The Class II MHC Molecule, Key to Fighting Disease

Whitefish Bay High School SMART Team

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Abstract

The class II major histocompatibility complex (MHC II) molecule is involved in immune responses to viral and bacterial diseases. When a peptide fragment of a protein is "loaded" into the molecule, the alpha helices of the Class II MHC unwind and the peptide is inserted in the gap. The class II MHC molecule is critical in the production of antibodies to fight illness and prevent future infections. The class II MHC helps the body identify antigens by presenting antigen fragments to helper T-cells. The helper T-cells then instruct B-cells to produce antibodies, which in turn alert other cells to the presence of a pathogen and instruct them to fight the intruder. We are focusing on influenza and the way in which a fragment of the influenza protein fits into the class II MHC molecule. In the case of influenza, macrophages ingest the virus, producing peptide fragments that the MHC molecules collect. We have designed a physical model of the class II MHC protein and a peptide fragment of influenza in the PDB file D8HATC pdb. Researchers like Dr. Gorski are working to understand how the MHC molecule opens for the peptide to be inserted. Understanding this peptide loading process is important for rational vaccine design, as vaccines should optimize the ability to load the class II MHC with pathogen-derived peptide fragments.

What happens when the class II MHC molecule doesn’t work?

Normally mild pathogens cannot be detected by the immune system until they infect cells and are left uninhibited in their attack on the body. Antibody production is severely inhibited. This leads to severe illness and even death. Occasionally children are born without the MHC II, a disease called bare lymphocyte syndrome.

What sort of medical treatments involve MHC II?

• No approved human treatments interact directly with MHC II yet, but mouse and human trials have shown that vaccines containing only fragments of antigens (peptide vaccines) may be able to prevent disease.
• Peptide vaccines are unique in that, unlike traditional vaccines in which a patient receives a whole pathogen, only a fragment of a virus is used to immunize against a pathogen; thus, there is little chance of accidentally contracting the disease.

The 1918 Flu Pandemic

Recent study of the 1918 flu is investigating the reasons for the flu’s unmatched deadliness. Researchers have concluded that hemagglutinin, a protein on the surface of the flu virus that allows it to attach to and penetrate lung cells, is a major factor in the flu’s deadliness. More common flu viruses that originate in birds are less deadly because they must “jump” from birds to pigs before spreading to humans. Usually the genetic changes in this extra “jump” diminish the power of the virus. It is believed that in the 1918 flu pandemic, the hemagglutinin changed to adapt to human cell receptors, thereby skipping over the pigs and, thus, maintaining its deadly features common to avian viruses.

Questions Yet to be Answered

• How does the molecule open to accept the antigen fragment?
• What features of the class II MHC determine which peptides are readily accepted into the protein?
• Could we create a vaccine that uses peptide fragments directly to stimulate antibody production?

The MHC II Model

• We chose to only model the section of the molecule that is involved in the binding of the peptide. Thus, we could focus on the way the molecule opens to accept the peptide.
• One of the more interesting portions of the molecule is the alpha helix that bends upward, a portion of which is not curled into a helix. One theory suggests that this portion may curl at pH 5, moving the entire helix aside to accept the peptide.

3D Model

The major advantage to building a physical 3D model is that people can actually hold it in their hands. This provides physical information not possible with a computer screen. The physical medium opens up possibilities for discoveries otherwise obscured by the 2-D plane of computer simulations.

Conclusion

The class II MHC is vital to our survival. With the never-ending onslaught of introduced new holidays, the class II MHC is crucial in our bodies’ defenses. Understanding how the molecule accepts antigen fragments can lead to more effective vaccines and to predicting future outbreaks of influenza and other harmful viruses.