IMMUNO

TRANSPLANTATION:

before blood transfusions: donor + recipient are matched for ABO + Rhesus D Ag

Blood types:

O = Universal DONOR
↳ can only receive O blood
they have anti-A + anti-B Abs

AB = universal RECIPIENT
↳ no anti-A or anti-B Abs

→ incompatibility of blood group antigens
↳ can cause TYPE 2 hypersensitivity ✡

A = anti-B Ab
↳ only A or O blood

B = anti-A Ab
↳ only B or O blood

↳ types of REJECTION:

hyperacute: (can occur within minutes)
✡type 2 hypersensitivity✡
↳ due to pre-existing Abs that attack graft
↳ causes: complement mediated lysis

✡ complete rejection can occur within 24 hours ✡
↳ ONLY treatment: graft removal
✡ avoid by typing + matching donor + recipient ✡

acute rejection: responses between 7-10 days after transplant
→ type 4 hypersensitivity
→ naive T cells are activated → differentiate into effector cells
↳ induces infiltration of M+ + lymphocytes
↳ prevention: treat patients w/ immunosuppressive drugs before + after transplant

chronic rejection: develops months/years after acute rejection reactions have subsided
→ type 3 hypersensitivity
↳ caused by IgG Abs made against HLA class I molecules in graft
↳ causes thickening of vessel walls + lumen narrowing = leads to ischemia, loss of function + eventual graft death

↳ anti-rejection drugs help, but are not perfect

due to indirect allorecognition
improve outcomes w/ transfusion effect:
→ alloreactive T cells stimulated by direct pathway wane after transplant
↳ can give rise to reg. CD4 T cells to suppress alloreactive CD4 + CD8
↳ IMPROVES outcomes

✡ Graft terminology:
autograft = self-tissue grafted to another self area
isograft = transplant between identical individuals
allograft = tissue transfered between genetically different members of same species
xenograft = tissue transfered between different species

transplant rejection: → type 4 hypersensitivity

↳ transplant of solid organ w/ alloreaction developed by individuals IS directed at graft cells

graft vs. host disease: → type 4 hypersensitivity

↳ after hematopoietic stem cell transplant

★ donor attacks recipient ★

★recipient's hematopoietic system is destroyed : gets healthy stem cells

↳ reaction due to donor T cells in graft that attack recipient's healthy tissues

↳ **Minimizing Rejection:**

★ use donor whose HLA is as similar as possible

↳ ↓ autoreactive T cells

↳ Administer immunosuppressive drugs

↳ interfere w/ activation of alloreactive T cells

Prednisone:

↳ prevents inflammation state

→ Adverse effects:
fluid retention
weight gain
diabetes
loss of bone mineral
skin thinning

Cyclosporin:

↳ inhibits T cell activation
= disrupts signal transduction

Tacrolimus:

↳ binds immunophilins

→ Adverse effects:
nephrotoxicity

≈ Corticosteroid Therapy:

ACTIVITY	EFFECT
↓ IL-1, iTNFα, GM-CSF, IL-3, IL-4, IL-5, CXCL8	↓ inflammation caused by cytokines
↓ NOS	↓ NO
↓ Phospholipase A ↓ Cyclooxygenase type 2 ↑ Lipocortin-1	↓ Prostaglandins ↓ Leukotrienes
↓ adhesion molecules	reduced emigration of leukocytes from vessels
induction of endonucleases	induction of apoptosis in lymphocytes & eosinophils

★ **Serum Sickness:**

extreme form of type 3 hypersensitivity

↳ occurs 7-10 days after administering therapeutic Ab

= chills, fever, rash, arthritis, vasculitis, glomerulonephritis

Blocking Allove active T cells:

Belatacept → targets co-stim of T cells; binds B7 on activated DC presenting alloantigens

Anti-CD25 Ab → given before transplant ↳ ? 2 months after

Rapamycin (sirolimus) → binds FK-binding proteins

↳ combo therapy

Direct Allorecognition:
↳ donor DC presents to recipient T cells
↳ activated T cells destroy tissue
★ leads to ACUTE rejection ★

Indirect Allorecognition:
↳ donor DC get degraded by recipient DC
↳ recipient DC present to donor
★ activated T cells will attack graft ★

★ leads to CHRONIC rejection ★

STEM CELL THERAPY:

↳ choice of therapy for many genetic / malignant diseases
within 2-3 weeks after transplant → new circulating blood cells begin to produce from transplant marrow

