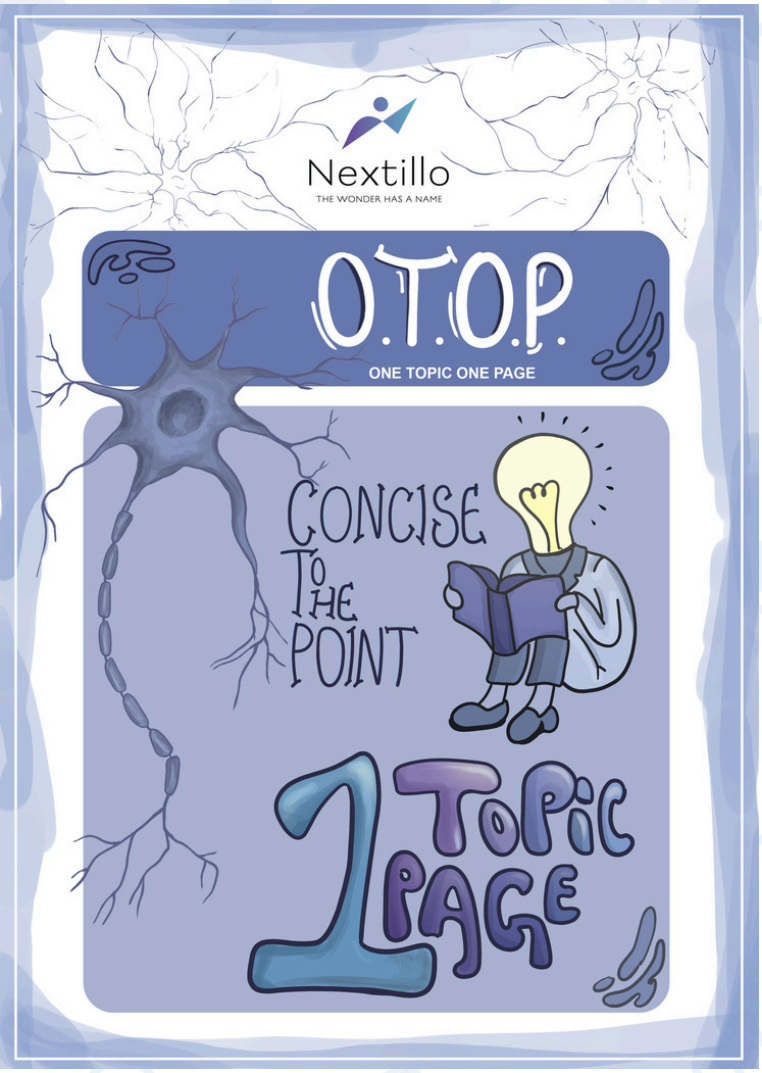
Table of Contents

Nextillo
THE WONDER HAS A NAME



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#OTOP BY NEXTILLO

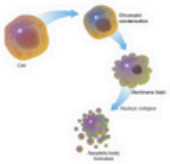
ONE TOPIC ONE PAGE BY NEXTILLO

CELL DEATH

It is a process by which cells get removed from the body or died as a result of an infection or insult to that body tissue like lack of supply of oxygenated blood. It can also be result of natural process to replace old cells with new. Forms include Apoptosis, necrosis, necroptosis, autophagy.

Apoptosis

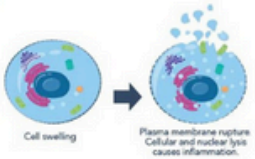
- ***It is caspase dependent Programmed cell death eliminates unwanted cells and it plays important role in normal development (e.g., tissue sculpturing)***
- ***Caspases: cysteine protease, Cleave after aspartate.***
- ***It takes place via 2 pathway extrinsic & intrinsic.***
- ***Cell-surface death receptors activate the extrinsic pathway of apoptosis.***
- ***The intrinsic pathway of apoptosis depends on mitochondria.***
- ***Bcl2 proteins regulates the intrinsic pathway of apoptosis.***
- ***Excess apoptosis leads to Tissue damage: heart attacks, strokes***
- ***Insufficient apoptosis leads to Autoimmune diseases***
- ***Cancer: mutations in Bcl2, p53.***



Apoptosis

Necrosis

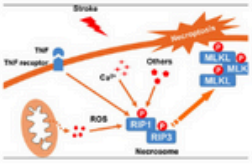
- ***Begins with swelling of cytoplasm and mitochondria***
- ***Ends with total cell lysis***
- ***No vesicle formation, complete lysis***
- ***Disintegration of organelles***
- ***No energy requirement***
- ***Random digestion of DNA***



