S. No	Topic	Class No	Date
1	Introduction	1 2	27/1 29/1
2	Fundamentals of Immunology • Definitions and basic terms • Types of immunity • Organs of immune system • Cells of immune system	3 4	3/2 5/2
	• Innate immunity • PAMPs • PRRs • Phagocytosis	5 6	10/2 12/2
3	• Antigens • Characteristic features of antigens • Types of antigens • Super antigens	7 8	17/2 19/2
4	• Humoral Immunity • Antibody – structure and functions	9 10	24/2 26/2
5	• Ig Biosynthesis • Monoclonal antibody production	11 12	3/3 5/3
6	• Complement system • 3 pathways of complement system	13 14 15	10/3 12/3 17/3
	Reserve	15	19/3
	First mid term (25 marks)	16	17/3 or 19/3
7	Cell mediated immunity • Macrophages • T cells • Th1 and Th2 response	17 18	24/3 26/3
8	MHC and transplantation immunity	19 20	31/3 2/4
9	Disorders of Immune system • Hypersensitivity • Immunodeficiency	21 22	7/4 9/4
10	Tumor immunology • Tumor specific antigens • TIL	23 24	14/4 16/4
11	Tolerance and autoimmunity	25	21/4
12	Antigen and Antibody reactions	26	23/4
	Reserve	27 28	28/4 30/4
	Second mid term(25 marks) (submit literature review – 10 marks)	27/28	27/4 or 28/4
	Final (40 marks)		

Immunological tolerance

Autoimmunity

By
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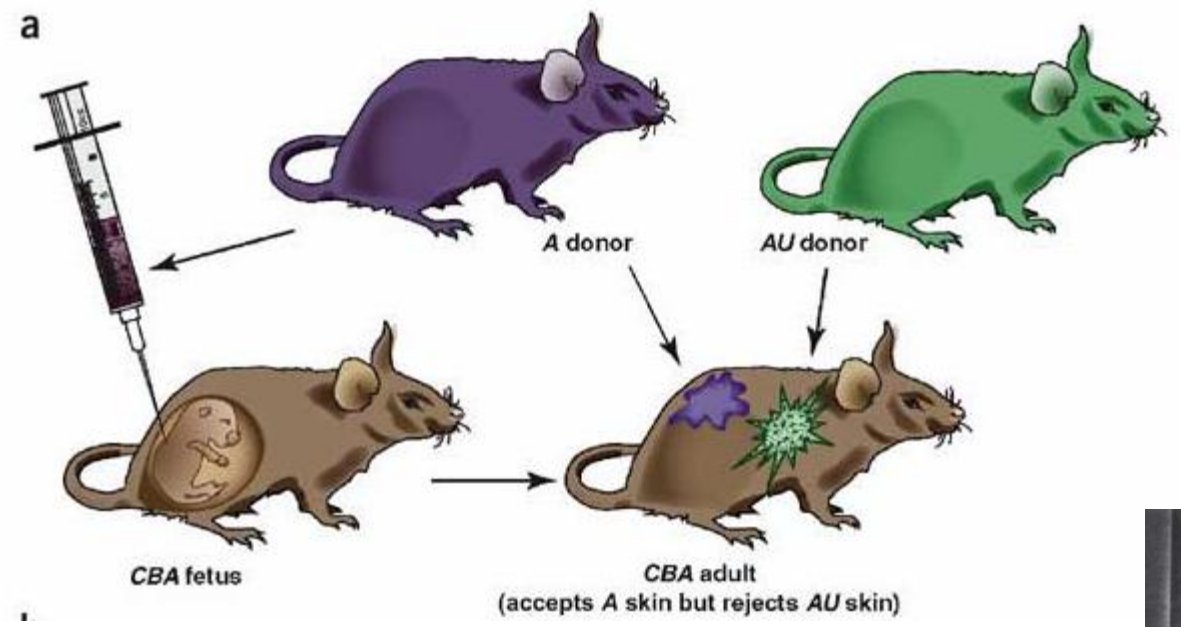
Tolerance