≈GVHD≈

→ can attack every tissue of body but
usually: skin, intestine, liver

↳ mature donor CD4 + CD8 T cells respond to recipient HLA allotypes

★ GVHD = type 4 hypersensitivity ★

4 grades:

GRADES of REJECTION:

Grade 1:	maculopapular rash <25% surface area serum bilirubin 2-3 mg/dL	>500 mL diarrhea
Grade 2:	maculopapular rash <25-50 % serum bilirubin 3-6 mg/dL	> 1000 mL diarrhea
Grade 3:	generalized erythroderma serum bilirubin 6-15 mg/dL	>1500 mL diarrhea
Grade 4:	generalized erythroderma w/ blistering + desquamation Serum bilirubin 15 mg/dL	Severe abd. pain w/ or w/out intestinal obstruction

★ begins 10-28 days after transplant ★
↳ creates inflammation

★usually restricted to first few months after transplant★
↳ ↑ liver enzymes
cramps, diarrhea
hyperbilirubinemia

★★ All patients getting stem cell transfer will have GvHD ★★
↳ severity depends on HLA match

↳ **HLA matching:** bone marrow is huge source of HSC
↳ using Ab specific for CD34 to extract stem cells
↳ could also use umbilical cord blood from placenta

↳ **haploidentical transplant:**
↳ donor = recipient share at least 1 HLA type

★★ **Graft vs. Leukemia Effect:**
↳ Alloreactive T cells in graft get rid of patient's residual leukemia cells
↳ after receiving stem cell graft: give patient transfusion of donor lymphocytes or T cells

- deplete graft of T cells : give recipient anti-T cell Abs
- NK cells will reduce incidence of leukemic relapse

Disrupting Healthy Tissue:

tolerance:

central:
- deletion of lymphocytes before they mature
- ☆ takes place in 1° lymph tissues ☆
- limits autoreactive T & B cells
- ☆ B cells can receptor edit ☆

peripheral:
- either renders self-reactive lymphocytes non responsive or actively generates inhibiting lymphocytes
- ☆ occurs outside 1° lymph tissues (outside bone marrow & thymus)
- regulates autoreactive cells in circulation

regulatory CD4+ T cells
- can be generated in the thymus or in periphery
  - nTREG
  - iTREG

dependent mechanism:
- occurs as TREG cells express ↑ levels of inhibitory CTLA-4

independent mechanism:
- rely upon secretion of cytokines to shut down nearby cell responses
- bystander suppression:
  - or Linned suppression = Tregs that interact w/ APC can suppress T cells that engage separate Ag-MHC Class 2 on APC

regulatory CD8+ T cells:
- ☆ not generated in thymus but in periphery during CD8+T cell activation induction events
- appear after Ag-MHC class I stimulation
- use a range of mechanisms:
  - ☆ APC lysis
  - ☆ inhibition of APC function
  - ☆ regulates effector cell that bind same Ag

regulatory B cells:
may exist → produce IL-10 to inhibit adaptive immunity

MDSCs:
can secrete inhibitory compounds to negatively regulate autoimmunity

AUTOIMMUNE DISEASES:
- all resemble type 1, 2, 3, or 4 hypersensitivities
- ☆ due to failure of tolerance ☆ → chronic diseases in which adaptive immune responses become misdirected

☆ Autoimmune hemolytic anemia:
- → IgM & IgG bind components on RBC & activates complement
  - → lysis of RBC (leads to ANEMIA)
- ↳ targets RBC

☆ Signs & Symptoms:
- Pale skin
- tiredness
- dizziness
- tachycardia

☆Neutropenia:

→ WBC are less susceptible to complement mediated lysis than RBC

deficiency of neutrophils → see ↑ risk of infection

☆complement fixation leads to opsonization☆

↳ spleen removes & destroys opsonized

= ONLY treatment is splenectomy

☆Goodpasture's syndrome: → Auto Ab for α3 chain of type 4 collagen in basement membranes

IgG is deposited along basement membranes of organs

↳ esp. glomeruli & tubules & causes inflammation

↳ kidney function is impaired leading to failure & maybe death

↳ treatment: plasma exchange to get rid of Abs & immunosuppressive

Signs & symptoms:

↳ anemia — bleeding from nose & urine

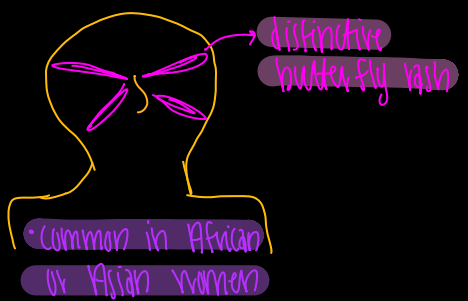
chest pain — respiratory problems

☆systemic lupus erythematosus (SLE): → type 3 hypersensitivity

IgG is made against cell-surface & intracellular self-Ag

↳ in kidney = glomerulonephritis

joints = arthritis



☆signs & symptoms:

