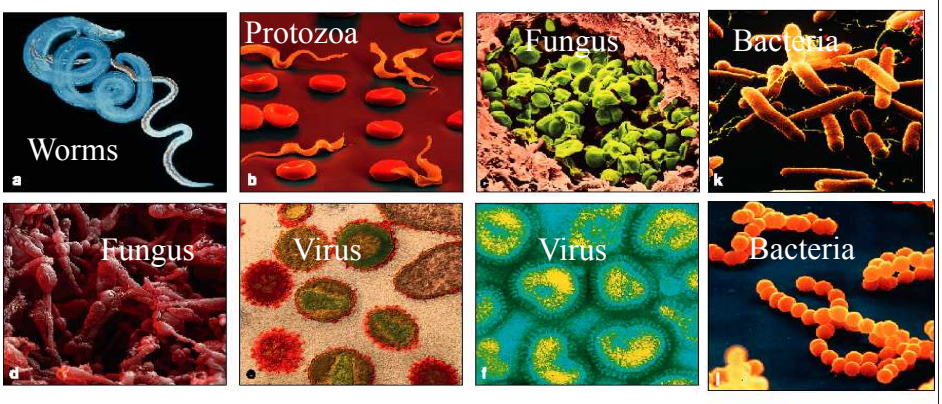
Basic immunological concepts and Cells of the immune system

BBS755 Infection and Immunity
Feb 5, 2015
Lecture 2
Prof. Stern

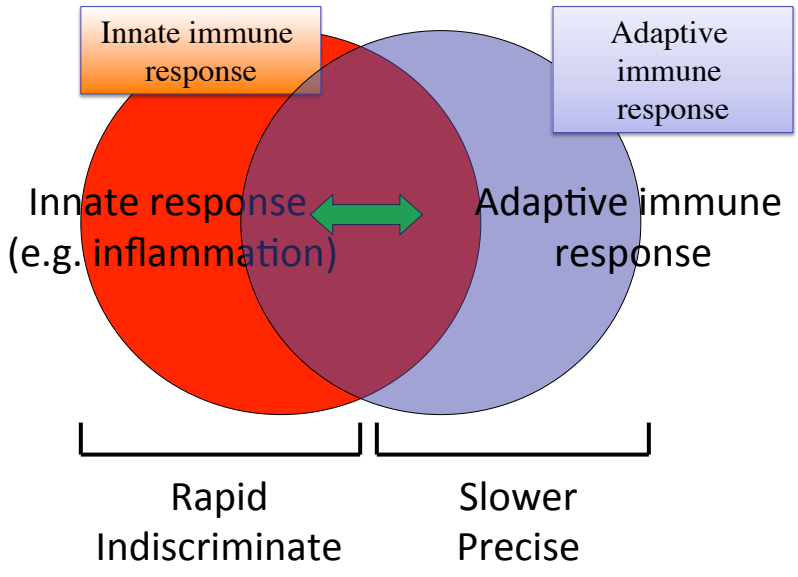
Immunology: study of how an organism responds to pathogens



What does the immune system need to do to deal with these threats?

- See everything
  - Viruses, bacteria, fungi, protozoa, helminths
- Look everywhere
  - All tissues, extracelllular, intracellular
- Mount an appropriate response
- Make a self-nonself discrimination

The Responses



Characteristics of innate vs adaptive responses

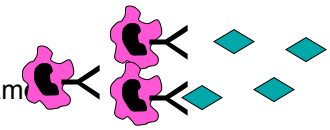
Inflammation (Innate immunity):
- Stereotyped response
- Same cell - same receptor
- Germ-line encoded receptors
- Immediate effect
- More easily subverted
- Evolutionarily older

Adaptive immunity:
- Specialized responses
- Each cell has a different receptor
- Somatic cell receptor variation
- Slower to respond, but "always gets their man"
- Evolutionarily more recent

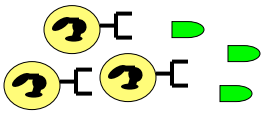
Specificity of innate versus adaptive immunity

Innate: Limited # specificities

- "Each policeman is looking for about the same thing"



- Limited number of different receptors looking for conserved features of pathogens or injury (e.g. bacterial cell wall components, DNA in cytosol)



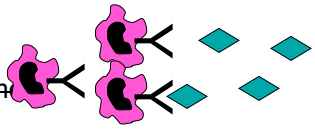
Adaptive: Numerous highly selective specificities

- "Each soldier is looking for a different thing"
- Many different receptors & each cell has a different receptor

Specificity of innate versus adaptive immunity

Innate: Limited # specificities

- ~~"Each policeman is looking for about the same thing"~~



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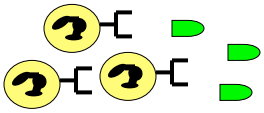


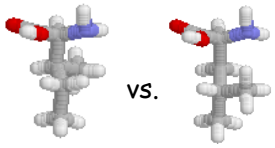
Adaptive: Numerous highly selective specificities

- ~~"Each soldier is looking for a different thing"~~
- Many different receptors & each cell has a different receptor

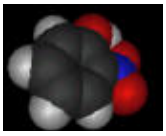
Specificity and Memory

Two key features of the adaptive immune system have puzzled, fascinated, and inspired researchers :

