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TOLERANCE, AUTOIMMUNITY & TRANSPLANTATION

Establishment & maintenance of ~~Tole~~ Tolerance :-

Tolerance : Process where B & T cells which are reactive to the ~~central~~ self host cells will eventually undergo apoptosis.
This process occurs in primary lymphoid organs.
- T-cells : Thymus [T-cells with Epithelial cells of Thymus]
- B-cells : Bone marrow [B-cells with Stromal cells]

* The tolerance the occurs in the Thymus or Bone marrow is called central Tolerance.
It limits growth of autoreactive T & B cells.

* Though the central Tolerance process is ~~big~~ quite effective, some Autoreactive B & T cells can escape the Primary & lymphoid organs.
To limit these escaped cells, peripheral tolerance mechanism activates in the secondary lymphoid organs.

If the naive lymphocytes ~~in~~ encounters a self-antigen, it will undergo one of the three fates: 1) APOPtosis
2) Anergy 3) Regulation

Signal (ii) is often absent due to presence of inhibitory molecules that prevents the interaction b/w adhesion molecules. It enters a state of Anergy.
eg: ~~CTLA~~ CTLA-4

Autoimmunity :-

- Autoimmune diseases can target diff. tolerances of the body.
- Most of the Autoimmune diseases are ~~ca~~ caused by Auto-Antibodies [Abs that targets self-antigens].

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- Some other cause include self-reactive T-cells.
- Autoimmune diseases are classified into -
  - ↳ Organ-specific Autoimmune disease: self-reactive T-cells or Auto-Abs targets a particular group of cells or organs.
  - ↳ systemic Autoimmune disease: more than one organ or group of cells are targeted.

(i) Organ-specific Autoimmune disease.

→ cellular lysis, chronic inflammation

→ eg: (i) Hashimoto's Thyroiditis

↳ Auto-Abs targets the thyroid cells / hormones & proteins secreted by thyroid ~~organ~~ glands.

↳ Efficiency of thyroid gland decreases but is not recognised initially (due to gland's ability to replenish the hormones & proteins).

↳ However, replenishment is upto a limit. Due to this fact, the symptoms when it occurs are much severe.

↳ Hypothyroidism is caused

↳ Observed often in middle-aged women

↳ As Auto-Abs target thyroid antigens, there is a condition of ~~itt~~ inflammation that leads to recruitment of immune cells to the site ~~leading~~ resulting in Goitre.

↳ Delayed-type hypersensitivity.

(ii) Autoimmune Anemia

↳ Anemia: loss of RBCs.

↳ Types - (i) Pernicious Anemia

- ~~Deadly that~~ Auto-Abs target an intestinal protein called as Intrinsic Factor Protein.

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- Function: Binds to vit B12 & helps in its absorption, so that vit B12 can be used for synthesis of RBC.
- The autoimmune disease, therefore, prevents absorption of vit B12 & subsequently synthesis of RBCs.
- Treatment: Monthly - infections of Vit B12.

(ii) Hemolytic Anemia
- ~~RBCs Underg~~ RBCs undergo lysis.
- Type II Hypersensitivity.

(iii) Good Pasture's Syndrome
↳ Auto-Abs attack kidney & the lungs
↳ Type II Hypersensitivity (due to involvement of IgG cells).

(iv) Insulin-dependent Diabetes Mellitus (Type 1 Diabetes)
↳ Auto-Abs are produced against β-cells of Pancreas that impers the production of insulin.
↳ Towards the later phase of the disease, T-cells are recruited to the site leading to Type IV Hypersensitivity.

(v) Myasthenia gravis
↳ Auto-Abs bind to Acetylcholine receptors (↳ required for ~~AA~~ smooth muscle contraction) on smooth muscles preventing muscle contraction.
↳ Skeletal smooth muscles will eventually weaken.

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(iii) Systemic Autoimmune disease

→ Eg: (i) Systemic Lupus Erythematosus

↳ Produce Auto-Abs to target DNA, histones, Platelets, leukocytes, clotting factors

↳ targets Middle-aged women.

(ii) Multiple sclerosis

↳ Inflammatory lesions in myelin sheath caused by T-cells

↳ T-cell dependent hypersensitivity.

(iii) Rheumatoid Arthritis

↳ Patients Produce rheumatoid factors (type of IgM Ab).

↳ These IgM Rheumatoid factors have affinity towards Fc region of IgG Abs. Upon binding, it forms very large immune complex.

↳ These complexes gets deposited at the bone joints.

↳ Results in chronic inflammation at the joints

↳ Type III Hypersensitivity.

Treatment:

- targets T- & B- cells depleting agents (signal (i))
- few targets to suppress signal (ii) by depleting adhesion molecules
- targets TCR signaling pathways
- few targets co-simulators or accessory molecules that suppress signal (ii)
- targetting cytokine signaling (signal (iii)).

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Transplantation Immunology :-

Introduction -

Transplantation: Transfer of cells, tissue or organ from donor site to receiver site.

→ use of immunosuppressive agents alongside Transplantation enhances transplant success rate.

→ However, these agents suppresses the entire immune system resulting in side effects.

Types of Transplants -

(i) Autograft: Self tissue transferred from one part of body to another.
eg: nose - construct, Gratting ~~fo~~ on burn patients

(ii) Isograft: Tissues transferred b/w two genetically identical species.

(iii) Allograft: Tissues are grafted b/w genetically ~~same~~ different members of same species.
Most common type of transplant.

(iv) Xenograft: Tissues are transferred b/w different species.
eg: Donor species are genetically modified to specifically Provide org cells/tissues/organs to receipients.

Notes:

- In Allograft, due to difference in cells/tissues, we can observe thrombosis (Clotting of blood ~~ve~~ cells) ~~due to during~~ First-set rejection (Days 10-14).
- However, second-set rejection (Days 5-7) is ~~more~~ much faster than First-set due to creation of memory cells from the first-set.

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Graft rejection follows predictable clinical course-

(i) Hyperacute : ~~Due 1 Graf~~ Immediate graft rejection due to pre-existing recipient antibodies.
Graft never gets vacularised.

(ii) Acute : Often observed in allografts where response is observed within weeks.

(iii) Chronic : Occurs over a longer duration ~~of ob~~ ranging from months to years. Often observed in patients using Immunosuppressive agents where the body slowly ~~Starts to~~ get used to these agents & starts to produce Antibodies against these agents.

Immunosuppressive Therapy-

→ Immunosuppressive agents targets signal (i) ~~&~~, (ii) and few ~~sr~~ down-stream ~~signal~~ signaling.

→ ~~These monoclonal antibodies Drugs like [illegible] prevents down stream signaling b/w Antigen / & foreign cell & immune cells by targeting CD complex.~~

→ Few drugs target complexes ~~#~~ responsible for signal (ii)

→ Some drugs target cell cycling. ~~or targets the cells as a~~

→ ~~wh~~ These drugs are often general (non-specific) in ~~T~~ target.

→ These monoclonal Antibodies (~~th~~ imm. sup. drugs) prevent down-stream signal ~~of b/w the~~ of the Foreign cell ~~& immune~~ upon encounter with immune cells.