Elucidation of mechanism of autoimmune diseases and drug development targeting neo-self

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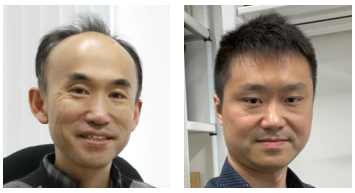


Abstract

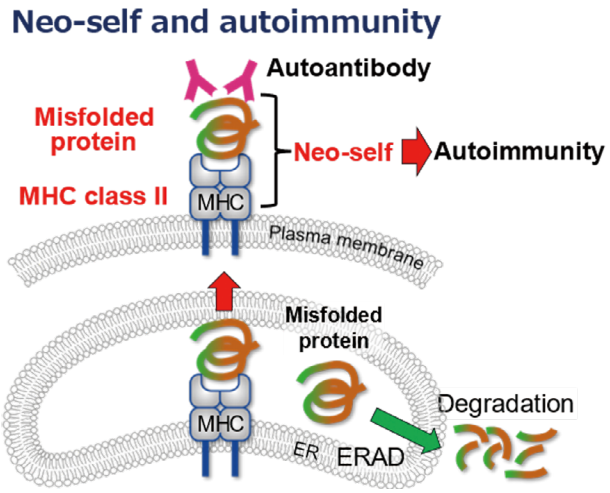
We have prevously shown that HLA class II molecules, which generally present peptide antigens to T cells, function like a molecular chaperone that transports intracellular unfolded proteins outside the cells. Furthermore, the complex of self-antigen and HLA class II molecules, neoself, is a target of autoantibodies produced in a variety of autoimmune diseases. In this study, we analyzed the function of neoself and found that the neoself abrogates self-tolerance and triggers autoimmune responses, indicating that the neo-self is one of responsible molecules for autoimmune diseases.

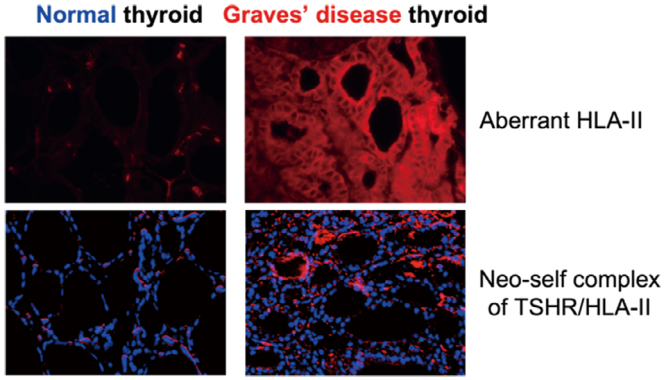
Background & Results

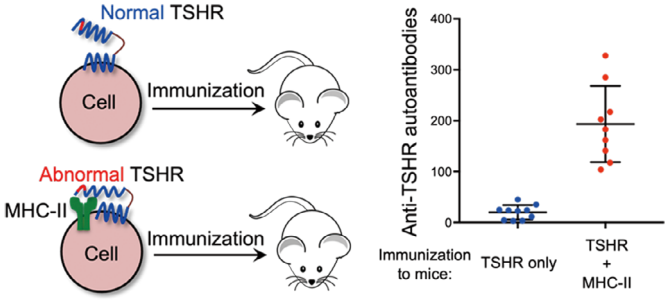
Immunity is a defense system against pathogens such as viruses, but autoimmune diseases develop when an immune response is triggered against self tissues and organs. The host gene that most strongly influences the development of autoimmune diseases is HLA class II, but how HLA class II is involved in disease development has remained unclear. We have shown that HLA class II molecules function like molecular chaperones, transporting unfolded intracellular proteins outside the cell. Furthermore, molecules bound to HLA class II molecules have been shown to be antigenically distinct from normal molecules and are the targets of autoantibodies produced in various autoimmune diseases as neo-self. In this study, we analyzed the pathogenicity of neo-self formed by HLA class II molecules, which are mainly expressed on specific immune cells and most cells in the body do not express HLA class II. In Graves' disease, an autoimmune disease against thyroid tissue, strong ectopic expression of HLA class II molecules was observed in the thyroid gland, and in addition, a neo-self complex composed of thyroid-stimulating hormone receptors (TSHR) and HLA class II molecules was detected. Furthermore, neo-self formed by HLA (MHC) class II molecules was found to be a pathogenic molecule that disrupts autoimmune tolerance and induces the production of autoantibodies. In summary, the present study demonstrates that the formation of neo-self is involved in the pathogenesis of autoimmune diseases. Therefore, elucidation of the mechanism of neo-self formation and inhibition of neo-self formation are important for elucidating the causes of autoimmune diseases as well as for developing therapeutic drugs.

Significance of the research and Future perspective

This study reveals for the first time that neo-self, a self-antigen/HLA class II complex, has pathogenic properties that disrupt self-tolerance and induce autoimmune reactions. Therefore, it is important to understand how neoselves are formed in order to understand the pathogenesis of autoimmune diseases. Current drugs for autoimmune diseases are all symptomatic drugs and require long-term administration. Elucidation of the mechanism of neo-self formation through this study is expected to lead to the development of a new type of therapeutic drug that targets neo-self to repair the cause of autoimmune diseases.







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