Necrosis

Necroptosis

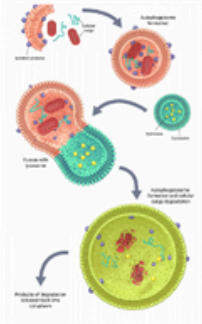
- ***Necroptosis participates in the pathogenesis of diseases including ischaemic injury, neurodegeneration and viral infection***
- ***An attractive target for the avoidance of unwarranted cell death***
- ***Death receptor, RIP1 and RIP3 are involved in these processes.***



Necroptosis

Autophagy

- ***Processes to remove unnecessary or non-functional organelles through lysosomes.***
- ***Inhibit accumulation of damaged or non-functional organelles by degrading them.***



Autophagy

Nextillo
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ONE TOPIC ONE PAGE BY NEXTILLO

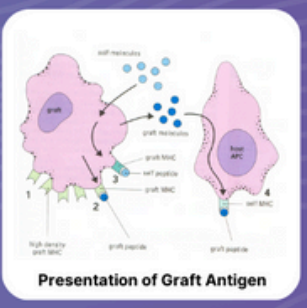
GRAFT REJECTION

It is a complex process in which "recipient immune system recognize the graft as foreign and attacks it". It involves 1. Cell mediated immunity 2. Circulating antibodies. It is caused by T-cell mediated reactions. Destruction of grafts occurs by CD8+ CTLs and CD4+ helper cells, Delayed hypersensitivity is triggered by CD4+ helper cells.

Types of Grafting

Based on genetic relationship between donor and recipient there are four types of Grafting methods:

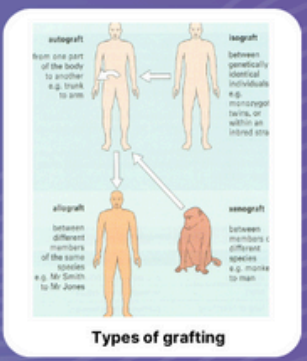
- ***Autografts: From one part of the body to another.***
- ***Isografts: Between isogenic individuals.***
- ***Allografts: Between genetically different individuals from the same species (most common).***
- ***Xenografts: Between members of different species (rapidly rejected by IgM or cell mediated rejection).***



Presentation of Graft Antigen

Mechanism

- ***Except for autografts and isografts, an immune response against allografts is inevitable/unavoidable.***
- ***Rejection of allografts involves both cell- mediated and humoral immunity.***
- ***Cell mediated reaction- Mainly responsible for graft rejection and are mediated by T cells (mainly by cytotoxic T cells).***
- ***T cells attack the graft and destroy it.***
- ***Humoral reaction- humoral antibodies cause certain rejection reactions.***



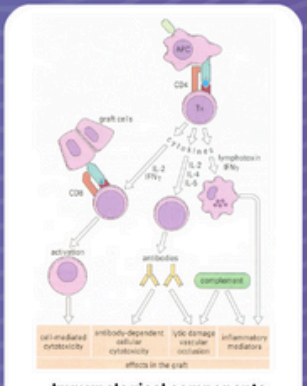
Types of grafting

Rate of Rejection

- ***Hyperacute- Time taken- Min-hours, cause- Anti-donor Ab and complement.***
- ***Accelerated- Time taken- Days, cause- activation of T cells.***
- ***Acute- Time taken- Days- weeks, cause- Primary activation of T cells.***
- ***Chronic- Time taken- Months- Years, cause- Unclear.***

Graft Versus Host

- ***The intensity of GVH reaction depends upon the extent of genetic disparity between the donor and recipient.***
- ***Clinical features- there is involvement of skin, GIT and liver (MC). Fever, - Weight Loss, - Anaemia, - Dermatitis, - Diarrhoea, - Intestinal Malabsorption, - Pneumonia, - Hepatosplenomegaly***



Immunological components of rejection

Nextillo
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#OTOP BY NEXTILLO

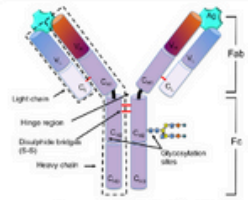
ONE TOPIC ONE PAGE BY NEXTILLO

ANTIBODY (PART- 1)

Specialized glycoprotein, produced from activated B cells (plasma cells) in response to an antigen. Capable of combining with the antigen that triggered its production. Antibodies are located in the γ-globulin fraction Immunoglobulin (Ig) constitutes 20-25 per cent of total serum proteins. There are five classes (or isotypes) of immunoglobulins recognised - IgG, IgA, IgM, IgD and IgE.

