Imunology12

Transplantation

The biggest problems

- infection
- genetic
- immunity processes
- immunotherapy

- Implantation – nonbiological material,
- transplantation – biological material,organ on other place
- graft – transplanted organ, tissue

Genetic bases of transplantation

- 20th century – Loeb, Tyzzar, Little – identification of genetic bases of transplantation
- **Genetic match** – condition of success
- Recipient´s IS recognise molecules (genetically based) – h**istocompatibility antigens** – on donor´s cells –
- recipient´s answer is paralel to reaction against external agenses

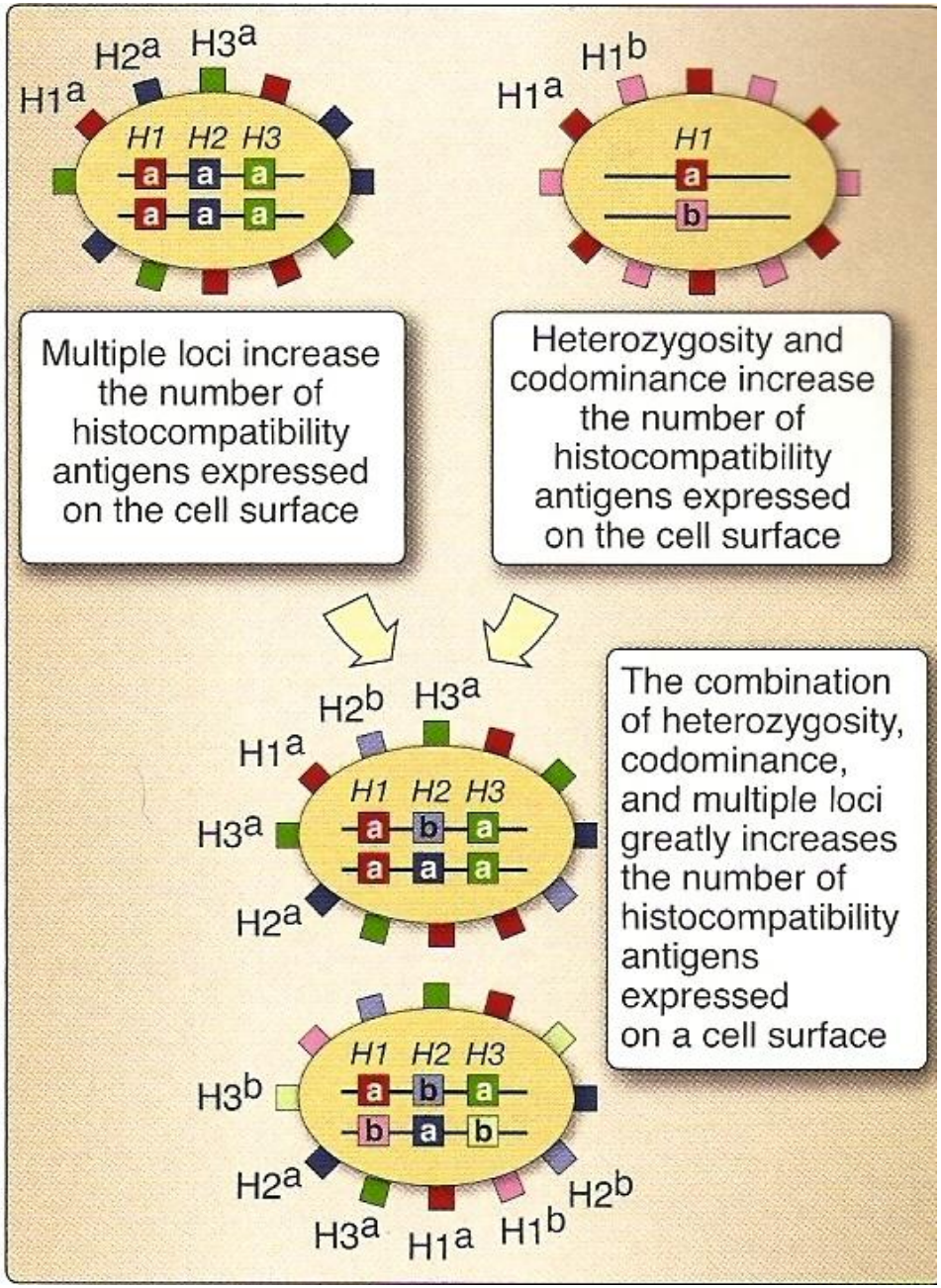
histokompatibility genes encode histokompatibility antigens

