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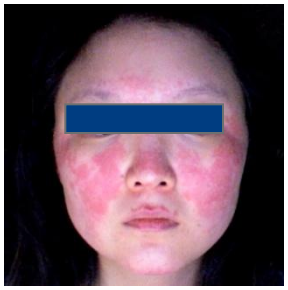
Autoimmunity: An Overview

BSc. Immunity and Infection

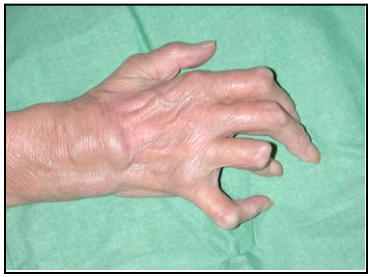
Module 3



Malar Rash - SLE

Dr Nicola Rogers

3rd January 2013



Joint damage - RA

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Autoimmunity – An overview

- What is it?
- How does it occur?
- Spectrum
- Pathogenesis
- Immunopathology
- Immunotherapy

Definition

- Immune response to self-antigen
- Breakdown in tolerance
  - Internal disregulation of the immune system
  - Resemble normal immune responses in that they are specifically activated by antigen

Central dilemma of immune system

How to provide effective defence against invading pathogens whilst avoiding unwanted activation of self-reactive T and B cells?

Healthy individuals

- Thymic negative selection is not 100%
  - self-reactive cells found in the peripheral T cell repertoire of healthy individuals
- MBP-specific $CD4^+$ in healthy individuals as well as MS patients
  - activation status different
- Up to 30% of population thought to carry self-reactive Ab, yet <1% develop SLE

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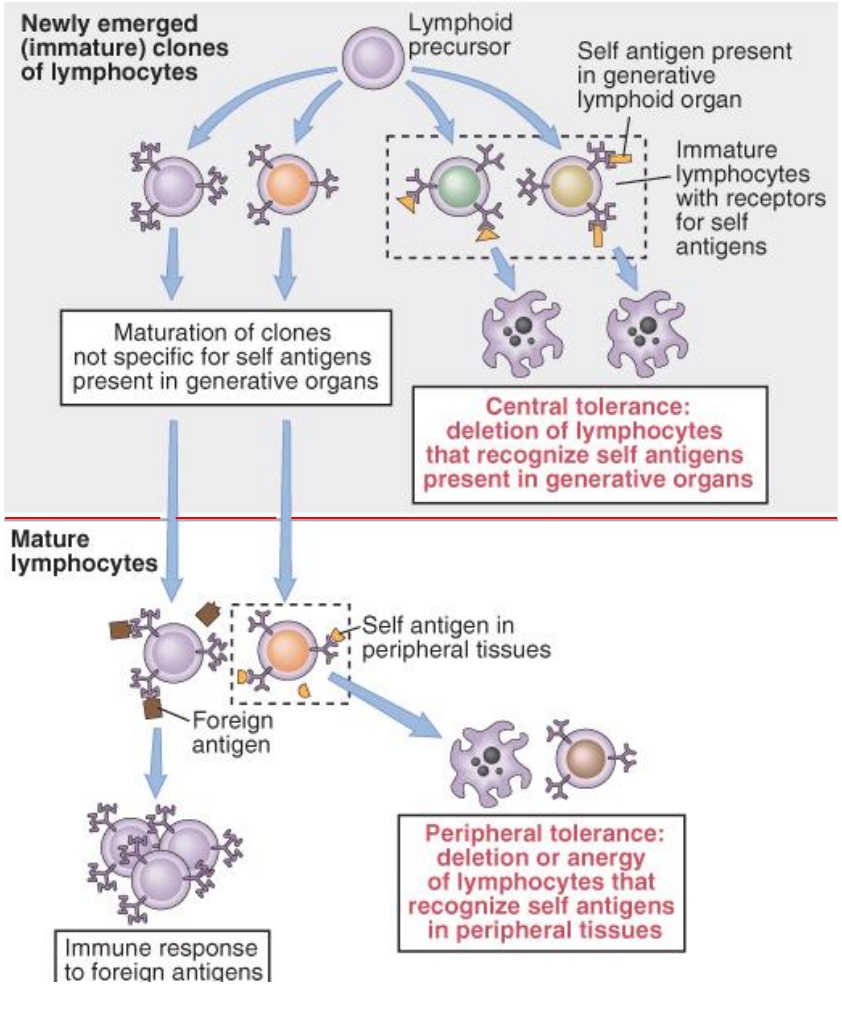
Tolerance mechanisms

Central
- Thymic deletion
- Lymphocyte selection
- Expression of Aire

Peripheral
- Anergy
- Deletion
- Regulation



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Breakdown in tolerance

- Failure of these mechanisms may result in a response to:
  - Innocuous non-self antigens
    - » Allergy
  - Self
    - »Autoimmunity

Prevalence – autoimmune disease

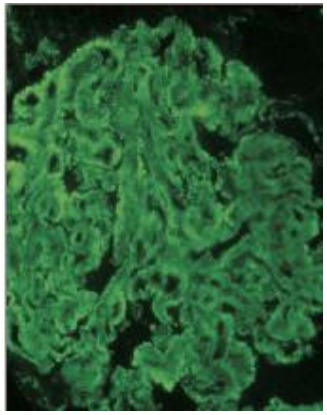
- 3-5% in developed countries
  - approximately 3 million in the UK
- Third major cause of morbidity and mortality
  - after cancer and atherosclerosis
- Incidence steadily increasing over last 3 decades

Spectrum

- Response elicited depends on antigenic target
- Extreme spectrum of disease
  - Systemic/Non-organ specific
    - »Systemic Lupus Erythematosus (SLE)
  - Organ-specific
    - »Type 1 Diabetes (T1D)

