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lecture #:	date:	professor:
28	Wednesday, March 28th	Dr. Desbarats
29	Friday, March 30th	Dr. Desbarats

announcements:

- ***PULS Computer Director***: *Application extended! Just send a blurb to PULS at puls@sus.mcgill.ca. The position is appointed by council and interviews will be held on Monday April 9th, 2007.*
- ***Last PULS Office Hours:*** *The PULS office is open until classes finish, therefore the last day to pick up NTCs will be Wednesday, April 11th, 2007 until 2pm.*

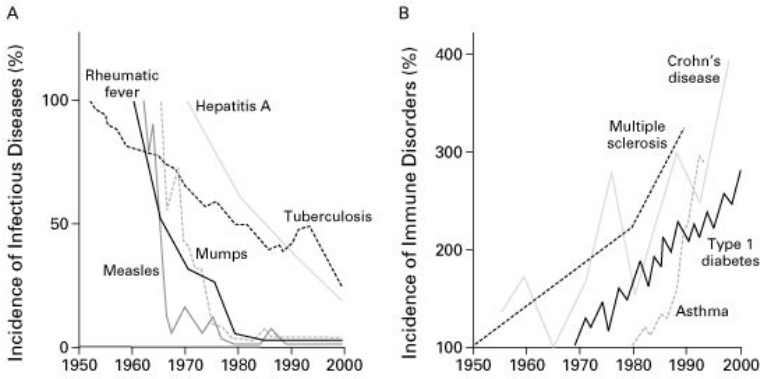
The last Immunology lectures will also be available on Athena:
http://athena.susonline.net/

Good luck on exams!

March 28, 2007
Autoimmune Disorders

LECTURE SEVEN: WHEN SELF-TOLERANCE FAILS
Autoimmune Diseases

OVERVIEW



- Like allergies, auto-immunity is on the rise dramatically.
- There seems to be an epidemiological correlation between the rise in autoimmunity and the decrease in infectious disease (*see the diagram on the right from last class and the discussion on why this is so*).
- Autoimmune diseases occur when your immune system reacts against **self-tissue**.
    - As of now, the causes are unknown as to why your immune system does not recognize self.
        - **1.** It could be a defect in the immune system to recognize self
        - **2.** It could be due to a disease that is currently unknown
            - e.g. a viral infection at a very low level

How does your immune system get to the point where it can react to dangerous microorganisms but does not react to your body?

Remember: T-Cells and B-Cells can make receptors and antibodies that can recognize **anything**, including self-components. Therefore, our immune system must **filter** out the self-recognizing components to protect the body from destruction. It does this through the following mechanisms:

- **1. Central Tolerance:** occurs in the primary lymphoid organs (bone marrow and thymus)
    - Uses mechanisms to **delete** or **kill** molecules that are potentially auto reactive
    - **B-Cells** are killed off in the **bone marrow** and **T-Cells** in the **thymus** are killed through the process of **negative selection** (*previously discussed*).
- **2. Antigen Segregation:** occurs in areas of the body where inflammation would be very dangerous; i.e. peripheral organs, such as the thyroid, pancreas, etc.
    - These areas have a physical barrier to block the immune system from access.
- **3. Peripheral Anergy:** occurs in secondary lymphoid tissues.
    - Is a secondary mechanism of protection, which is especially used in the case of a cell that escapes from the bone marrow or thymus that is still auto-reactive.
    - Consists of cellular inactivation via weak signaling without a co-stimulus
- **4. Regulatory Cells:** occurs in secondary lymphoid tissue and other sites of inflammation.
    - There exist some CD4 cells that are neither Th1 nor Th2. Although these are only 5-10% of all T-Cells, they are crucial to the regulation of parts of the immune response because they can turn off dangerous auto-reactive cells.

- ***All of these mechanisms will help to prevent autoimmune disease.***

Take–Home Message: *autoimmune diseases consist of your immune system not being able to recognize self. These diseases are on the rise and the cause still remains unknown. However, the body has developed numerous mechanisms to aid in prevention of their development. These mechanisms include central tolerance, antigen segregation, peripheral anergy, and the use of regulatory cells. Each of these will be discussed in further detail below.*

CENTRAL TOLERANCE

- *Remember:* the consequence of **negative selection** is **tolerance.**
- ***However, if the self-antigen is never present in your thymus, how can you develop tolerance against it?***
    - To illustrate this, we will be using the example of the eyes and the ovaries.
    - These contain antigens that you need to be tolerant to in order to avoid organ destruction.
        - *In the ovaries and testes, the antigens are altered during puberty. Therefore, we must have protection against self to prevent destruction of these organs.*

The thymus is able to express a special protein, the **autoimmune regulator** [AIRE]. This protein can act as a **transcription factor** to produce proteins that are normally tissue specific.

- Therefore, proteins that are usually locally expressed can be produced in the thymus.
- Not enough are produced to create an external effect, but enough is produced to allow the peptides to be exposed to developing cells in the thymus.
    - **This means that you can become tolerant to these peptides.**
- The regulator mostly controls gene products from **endocrine organs**, although it is not understood why.

Mutations against this regulator are very dangerous because T-Cells that are reactive to self-tissue are allowed to mature and leave the thymus.