- more than 100 locuses
- most strong between them MHC complexes – encode molecules MHC I and II
- Productes of these genes are usually c**odominant** expresse always whether in one (heterozygot, hemizygot) or two copies (homozygot)
- other non MHC antigens are not so strictly inherited – many genes scatter on several chromozomes incl. X or Y chromosome

- **MHC I and II**

- **Codominance**
- **Heterozygot**
- **Multiple locuses**

- increase the number of histokompatibility antigens combinations expressed on the cell surfaces



Presentation of antigen

- Any peptid fragment – produced in cytoplasma or from fagocytosis – is expressed on the surface and presented via MHC I or II molecules and serves as antigen of histocompatibility.

Terminology

Localisation

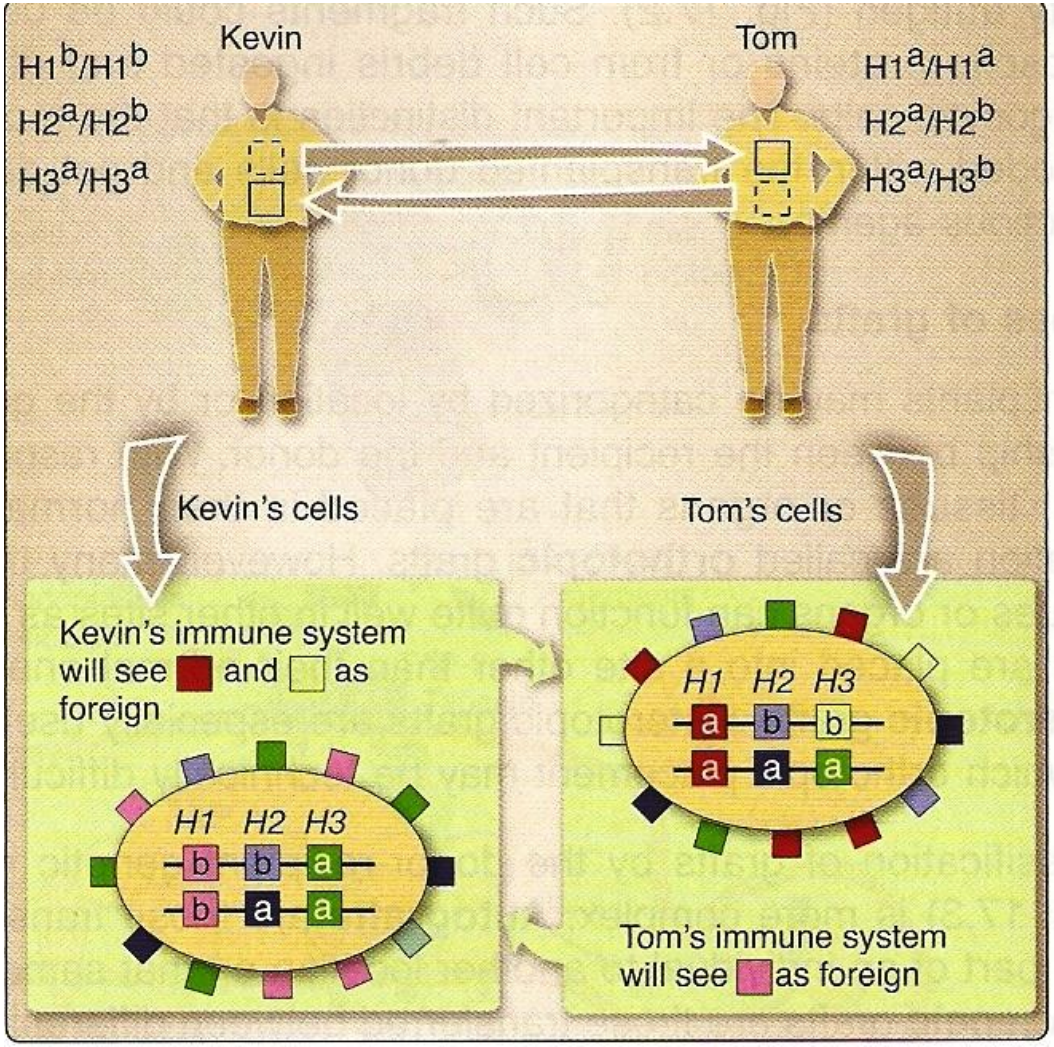
- Orthotopic grafts
- Heterotopic grafts – if technical problems

