

How Does Autoimmunity Occur?

OK, this refers to autoimmunity and hypersensitivity reactions. Sorry this wasn't on the original (I was going to have it under the review section at the beginning.) But, I finally got everything figured out. Let me know if you have questions.

Normal Immune Response

1. The macrophage recognizes a pathogen, due to a PAMP (pathogen-associated molecular pattern) on that pathogen, such as mannose, double-stranded RNA, etc. Remember Toll-like receptors?
2. Once the macrophage is activated, it upregulates B7 receptors. B7 is what will bind to the CD28 on T cells.
3. The macrophage takes peptides from the pathogen and presents them on MHC II class receptors to T cells that recognize that particular pattern.
4. The TCR and MHC II bind (the first signal.)
5. The CD28 and B7 bind (the second signal). Remember, without this second signal, **ACTIVATION OF THE T CELL DOES NOT OCCUR!!** The T cell will become nonfunctional (anergic), will undergo apoptosis, or becomes regulatory. It needs the second signal to become activated to the pathogen.
6. T cell is now active and begins replicating, etc, etc.

If a second signal is needed, how to self-peptides and harmless environmental antigens initiate an immune response?

This occurs in two ways, one of which is explained in my previous handout, although maybe not as well.

I. MOLECULAR MIMICRY

1. A pathogen that has an identical peptide sequence to a host protein enters the host.
2. This pathogen also has PAMPs, which activate the macrophage, causing it to upregulate B7.
3. The T cells are activated by this macrophage.
4. T cells activate B cells, etc.
5. These macrophages, T cells, and antibodies combat the pathogen, but also the host tissue with the identical peptide sequence.

II. COINCIDENCE

1. A pathogen with a PAMP activates a macrophage, like above.
2. While the macrophage is displaying peptides from the actual pathogen, it also picks up peptides from host debris caused by inflammatory damage.
3. Both the host cell peptides and pathogen peptides are presented along with B7.
4. T cells that recognize this host cell sequence are activated.

These two events occur only if central tolerance has failed. Obviously, peripheral tolerance has not occurred either. So basically, you can't have an autoimmune reaction without the macrophage being activated by some other pathogen or tissue damage first. I hope that makes sense. Let me know if you have questions on this!

I also know that specific MHC alleles make someone more susceptible to autoimmunity and/or allergic reactions, but I'm not positive how this fits it. Even so, some type of inflammation or infection is still required to initiate the disease.