↳ ↑ risk of CVD — joint pain — skin lesions/rashes

anemia — headaches

fatigue — confusion

☆multiple sclerosis: → type 4 hypersensitivity

autoimmune effector cells attack myelin sheath of nerve cells

onset: between 25 & 35 yrs. old

↳ death can occur within a year w/ severe cases

☆symptoms:

↳ muscle weakness
impaired vision
lack of coordination
spasticity (muscle contrac.)

→ causes permanent damage & nerve deterioration

☆motility & gait issues☆

↳ progression can be slow or alternate between acute attacks & gradual recovery

↳ activated TH1 cells activate Mf to release proteases

↳ causes plaque formation & demyelination

to treat:

↳ injection of IFN-β1 to reduce attack incidence & immunosuppressive drugs

★ APECED:
↓
lack of AIRE → without AIRE: can't get rid of Ag that are autoreactive to self

↳ common in Finns

★ B + T cells are directed against tissues + endocrine glands ★

★ persistent candida infections ★
↳ can lead to carcinoma or fulminant hepatitis

★ IPEX: → X-linked ★
↓
immune dysregulation polyendocrinopathy enteropathy

↳ caused by: FOXP3 mutation
↳ master regulator for Tregs

MAINLY AFFECTS Boys → (X-linked)

★ no abn. at birth
↳ but develop enteritis w/ intractable diarrhea, type 1 diabetes, + eczema within first months of life

★ ↑ TH17 + eosinophils w/ ↑ IgE levels ★

★ stem cell transplant to survive ★

★ Ankylosing spondylitis:
↓
more prevalent in MEN → only one

↳ onset between 20-30 yrs old

★ signs + symptoms: inflammation of joints in spine
★ back pain ★
stiffness worsens w/ time

★ treatment: medicine + exercise

★ Graves' Disease:
↓
chronic overproduction of T3 + T4 due to agonist Ab specific to TSH response = hyperthyroid

★ other symptoms: ← = heat intolerance, nervousness, irritability, moist skin, weight loss, enlarged thyroid (goiter)

↳ bulging eyes (Ab binds eye muscles)

long-term → removal w/ surgery or irradiation

★ myasthenia Gravis: → type 2 hypersensitivity
↓
impaired signaling from nerve to muscle across nm junction

↳ auto Ab bind Ach on muscles → progressive muscle weakening, droopy eyelids, difficulty breathing (impaired chest muscles)

treat by inhibiting Acetylcholinesterase + immunosupp. drugs

☆ Hashimoto's thyroiditis:

↙ caused by TH1 response that makes Ab + CD4 T cells specific for thyroid Ag

↳ destruction of tissues leads to hypothyroid

treatment = hormone replacement

☆ goiter due to inflammation → massive IR A

↳ ECTOPIC LYMPH TISSUES:

↙ seen in RA + MS
Graves'

↳ form in tissues that are chronically infected w/ pathogen → (like liver during hep C)

☆ Pemphigus vulgaris: → IgG Ab against desmoglein in cell junctions → interferes w/ integrity of skin

↙ skin blistering

↳ Ab made to EC5 = made 1st + don't cause immunopathology
↳ Ab to EC1 + EC2 = immunopathology

☆ Rheumatoid Arthritis: → type 3 hypersensitivity

↳ onset between 20-40 yrs old

↙ chronic: episodic joint inflammation

↳ immune complexes are deposited in tissues

↳ 80% of patients make IgM IgG IgA Ab for Fc region of IgG

↳ treatment: anti-inflammatory + immunosuppressive drugs

↳ synovium is infiltrated w/ neutrophils + Mϕ + CD4, CD8 + B cells + plasma cells

☆ Type 1 diabetes: → type 4 sensitivity

↙ T cell mediated
↳ CD 8+ T cells mediate destruction of beta cells + islets get infiltrated w/ lymphocytes

manifests early in childhood or adolescence

↳ Islets of Langerhans: → Alpha: glucagon, Beta: insulin, Delta: somatostatin

↳ treat w/ synthetic insulin

☆ Celiac disease: → type 4 hypersensitivity

↳ caused by IR to wheat flour or rye

↙ inflammatory disease of gut mucosa
↳ inflammation becomes chronic w/ persistent gluten

gluten digested to: gliadin + glutenin

CD4+ T cells respond to gluten peptides in GALT + activate tissue Mϕ

treat w/ removal of Gluten

CANCER

→ abnormal ÷ invasive cell proliferation

→ Median age = 70 yrs. old

due to several mutations

Benign vs. **Malignant**

Benign
- warded off
- DOES not spread
- mode of spread ↳ (metastasis)

