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Complement receptors and lupus

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Keywords

Animal model, complement receptors, systemic lupus erythematosus

Context

Among the genetic factors contributing to lupus susceptibility, the *Sle1* locus, conserved in mouse and human chromosome 1, has been linked to murine and human lupus. In mouse models, the specific contribution of *Sle1* to the pathogenesis of lupus has been dissected by individually segregating this locus from the original lupus prone NZBM2410 strain to a C57BL/6 background (B6.*Sle1*). B6.*Sle1* mice show a loss of tolerance to chromatin, as indicated by the development of high levels of antinuclear antibodies, whereas additional loci are needed for the full spectrum of immunological and clinical manifestations. The *Sle1c* locus contains the *Cr2* gene, which encodes complement receptors 1 and 2 (CR1 and CR2) by alternative splicing.

Significant findings

The authors identified structural differences, when comparing CR1 and CR2 proteins, between B6.*Sle1c* lupus mice and their normal counterparts. The difference is due to a single nucleotide polymorphism that introduces a novel N-linked glycosylation site in the ligand binding domain of CR1/CR2 receptors. By using tetrameric C3 degradation products, the ability of B6.*Sle1c* splenic cells to bind this ligand was shown to be decreased. Intracellular calcium responses of B6.*Sle1c* B cells to C3 degradation products were decreased, and *in vivo* these mice displayed diminished immune responses to a T-dependent antigen. Molecular modeling of the mouse CR2 sequence suggests that the glycoslyation at the polymorphism site interferes with dimerization of the CR2 receptor rather than with ligand binding.

Comments

The authors demonstrated a functionally significant phenotype associated with the lupus prone allele *Sle1c* that has been linked to lupus in multiple human ethnic groups and mouse strains. These observations suggest that the antichromatin humoral response is associated with defective binding and signaling of C3 and C4 degradation products through CR1/CR2 receptors, although the mechanism of this association remains to be elucidated. The authors propose defective induction of B-cell tolerance or qualitative changes in processing of autoantigens through this pathway as the potential mechanisms operating in mice and humans with genetically diminished CR1/CR2 responses.

Methods

Immunoprecipitation, sequence analysis, flow cytometric analysis, fluorescent intracellular calcium analysis, immunization of mice with dinitrophenol (DNP), ELISA analysis of anti-DNP antibodies, molecular modeling.

Additional information

References

1. Boackle SA, Holers VM, Chen X, Szakonyi G, Karp DR, Wakeland EK, Morel L: *Cr2*, a candidate gene in the murine *Sle1c* lupus susceptibility locus, encodes a dysfunctional protein . Immunity. 2001, 15: 775-785. ,