- Therefore, numerous autoimmune disorders can be developed in infants.
- These mutations are called: **autoimmune Polyendocrinopathy Candidiasis/Ectodermal Dysplasia [APECED].**
- Essentially what happens is that at the age of approximately one year, the child will develop his first autoimmune syndrome. Over the next five or six years, the child will develop syndrome after syndrome until he accumulates around six. If not treated, the child will die from this. *The diagram to the right shows the most common diseases acquired.*

APECED patients suffer a variety of autoimmune diseases and candidiasis

Symptom	Frequency in Finnish patients (%)
Endocrine glands	
Hypoparathyroidism	85
Adrenal failure	72
Ovarian failure	60
Insulin-dependent diabetes mellitus	18
Testicular atrophy	14
Parietal cell atrophy	13
Hypothyroidism	6

Figure 11-19 part 1 of 2 The Immune System, 2/e (© Garland Science 2005)

- All of the most common autoimmune symptoms are endocrine related, indicating that the affected individuals will probably not make it past puberty without dying.

Take-Home Message: *through the mechanisms in place by central tolerance, negative selection accounts for the deletion of T-Cells that recognize self-peptides when the self-peptides are present in the thymus. In addition, the autoimmune regulator (a transcription factor) is able to upregulate the production of hormones in the thymus that are not normally present. This confers the ability for T-Cells to create tolerance to these endocrine molecules. Mutations against this regulator are severe, since no tolerance will be formed against any of the hormones in your circulation.*

ANTIGEN SEGREGATION

Now, let's discuss what happens to self-proteins that are not expressed in the thymus and are not affected by the regulator…

- *Remember that the regulator only affects endocrine peptides.* To solve the problem of all other peptides, we use **antigen segregation.**
- This affects peptides in the **brain, eye, testis, uterus [and therefore fetus], and the hamster cheek pouch** and collectively these are considered **immunologically privileged sites.**
  - Commonalities in these areas include the fact that: if you have a strong inflammatory reaction, there are many, many consequences, including death or infertility.
  - The brain, eye, testis, and uterus have obvious consequences. But as for the hamster cheek pouch: this is where the hamster stores its food. If there is reaction here, the hamster will not be able to store food anymore and it is the equivalent of inflammatory bowl disease in the human.

- All of these places have **tight epithelia** that to do allow T-Cells and B-Cells to cross easily. If there is an infection in any of these places, the barriers to become more leaky and there is the possibility of an inflammatory reaction. Normally though, there are no T-Cells or B-Cells located there.
- **Upon injury in these places,** there is the release of sequestered antigens. These antigens are carried to the lymph nodes and activate T-Cells, which attack the location of injury.
  - **This shows you that you have T-Cells in your body that have the potential to react to these proteins, but they normally do not have contact.**

- **An important thing to note**, is that if one eye is injured the activated T-Cells return and attack **both** eyes.
  - ***Therefore, the barriers that keep these areas free of T-Cells only work against naïve T-Cells. Activated T-Cells are unaffected by these barriers.***

- ***Take-Home Message:*** *since not all proteins have access to the thymus and can be produced in the thymus [via the autoimmune regulator], there are still free proteins that are not accounted for by the T-Cells. The protection these proteins have is segregation from T-Cells. Normally, the barriers to the eye, brain, testes, and uterus [immunologically privileged sites] are very tight and do not allow passage of T-Cells or B-Cells and therefore, no attack can take place. However, upon injury, the epithelium becomes looser and invasion and attack is possible.*

PERIPHERAL ANERGY

- ***Again though, there are still peptides unaccounted for. How do we account for these to be protected?***
- These locations include the **liver, the heart**, and basically any other location that is not expressed in the thymus, controlled by the AIRE, or is protected by specific barriers.
- The mechanisms employed here are **essentially valid for all antigens** in the body. This is the **two-signal system** *that was discussed earlier.*
  - **Signal One** [the antigen presented by the APC] is the trigger. But **Signal Two** is the safety-signal. The attack on the pathogen cannot happen without this second signal.

- ***But where does the co-stimulator signal come from?***
  - The co-stimulatory signal only comes with an **activated APC: macrophage or dendritic cell** that has been **stimulated through a TLR** or other signal

- *Therefore, this should **only** occur if there is a microbe in the vicinity.*

In the last lecture, we learnt that other molecules that should not be present, like diesel fuel, could trigger this system. This is why one reason why people living in polluted first-world nations have increasing statistics of autoimmune disorders [*see above*].

  - **Normally,**
    - **1.** The T-Cell encounters the antigen through contact with an activated APC.
    - **2.** The T-Cell then receives a co-stimulatory signal and becomes activated, so it can go on to kill the microbe that is present.
  - **In this case,**
    - **1.** The T-Cell encounters the **self-**antigen through contact with an activated APC.
    - **2.** The T-Cell does not receive the secondary signal, and the T-Cell becomes **anergic**: unresponsive. These cells can remain un-responsive and stick around in the body or some of them can die. *It is unknown how the choice between death and unresponsive T-Cells is made.*

- ***Are there any other problems with this? Yes!***
  - *Remember* that the end of the immune response consists of death of all the proliferated T-Cells: **peripheral deletion**.
  - If you have a mutation in the suicide pathway [i.e. the **Fas ligand**], there is an accumulation of the proliferated activated cells. This is a problem because activated cells are able to cross barriers and since there are so many of them, although normally they have no effect, now they are able to "gang-up" the body. Over the years, these cells may begin to react to self-components and cause disease.
    - Diseases that are caused include autoimmune lymphoproliferative syndrome, which has been explained in previous lectures, but is essentially the accumulation of proliferated T-Cells in the lymph nodes, causing enlargement of the area.

