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Tumor cell expression of CD59 is associated with resistance to CD20 serotherapy in patients with B-cell malignancies.

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The anti-CD20 chimeric monoclonal antibody rituximab (Rituxan) is used to treat patients with various B-cell tumors, including patients with plasma cell dyscrasias who have CD20+ disease. Many patients with CD20+ disease have either primary unresponsive disease or progress after initially responding to rituximab; therefore, understanding how tumor cells are, or become, resistant to rituximab is of clinical relevance. In this report, we determined whether tumor cells express antigens that block complement-mediated lysis or antibody-dependent cell-mediated cytotoxicity (ADCC) and thereby contribute to rituximab resistance. We demonstrate that expression of the complement regulator CD59 is associated with resistance to rituximab-mediated complement lysis of multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL) cell lines. Moreover, neutralization of CD59 using a blocking monoclonal antibody reversed resistance to rituximab-mediated complement lysis of CD20++ CD59++ ARH-77 MM cells. In addition, we demonstrate the presence of CD59 and rituximab binding on viable tumor cells from patients with MM and Waldenstrom's macroglobulinemia with progressive disease despite rituximab therapy. Last, we also examined MM and NHL B-cell lines, as well as patient tumor cells, for the expression of other antigens that may have a role in blocking ADCC activity, such as Fas ligand (FasL), MUC1, or TRAIL. FasL, MUC1, and/or TRAIL were coexpressed with complement regulators on many of these cells. These studies therefore show that complement regulators, particularly CD59 and antigens that may block ADCC, are present on various B-cell tumors and associated with rituximab resistance in patients. A prospective, clinical study is assessing the role of these antigens in mediating rituximab resistance.