PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

H-chain CDR3 contribution in specificity of autoantibodies

ArticleInfo		
ArticleID	:	119
ArticleDOI	:	10.1186/ar-2001-66875
ArticleCitationID	:	66875
ArticleSequenceNumber	:	76
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 2001–1–12 OnlineDate : 2001–1–12
ArticleCopyright	:	Biomed Central Ltd2001
ArticleGrants	:	
ArticleContext	:	130753311

Fanny Monneaux,[Aff1]

Aff1 CNRS, Strasbourg, France

Keywords

Autoantibody, complementarity-determining region, lupus

Context

Systemic lupus erythematosus is characterized by the production of antibodies directed against various nuclear antigens. Many groups have focused on the sequence of the V region genes of antinuclear antibodies and several features accounting for DNA binding have emerged from these sequences, especially in VH-CDR (H3). In this study, the authors exchanged H3 domains between the 3H9 antibody and two donor antibodies, LG8-1 (closely related to 3H9) and ASWA1 (divergent from 3H9). The H3 domain of these three antibodies differed in the number of arginine residues and in overall charge and these antibodies share different specificities. Variant H chains were expressed together with the 3H9 light chain as single-chain Fv (scFv), and the five antibodies were then tested for their ability to bind nucleosomes, DNA and cardiolipin.

Significant findings

The five scFvs equally bind cardiolipin, suggesting that this recognition is not due to junctional or somatic diversity mechanisms. In contrast, the DNA and nucleosome binding activity was only observed for 3H9 scFv with its own H3. It is surprising that the exchange with LG8-1 H3, which is arginine-rich, is not sufficient to restore the ability of this antibody to bind DNA. These results suggest that conformation, flexibility or additional sidechain contributions of 3H9 H3 are crucial, and are directly involved in DNA and nucleosome binding.

Comments

This study demonstrates that binding of autoantibodies to DNA, nucleosomes or cardiolipin is due to more than attraction between opposite charges. Indeed, the authors show that the presence of arginine in H3 is not sufficient to explain binding to DNA. Another important point in this paper is the

demonstration that binding to antigens that share common epitopes (DNA, nucleosomes and cardiolipin) does not require similar contributions from H3. The authors propose that the germline of the 3H9 VH domain is directly involved in cardiolipin binding, whereas structural features of H3 guide the maturation of antibody binding toward nuclear autoantigens such as DNA or nucleosomes. This paper highlights the contribution of somatic mutations to binding constraints imposed by H3. Because only five combinations were tested here, further studies will be needed to validate the model proposed by the authors. X-ray structures would help to delineate the fine 3D interactions between antigen and antibody.

Methods

scFv construction and expression, ELISA, DNA sequencing

References

1. Seal SN, Monestier M, Radic MZ: Diverse roles for the third complementarity determining region of the heavy chain (H3) in the binding of immunoglobulin Fv fragments to DNA, nucleosomes and cardiolipin. Eur J Immunol. 2001, 30: 3432-3440.