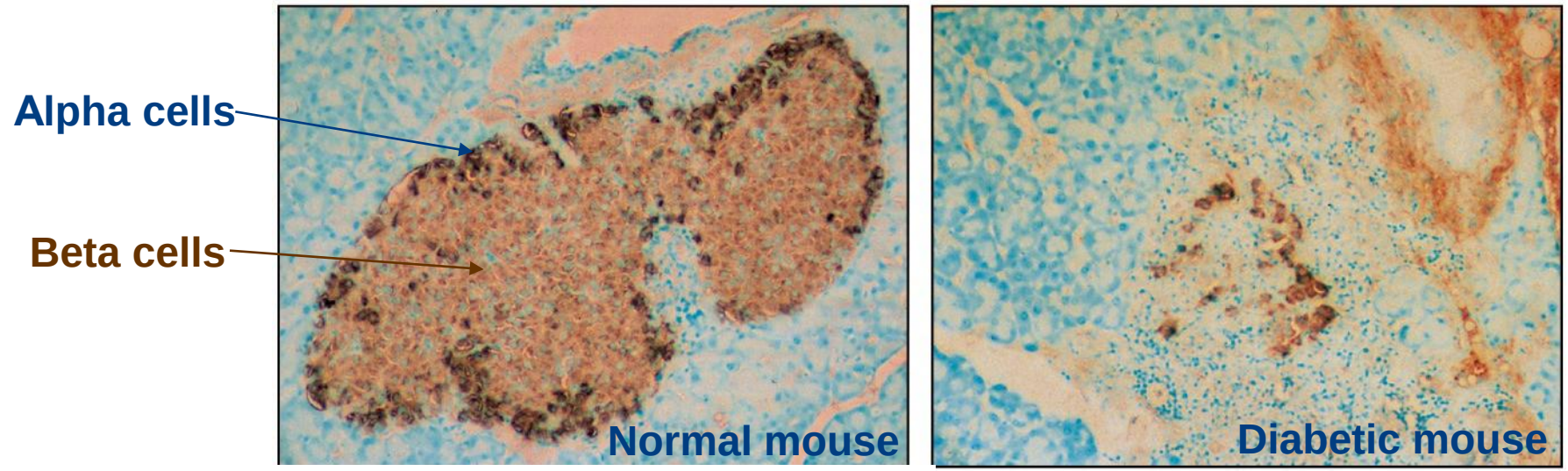
Systemic - SLE

- Immune-mediated damage to many organs
- Self-reactive T and B cell activation
- Production of AutoAb
  - Histones, chromatin, DNA, RNA
- Deposition of immune complexes in microvasculature
  - Glomerulonephritis
  - Splenomegaly,
  - lymphadenopathy



Organ specific – T1D

- Immune mediated damage to β cells
- Cytotoxic T cells kill β cells resulting in inability to produce insulin
- α cells within the islets of langerhans are unharmed



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Pathogenesis

- Genetic factors
- Gender
- Environment
- Immune response

Pathogenesis – Genetic Factors

- HLA and non-HLA associations
- Sibling risk and family studies
- Population studies
- Linkage studies

Genetic factors

- Monozygotic and dizygotic twins
  - 20% concordance for monozygotic vs 5% for dizygotic twins in both SLE and T1D (IDDM)
    - »HLA genes

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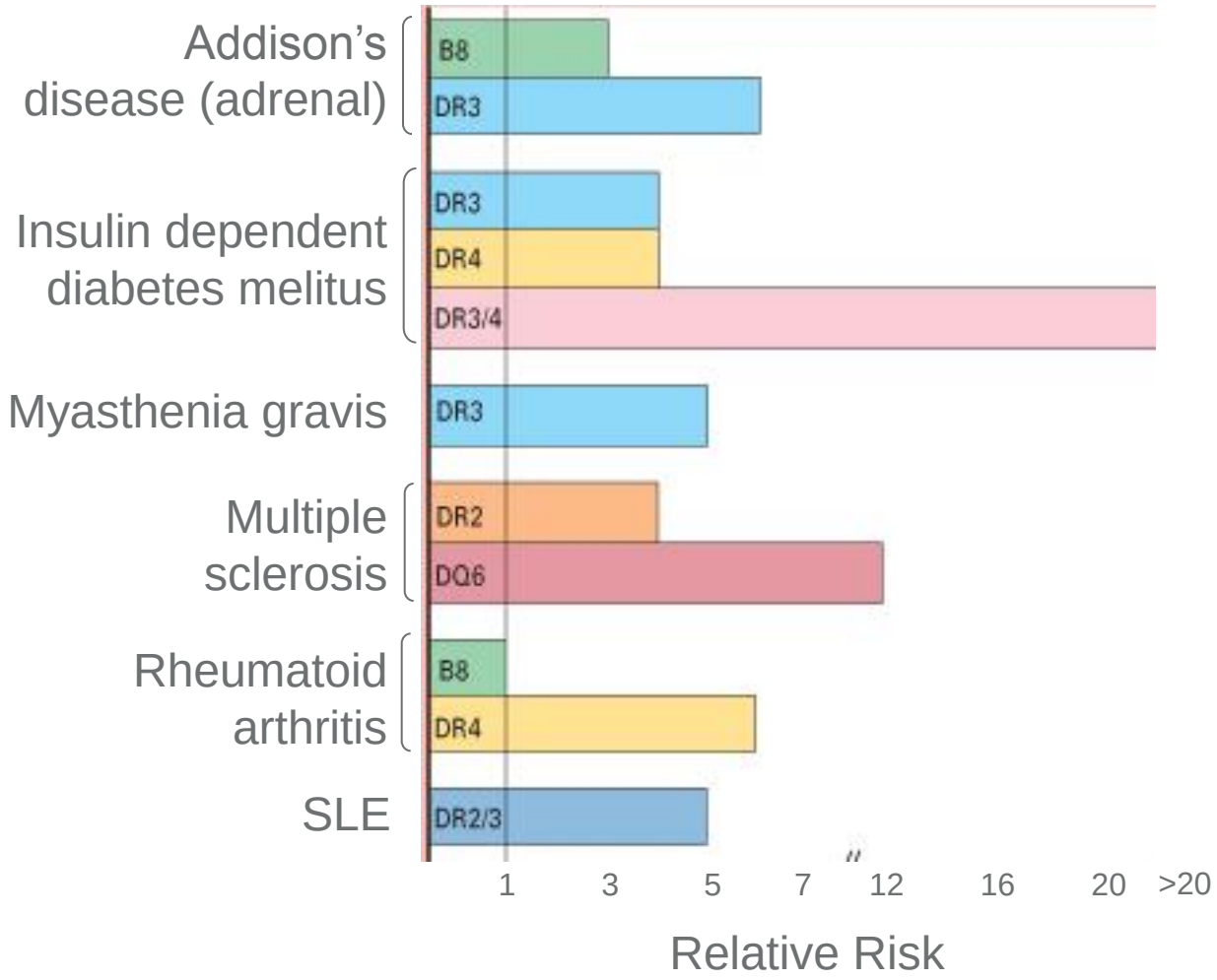
HLA