The immune system is amazingly specific

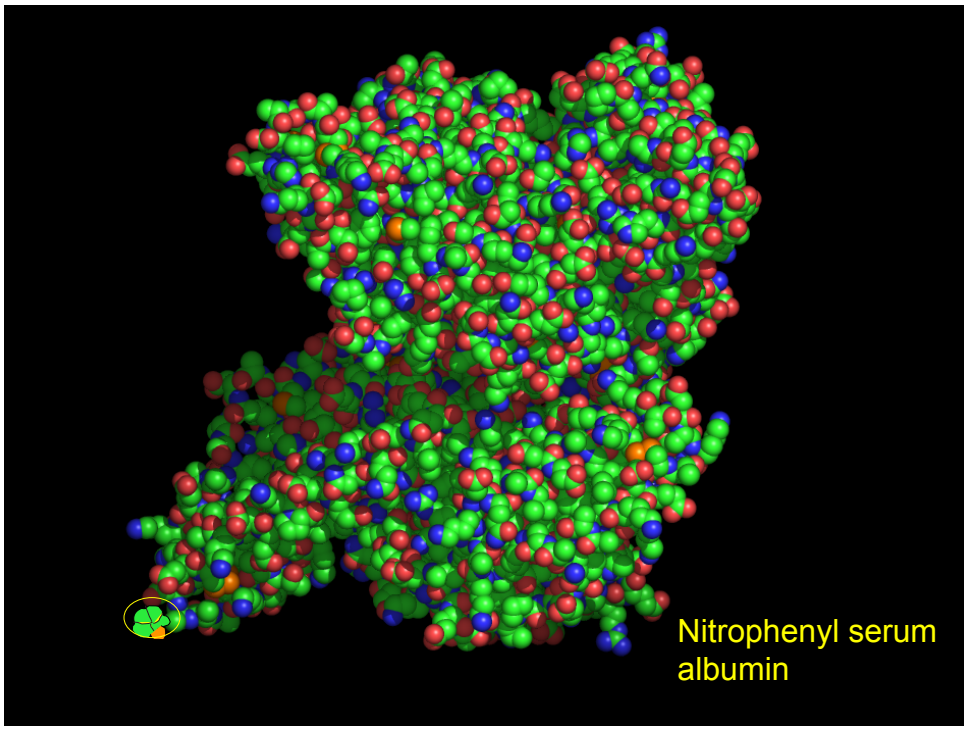


isoleucine leucine



Dinitrophenyl hapten

hapten: a small molecule covalently coupled to a macromolecule to make it "foreign" so it can be recognized by the immune system



Immunological memory

The immune system responds more quickly and more effectively to pathogens to which it has been previously exposed

Immunological memory

Thucydides, on the plague of Athens, 430 BC

"Yet is was with those who had recovered from the disease that the sick and the dying found most compassion. These knew what is was from experience, and had now no fear for themselves, *for the same person was never attacked twice - never at least fatally*."

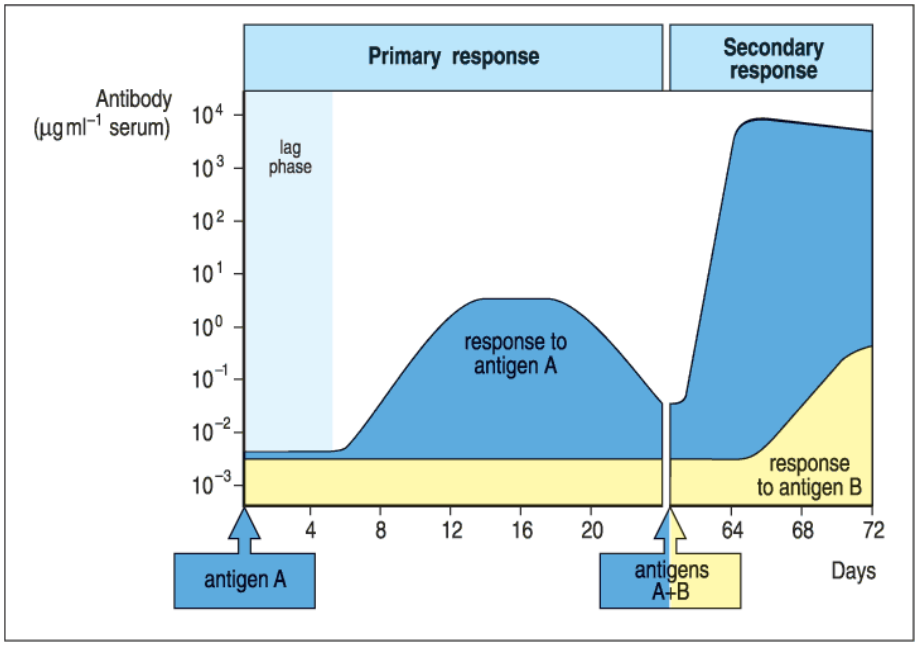


Fig 1.20 © 2001 Garland Science

Immune defenses

Immune defenses

First line of defense: barriers (epithelial surfaces)

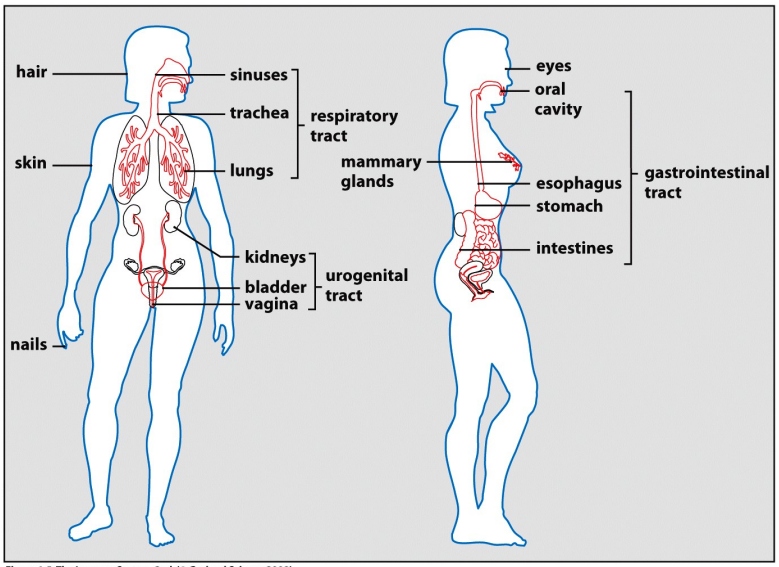


Figure 1.5 The Immune System, 3ed. (© Garland Science 2009)

Once barrier has been breached…

…immune system takes over

To deal with diverse threats, many different defenses are needed

What are the components of the immune response?