Structure Of Antibody

- **An antibody molecule is a 'Y-shaped' heterodimer; composed of four polypeptide chains - Two identical light (L) chains, and Two identical heavy (H) chains.**
- **There are five classes of H chains and two classes of light chains.**
- **L chains are of two types- kappa (κ) and lambda (λ).**



Immunoglobulin G

Immunoglobulin G

- **Constitutes about 70-80% of total Igs of the body.**
- **IgG has maximum daily production.**
- **it has longest half-life of 23 days.**
- **Highest serum concentration.**
- **It has four subclasses- IgG1, IgG2, IgG3 and IgG4**
- **It can cross placenta, IgG2 has the poorest ability to cross placenta.**
- **It plays a major role in neutralization of toxins.**

Immunoglobulin M

- **IgM has highest molecular weight.**
- **IgM exists in both monomeric and pentameric forms- on B cells, it exists in monomeric form, in secreted form, it is pentameric in nature.**
- **Raised in Acute infection**
- **Acts as an opsonin**

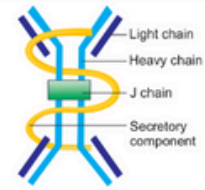
Immunoglobulin M

Immunoglobulin A

- **IgA is the second most abundant class, 10-15% of total serum Ig.**
- **IgA in serum is predominantly in monomeric form.**
- **Breast milk is rich in IgA.**
- **The majority of plasma cells producing IgA are located within mucosal membranes lining the intestines.**

Immunoglobulin D

- **IgD is found as membrane Ig on the surface of B cells and acts as a B cell receptor along with IgM.**
- **Has the highest carbohydrate content among all the Igs.**



Immunoglobulin A

Nextillo
THE WONDER HAS A NAME

#OTOP BY NEXTILLO

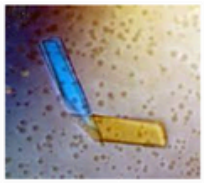
ONE TOPIC ONE PAGE BY NEXTILLO

ANTIBODY (PART- 2)

The five classes of Igs and their subclasses are called as isotypes.Vary from each other in the amino acid sequences of the constant region of their heavy chains. Idiotypes in an individual arise continuously from mutations (somatic hypermutations) in the genes of variable region.

Bence Jones Proteins

- ***Seen in a neoplastic condition of plasma cells called multiple myeloma (light chain disease)***
- ***Cancerous plasma cells produce excess of light chain (Bence Jones proteins) which accumulates in patient's serum and excreted in urine.***



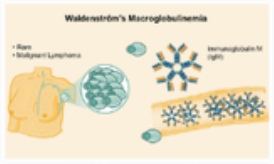
Bence Jones protein

Waldenstrom's Macroglobulinemia

- ***Lymphoma affecting B cells produces excess of IgM. It is seen in multiple myeloma.***
- ***Somatic mutations in MYD88 gene occur in over 90% of patients.***

Heavy Chain Disease

- ***It is characterized by an excessive production of heavy chains that are short and truncated.***
- ***Four types of heavy chain disease have been recognized based on H chain involved- alpha chain disease (Seligmann's disease); gamma chain disease (Franklin's disease); mu chain disease; delta chain disease.***



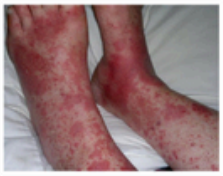
Waldenstroml's Macroglobulinemia

Cryoglobulinemia

- ***Condition where the blood contains cryoglobulins; a type of Ig that becomes insoluble (precipitate) at low temperatures but redissolvesagain if the blood is heated.***
- ***Cryoglobulins usually consist of IgM directed against the Fc region of IgG.***
- ***Cryoglobulins have been associated with multiple myeloma and hepatitis C infection.***

Monoclonal Antibody

- ***Antibodies derived from a single clone of plasma cell; all having the same antigen specificity- i.e. produced against a single epitope of an antigen.***



Purpura of Cryoglobulinemia

Nextillo
THE WONDER HAS A NAME

#OTOP BY NEXTILLO

ONE TOPIC ONE PAGE BY NEXTILLO

X-LINKED DISORDERS

X-linked disorders are genetic conditions caused by mutations in genes located on X chromosome. Since males have only one X chromosome (XY), they are more commonly affected by the X-linked disorders than females, who have two X chromosomes (XX).