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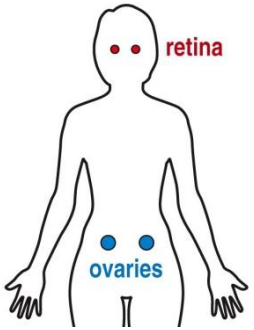
Genetic factors

- Monozygotic and dizygotic twins
  - 20% concordance for monozygotic vs 5% for dizygotic twins in both SLE and T1D (IDDM)
    - »HLA genes
  - Only 20% concordance for HLA identical sibs, therefore other genes also involved
    - »Non-HLA

Non-HLA alleles

- Incidence of autoimmune disease is higher in identical twins than in HLA-identical sibs
  - Eg: Type 1 Diabetes
- Involvement of non-HLA genes
  - Genes affecting different aspects of tolerance
    - »AIRE
    - »FoxP3 ($CD25^+$ Tregs)
    - »CTLA-4

AIRE



- *Aire*: Autoimmune regulatory gene
  - Aire$^{-/-}$ mice
- Regulates the presentation of peripheral self-antigen in the thymus
  - tissue-specific antigens
  - developmental antigens
- APECED (autoimmune polyendochrinopathy, candidiasis-ectodermal dystophy) ; APS-1

IPEX

- IPEX:
  - X-linked polyendocrinopathy
  - Fatal disorder
  - Mutations in Foxp3 gene in patients
    - »13/14 patients
  - Same symptoms as *scurfy* mice

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Autoimmunity and Gender

	F:M
Anklyosing spondylitis	0.3
Acute anterior uveitis	0.5
Goodpastures syndrome	1
Myaesthenia Graves	1
Type I Diabetes	1
Pemphigus vulgaris	1
Rheumatoid Arthritis	3
Grave's Disease	4-5
Hashimoto's thyroiditis	4-5
Multiple Sclerosis	10
Systemic Lupus Erythematosus	10-20

Gender and Autoimmunity

- Females mount more vigorous immune responses:
  - produce higher Ab titres
  - have higher levels of $CD4^+$ T cells
  - have significantly higher levels of serum IgM
  - tend to drive towards Th1responses

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Gender and murine studies

- Female mice more likely to generate Th1 responses
- Immune response can be modified by:
  - castration
  - injection of testosterone

- Prolactin directs towards to Th1
- Estrogen demonstrated to be immunostimulatory
- Female NOD more susceptible to spontaneous diabetes

Environment and Autoimmunity

- Goodpasture's Disease
  - Autoantibodies to GBM
  - All patients develop glomerulonephritis
  - 40% develop pulmonary haemorrhage
    - »40% are smokers
    - »Capillary damage and exposure of autoAg
- Infection
  - Molecular mimicry
  - Superantigen

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Famous person and “discovery”

A C I H H E R P L L U

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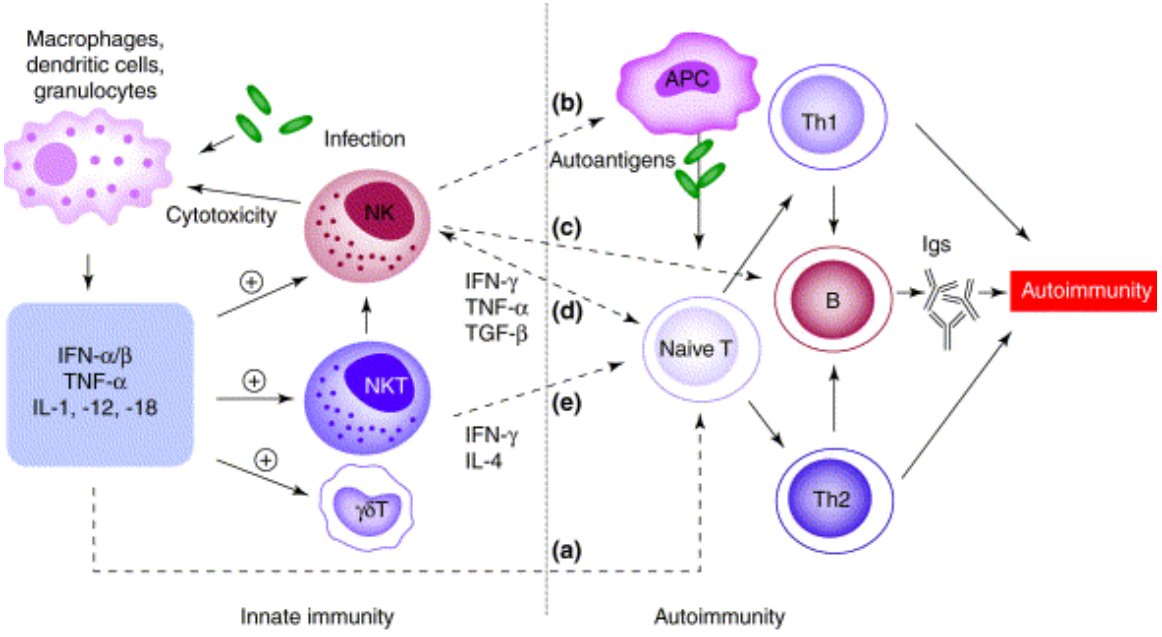
Immunopathology