Soluble defenses: antibodies, complement proteins, cytokines, chemokines, lipid mediators

Cells: lymphocytes, macrophages, dendritic cells, granulocytes, mast cells

Immune defenses

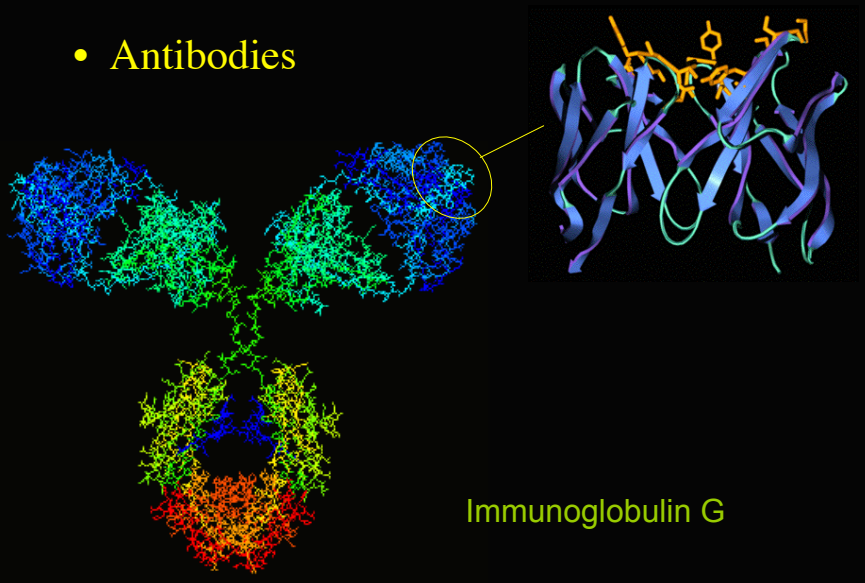
- Soluble molecules

Humoral immunity, from "humor" : according to ancient theory, four bodily fluids or humors (blood, phlegm, black bile, yellow bile) determined health and temperament, with imbalances among the humors responsible for pain and disease

- serum antibodies (Abs)
- serum complement (C')

Immune defenses

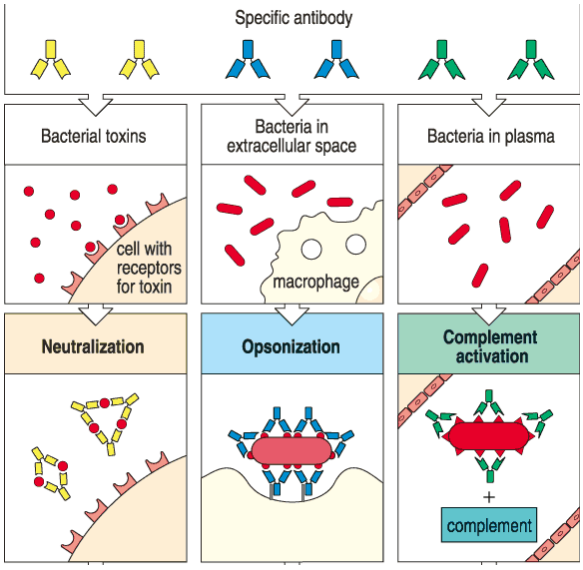
- Antibodies



Immunoglobulin G

Immune defenses

- Antibody-mediated immunity



Opsonize:
fr. Greek *opson*,
condiment, delicacy

Complement:
a cascade of serum proteins that results in bacterial lysis and immune recruitment

The complement system

Recognition of microbial surface

↓

Proteolytic signaling cascade

↓

All pathways lead to:
1) Covalent deposition of complement components on surface
2) Generation of pro-inflammatory peptides

↙ Membrane damage

↓ Target for destruction by phagocytes "opsinization"

↘ Inflammation

Immune defenses

- Cellular responses - T cells (CTL and NK cells) directly lyse infected cells…

Credit: STEVE GSCHMEISSNER/SCIENCE PHOTO LIBRARY

CYTOTOXIC T-LYMPHOCYTE:
A specialized white blood cell responsible for eliminating unwanted body cells (e.g. cancer) is killing a cell infected with the influenza virus

© James A. Sullivan CELLS alive!

… by induction of apoptosis to destroy infected cells and their contents

Immune defenses

- Cellular responses – macrophages phagocytose bacteria and fungi …

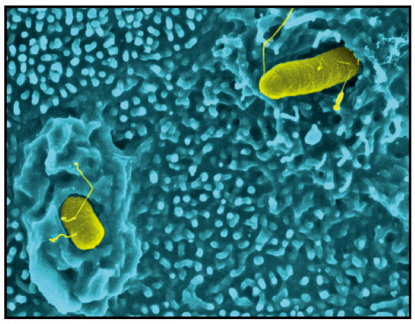


Figure 2-13 Immunobiology, 6/e, (© Garland Science 2005)

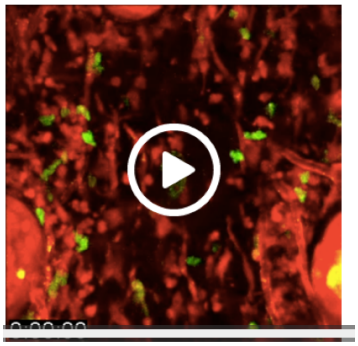
MACROPHAGE:
Another white blood cell responsible for killing microbes is ingesting the yeast *Candida albicans*

© James A. Sullivan CELLS alive!

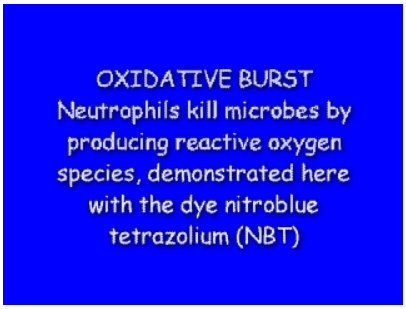
… and kill them by phagosome-lysosome fusion (pH ~5: proteases, lipases, lysozyme, antimicrobial peptides, iron chelators)

Immune defenses

- Cellular responses: neutrophils phagocytose and kill bacteria…



Neutrophil swarms require LTB4 and integrins at sites of cell death in vivo Tim Lämmermann et al Nature 498, 371–375



… by releasing reactive oxygen (ROI) and nitrogen (RNI) species that react with proteins, lipids and DNA.

