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Does elevated DR on RA B cells reveal cryptic epitopes?

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Keywords

Allele specific monoclonal antibodies, antigen presentation, MHC class II

Context

Human leukocyte antigen (HLA)- DR molecules present antigens to $CD4^+$ T cells. DR alleles sharing a common polymorphism at residues 67-74 of the DR? chain confer susceptibility to severe rheumatoid arthritis (RA). However, the biological role of HLA-DR remains poorly understood. The authors previously reported that expression of HLA-DM, a catalyst of DR/peptide binding, is decreased in B cells of RA patients, suggesting a role for antigen presentation defects (see Additional information). The aims of this study were to quantify DR expression in RA and to examine consequences of quantitative differences in DR levels for T-cell responses.

Significant findings

RA-associated DR4 molecules were elevated twofold to threefold on RA patients' (n = 6) B cells compared to controls (n = 5). This was true for RA-associated DR4 variants such as DR0401, for nonassociated DR variants such as DR0402, and for the nonassociated DR11 allele. Upregulation was less for other DR alleles, such as DR1 (weakly RA-associated) and DR7 (nonassociated), and for DR molecules containing an alternate ? chain (DR53). Levels of DR15 molecules were reduced in RA. No correlation with B-cell activation, disease activity, or use of anti-inflammatory drugs was observed. Increased DR1 levels on transfected fibroblasts resulted in improved presentation of antigenic peptides to T cells and in improved responsiveness to mutated peptides. The authors concluded that elevated DR levels during RA could cause presentation of normally cryptic self peptides to T cells.

Comments

This study introduces increased surface expression of some DR alleles as a potentially relevant variable in RA pathogenesis. However, there are caveats: firstly, the allele-specific antibodies used here might differentially detect subpopulations of DR molecules due to heterogeneity of conformational states or the bound peptide repertoire, these differences between alleles and between RA patients and controls could confound these results; secondly, the size of the study is small; furthermore, disease controls are lacking, so selective DR elevation could be either RA-specific or a generalized response to inflammation. Further work is needed to evaluate the possible etiologic role of variation in DR levels, to explore the mechanisms involved in altered DR levels, and to see if similar phenomena occur in other cell types.

Methods

Quantitative flow cytometry, cytotoxicity assay, transfection

Additional information

Louis-Plence P, Kerlan-Candon S, Morel J, Combe B, Clot J, Pinet V, Eliaou JF: **The down-regulation of HLA-DM gene expression in rheumatoid arthritis is not related to their promoter polymorphism.** *J Immunol* 2000, **165**:4861-4869 (PubMed abstract).

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