Innate and adaptive immune components



Autoimmune disease – immunopathology

- Majority of pathology attributed to the adaptive immune response and dominated by either:
  - Cell mediated
    - »Inflammatory cytokine production
  - Humoral (antibody) mediated
    - »Immune complexes
  - Reminiscent of hypersensitivities (Types II-IV)
- Increasing evidence for innate component

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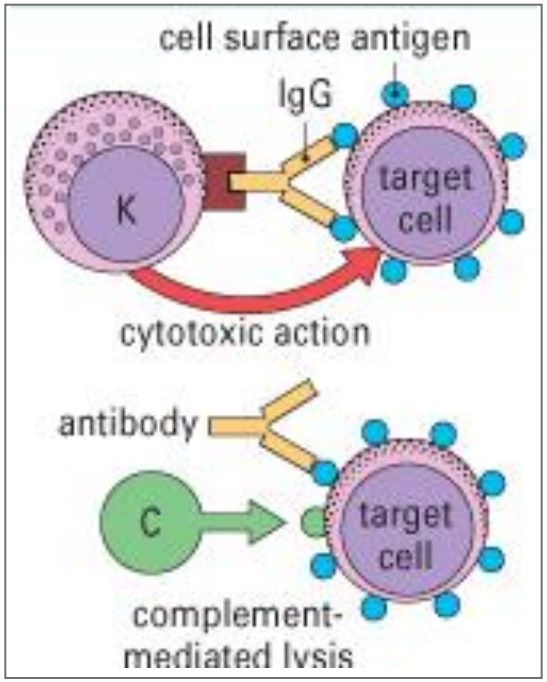
Adaptive - immunopathology

Surface Ag



Organ Specific
Systemic

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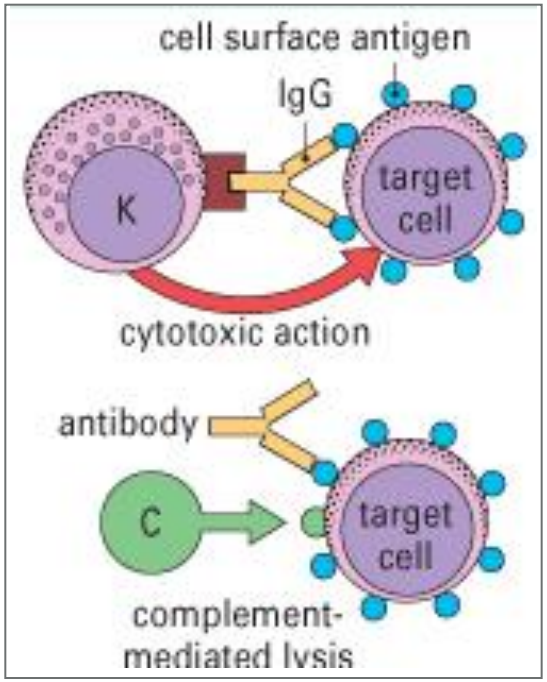
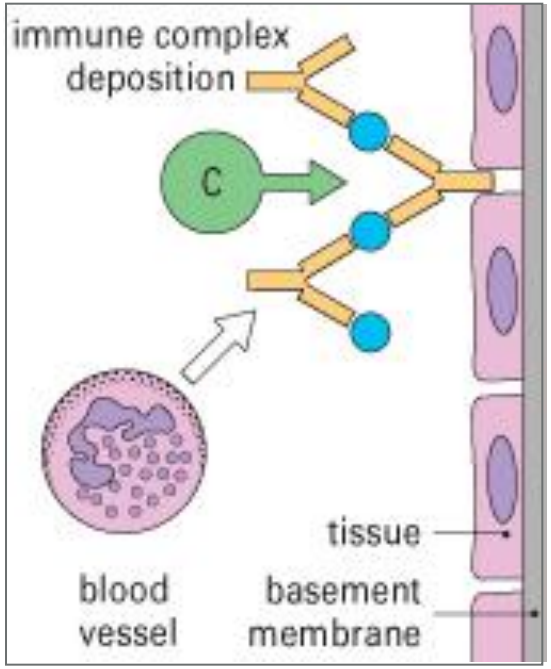
Adaptive - immunopathology