- superoxide (O_2^-) generated by the NADPH oxidase complex
- nitric oxide (NO) produced by inducible nitric oxide synthase (iNOS)

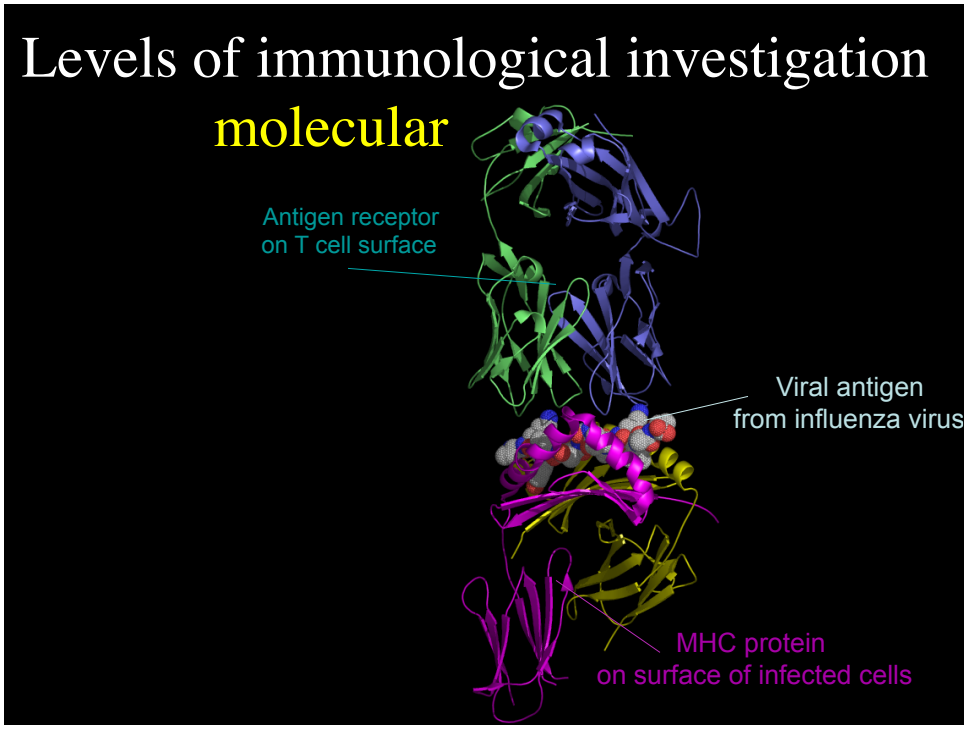
How do we learn about the immune system?

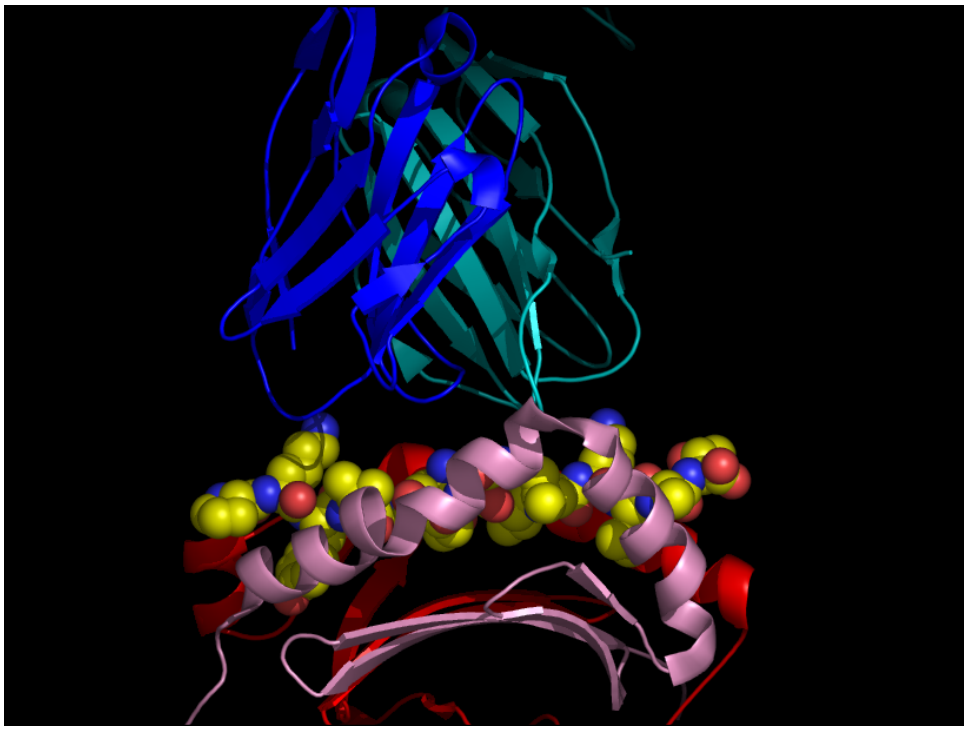
Many branches of experimental science have contributed to our current understanding of immunology

Chemistry
Biochemistry
Molecular biology
Microbiology
Microscopy
Cellular biology
Genetics
Population biology

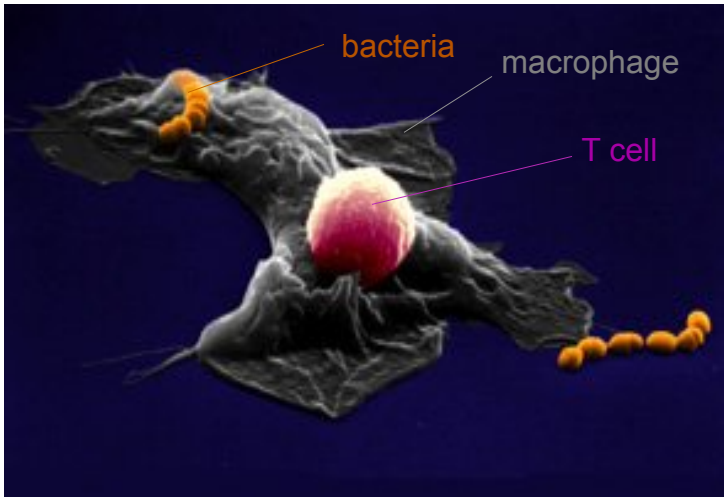
Levels of immunological investigation

molecular





Levels of immunological investigation: cellular



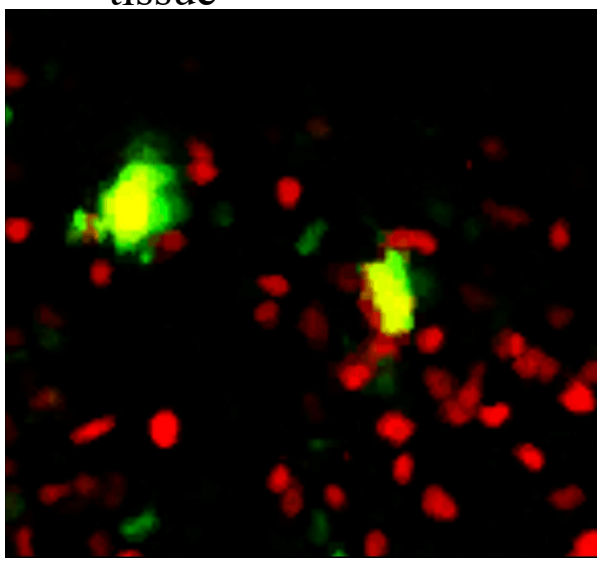
Levels of immunological investigation: tissue

