# Immune Responses: The Good, the Bad and the Ugly

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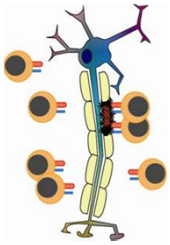
## Overview

- Where does immunology come from?
- Where is the immune system?
- How does the immune system recognise infection?
- What happens when this goes wrong?



## How old is the study of immunology?

- The concept of immunity is an ancient one
- Exploited by Edward Jenner who used cowpox inoculation to prevent smallpox (1796)
- Modern understanding of immunology – that it depends on cells – required the formulation of the germ theory of disease towards the end of the 19th century by Louis Pasteur, Robert Koch, Eli Metchnikoff, Paul Ehrlich and others

## Rabies

Number of people who have survived symptomatic rabies (2009) **6**

Louis Pasteur by Patrice Debré

Johns Hopkins University Press 1998

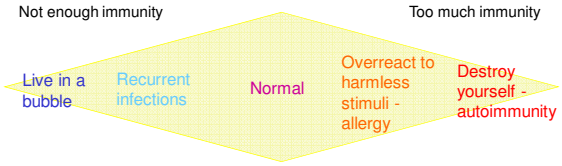
'… here Pasteur left the field of bacteriology, itself still in its infancy, to become the first to venture into … immunology … a new science that would provide the means of understanding and manipulating natural immunity.'

'At the beginning of each session, a loaded revolver was placed within their reach. If a terrible accident were to happen to one of them, the more courageous of the two others would put a bullet in his head.'

## Complications of the rabies vaccine

- Attenuation was used to develop a rabies vaccine. Rabid rabbit spinal cords were dried in air and used to treat patients.
- Approximately 0.1% of vaccine recipients developed an acute paralytic illness; most recovered.
- The immune system is confusing the rabbit brain and the human brain

## The Immune Response is a Two Edged Sword




A spectrum of possible immune responses

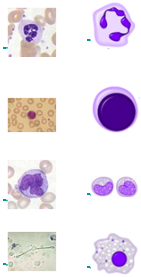
## Immune function depends on cells

Neutrophil (60%)

Lymphocyte (30%)

Monocyte (5%)

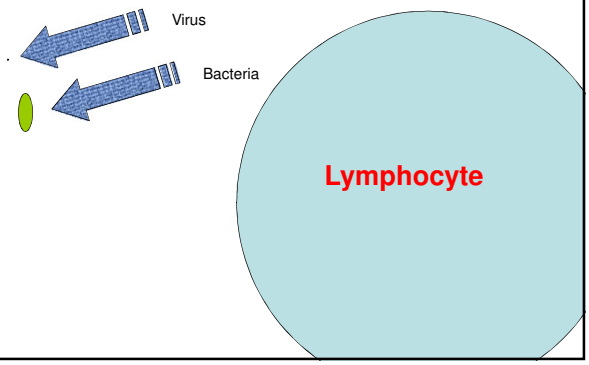
Macrophage (in tissues)



- How many cells are there in a millilitre of blood?
- Red cells – 500m
- White cells - 1,000,000

en.wikipedia.org/wiki/White_blood_cells

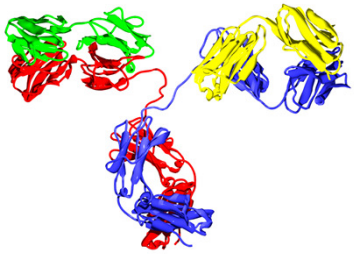
## Pathogens and lymphocytes drawn to scale




## How does the immune system recognise infection

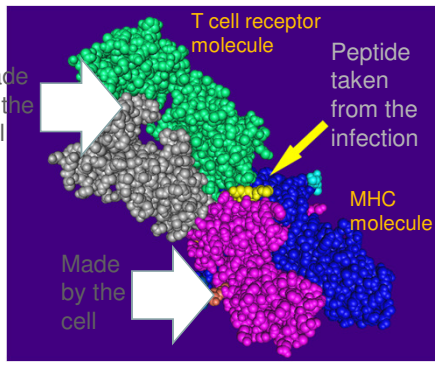
- 1. Antibodies recognise infection directly
- 2. Lymphocytes recognise infection indirectly

## Antibodies bind directly



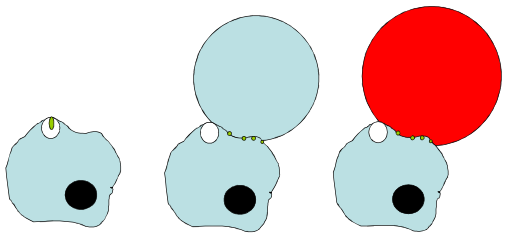
commons.wikimedia.org/wiki/File:Antibody_IgG2.png