- ***Take-Home Message:*** *Since T-Cells need both a direct antigen signal and a co-stimulatory signal to become active, this signaling system can be exploited to prevent self-attack. Normally after both signals, the T-Cell can proliferate and kill. However, if the T-Cell encounters a self-antigen, there is no secondary signal present and the T-Cell becomes anergic [unresponsive]. Another problem that may occur is mutations in peripheral deletion. Normally, at the end of an immune response, all of the proliferated cells die. However, if there is a mutation in the Fas ligand, which causes self-death, these cells will not die, accumulated, and over the years can cause numerous autoimmune problems.*

REGULATORY CELLS

- The last mechanism we are going to discuss is that of the **regulatory T-Cells.**
- It is the **final layer** of protection for autoimmunity.
- Present in your body is a class of cells called **regulatory T-Cells**. *As we have already learnt,* CD4 cells mostly differentiate into **Th1 helper cells or Th2 helper cells**. However, these regulatory T-Cells consist of the 5-10% that do not differentiate into either. These cells are called **Th3 cells** or **T-Reg cells**.

TH3 CELLS:

- Th3 cells are mainly located in you **intestinal tract**. Like the hamster cheek pouch, foreign antigens coming from the food consumed continuously bombard the intestine. In addition, the GIT tract has lots of bacteria, which are able to stimulate your immune response, via TOLL-like receptors.

- Since this area needs to be protected, Th3 cells have evolved to secrete **immunosuppressive cytokines,** such as TGFβ, which is the **most potent immunosuppressive cytokine** your body makes.
    - Th3 cells, by secreting TGFβ, act to **suppress Th1** and **Th2** cells.
- If you lose these cells, or have mutations, you will have vicious autoimmunity against her gut, which results in ulcerative colitis or Crohn's disease [**inflammatory bowel diseases**].

T-REG CELLS:

- These cells are present **throughout** your body.
- They secrete both TGFβ and **IL-10**, which tends to suppress Th1 cells.
    - Therefore, these cells are crucial for prevention of autoimmune diseases caused by Th1 cells.
- In addition, there is crucial expression of a gene called **foxP3** for development of regulatory T-Cells in the thymus.
    - Without it, there is no production of regulatory T-Cells and you will develop and autoimmune/inflammatory disease, such like individuals with a mutation in the autoimmune regulator [AIRE] transcription factor.
- ***Therefore, T-Reg cells are just as important as negative selection in the thymus, proving that all levels of protection against autoimmunity are crucial.***

- ***Take-Home Message:*** *The final method of protection against autoimmunity is that of regulatory cells. We know that most CD4 cells develop into Th1 or Th2 cells. However, there are some remaining cells that develop into Th3 or regulatory [T-Reg] cells. The Th3 cells are present in the intestine and secrete TGFβ to suppress the activity of Th1 and Th2 cells. T-Reg cells are present everywhere in the body and secrete both TGFβ and IL-10, which inhibits Th1 cells. In addition, foxP3 is required for the proper development of T-Reg cells in the thymus. If any of these three genes acquire mutations, there is the development of autoimmunity.*

- **A question:** ***in which gene do you think you could have a mutation without developing an autoimmune disease?***
    - **RAG.** ***Why?***
        - Without RAG, there is no development of T-Cells **or** B-Cells. Therefore, since you have no immune system, it cannot attack the self. However, because there is no immune system, you will die.
    - *Luckily, these diseases are very rare.*

MOLECULAR MIMICRY

- Not all people who have autoimmunity have developed one of the mutations we have discussed. Therefore, how do these people get autoimmune diseases?
    - **Molecular Mimicry**
- Although you are tolerant to self-proteins, what if you have a pathogen that has an **identical** protein as the self-protein. It doesn't have to have the same amino acid sequence, just the **same shape when presented by the MHC.**
- With the abundance of different pathogens and self-peptides, this is bound to happen. One example of this is **rheumatic heart disease.**
    - In this case, there is first infection by streptococcal bacteria in the cell wall, leading to strep throat and stimulating the antibody response. One of the streptococcal antigens is similar to a protein in the heart valve.
    - Therefore, when you have an antibody response, some cross-react with the heart tissue causing rheumatic fever.