Intravital imaging of a lymph node

Immunity Vol 21, 231-339, 2004.
Alex YC Huang, Hai Qi, Ronald Germain
Illuminating the landscape of in vivo immunity: insights from dynamic in situ imaging of secondary lymphoid tissues

Two-photon microscopy of a murine lymph node. Images taken at 30s intervals at a depth of ~100um below the capsule. Total length of movie = 25min (300x).

Image shows capture of CD4+ T cells (red) and CD8+ T cells (green) specific for chicken ovalbumin by dendritic cells (yellow) expressing ovalbumin peptides bound to cell surface MHC II molecules.



Levels of immunological investigation: organism

Transgenic mice and gene knockout technology allow
the function of a gene to be tested in vivo at the whole organism level

Levels of immunological investigation: population

Science. 2011 Oct 7;334(6052):89-94. Epub 2011 Aug 25.

The shaping of modern human immune systems by multiregional admixture with archaic humans.

Abi-Rached L, Jobin MJ, Kulkarni S, McWhinnie A, Dalva K, Gragert L, Babrzadeh F, Gharizadeh B, Luo M, Plummer FA, Kimani J, Carrington M, Middleton D, Rajalingam R, Beksac M, Marsh SG, Maiers M, Guethlein LA, Tavoularis S, Little AM, Green RE, Norman PJ, Parham P.

Department of Structural Biology, Stanford University School of Medicine, Stanford, CA 94305, USA.

Abstract

Whole genome comparisons identified introgression from archaic to modern humans. Our analysis of highly polymorphic human leukocyte antigen (HLA) class I, vital immune system components subject to strong balancing selection, shows how modern humans acquired the HLA-B*73 allele in west Asia through admixture with archaic humans called Denisovans, a likely sister group to the Neandertals. Virtual genotyping of Denisovan and Neandertal genomes identified archaic HLA haplotypes carrying functionally distinctive alleles that have introgressed into modern Eurasian and Oceanian populations. These alleles, of which several encode unique or strong ligands for natural killer cell receptors, now represent more than half the HLA alleles of modern Eurasians and also appear to have been later introduced into Africans. Thus, adaptive introgression of archaic alleles has significantly shaped modern human immune systems.

PMID: 21868630 [PubMed - indexed for MEDLINE]

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Not Exactly Rocket Science

« Ostriches sleep like platypuses (and look wide awake when they do)
I've got your missing links right here (27 August 2011) »

Did sex with Neanderthals and Denisovans shape our immune systems? The jury's still out

The Neanderthals may be extinct, but they live on inside us. Last year, two landmark studies from Svante

Summary of key points

- Diverse threat from infectious agents
  numerous, ubiquitous, adaptable

- Innate (rapid, germ-line encoded) and adaptive (slower, encoded by rearranged/mutated receptors) responses

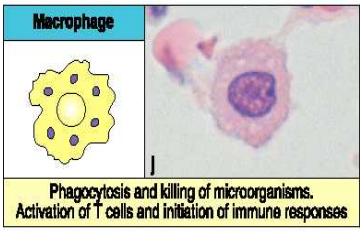
- Flexible, multilevel protection strategy
  soluble defenses (humoral immunity)
  phagocytes and cytoxic cells (cellular immunity)

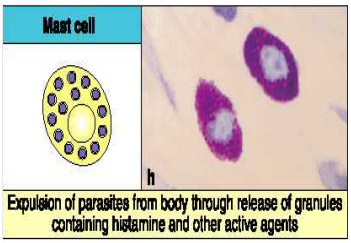
Cells of the immune system

There are a variety of types of immune cells, but all arise from a common bone-marrow progenitor

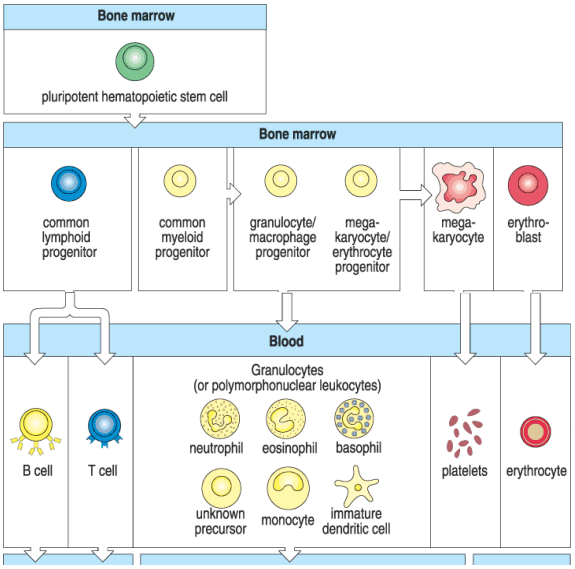
How can we tell the various immune cells apart from one another?

