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Autoantibodies to nucleolin are detected very early in sera from MRL/lpr mice

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Keywords

Autoantibody, lupus mice

Context

Systemic lupus erythematosus (SLE) is characterized by the presence of high titers of autoantibodies reacting with complexes such as nucleosomes and spliceosomes. In most cases autoantibodies directed against nucleic acids (DNA or RNA), and proteins that bind to them, coexist in the serum of lupus patients, as well as in sera derived from several mouse strains that are susceptible to the development of SLE. One explanation for the diversity of the immune response observed in lupus is an 'intermolecuar epitope spreading' mechanism in which an initial response directed against one of the autoantigens spreads to other components of the complex. To identify the putative triggering antigen, the authors studied the reactivity of autoantibodies produced in the earliest phase of the disease in NZB/NZW F1 and MRL/lpr mice.

Significant findings

All mice tested produced autoantibodies reacting with at least one of four molecules migrating on SDS-PAGEat 150, 110, 75 or 55 kDa. The sera from all 10 MRL/lpr mice and from six of ten NZB/ NZW F1 mice at the age of 4-8 weeks strongly reacted with either the 150 kDa or the 110 kDa protein. Seven NZB/NZW F1 mice produced antibodies initially recognizing the 75 kDa or the 55 kDa protein. The 150 kDa and 110 kDa proteins bound DNA. The 110 kDa protein was identified as nucleolin.

Comments

This study demonstrates that nucleolin is a very early target of autoantibodies produced in MRL/lpr mice. Because nucleolin binds nucleic acid and is cleaved by granzyme A, the authors propose that nucleolin could be the immunodominant molecule that breaks down self-tolerance. Starting from this protein, a larger, diversified Th response might then be generated, extending via intramolecular and

intermolecular spreading of the T and B cell responses. However, data and/or a hypothesis to explain the nature of the other proteins (150 kDa, 75 kDa and 55 kDa) are missing in this work. Moreover, no data are presented addressing whether there is also T cell responsiveness to nucleolin. Finally, nucleolin was not consistently targeted early in the observed response in NZB/NZW F1 mice.

Methods

Immunoblotting, ELISA

References

1. Hirata D, Iwamoto M, Yoshio T, Okasaki H, Masuyama J, Mimori A, Minota S: Nucleolin as the earliest target molecule of autoantibodies produced in MRL/lpr lupus-prone mice. Clin Immunol. 2000, 97: 50-58.