- *Today, this disease is prevented with antibiotic treatment at the onset of strep throat.* In the past, rheumatic heart disease caused first a heart murmur, which over the years can destroy the valves in your heart.
- Not everyone with strep will develop rheumatic heart disease. For this disease to occur, you need to have **presented an identical peptide on your own MHC.**
    - This is because depending on the MHC presented, not all the peptide presented will be identical to the heart valve protein. *Remember that each individual will develop slightly different MHC molecules.*

- ***Take-Home Message:*** *even though we have these mechanisms of protection [central tolerance, antigen segregation, peripheral anergy, peripheral deletion, and regulatory cells], there are still some individuals who can acquire autoimmune disease without the development of mutations in regulatory molecules. To account for this, we use the concept of molecular mimicry. This consists of the fact that pathogen peptides may be structurally identical to self-peptides. Therefore, when they are presented in the context of MHC, the antibodies that attack can bind to self-peptides and cause disease. However, this does not occur for all people because MHC presentation works on a person-to-person basis, meaning that the peptides presented in one individual will differ from those in a different person and therefore, may not match the self-peptide.*

AUTOIMMUNE DISEASES

- Classified in two categories:
    - **Organ-Specific:** caused by **T-Cells** attacking only one organ system
        - **Type I diabetes mellitus**
        - Goodpasture's syndrome: against the basement membrane in the lungs and kidneys
        - **Multiple sclerosis**
        - Grave's disease: *against the thyroid*
        - Hashimoto's thyroiditis: *against the thyroid*
        - Autoimmune pernicious anemia: *against RBC precursors*
        - Autoimmune Addison's disease: *against the pituitary adrenal axis*
        - Vittiligo: *against pigmentary cells in the skin [melanocytes]*
        - Myasthenia gravis: *against ACh receptor in muscle endplate*
    - **Systemic:** caused by **antibodies**
        - Rheumatoid Arthritis: *against your joints, but is also mediated by antibodies that can circulate through your system to attack joint anywhere*
            - *Therefore, can possibly can fit into both categories*
        - Scleroderma: *"skin of stone"; antibodies against your skin cause thickening and hardening, but also causes a thickening and hardening of the internal epithelia, which is very dangerous*
        - **Systemic lupus erythematosus:** *make antibodies against numerous self-components, including intracellular component, such as DNA, etc*
        - Primary Sjogren's syndrome: *against the salivary glands*
        - Polymyositis: *against the muscles*

- ***Essentially, there is no part of you that is immune to attack.***

TYPE I DIABETES: INSULIN-DEPENDENT DIABETES MELLITUS [IDDM]:

- Very common in North America, but the most common type of diabetes is Type II
- Usually occurs in young children, before the age of ten, although it can happen in adults.

- The disease consists of an attack of the **β cells in the islets of Langerhans.**
    - *Remember that the islets of Langerhans in the pancreas have three different cells, which produce three different hormones. In this case, the attacking T-Cells are only specific for B-Cells, which secrete insulin.*
        - **It is this specificity for cells that normally allows the body to kill one molecule while leaving the neighboring one alone.** Unfortunately here we are killing something that is useful.
- Since we are killing off our cells that produce insulin, there is no more circulating in the blood. By the time that you show symptoms, over 90% of the beta cells have been killed and attempts to salvage the cells is essentially useless. Therefore, the treatment is **injection of insulin** to account for the loss.

Consequences:

- The increased blood sugar causes damage to pretty much all of your tissues.
- There is **vascular damage** that can result in amputation, heart attacks, or strokes; **retinal damage** that can result in blindness; and **vascular and tissue damage** that can result in kidney failure.

- The only **treatment** is insulin replacement and the only **cure** is pancreatic transplantation.
    - Pancreatic transplantation is usually done in concert with kidney transplantation. It is extremely difficult because it has exocrine functions [including proteases], as well as endocrine function. Therefore, the proteases can digest the pancreas if there is significant damage, causing their release.
    - It would be ideal to have an immunological cure or a way to predict who will develop diabetes type I, in order to prevent destruction of the beta cell before it happens.
        - This may be possible because there is a **genetic** component.
        - Many studies are currently on-going taking prospective children and giving them treatments of drugs to modulate their immune system, including immunosuppressive drugs. However, there are many problems with immunosuppressive drugs *that will be discussed in the transplant lecture*.

- **Causes:** molecular mimicry is a hypothesis, although there is no conclusive evidence as to which pathogen could be causing this. *Remember that molecular mimicry is the similarity in shape between a pathogen and a self-peptide, causing the antibody response to the pathogen to be able to affect the self-proteins.*
    - Therefore, individuals with a certain type of MHC are more prone to obtaining this disease. **This has been proven to be true.**

MULTIPLE SCLEROSIS:

- This disease is increasing in prevalence, mainly in people in their early 20s and 30s. More women than men develop this disease due to the effect of sex hormones. However, if a man does develop MS, it will develop it younger and a more aggressive form.
- If you are born or grew up in the **temperate** regions of the world, or in **Scandinavia**, there is a greater likelihood of developing this disease that compared to people from the tropics.
    - It is unknown why this occurs, but possible reasons include the pathogens you were exposed to or the amount of sunlight you get [due to the **activated of vitamin D**].
- It is an autoimmune disease against your **brain, specifically against the oligodendrocytes,** which are the **myelin-producing cells** of the CNS.
    - *Remember that myelin surrounds your axons as insulation to allow sufficient nerve propagation. Without it, there is no nerve conduction.*