Surface Ag



Immune complex

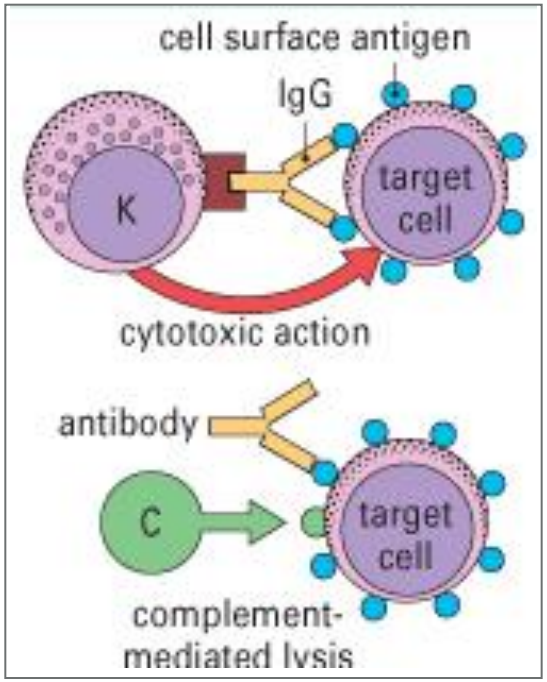


Organ Specific
Systemic

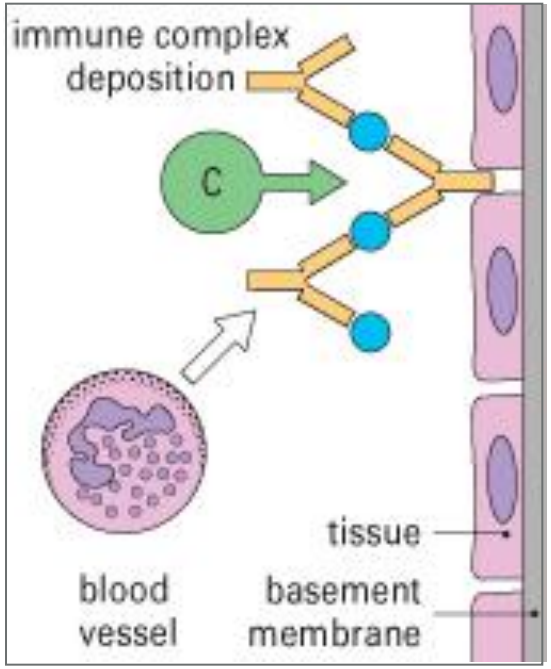
Systemic

Adaptive - immunopathology

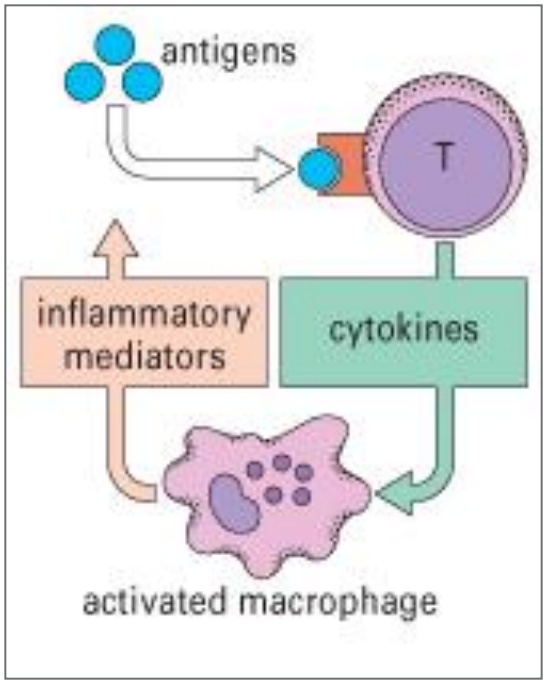
Surface Ag



Immune complex



T cell driven



Organ Specific
Systemic

Systemic

Organ Specific
Systemic

[2]

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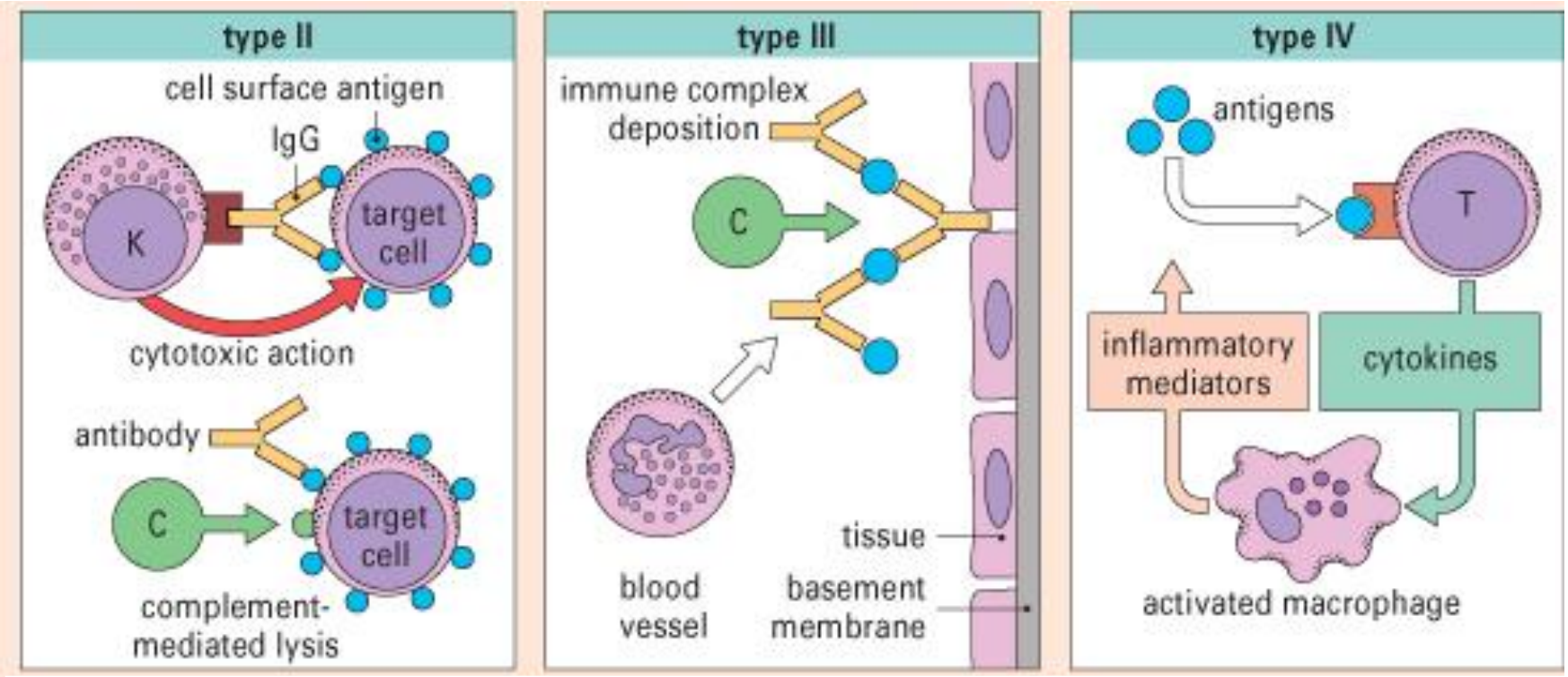
Autoimmune pathology