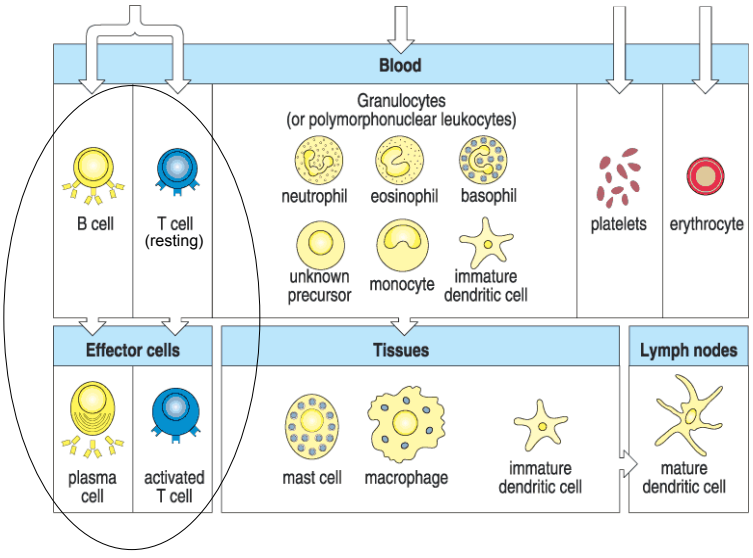
1. Morphology
2. Surface molecules that are cell type-specific





Differentiation of immune cells





Lymphocytes
(adaptive immunity)

B and T Lymphocytes

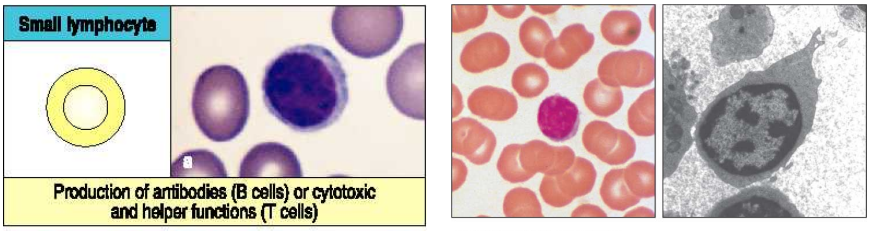


Fig 1.5 © 2001 Garland Science

- Mediators of adaptive immunity
- distinguish self / non-self
- resting and activated appearance is different

Type of Lymphocytes

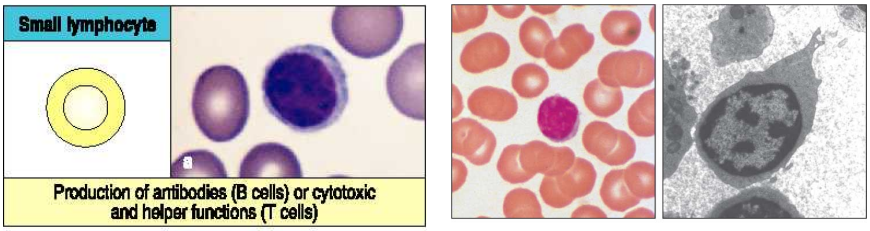
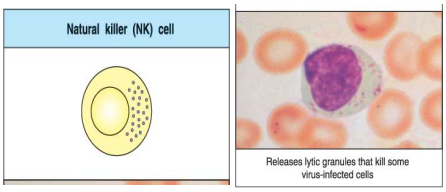
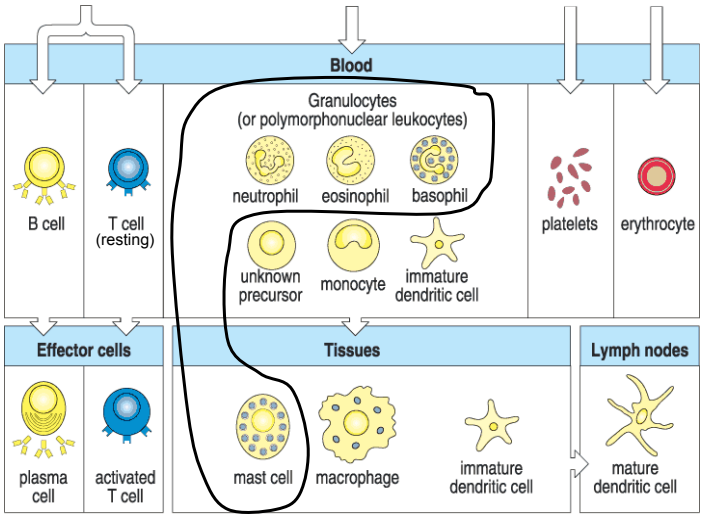


Fig 1.5 © 2001 Garland Science

- Killer T cells (CTL): recognition and lysis of infected cells
- Helper T cells (T_{H1}, T_{H2}, T_{H17}, T_{reg}):
  recognize infection,coordinate response, activate or inhibit effector cells
- B cells: antibody production
- NK cells: lyse infected cells
- Innate-like lymphocytes:
  B-1 cell, γδ T cells, NKT cells





Myeloid cells
phagocytes, granulocytes
(innate immunity)

Myeloid cells

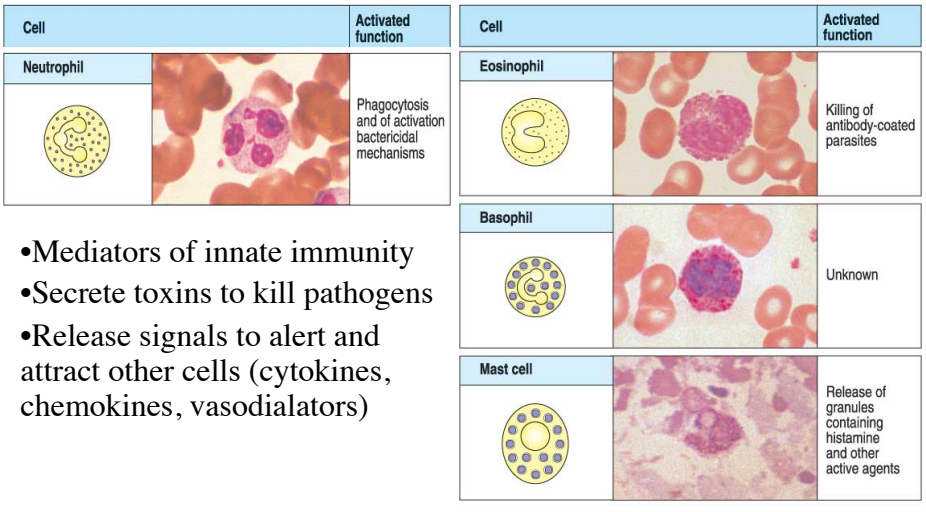
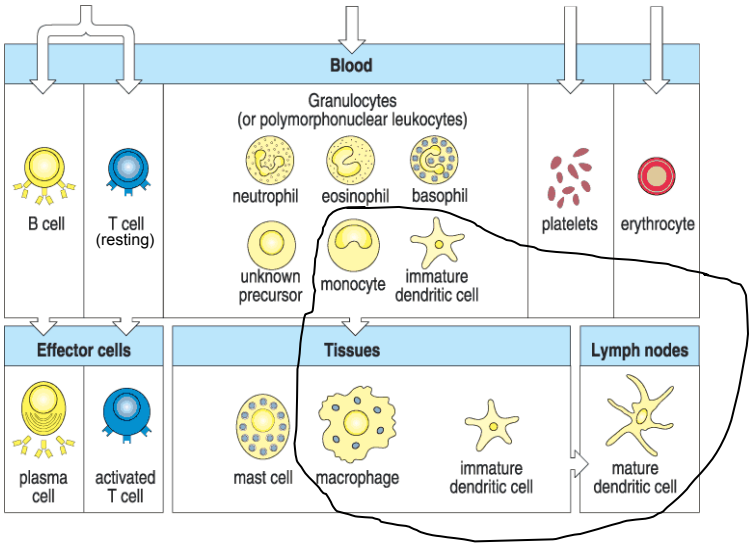