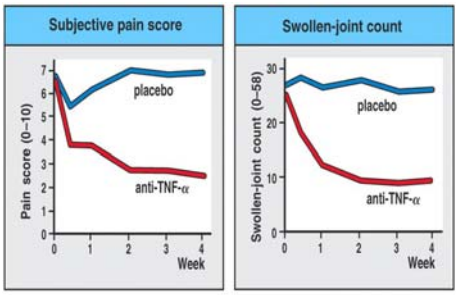
- The physiological consequences of myelin degeneration depend on the **location of the lesion.**
  - e.g. if the lesion is in the optic tract, you can go blind
  - e.g. if the lesion is in the motor tract, you can become paralyzed
- The problem with disease is that you never know where your next lesion will be. There are no predictive measures.
- ***There is more unknown than known about multiple sclerosis.***
  - We do not know what triggers it, how to prevent it, or how to treat it.
  - What we do know is that **T-Cells and B-Cells infiltrate the brain,** which is a normally immuno-privileged site and cause demyelination lesions.

INFLAMMATORY BOWEL DISEASE:

- Consists of an autoimmune attack of **any section of the GIT.**
- Predisposing factors include:
  - **Eating disorders,** due to the damage that is already caused to your body.
  - **Genetics,** due to specific MHC molecules, which may indicate molecular mimicry.
  - **Disease that prevents formation of regulatory T-Cells,** due to the antigens present in food.

RHEUMATOID ARTHRITIS:

- Is a disease of both **T-Cells and B-Cells,** which infiltrate into joints and destroy the **cartilage.**
- Uses some of the same mechanisms as inflammatory bowel disease.
  - Both of the diseases respond to the same treatment, which is ineffective for IDDM and MS.
  - This therapy **neutralizes tumor necrosis factor,** which is secreted by Th1 cells. When antibodies are made for TNF, they bind and remove it from circulation. This decreases the subjective (what **you** feel) and objective (what the **doctor** sees) symptoms.



    - Downsides to this therapy consist of:
      - **Administration:** it is an antibody, so it cannot be eaten because it will be degraded, so it has to be injected. After several injections, there can be the development of **type III hypersensitivity reactions** [*see previous lecture*], such as serum sickness.
      - TNF is naturally produced by the body to prevent cancer, so side effects include an increase in cancer. This is especially true of inflammatory bowel disease, in which polyps develop along the intestinal wall. These polyps can then later develop into cancerous tumors.

- ***Take-Home Message:*** *Autoimmune disorders can cause many problems, both organ-specific and systemically. The problem with these diseases is that they are also difficult to treat because of the potential side effects of treatments and the unknown factors of the disease.*

AS A REVIEW

- Remember that the **AIRE** transcription factor is only located in the **thymus** and controls the expression of many genes and many endocrine hormones. A defect in this gene does not mean defective endocrine organs or hormones; it means a defect in the tolerance to them.
- Proteins that are segregated by **barriers** are protected anatomically; they are not protected in other ways.
- Last class we discussed autoimmune disorders that were **organ-specific**. Remember that these diseases are induced by **T-Cell** attack. Now, we will talk about **systemic autoimmunity.**

SYSTEMIC AUTOIMMUNITY

- This is controlled by B-Cells, which require T-Cell help. Therefore, to get systemic autoimmunity, you need to break tolerance at 2 levels.
    - The T-Cells need to be broken at the level so that they cant present the self-antigen to the B-Cell.
    - B-Cell protection then needs to be broken so that they recognize self-components. The antibodies that are created to these then have the ability to circulate through your body and find these self-peptides in any location of the body.

PEMPHIGUS VULGARIS:

- In this case, the antibody reacts with a protein that is expressed in the **tight junctions of skin** that attempts to hold your skin together.
- When the antibodies prevent your skin from being held together, the skin bubbles off. The bubbles can form anywhere on your body, since the B-Cell antibodies have access to every area through the circulation.

LUPUS:

- Lupus is the most common systemic autoimmune disease.
- Lupus comes from the Latin word for wolf. This is derived from the fact that one of the outcomes of lupus is markings on the skin, which to some people resembled the markings on a wolf's face.
- Not all affected individuals have the same extent of rash on their skin.
- However, it is **important** to remember that the rash is occurring **everywhere** in the body, including the **internal organs.**
    - This can causes side effects, such as kidney failure and dementia. Luckily though, the severe forms that cause these side effects are very rare.
- In the case of lupus, the antibodies are responding to **multiple self-components**, such as your DNA, RNA, antibodies, etc. This is the cause for affecting multiple organs.

- ***Take-Home Message:*** *systemic autoimmunity is a result of a malfunction in both B-Cells and T-Cells. It occurs when antibodies are able to attack various parts of the body with accessibility provided via the circulation. Examples of systemic autoimmunity include pemphigus and lupus.*