Surface Ag | Immune complex | T cell driven



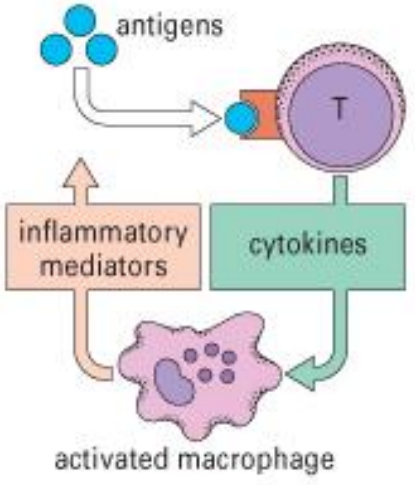
Hashimotos Thyroiditis
Goodpastures Disease

SLE

T1D
RA

Thelper profile

- Upsetting the Th1/Th2 balance
- Majority demonstrate a Th1 profile
- Inflammatory cytokines
  - RA
  - T1D
- Role of recently identified Th17 cells
  - EAE
  - CIA



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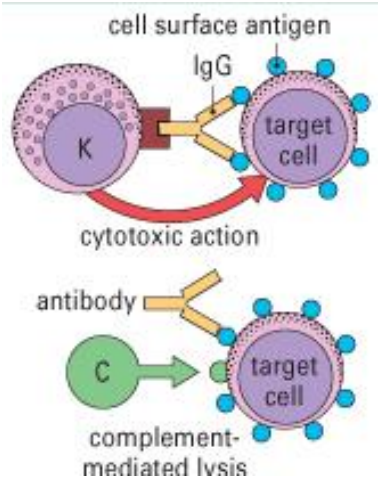
B cells and autoAb

- Frequency of auto-reactive B cells higher
- Auto-reactive antibodies capable of
  - Recognising and binding to self
  - Complement mediated lysis



B cells and autoAb

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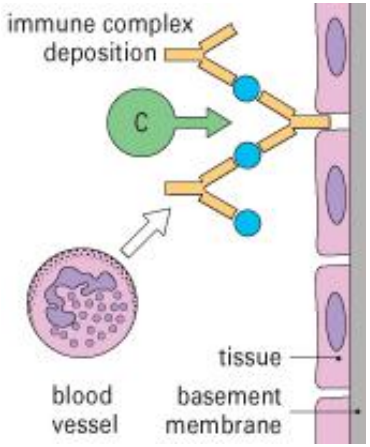
  - Formation of immune complexes



[2]

B cells and autoAb

- Frequency of auto-reactive B cells higher
- Auto-reactive antibodies capable of
  - Recognising and binding to self
  - Complement mediated lysis
  - Formation of immune complexes
- Class switched Ab requiring T cell help
  - Th2

Regulatory T cells

- Peripheral tolerance mechanism
  - $CD25^{+}FoxP3^{+}$
  - NKT
- Absence or defective function associated with autoimmunity
- Presence associated with tolerance
- Preclinical animal models – antigen specific immunotherapy

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Immunopathology - Tregs

- Peripheral tolerance mechanism
- Aberrant role demonstrated:

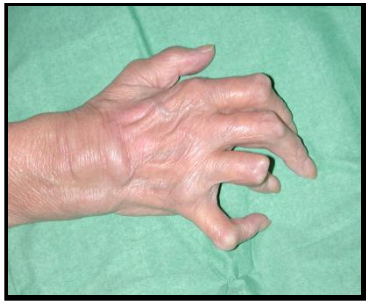
NKT

- T1D
- EAE
- RAE
- SLE
- Myaesthenia Graves
- Prostatitis
- IBD

$CD25^+$ FoxP3

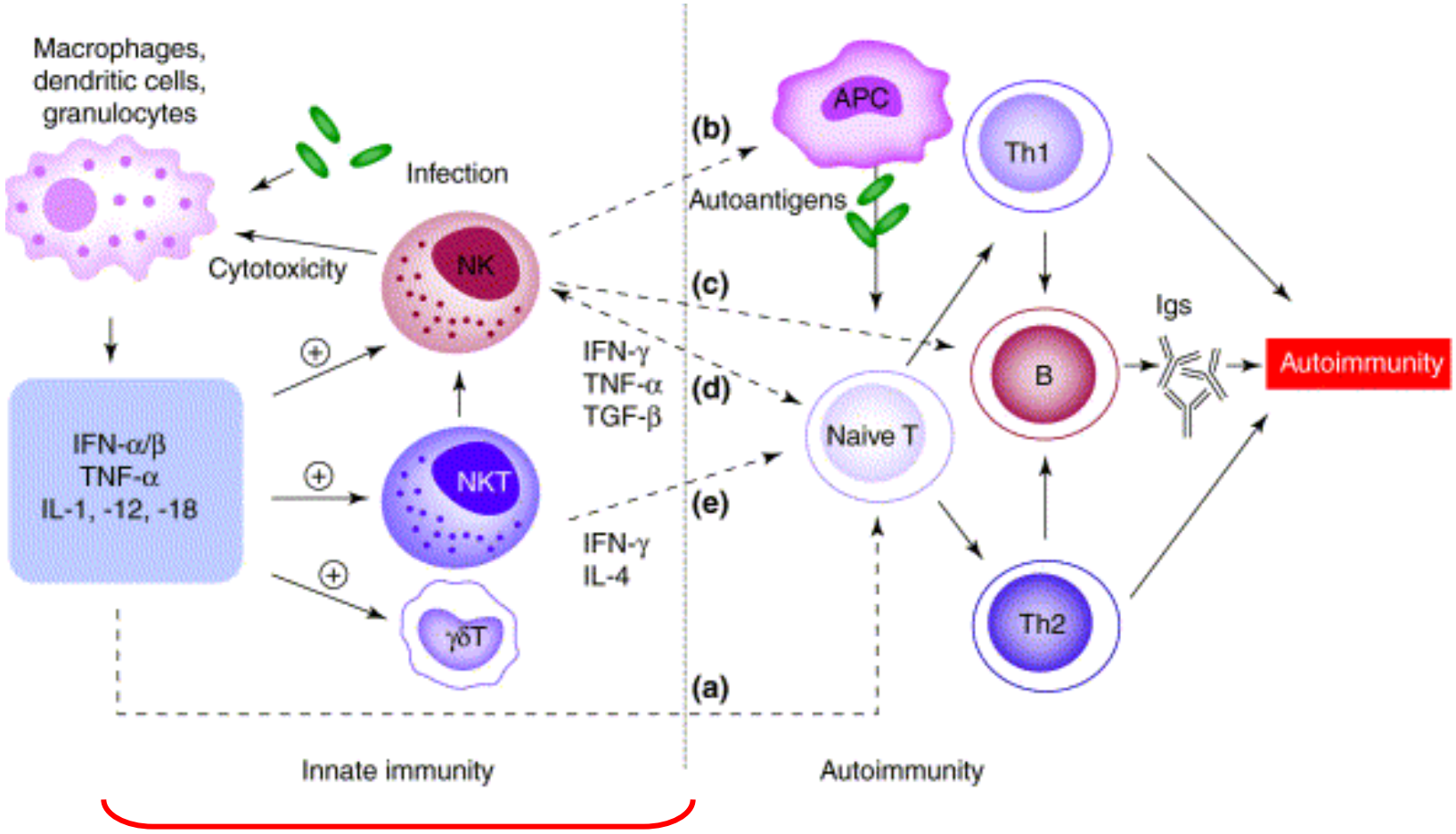
- Cutaneous AI
- T1D
- Thyroditis
- AI ovarian disease
- AI prostatitis
- SLE
- IBD