## T cells recognise infection indirectly




commons.wikimedia.org/wiki/File:TCR-MHC_II.png

## How T cells recognise infections

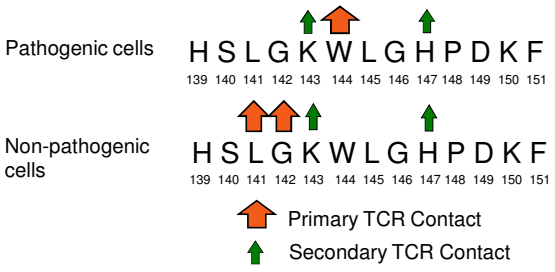


1. Antigen presenting cell digests infection to produce peptides

2. Peptides are shown to T cell

3. T cell with specific receptor activated to produce helper cells and killer cells

## T cells focus on a limited set of amino acids



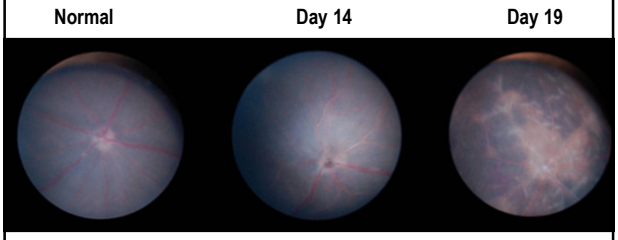

Prabhu-Das et al. J. Exp. Med. 186: 867 1997

## The immune system constantly patrols the body

- Samples the environment for evidence of infection
- Examines cells to see if they are infected
- Examines cells to see if they are cancerous

Calls for Help
Starts killing
Produces inflammation

## Inflammation of the retina




Invest. Ophthal. Vis. Sci. **49**:5458 (2008)

## Autoimmunity occurs because…

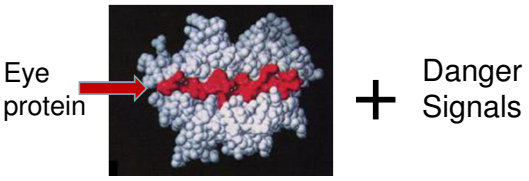
- … the sufferer has a 'permissive' set of genes (so it runs in families)
- …the environment triggers disease (e.g. some viral or bacterial infections)
- …the immune system mistakes a healthy cell for an infected or a cancerous cell

## How do the T cells get activated?

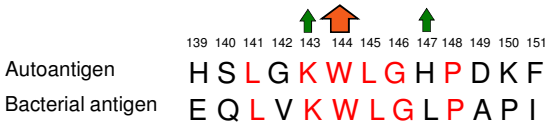
### Sympathetic Ophthalmia

- In 1583 George Bartisch wrote that after injury the eye may shrink and become painful, "in this case the other eye is in great danger"
- 80% of cases develop within 3 months; can occur up to 50 years after initial injury

## Bystander Activation



## Molecular Mimcry

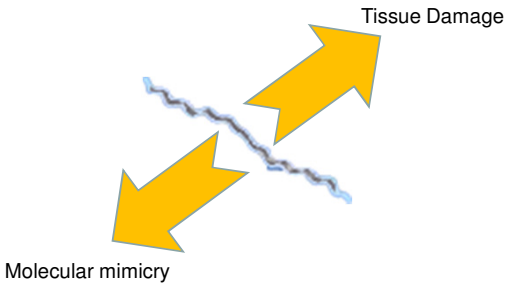



Carrizosa, A. M et al. (1998) Journal of Immunology **161(7): 3307-3314.**

## What amino acid substitution studies tell us

- TCRs can be exquisitely sensitive to single amino acid changes
- TCRs can accept multiple substitutions without losing the ability to respond
- TCRs can be activated by two peptides of completely different sequence
- A single TCR in a mouse has the potential to be stimulated by about 13 self-peptides

## The Complexity of Infection




## What can we study

- Genetics:
  - To find all the genes that play a role and to establish the effect of individual genes on disease
- Immune mechanisms:
  - To find out which cells are important and what molecular programmes they use to cause disease
- Treatments:
  - To test new drugs or therapies quickly before trying them in patients

## Treatments for autoimmune disease

- Anti-inflammatory (Aspirin-like; steroids)
- Immunosuppressive (Killing immune cells or inhibiting their function)

- Antigen specific 'anti-vaccination'
- Modulate immunity selectively in the affected organ

## Important questions for future research

- Understand what triggers human disease
- Predict how bad disease is going to be
- Target drugs to a specific immune response not to the whole immune system

## Summary

- The 'immune system' is a collection of cells that respond to pathogens.
- This response causes inflammation
- The response can be life saving (e.g. rabies vaccination)
- The response can destroy normal life (e.g. multiple sclerosis; uveitis)
- There is still lots to learn

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