Donor – recipient

- autotransplantation – the same (transfussions) genetically indentical - syngeneic
- allotransplantation – genetically different from the same genus
- xenotransplantantion – different genus (pig/man)

Laws of tansplantation

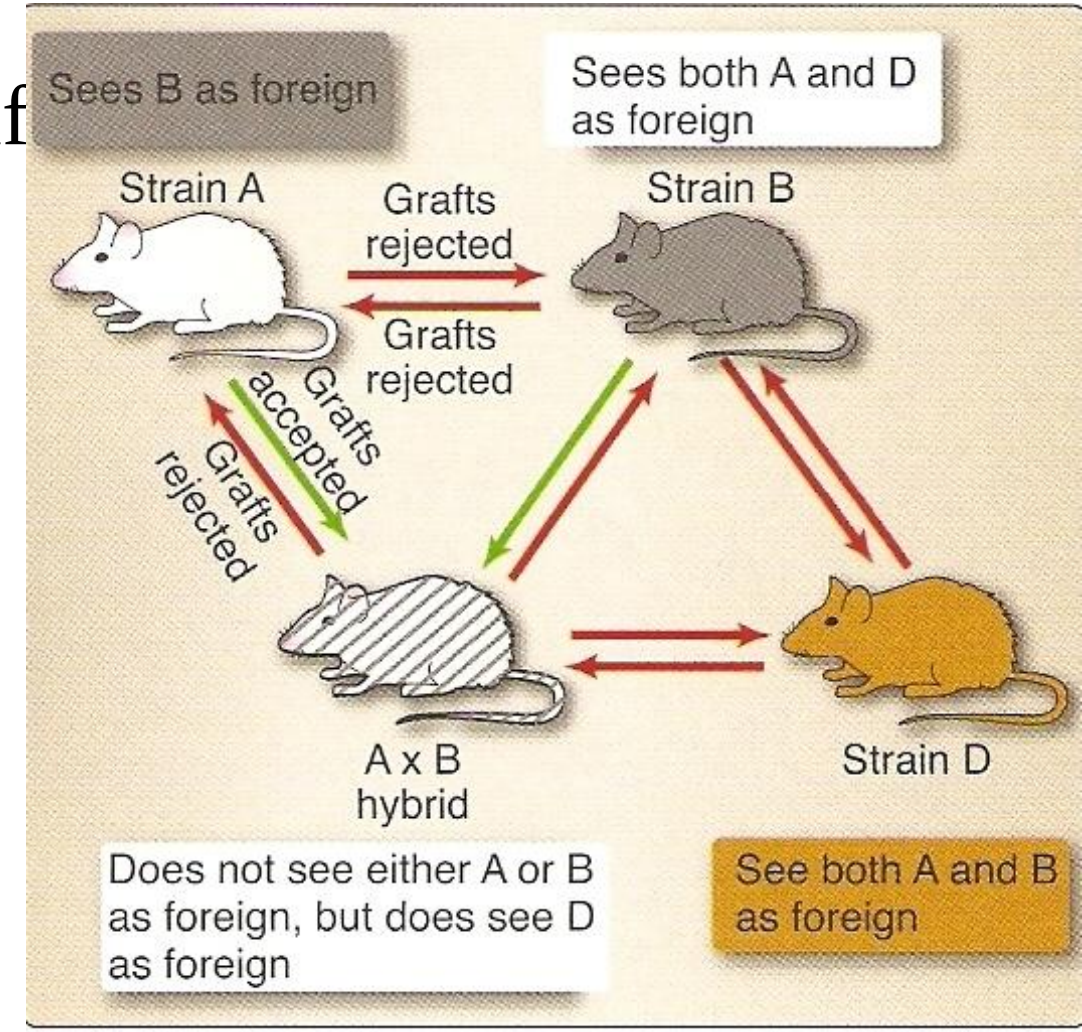
Depent on individual combination of genetic impairment or match between donor and recipient



