THERAPY

Rituximab targets short-lived autoreactive plasmablasts

The production of autoantibodies is a key pathogenetic component in autoimmune diseases such as rheumatoid arthritis. B cells are prolific producers of these autoantibodies, and as such have been targeted by numerous antirheumatic therapies. One of these therapies, rituximab, a chimeric monoclonal antibody against human CD20 (hCD20; a B-cell-specific surface marker), depletes B cells and has been effective in several autoimmune diseases, including rheumatoid arthritis. However, the precise mechanisms by which rituximab induces B-cell depletion and ameliorates autoimmunity are not fully understood. Huang and colleagues studied the action of rituximab in the K/BxN mouse model of inflammatory arthritis.

The mice were transfected with a bacterial artificial chromosome harboring the hCD20 transgene. Control mice did not possess this transgene. After the spontaneous development of arthritis in response to the ubiquitously expressed autoantigen glucose-6-phosphate isomerase (GPI), the mice received weekly injections of 1 mg rituximab. Serum titers of anti-GPI antibodies decreased over time in $hCD20^+$ mice, whereas total antibody titers did not change markedly. No similar decrease in anti-GPI titers was observed in control mice.

> “...pathogenetic plasma cells [were] short-lived with a higher turnover rate than normal plasma cells...”

As rituximab led to a decrease in serum titers of anti-GPI, but not in total antibody titers, it was thought that anti-GPI-producing cells were somehow being specifically targeted by rituximab. In cell samples harvested from the bone marrow, spleen, lymph nodes, peripheral blood and peritoneal cavity of 8-week-old arthritic mice, enzyme-linked immunosorbent spot assay revealed that by far the highest numbers of anti-GPI-producing cells were in the spleen and lymph nodes, whereas numbers in the bone marrow—where long-lived plasma cells are usually located—were very low. Further analysis of these antibody-producing cells revealed that they were plasmablasts (that is, at an early stage of differentiation into plasma cells). As plasma cells are thought to express CD20, the presence of hCD20 on anti-GPI-producing plasmablasts in these mice, albeit at lower levels than on B lymphocytes, was an unexpected finding, and explains why they are susceptible to depletion by rituximab. These pathogenetic plasma cells in the spleen and lymph nodes were also found to be short-lived with a higher turnover rate than normal plasma cells, which tend to be long-lived.

The data presented in this paper indicate that the efficacy of rituximab is likely to be greatest in autoimmune diseases that are characterized by a major pathogenetic role of autoantibodies produced predominantly by CD20-expressing, short-lived plasmablasts. Further study, particularly in similar animal models, is likely to shed further light on this subject and help identify diseases susceptible to rituximab therapy.

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Original article Huang, H. *et al.* Rituximab specifically depletes short-lived autoreactive plasma cells in a mouse model of inflammatory arthritis. *Proc. Natl Acad. Sci. U. S. A.* **107**, 4658–4663 (2010)