THE EARLY MARGINAL ZONE B CELL INITIATED T INDEPENDENT TYPE 2 RESPONSE RESISTS THE PROTEASOME INHIBITOR BORTEZOMIB

V Lang,1 D Mielenz,2 H Martin Jäck,2 K Neubert,1 C Böhm,1,3 G Schett,3 R E Voll,1,3 S Meister1

1Interdisciplinary Center for Clinical Research, Research Group N°, Nikolaus Fiebiger-Center of Molecular Medicine, University Hospital Erlangen, Erlangen, Germany; 2Division of Molecular Immunology, Department of Internal Medicine2, University of Erlangen-Nuremberg, Erlangen, Germany; 3Department of Internal Medicine3 and Institute of Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany

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The proteasome inhibitor bortezomib is clinically approved for the treatment of multiple myeloma. Recently, we demonstrated that bortezomib eliminates autoreactive plasma cells in SLE mice, thereby representing a promising novel treatment for antibody-mediated diseases. Here, we investigated the effect of bortezomib on the developing and pre-existing T dependent antibody response towards dinitrophenylated keyhole limpet hemocyanin and the T independent type 2 response towards NIP-Ficoll in BALB/c mice. Bortezomib treatment strongly reduced T dependent antibody titres mainly due to depletion of plasma cells. In contrast, the early T independent type 2 response, predominantly initiated by marginal zone (MZ) B cells, resisted bortezomib. Immunoproteasomal subunits and the antiapoptotic unfolded protein response were induced in NIP-Ficoll-stimulated MZ B cells after bortezomib treatment, but not in plasma cells. This induction might be cell autonomous and not a consequence of the microenvironment since mobilisation of MZ B cells out of the spleen did not render them susceptible towards bortezomib. We conclude that the resistance of MZ B cells against bortezomib leaves early T independent responses protecting against bloodborne pathogens largely intact. This fact may account for a relatively low risk of bacterial infections compared to most other immunosuppressants and cytotoxic drugs.