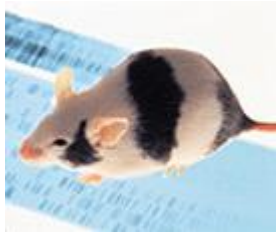
Tolerance refers to an antigen induced specific unresponsiveness

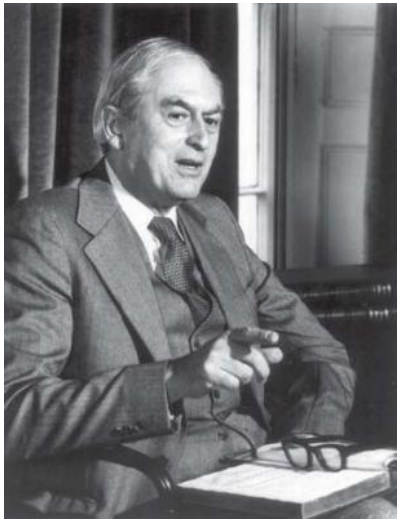
Tolerance

- Different from immuno-suppression
- We are tolerant to our tissues
  - Central tolerance
    - Result of thymus or bone marrow
  - Peripheral tolerance
    - Result of other factors out of thymus or bone marrow
- Breaking of tolerance leads to Autoimmunity
- Tolerance first observed in dizygotic twin cows (non responsiveness to each other)

Experimental induction of Tolerance







- Medawer's observation

Chimeric mice, is it possible in humans

Factors effecting tolerance

Factors that determine induction of immune response or tolerance following challenge with antigen		
Factors that affect response to Ag	**Favor immune response**	**Favor tolerance**
Physical form of antigen	Large, aggregated, complex molecules;	Soluble, aggregate-free, relatively smaller, less complex molecules, Ag not processed by APC or processed by cell without class II MHC
Route of Ag administration	Sub-cutaneous or intramuscular	Oral or sometimes intravenous
Dose of antigen	Optimal dose	Very large (or sometime very small) dose
Age of responding animal	Older and immunologically mature	Newborn (mice), immunologically immature
Antigen processing	Properly processed	Improperly processed

Immunological features of tolerance

- It is an antigen-induced, active process
- Like immunological memory it is antigen dependent
- Like immunological memory it can exist in T cells and / or B cells
- In T cells it is easy to induce and lasts longer