Cytokines



- Bridging innate and adaptive autoimmunity
  - Innate and adaptive cellular communication
  - Distinct innate and adaptive cytokines
- Inflammatory mediators
  - IFN-γ and TNF- α are two key players
- Mice deficient in IL-18, IL-1β, IL-12 and TNF-α
  - resistant to induction of autoimmunity

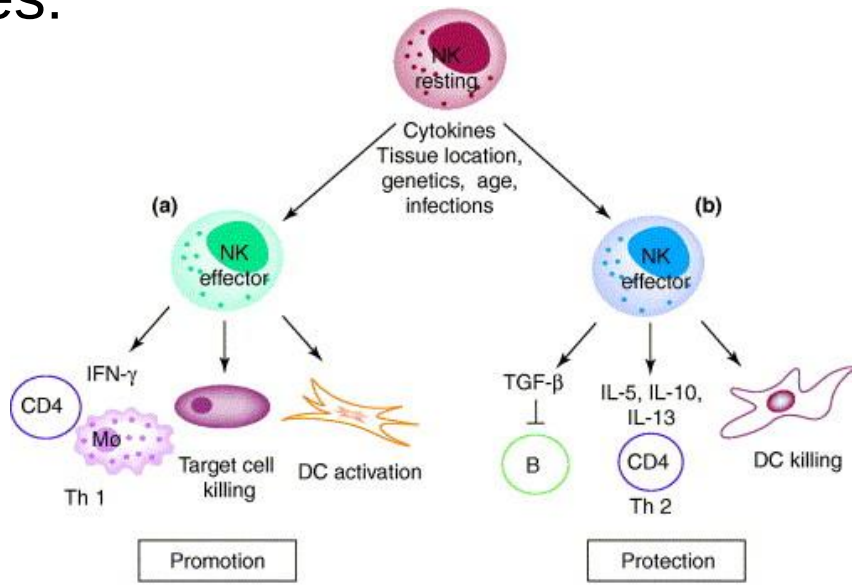
Innate - immunopathology



[Trends in Immunology]

NK cells

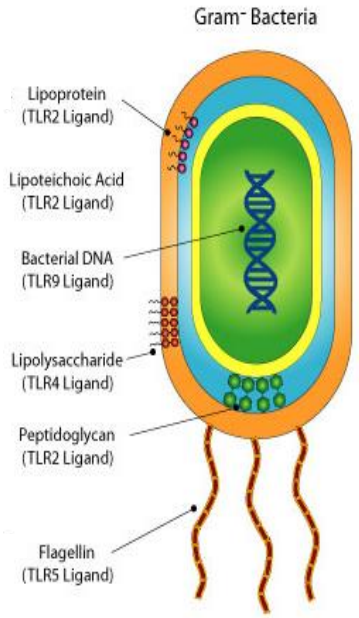
- Frequently present in target organs during disease progression
  - Protection or promotion?
  - Primary or secondary to immunopathology?
- NK cell depletion enhances:
  - MS, EAE, Colitis

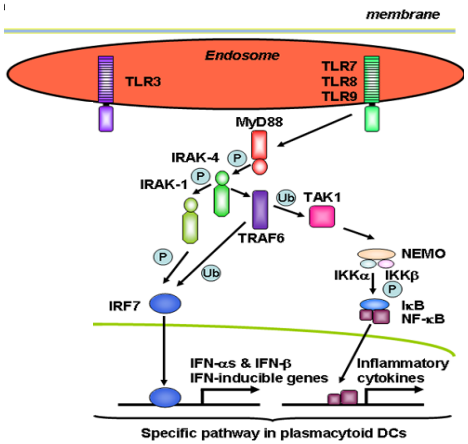


[Trends in Immunology]