PREGNANCY AND SYSTEMIC AUTOIMMUNITY

- ***Consider the case of pregnancy:*** if you become pregnant, the diseased IgG antibodies can cross the placenta and affect the fetus. However, *remember that only IgG can cross the placenta; not T-Cells or other classes of antibodies.* Other diseases that can be transmitted this way include:
    - **Myasthenia Gravis:** this is when antibodies are present that are directed towards the **ACh receptor** on the muscle endplate. This can cause weakness or eventually paralysis.
    - **Grave's Disease:** This is a disease in which there are antibodies developed against the **thyroid gland**, causing hyperthryroidism.
    - **Thrombocytopenia:** In this case, you make antibodies that attack your **platelets**, making your

body more susceptible to bruising and hemorrhage.
    - **Lupus**
    - **Pemphigus**
- There is nothing that can be done for the baby *in utero*, but once it is born you can use **plasmaphoresis:**
    - The baby is hooked up to a system, such like that of kidney dialysis. The blood is completely removed from the system and filtered through a system before being re-inserted. The filtering system is able to **remove all of the anti-bodies** in the blood. Although this makes the baby very immune susceptible, it prevents these autoimmune diseases from occurring.
    - This concept cannot be used in the mother or other adults. This is because you cannot remove the B-Cells and T-Cells effectively. If someone has the disease, their B-Cells and T-Cells are already programmed and they just make more. *The baby does not have these B-Cells and T-Cells; it only has the antibody from transfer of IgG from the mother.*

- ***Take-Home Message:*** *Remember that since IgG molecules can cross the placenta, autoimmune diseases that afflict the mother can be inflicted onto the baby. Although this cannot be dealt with in utero, once the baby is born, its blood can be filtered to remove the antibodies made. Although this works, it causes the child to be very immune suppressed. This mechanism does not work with adults because the B-Cells have already been programmed to recognized specific peptides. Therefore, even if antibodies were filtered out, new antibodies would form.*

HLA MOLECULES

- *Remember that last time we discussed how* it is unknown why autoimmune disorders develop. Most are **linked to the type of MHC you have.** It means that you may be more resistant to more pathogenic diseases, but possibly more susceptible to more autoimmune diseases [*see diagram*].
    - Different alleles for MHC can be implicated in different diseases.
    - This supports the idea of **molecular mimicry** because if you have a specific MHC molecule, it will affect which pathogens and self-peptides it responds to.

- In addition, different autoimmune diseases affect men differently than women.
    - *See the diagram to the right.* If the sex ratio is less than one, men are more susceptible. Notice though, that in most cases, affected women are more common.
    - The sex-based infliction is due to that fact that **hormones affect your immune system** and can affect which type of autoimmunity you can get.
        - Female hormones, e.g. progesterone, tend to bias your immune response towards a **Th2** response, meaning that **antibody-mediated** autoimmunity is more common.
            - It is unknown why this occurs, but the amount of diseases acquired or the extent of disease **increases during pregnancy**.
                - However, T-Cell mediated autoimmune diseases seem to alleviate during this same time

- ***Take-Home Message:*** *women are more afflicted than men with autoimmune disorders, due to hormones present in the*

Associations of HLA serotype with susceptibility to autoimmune disease

Disease	HLA allele	Relative risk	Sex ratio (♀:♂)
Ankylosing spondylitis	B27	87.4	0.3
Acute anterior uveitis	B27	10	<0.5
Goodpasture's syndrome	DR2	15.9	~1
Multiple sclerosis	DR2	4.8	10
Graves' disease	DR3	3.7	4–5
Myasthenia gravis	DR3	2.5	~1
Systemic lupus erythematosus	DR3	5.8	10–20
Type I insulin-dependent diabetes mellitus	DR3/DR4 heterozygote	~25	~1
Rheumatoid arthritis	DR4	4.2	3
Pemphigus vulgaris	DR4	14.4	~1
Hashimoto's thyroiditis	DR5	3.2	4–5

Figure 13-20 Immunobiology, 6/e. (© Garland Science 2005)

body. Female hormones seem to activate a Th2 response and therefore cause organ-specific autoimmunity.

A REVIEW

- *Remember that **positive selection** does not affect autoimmune disease. It aids in increasing the response your body has to the microbe. A defect in **negative selection** will cause autoimmunity [Recall, mutations in the AIRE]*
    - ***Therefore, remember that autoimmunity is not a hyperactivity response; it is a defect in regulation.***
        - ***Th1:** causes MS or IDDM*
        - ***Th2:** lupus or pemphigus*
        - ***Negative selection:** PAMPs*
        - ***Regulatory T-Cells:** multiple autoimmune disorders*
    - *The fact that they are caused by a defect in regulation is further proven by the fact that most affected individuals are also **immunosuppressed**, due to the regulatory mutations.*

LECTURE EIGHT: IMMUNITY IN TRANSPLANTATION AND PREGNANCY

OVERVIEW

- Throughout ages there has been the need to transplant limbs, due to loss of the limbs, mainly in battle. Specific grafts in history have been documented as being successful. Typically though, grafts were initially fine and then **later** became infected.
    - Your blood supply is initially very good, blood vessels are re-growing into the graft. However, this can only last so long.
    - Eventually, it turns black and falls off.
    - *This is because your body recognizes the part as foreign and rejects it.*

