

MHC class II-induced neo-self antigens in autoimmune diseases

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Cellular misfolded proteins are generally not transported outside the cells and thus may not be exposed to immune cells. This suggests that immune tolerance may not be induced to the cellular misfolded proteins. However, we recently found that such misfolded proteins in the endoplasmic reticulum are rescued from protein degradation and are transported to the cell surface by aberrantly expressed MHC class II molecules without being processed to peptides. Because structures of misfolded proteins associated with MHC class II molecules are different from normal proteins, antigenicity of the misfolded proteins are different from that of normal proteins. Indeed, it has been well known that MHC class II molecules are aberrantly expressed in many autoimmune-diseased tissues. Extensive studies on the misfolded proteins rescued by MHC class II molecules have revealed that misfolded proteins associated with MHC class II molecules are specific targets for autoantibodies produced in autoimmune diseases. Furthermore, a strong correlation has been observed between autoantibody binding to misfolded proteins associated with MHC class II molecules and the autoimmune disease susceptibility conferred by each MHC class II allele. These findings suggest that misfolded proteins rescued from protein degradation by aberrantly expressed MHC class II molecules function as a 'neo-self' antigens that might induce abnormal immune response in autoimmune diseases.