Imbred individuals - experiment

- Moses combined in siblings line in more than 20 generations – 99% of the same genetic material.
- Detection and study of genetic laws:
- Host can recognise as false and react on any histokompatibility antigens, that are not encoded by own cells

Heterosygot accepts graf
from homozygotic
parent.
Homozygotic parent
refuses graft from
heterozygotic donor



MHC I or II molecules are polymorfic differs also in non MHC locuses

Rejection – no acceptation

- **Hyperaccute** – minutes or hrs – preexistence of preformed antibodies against donor (AB0).
- **Accelerated** – days - reactivation of sensibilised T lymphocytes in the 2nd transplantation
- **Accute** – days and weeks – primáry activation of T cells
- **Chronical** – rejection caused by infection or loss of tolerance

Rejection reactions

Recipient reject foreign antigens

- **directly**: donor´s APC and recipient´s T cells

If some MHC I molecules of the donor are idnetical to the recipient´s. APC of the donor present via MHC I peptids and they are bound on T CD8+ of recipient.

APC of the donor process cell debris of the donor and present them via MHC II to recipient´s T CD4+

- **indirectly**: recipient´s APC a donor´s T cells

APC of the recipient process and present peptid fragments from the donor´s cell (his antigens) and present them to T cells of the recipient

Terminology

- HvG reaction – host versus graft

immunocompetent recipient recognises foreign antigens of transplanted tissue and reacts by mechanisms that lead to tejection

Survival rise in direction xeno, allo, iso, auto.

Present in

– MajorHC but also in minorHC.

– imunological memory and secondaty reaction.

2nd transplantation of the tissue with the same MHC produce more fast rejection. , T memory cells produced during 1st transplantation

Terminology

- GvH reactiona – graft versus host

Imunosupresed recipient receive immunocompetent lymfoid cells of the donor, and they recognise foreign antigens of the host and produce destruction

.

Symptoms: diarrhoe, erytema, loss on weight, fever malaise, arthralgy..)

Types of immune reactions – almost any immunological reactions can be present

- **Natural antibodies**:AB0 antigens – transffusions **-** IgM, produced after mi exposition and cross reactiong
- **Newly generated Ab**: activation of B cells and production of plasma cells and Ig against graft. Longer expositione. Present during 2nd transplantation => ADCC, C´, opsonisation
- **DTH – CTL** – recognision of pMHC I and II **Activation C´ -**
- **NK cells –** recognise the lack of MHC I on transplanted tissue => destruction of graft

Immunotherapy

- Basical condition –high genetical identity
- mostly not present
- 2 ways how to influenc:

- **specific immunotolerance** – experimental no in humam
- **immunosupression –** whole-body irradiation, chemotherapy, side iffects (opportune infection)., antibodies against surface molecules of imunocompetent cells (APC, ly, anti MHC I and II molecules, anti CD4, CD8 molecules