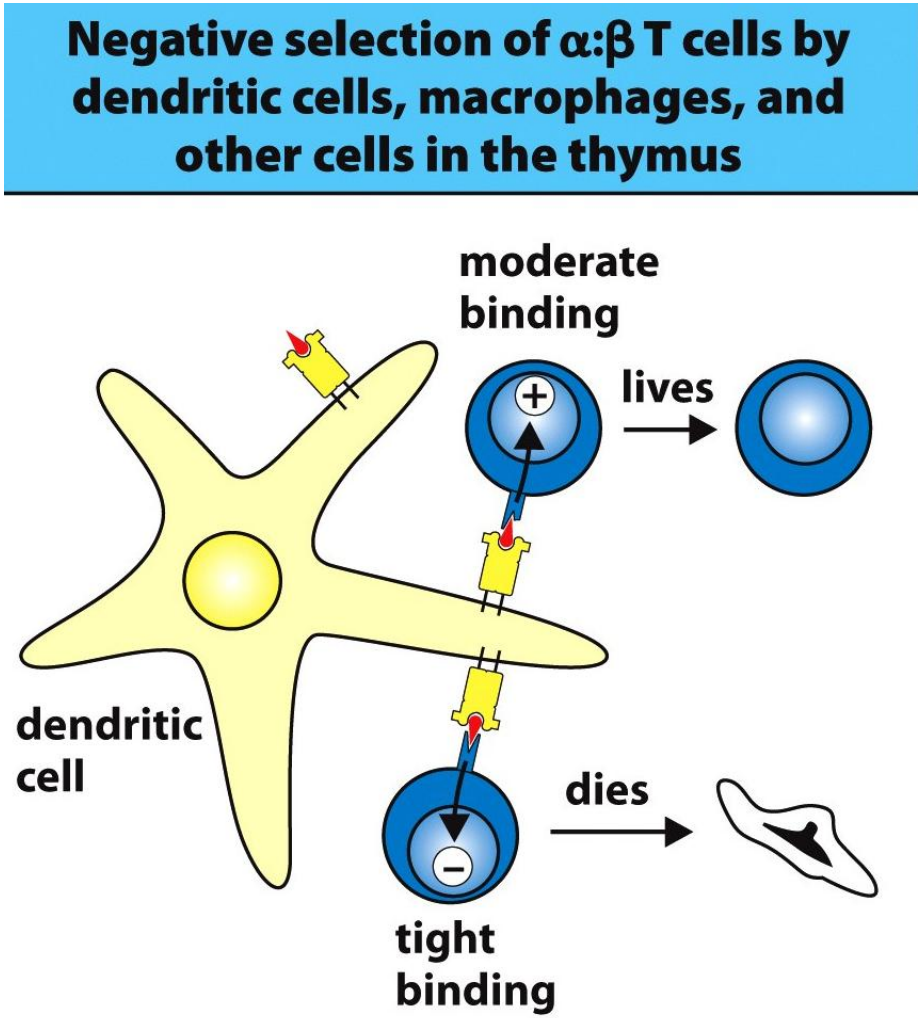
Mechanism of tolerance induction

- Clonal deletion
  - Thymus – negative selection
  - Bone marrow – negative selection
- Clonal anergy
  - Lack of Co-stimulatory molecules
  - Exposure to large amounts of Ag
  - Improper antigen presentation
- Receptor editing
  - High Ag conc. Leads to re-rearrangement of VDJ regions by activating RAG1 and RAG2

Mechanism of tolerance induction

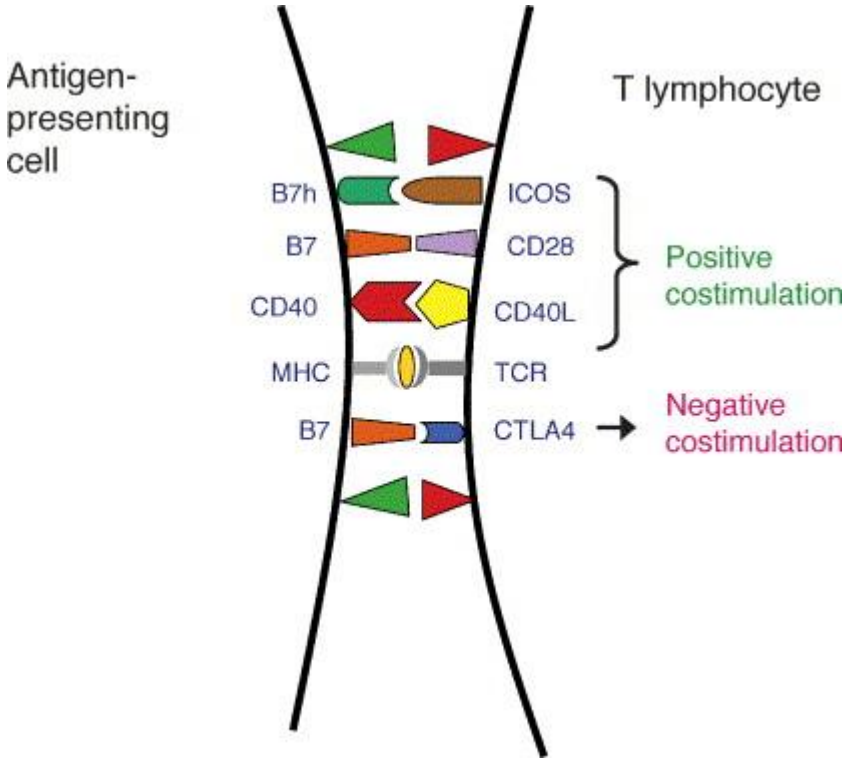
- Anti-ideotype antibodies
  - Can be used to suppress immune response
- Suppressor T cells / Regulatory T cells (Treg)
  - Big debate over their existance
  - Both CD4+ and CD8+ exist
  - They are +ve for Foxp3
  - Mutation in foxp3 leads to Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX)syndrome