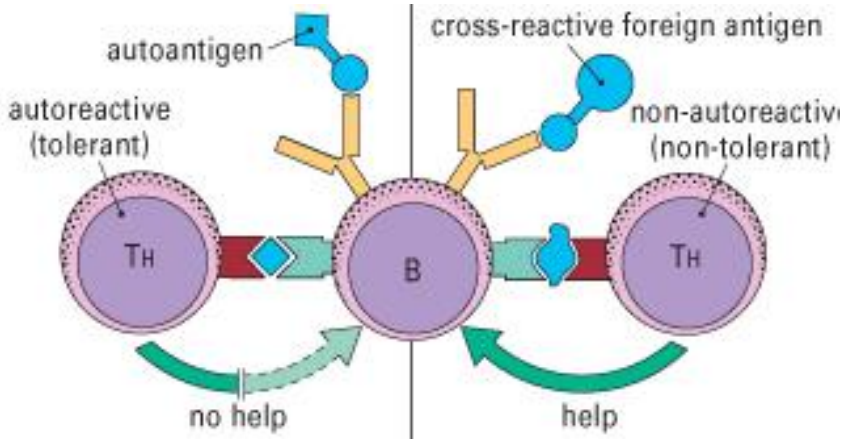
Toll Like Receptors

- Widely expressed (DC, NK, T)
- Endogenous ligands identified
- Activation of auto-reactive T and B cells
- Onset of autoimmunity following TLR triggering
  - EAE, T1D, Myocarditis, Arthritis
- Link to IFN-α
  - SLE, autoimmune hepatitis





Infection



- Cause or trigger?
- Infection triggers in MS
- EAE relapses – viral infection
- Diabetes induced by coxsackie virus
- Experimental models of induced immunity often involves use of bacterial adjuvant

- Or

TLR-mediated?

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Molecular Mimicry

Protein	Sequence
Human Cytomegalovirus IE2	PDPLGPDED
HLA-DR	VTELGPDEA
Poliovirus VP2	STTKESRGTT
Acetylcholine R	TVI KESRGTK
K.Pneumoniae nitrogenase	SRQTDREDE
HLA-B27	KAQTDREDL

Shown to exhibit immunological cross reactivity

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Immunotherapy

Inhibit on-going immune responses and reverse immunopathology

Current immunotherapy -1

- Non-specific immunosuppression
  - Prednisolone SLE
- Neutralising key inflammatory cytokines
  - TNF-α and RA
  - Infliximab
    - »Long-term safety overall good
    - »Increase in TB susceptibility

Current immunotherapy -2

- Targeting B cells
  - Rituximab (anti-CD20 B cell)
  - RA, SLE, Autoimmune haemolytic anaemia
- Targeting T cell signalling R (CD3)
  - Mitogenic, ck storm (FcR mediated – can be overcome)
  - T1D
  - Well tolerised Fc mutated non-mitogenic humanised Ab

Immunotherapy research

- Antigen-specific tolerance strategies
  - Peptide-specific tolerance for
    - »MS, RA, Type 1 diabetes
  - Ability to treat pre-existing disease, rather than prevent onset?
- Adoptive transfer of regulatory T cells

Immunotherapy - $CD25^{+}FoxP3^{+}$

- T1D; MS; IBD; RA
  - 14 prevention,
  - 2 remission
  - 2 inhibition of early progression
  - 1 reversal
- Limited success in reverting active disease
  - likely to require specificity for the pathogenic antigen

Autoimmunity - Summary

- Potent cause of immune disease
- Balance between preventing autoimmunity and not impairing specific immune responses
- Resemble normal immune responses
- Both cell mediated and Ab driven adaptive immune responses
- Role of innate immunity
- Complex pathogenesis
- Clearer understanding of pathology will facilitate immunotherapy

Figure Sources

1: Abbas & Litchman. Basic Immunology

2. Male *et al*. Immunology

3: Janeway *et al*. Immunobiology

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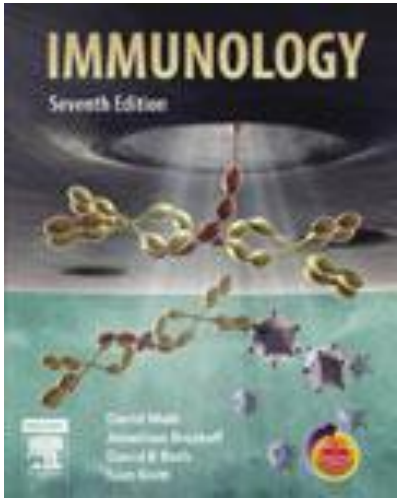
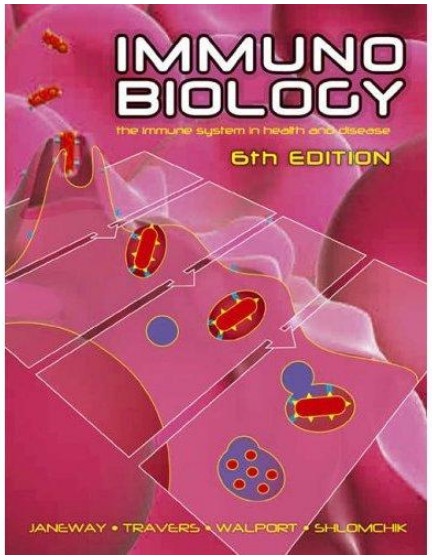
References





- Diamond, B. (2005). Autoimmunity. Immunological Reviews. 204: 5-8.
- Christen, U. and von Herrath, G. (2004). Initiation of Autoimmunity. 16: 759-767.
- Olsson, T. and Martin, R. (2006). Basic and clinical science approach complex diseases. Current Opinion in Immunology. 18: 1-4

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Related lectures

- All autoimmunity lectures
- All tolerance lectures
- Tregs
- Immunosuppression
- Thelper subsets

Self Study

- Identification of defined autoantigens
- Identification of animal models

Defined Autoantigens

Disease	Autoantigen
Grave's disease	
Type I Diabetes	
Myasthenia gravis	
	Gastric parietal cells IF
	Vertebrae
	ss and dsDNA, chromatin
	Brain and White matter
	Connective tissue, IgG

Animal Models

Animal Model	Human Disease	Autoantigen
NOD		
BXSB		
EAGM		
EAE		
AI arthritis		
EAT		