Fig 1.4 part 2 of 2 © 2001 Garland Science

- Mediators of innate immunity
- Secrete toxins to kill pathogens
- Release signals to alert and attract other cells (cytokines, chemokines, vasodialators)

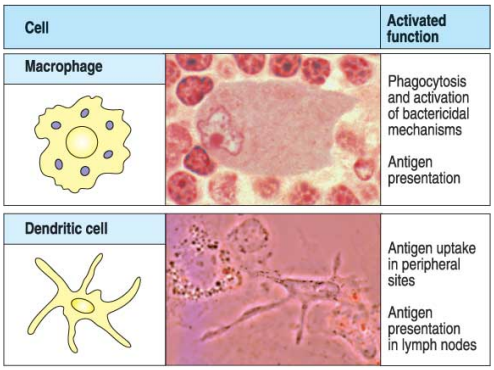


Antigen presenting cells
(bridge between adaptive and innate immunity)

Antigen presenting cells

Functions of APC

- sentinels / warning
- sample environment by phagocytosis and surface receptors
- process antigens and "present" them to helper T cells



Other functions

- Mϕ: phagocytic effector cells
- DC: carry antigens to lymph nodes

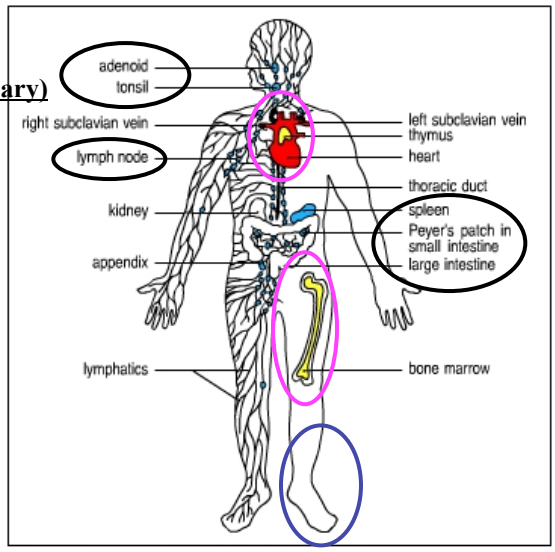
Where are immune cells in the body?

Primary immune organs
Bone marrow
Thymus

Peripheral (secondary) Lymphoid tissue
Lymphocytes
Macrophages
Dendritic cells

Blood
Granulocytes
Monocytes
Lymphocytes

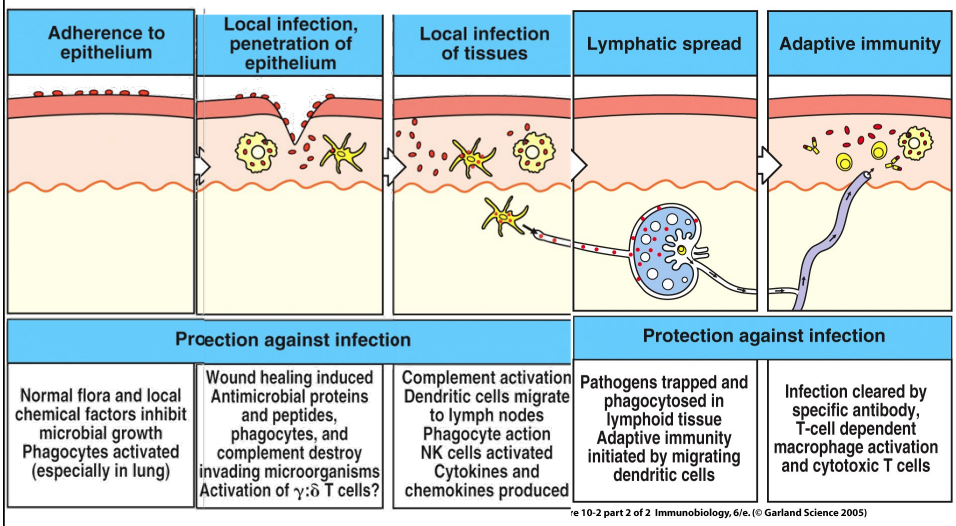
Tissues
Macrophages
Dendritic cells
Mast cells



Summary of key points

- Immune cells arise from a common precursor
- Different types of immune cells have different functions
- Phagocytic and secretory myeloid cells (neutrophils, PMN, mast cells, basophils, mϕ) provide immediate response, sound alarm
- Lymphocytes (B, T, NK cells) are specialized for specific antigen recognition
  - –Activated B cells secrete Ab
  - –Activated CTL lyse infected cells
  - –Activated TH cells recognize infection, coordinate response