- It was only in the 1950s and 60s that transplantation became recognized as an immunological process. The **first successful transplant** then occurred in the 1950s and was a kidney transplant between identical twins.
    - Once it was concluded that the cause of failure was the immune system, you could now take people who were genetically and immunologically identical and have success.
    - This also means you can have grafts from your own body. For example, in a burn, it is possible to take skin from other areas of your body and graft it to the burn area and have it take. This is called an **auto-graft.**
        - You can do the same thing with your identical twin, if you have one.
- There were very few transplants that were successful, until there were drugs discovered that could **suppress the immune system.**
    - With these drugs, the success of transplants sky-rocketed.
        - Blood and bone marrow transplants have their own specific problems, but the *diagram to the right shows the common organ transplants.* Cornea transplants are increasing. *Remember that the cornea is an immunologically privileged site, so there are no T-Cells or B-Cells that are present to begin with.*

Tissue transplanted	5-year graft survival*	No. of grafts in USA (2002)
Kidney	65–75%	15,680
Liver	65–75%	5594
Heart	68%	2231
Pancreas	30%/80%#	1492
Lung	40%	1077
Cornea	~70%	~40,000†
Bone marrow	40%/60%	15,000‡

Figure 13-41 Immunobiology, 6/e. (© Garland Science 2005)

- ***The problem right now with organ transplant is the availability of organs.*** They need to be acquired from only brain-dead patients, so that the organs are still alive for the transplant. As well, individuals need all of their organs, except possibly for one kidney [if the other is healthy], so the availability of useable organs is few and far between.

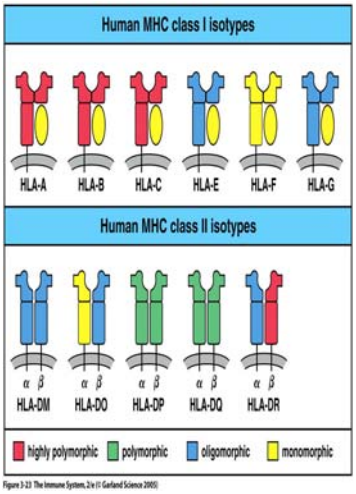
- ***Take-Home Message:*** *Until recently organ transplants were failures. Upon the discovery of both the fact that it is the MHC molecules that cause rejection and the invention of immunosuppressive drugs, transplants became much more popular. As of right now, the two major problems with transplants are availability and transplant rejection.*

TRANSPLANT REJECTION

- ***Why does this happen?*** We share 99.9% of genes, which totals a difference in less than one in thousand genes in our body. In addition, the genes in which we do differ in are usually only single base pair differences. Therefore, since we are almost entirely identical, what is the big deal?
    - **Where we differ is called the MHC, or HLA, in humans.**

- At the MHC locus, the genes are **polymorphic**. This is the key to rejection because the MHC molecules will never be the same between individuals, unless they are identical twins. Sometimes brothers and sisters can be very similar or identical.

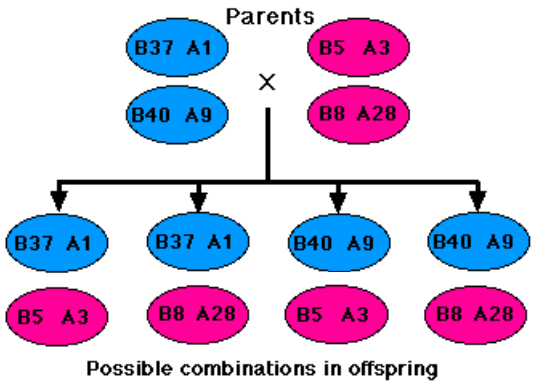
- *As of now, we have be taught that there is one type of MHC I molecules and one type of MHC II molecules.* **This is not true.**
    - There are **three different isotypes** of **MHC I** and **three** of **MHC II.**
        - These are called HLAa, HLAb, and HLAc for MHC I and HLAvr, HLAvp, and HLAvq for MHC II.
        - *The diagram to the right shows the numbers of variants that there are in the population.* You can see that there are hundreds.
            - There is no way that in a given population you will have anyone who has all three of the same MHC molecules.
    - When they check typing between individuals, they first check **HLAa and HLAb** because these are the two most **common** types.
    - Individuals who are related have a much better chance at having some of the same isotypes.



- *The diagram to the right is just to show you the different types of MHC isotypes. The Class I isotypes are not expressed everywhere. They are expressed in certain areas, such as your brain, the placenta, etc. and are probably not involved in antigen presentation.*

- There are three class I molecules that are expressed on every cell. The same thing goes for class II molecules: vp vq, and vr are all involved in antigen presentation.

- *Remember that these molecules are inherited as DNA on a molecule,* ***one from each of your parents****.* During inbreeding, you can consider the both of the molecules inherited as a unit,



since every individual will have the same inherited genes.

- Because humans are outbred, you cannot do this. Each of the mother and father will have two different MHC molecules, one of which they pass on to the child, for a total of four possible combinations. [*See the diagram to the right for visual presentation*].
    - So even in a family of four, the likelihood of having the same MHC molecules is small. As the number of children increases, the probability of having the same MHC molecules increases. In addition, the children will not match the mother or father since there is only one of the molecules inherited from each of them. However, your best chance is still your family.
        - If a transplant is needed, a doctor will tissue type each member of the family to determine the MHC molecules they have present. If two of the siblings are the same, this would be the individual to use for transplant [e.g. kidney].
- **It is important to note that on each of your cells you have an MHCa from each of your parents, and MHCb from each of your parents, and an MHCc from each of your parents.** This means there are lots of different possibilities for presenting peptides on your cells.

