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

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

Pathogens and lymphocytes drawn to scale

How does the immune system recognise infection

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

T cells recognise infection indirectly

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

Pathogenic cells: H S L G K W L G H P D K F
Non-pathogenic cells: H S L G K W L G H P D K F

Primary TCR Contact
Secondary TCR Contact


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

Normal Day 14 Day 19


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 Bartsch 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

Danger Signals

Eye protein
Molecular Mimicry

Autoantigen: 
H S L G K W L G H P D K F

Bacterial antigen: 
E Q L V K W L G L P A P I

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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