Role of B7 costimulation pathway in the development and progression of lupus in MRL/lpr mice

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Context

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of autoantibodies to nuclear proteins and nucleic acids, accompanied by clinical manifestations. To initiate this type of mature humoral response, both T and B cell costimulatory interactions are required. The best-characterized and strongest costimulatory signal for interaction is provided by CD28 and CTLA-4 (on T cells) binding to B7-1 and B7-2 (on antigen presenting cells). Blockade of the B7 pathway using receptor antagonists and antibodies has provided insight into the importance of these costimulatory molecules in autoimmune disease. However, the role of B7-1 and B7-2 as individual ligands in the development of autoimmunity is unclear. The aim of this study was to investigate the role of B7 costimulation in a murine model of SLE by inhibiting the B7 pathway using blocking antibodies, or using B7-deficient mice backcrossed into the MRL-lpr/lpr background.

Significant findings

MRL lpr mice treated with B7 blocking antibodies, or deficient in B7-1 or B7-2 molecules, produce autoantibodies recognizing small nuclear ribonuclear proteins (snRNPs) and DNA. Mice treated with B7 antibodies demonstrated changes in isotype switching as compared with untreated animals. This was not observed with B7-deficient mice. For example, coadministration of anti-B7-1/B7-2 antibodies significantly reduced the production of IgG1 and IgG2b autoantibodies specific for snRNP as compared with anti-B7-2 antibody treatment alone. The authors also demonstrated that the previously observed high proportion of activated (23% for CD4 and 29% for CD8) and memory (77% for CD4 and 70% for CD8) T cells is unchanged in B7-1-deficient mice. In contrast, B7-2-deficient mice possessed significantly fewer activated (13% for CD4 and 17% for CD8) and memory (2% for CD4 and CD8) T cells. They next examined specific antibody deposition in the kidney, demonstrating that IgG and C3 complement deposition was less pronounced in the kidney of B7-2-deficient MRL-lpr mice, and this correlated with less severe glomerulonephritis. In conclusion, this work demonstrates that blocking both B7-1 and B7-2 does not completely eliminate autoantibody production, and suggests the possible involvement of alternative costimulation pathways for T cell activation (eg CD40-CD40L pathway).

Moreover, the authors speculate about the possible role of new molecules, including inducible costimulator (ICOS) and B7-h, that may replace the CD28/B7-1/2 pathway.

Comments

Contrary to other studies, this paper demonstrates that blocking B7-1 or B7-2 is not sufficient to prevent the development and progression of lupus, and suggests that manipulation of costimulatory pathways for therapeutic applications needs further study. One interesting result in this study is the demonstration that B7-1 and B7-2 expression at the cell surface of splenocytes is reciprocal (eg increased B7-1 expression in B7-2-deficient mice and vice versa), suggesting that B7-1 and B7-2 have the ability to compensate for each other in the absence of the other B7 molecule.

Methods

B7-1 and B7-2-deficient MRL/lpr mice

References

1. Liang B, Kashgarian MJ, Sharpe AH, Mamula MJ: Autoantibody responses and pathology regulated by B7-1 and B7-2 costimulation in MRL/lpr lupus. J Immunol. 2000, 165: 3436-3443.

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