Malignant
- continue to ↑ size ÷ invade other tissues

metastasis: where cells are carried by lymph or blood to distant sites

Mutations → insertions / deletions
substitutions
recombinations

types of cancer:

- ☆ carcinoma:
  - most cancers → cancer of epithelial cells
  - ↳ breast / prostate cancer
- ☆ sarcoma:
  - cancer of other cell types
  - ↳ mesodermal CT → bone, fat ÷ cartilage
- ☆ lymphoma:
  - cancer of solid lymph tumors
  - cells within glands
  - ☆ Hodgkin's
    - ↳ only B cells
  - ☆ Non-hodgkins
    - ↳ T ÷ B cells
- ☆ Myeloma:
  - cancer involving bone marrow
  - plasma cells

☆☆ leukemia, lymphoma, myeloma } involving some part of immune sys.

≈ Gene classes ≈

- proto-oncogenes
  - ↳ contribute to normal cell division
  - ↳ code for GF ÷ proteins involved in signal transd. ÷ gene trans.
  - ↳ Ras, Her2, Myc
- tumor suppressor
  - ↳ normally code for proteins that prevent unwanted proliferation
  - ↳ p53, Rb, Apc ÷ DCC
- apoptotic genes:
  - ↳ proapoptotic: act as tumor suppressors
  - ↳ antiapoptotic: behave like oncogenes
    - ↳ Bcl2: suppressor, Bin: inducer

☆ need at least 5-6 independent mutations ☆

Characteristics of cancer cells:

- ☆ stimulate own growth
- ☆ ignore growth-inhibiting signals
- ☆ avoid death by apoptosis
- ☆ develop blood supply
  - ↳ angiogenesis
- ☆ metastasis
- ☆ replicate constantly
- ☆ evade ÷ outrun IS

Immune responses to cancer:

innate inhibitors of cancer
- NK cells can target neoplastic cells
  - ↳ mutations that ↓ NK, ↑ certain cancers
- activated Mϕ bind Ab coated tumor cells ÷ secrete TNFα

adaptive cell types involved in certain cancers
- ↳ lack of T cells = ↑↑ cancer
- B cells generate antitumor Ab against tumor specific Ag

TILs
- → T cells
- → NK cells
- → NKT cells

↑↑ # = better prognosis

↳ cytokines ∴ cancer:

- IFN-γ: ↳ All IFN enhance tumor cell removal
- IL-12: ↳ encourages DC to activate strong TH1 ∴ CTL response
- TNF-α: ↳ may promote or inhibit anticancer effects

TUMORS:

- tumor specific Ag: not found on normal cells ↳ just tumor cells
- tumor associated Ag: found on certain normal cells ∴ tumor cells
  - ⭐ CT antigen: ↳ MALE germ cells

SUCCESSFUL TUMORS:

- ⭐ can evade ∴ manipulate IS
- ⭐ MIC is not found on healthy cells ↳ expressed when cells are under ≈STRESS≈
- tumors have ↑ MIC
  - ↳ variant tumor cleaves MIC
  - soluble MIC binds NKG2D on lymphocytes
  - ↳ cell is not killed ∴ allows proliferation
- ⭐ tumors can manipulate IS ↳ Ag can be processed / presented by DC w/out B7 ↳ no activation bc no B7 to bind CD28 ∴ cause signal
- ⭐ tumors can also secrete TGFβ = immunosupp. environment

VACCINATIONS:

HPV → links to anal, mouth, throat, genital cancers

w/ infections that last longer → infected cells integrate HPV DNA & ∴ express viral proteins

- inactivates p53 ∴ Rb = excessive replication → protein E5, 6, 7 } contribute to malignant transformation
- ⭐⭐ spread ∴ incidence ↓↓↓
  - ↳ vaccination have NO EFFECT w/ ACTIVE infections

MONOCLONAL AB:

- BRAF
- PD-1

Can boost T cell response

⭐ multiple myeloma: ↳ tumor of plasma cells that disrupts bone marrow

⭐ treatments: ↳ medications that block vessel formation, immunosuppressant drugs, inducers that cause tumor cell apoptosis