Stages of response to infection



Classic signs of inflammation

Calor, dolor, tumor, rubor

warmth, pain, swelling, redness

Aulus Cornelius Celsus
25 – 50 AD
De Medicina

Inflammation

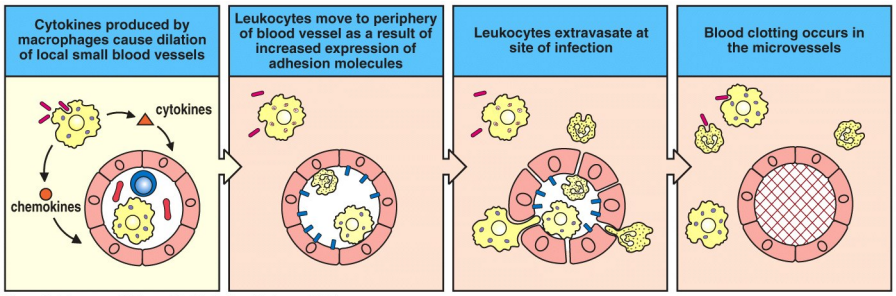


Figure 2-8 Immunobiology, 6/e. (© Garland Science 2005)

- Induced by resident leukocytes, complement activation, or tissue damage
- Results in:
  - Increased vascular diameter, local blood flow
  - Upregulation of endothelial cell adhesion molecules
  - recruitment of leukocytes from blood (extravasation)
  - plasma leakage (edema)

Dendritic cells deliver tissue antigen to lymph nodes and present it to lymphocytes

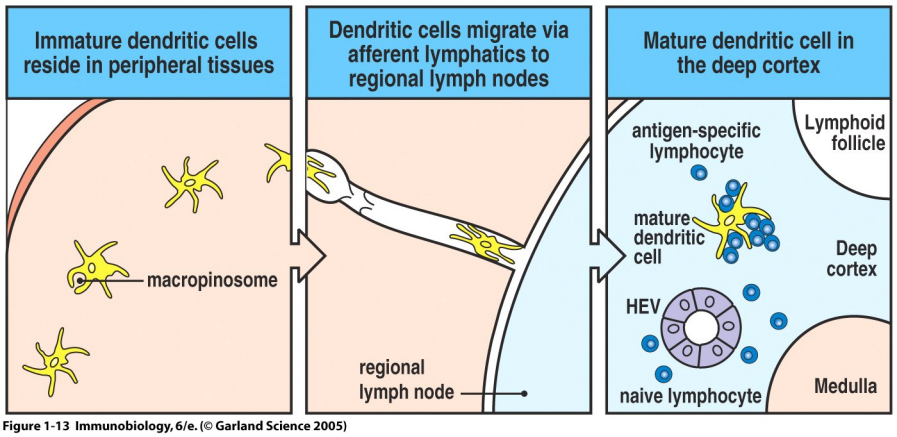
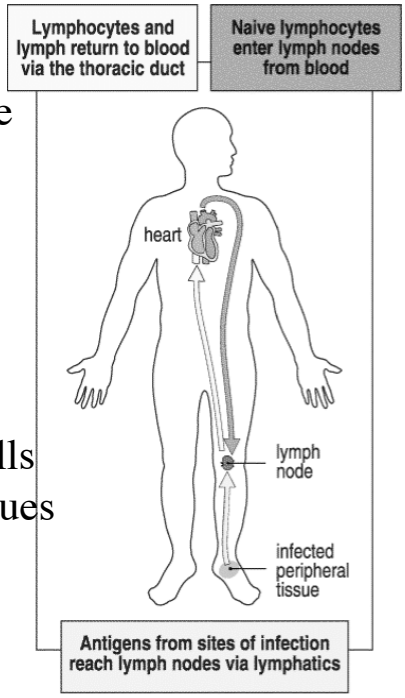


Figure 1-13 Immunobiology, 6/e. (© Garland Science 2005)

Lymphocytes circulate between blood and lymphatic fluid

Antigen-presenting cells carry antigens from tissues to lymph nodes



Lymph nodes - and other peripheral lymphoid tissue - where lymphocytes meet antigens

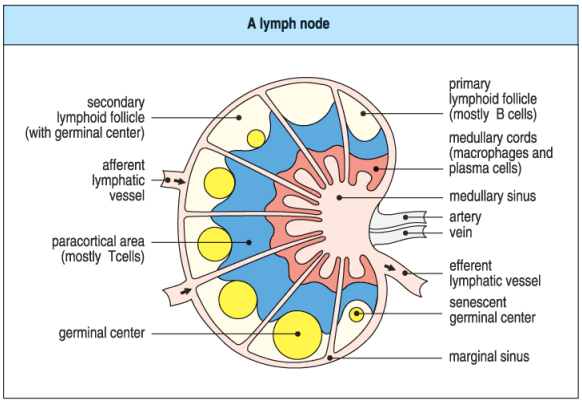
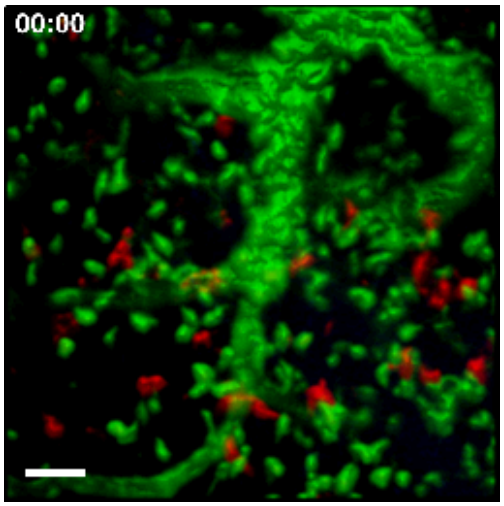


Fig 1.8 part 1 of 2 © 2001 Garland Science

Fig 1.8 part 2 of 2 © 2001 Garland Science

T cells searching for antigen in lymph node



Meeting of lymphocytes and antigen is important in the conversion of naïve lymphocytes to active forms that can perform their respective immune functions

Naïve: simple and guileless, unsuspecting
In immunology, having been never exposed to antigen

Summary of key points

- Inflammation is a rapid response to penetration of the epithelial barrier, and serves to deliver effector molecules and cells to sites of infection
- Inflammation is triggered by soluble mediators released by tissue-resident leukocytes: mΦ, mast cells, and causes monocytes, neutrophils, and lymphocytes to extravasate near sites of infection
- antigen presenting cells acquire antigens and carry them to lymphatic tissue to initiate adaptive responses
- naïve lymphocytes (B cells and T cells) meet antigens on APC in lymph nodes, inducting lymphocyte maturation
- yin/yang of immunity:
  - possibility of collateral damage by innate system
  - possibility of autoreactivity by adaptive system

The end