X-linked Dominant Inheritance

- *Affected females have 50% chance of passing trait to each of their offspring, regardless of gender.*
- *An affected father passes trait to all his daughters but none of his sons, as males inherit their X chromosome from their mother.*
- *In males, the X-linked dominant disorders are typically more severe because they only inherit one X chromosome, making them hemizygous for the trait.*
- *In females, the severity of the disorder can vary depending on X inactivation.*

X-linked Recessive Inheritance

- *Affected males inherit trait from their carrier mothers, as males receive their X chromosome from their mothers.*
- *Carrier females (heterozygotes) are typically asymptomatic but can pass trait to their sons or daughters equally .*
- *Males are more commonly affected by the X-linked recessive.*
- *Females carrying recessive allele on one X chromosome are generally unaffected due to X inactivation, but they can be carriers and pass traits to their offspring.*

X-linked dominant disorders

Disorder	Mnemonic
Incontinentia Pigmenti	IP (Incontinentia Pigmenti)
Rett Syndrome	Rett (Rett Syndrome)
Vitamin D-Resistant Rickets	X-linked dominant rickets is VDR, think "vitamin D resistant"
Hypophosphatemic Rickets	XLH (X-linked Hypophosphatemic Rickets)
Aicardi Syndrome	Aicardi (Aicardi Syndrome)
Oral-Facial-Digital Syndrome Type I	OFD1 (Oral-Facial-Digital Syndrome Type I)
Focal Dermal Hypoplasia	Goltz (Goltz Syndrome)
Conradi-Hünermann Syndrome	Conradi (Conradi-Hünermann Syndrome)

X-linked recessive disorders

Disorder	Mnemonic
Hemophilia A	"A" for "Absent" clotting factor VIII
Hemophilia B	"B" for "B Factor" (Factor IX deficiency)
Duchenne Muscular Dystrophy (DMD)	"Duchenne Distorts Muscles"
Becker Muscular Dystrophy (BMD)	"Becker Builds Muscle" (milder form of DMD)
Color Blindness	"R-G" for "Red-Green" (most common type)
Androgen Insensitivity Syndrome (AIS)	"Complete Insensitivity" to Androgens
X-linked Agammaglobulinemia (XLA)	"Agammaglobulinemia Leaves Immune System Vulnerable"

Nextillo
THE WONDER HAS A NAME

#OTOP BY NEXTILLO

ONE TOPIC ONE PAGE BY NEXTILLO

Y-LINKED DISORDERS

Y-linked inheritance refers to transmission of the genetic traits or disorders through genes located on Y chromosome. Since Y chromosome is passed only from father to the son, Y-linked inheritance is following the strict paternal lineage.

Y - Linked Dominant Inheritance

- *Y-linked dominant traits are passed directly from fathers to their sons, as daughters do not inherit Y chromosome.*
- *Y-linked dominant traits are passed vertically through successive generations along paternal lineage without skipping generations.*
- *There is no female-to-female transmission in Y-linked dominant inheritance because only males carries Y chromosome.*

Y - Linked Recessive Inheritance

- *Similar to Y-linked dominant traits, Y-linked recessive traits are passed exclusively from the fathers to their sons.*
- *Y-linked recessive disorders are even rarer than Y-linked dominant disorders due to limited genetic information carried on Y chromosome and need for both copies of the Y chromosome to carry mutant allele for expression.*
- *Unlike X-linked recessive inheritance, there is no carrier state for Y-linked recessive traits in females because they do not carries Y chromosome.*

Y-linked dominant disorders

Disorder	Mnemonic
Hypoparathyroidism,	"HYPO"
sensorineural deafness,	
and renal dysplasia	
Retinitis pigmentosa	"RP on Y"
Infertility	"Y-not Fertile"
Swyer syndrome	"SWY Y"
Hanhart syndrome	"HAN on Y"

Y-linked recessive disorders

Disorder	Mnemonic
Male infertility	Y U NO FERTILE
Swyer syndrome	SWYER
Retinitis pigmentosa	RP (Retinitis Pigmentosa)
Deafness	DEAF
Congenital adrenal hypoplasia	YACHT (Y-linked Adrenal Cortical Hypoplasia with Testicular Regression)
Hypergonadotropic hypogonadism	HGH (Hypergonadotropic Hypogonadism)
Holt-Oram syndrome	HOS (Holt-Oram Syndrome)
Cerebrooculofacioskeletal syndrome	COFS (Cerebrooculofacioskeletal Syndrome)
Hereditary nephritis	YOLO (Y-linked Hereditary Nephritis with Hearing Loss)