Negative selection in Thymus



Clonal deletion

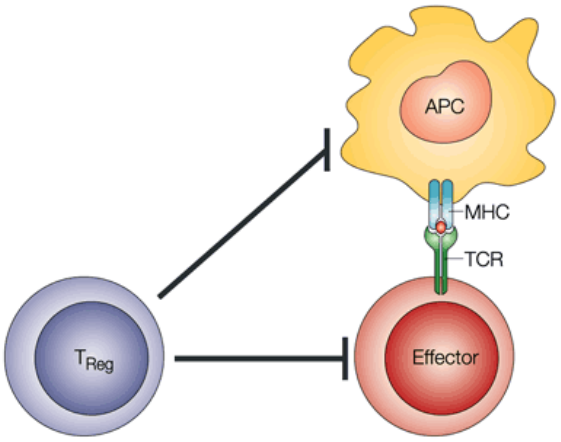
Clonal anergy



Co-stimulatory molecules involved in +ve and –ve clonal selection of T cell

Clonal anergy

T regs



Nature Reviews | Immunology

$CD4^+CD25^+$ T cells have been shown to regulate immune responses in vivo. This might be the result of the suppressive effects of regulatory T (T_{Reg}) cells on effector T cells directly or on antigen-presenting cells (APCs). This can be beneficial to the host by preventing autoimmunity and enabling tolerance to organ, tissue and cell transplants to develop. However, it can also be detrimental as T_{Reg} cells can prevent effective immune responses to tumours and infectious agents. GVHD, graft-versus-host disease; TCR, T-cell receptor.

Breakdown of tolerance

- Breakdown of tolerance leads to autoimmunity
  - By using immunosuppresive drugs one can minimize the presence to tolorogenic antigen
  - This leads to lack of antigen during new cell differentiation
- Cross reactive antigens
  - Antigenic mimicry leads to autoimmunity

Breakdown of tolerance

- Sequestered antigens
  - Antigens hidden from immune system often exposed by injury
- Escape of auto-reactive clones
  - Negative selection in thymus may not be efficient. Not all antigens are present in thymus
- Lack of regulatory T cells (Tregs)

Autoimmunity

- Autoimmune diseases are classified on the basis of organ involved
  - Organ-specific
  - Non-organ-specific (systemic)
- Genetic predisposition for autoimmunity
  - Association of certain HLA types

Autoimmunity

Spectrum of autoimmune diseases, target organs and diagnostic tests

Disease	Organ	Antibody to	Diagnostic Test
Hashimoto's thyroiditis	Thyroid	Thyroglobulin, thyroid peroxidase (microsomal)	RIA, Passive, CF, hemagglutination
Primary Myxedema	Thyroid	Cytoplasmic TSH receptor	Immunofluorescence (IF)
Graves' disease	Thyroid		Bioassay, Competition for TSH receptor
Pernicious anemia	Red cells	Intrinsic factor (IF), Gastric parietal cell	B-12 binding to IF immunofluorescence
Addison's disease (Fig 1)	Adrenal	Adrenal cells	Immunofluorescence
Premature onset menopause	Ovary	Steroid producing cells	Immunofluorescence

Autoimmunity

Phacogenic uveitis	Lens	Lens protein	
AI hemolytic anemia	Red cells Platelet	Red cells	Passive hemagglutination Direct Coomb's test
Idiopathic thrombocytopenia		Platelet	Immunofluorescence
Primary biliary cirrhosis	Liver	Mitochondria	Immunofluorescence
Idiopathic neutropenia	Neutrophils	Neutrophils	Immunofluorescence
Ulcerative colitis	Colon	Colon lipopolysaccharide	Immunofluorescence
Sjogren's syndrome	Secretory glands (Fig 5)	Duct mitochondria	Immunofluorescence

Autoimmunity

Vitiligo	Skin Joints	Melanocytes (fig 6)	Immunofluorescence
Rheumatoid arthritis	Skin, kidney, joints etc	IgG	IgG-latex agglutination
Systemic lupus erythematosus	joints, etc.	DNA, RNA, nucleoproteins	RNA-, DNA-latex agglutination, IF (granular in kidney)

Systemic autoimmune dieseases

Next class

Immunity against tumors