Possibilities to influence surviving of transplanted tissues

- Choose the donor
  – MHC identity with recipient – identical sigblings, HLA 95-100% .....
  – AB0 compatibility must be present
- Preparation of the recipienty
  – skreening for anti HLA Ab donor specific – must be negative,
  – pacient withou infection

+ imunosupressive therapy (cyclosporin – inhibiítion of IL2 synthesis, blocking T cell proliferation), whole body irradiation

Immunesupresive - examples

Agent	Affected Cells	Mode of Action
Azathioprine	Multiple cell types	Inhibition of nucleotide synthesis
Corticosteroids (e.g., prednisone)	Multiple cell types	Inhibition of transcription for numerous cytokines and other products involved in inflammation
Cyclophosphamide	Multiple cell types	Inhibition of nucleotide synthesis
Cyclosporine	Lymphocytes	Inhibition of transcription for multiple cytokines (e.g., IL-2, IL-4)
Mycophenolate mofetil	Lymphocytes	Inhibition of lymphocyte nucleotide synthesis and proliferation
Sirolimus (rapamycin)	T cells	Inhibition of some signal transduction induced by cytokines (e.g., IL-2)
Tacrolimus (FK506)	T cells	Inhibition of gene transcription in lymphocytes, inactivation of calcineurin
Irradiation	Many cell types	Induction of DNA damage, especially in rapidly proliferating cells
Antibodies against lymphocytes or against T cells	Lymphocytes, T cells	Destruction or inhibition of lymphocytes or lymphocyte subsets
Anti-CD4 antibodies, anti-CD8 antibodies	$CD4^+$ T cells, $CD8^+$ T cells	Interference with TCR binding
Anti-MHC I/II antibodies	Antigen-presenting cells	Interference with antigen presentation and T cell activation by blockading

Blood transffusion

- Blood = ery, leu ...., Ery have more than 400 types of antigens – mostly without clinical impact

AB0: surface structures on ery and some epitelial and endotelial cells. – synthesis encoded by H (2alels – for production of H substance) (HH,Hh,hh) a AB0 lokusoch (antigens recognised by natural antibodies - IgM)

Transfussion of blood

Rh: antigen on the surface of ery: Rh- exposed to Rh+ blood produces IgG.

Rh incompatibiliy of pregnant
(DD, Dd, = Rh+., dd = Rh-)

Rh-mother can have Rh+fetus and produce antiRh IgG

- 1st. pregnancy – no complication, small amount of IgG
- 2nd and next pregnancy (or aborts) – antibodies circulate in the fetus (Rh+ vs. anti Rh IgG) => hemolytical anemia of newborn– activation of C´, reactive release of inmature erytroblast - erytroblastosis fetalis

Prevention: antiRh Ab after the 12th week of pregnancy, abortuses, transfussions, delivery if Rh-women

Bone marrow transplantation

- Bone marrow contain stem cells for the whole hemotopoesis – source for pationts with deficientcies of cells (risk also).
- Transplantation of immunocompetent cells to immunodeficient recipient
- GvH rejection
- Preparation of bone marrow – T cell elimination before transplantation. Cells of BM undergo posit and negat selection in thymus of recipient
- Time to production of functionnal system – risk of oportunie infection

Immunologically privileged places

- allo and xeno transplantation possible

Eye – intraoccular liquid of the anterior chamber – nutrition of the eye without blood cells, inhibition of apoptosis = transplantation of cornea

Lumen testes – closed before development of IS is finished – spermatogonia not recognised as self

Brain– hematoencefalic barriére – limited interchange of molecules + immunity reactions

Placenta – existence of nonself histocompatibility antigens without stimulation of mother immunity

Sources of tissues

Human

- Donors – live or dead
- Stem cells – adult, embryo, self, fetal
- Etic and law

Xenotransplantation