- ***Take-Home Message:*** *on each of your cells, you have **six types of MHC on the surface**. These include HLAa, HLAb, HLAc, HLAvp, HLAvq, and HLAvr. The first three belong to MHC I and the latter three are MHC II molecules. However, the cell has a **multitude** of MHC **molecules** on the surface, which in total can present **six antigens** at a time [one for each MHC isotype]. The molecules are inherited as a gene locus, so you get one from your mother and one from your father. This means that even between family members there is large diversity, let alone between random individuals.*

- When we do experiments, we used inbred mice, who then have the same MHC molecules and are entirely genetically identical. If you carry out a transplant between these mice, there is no rejection. However, if you carry out a transplant with a mouse that is not part of the inbred strain, there is rejection.
    - *When we consider analysis of MHC molecules, we consider only one of the isoforms [i.e. HLAa, HLAc, etc] to refer to the entire locus. This is to simplify the nomenclature used. If we considered all six isoforms upon each analysis, it would become very complicated.*

GRAFTING:

- Upon first graft, the healing time totals 10 days - two weeks to determine whether it will be accepted or not. Upon rejection: the foreign skin graft can activate **macrophages and dendritic cells**, which migrate to the local lymph node and activate T-Cells, which move back to the location of the graft and restrict blood flow. The graft then becomes black and falls off. This rejection is called **first set rejection** because it is the first time the mouse is seeing foreign MHC molecules and it has not formed memory cells yet.
- If you do the same experiment again, the mouse will have memory cells to recognize the previous molecules. That means, that upon grafting, the mouse will attack the new graft quicker than the first graft [e.g. in a week]. This is **second set rejection** and is mediated by **T-Cells.**

- **ASIDE:** silicone has no molecules to react to, which is why it is a good material for transplantation. However, over time pieces may degrade and fall off the whole. If these smaller particles become oxidized, your immune system can attack them. These molecules cannot be degraded, but upon attack they can be surrounded by scar tissue. So, if your immune system recognizes something as foreign in your body, it will be attacked.

- ***So what happens if you have identical MHC molecules and you give a graft?***
    - If you transplant between a boy and a girl who have the same MHC molecules, the body will recognize some of the opposite sex proteins [e.g. male antigens] as foreign. This causes a **very slow** graft rejection because there are not many proteins that are being recognized. This is

called a **minor incompatibility.**

- ***Take-Home Message:*** *self-grafts and grafts between identical twins are very successful. However, grafts between individuals are difficult, due to the presence of different MHC molecules. The first time there is rejection it is called first-set rejection because it is the equivalent of an immune response attacking foreign particles [i.e. the build-up of B-Cells, T-Cells and formation of memory cells]. If there is a second graft with the same tissue, there will be second-set rejection. This would be a by-product of the memory cells that were formed form the first reaction. In addition, further rejection can take place if there are other minor antigens present, such as the presence of opposite sex proteins.*

TYPES OF REJECTION:

- **Hyperacute:** occurs immediately
    - This should never happen unless there is a medical mishap.
    - It occurs when the two blood types do not match.
    - It is almost impossible to survive this rejection reaction because it activates the complement system, which attacks the entire body.
        - The only treatment is to take this organ out, but if it is a major organ and there is no back-up, it is impossible.
    - Therefore, in addition to blood typing, you mix the two blood samples prior to transplantation to ensure that there is no reaction.
- **Acute:** occurs within weeks
    - This is the most common type of rejection if you transplant a graft that is not HLA-matched.
    - The new organ will have antigens on it, due to the damage that it sustained during the trauma of dying and transport. These APCs are transported to the lymph nodes, where the APCs are recognized as foreign and an immune response is initiated. This is called **direct allorecognition:** direct recognition of an MHC.
    - The debris from the kidney is phagocytosed by the recipients own macrophages and presented in the context of MHC II. If there are minor differences, [i.e. male into female, etc], these will be recognized as foreign and there will be an immune response. This is called **indirect allorecognition:** recognition of foreign peptide.
        - Both of these responses occur in the **draining lymph node** or **spleen**, just like any other immune response.
- **Chronic:** if it keeps happening after months or years
    - This type occurs mostly in transplantations who are MHC matched. In this case, the only thing that your body can recognize as foreign is the **peptides that come with the organ.**
    - There is no direct allorecognition here.
    - It can take a very long time to develop because it is based on the circulation of the foreign peptide and its probability of contacting the correct, matching T-Cell in a given lymph node is quite low. If this contact is never made, there will never be rejection.
        - Once it starts though, the T-Cells will return to the organ and attack. Upon attack, the organ gets damaged and more peptide is released. This activates more T-Cells for further attack. In addition, they can activate B-Cells, which cause an **inflammatory response.**
            - Once this starts it is **very, very hard to stop**.

- **Take-Home Message:** there are three different types of rejection. This includes: hyperacute, which is a by-product of mismatched blood cells. Acute rejection, which is due to antigens present on the organ being transplanted as a result of the damage it went through during the humans' death. It consists of both indirect and direct allorecognition. The last type of rejection is chronic rejection, which occurs over a long period of time from left-over peptides on the organ being transplanted.