CELLULAR IMMORTALITY

Early old age

Werner syndrome is an autosomal recessive disease caused by inactivation of the gene encoding the DNA helicase WRN and is characterized by premature ageing, genomic instability and increased non-epithelial cancer incidence. It is thought that the erosion of telomeres — structures that cap chromosomes and are essential for chromosomal stability — has a role in the pathogenesis of this syndrome. Ron DePinho, Sandy Chang and colleagues have developed a mouse model that is null for both *Wrn* and the RNA component of telomerase (*Terc*) — an enzyme essential for telomere maintenance — that shows many of the classic features of Werner syndrome.

WRN is involved in DNA recombination, replication and repair, and hyper-recombination and numerous chromosomal aberrations have been observed in individuals with Werner syndrome. DePinho and Chang hypothesized that a combination of impaired DNA repair and telomere dysfunction might drive Werner syndrome pathogenesis.

The authors carried out successive intercrosses between $Wrn^{-/-}$ mice and $Terc^{-/-}$ mice to produce cohorts with progressively shorter telomeres and increasing telomere dysfunction. In first- and second-generation $Terc^{-/-}$ mice, *Wrn* status had no impact on clinical appearance, but the fourth- to sixth-generation $Terc^{-/-}Wrn^{-/-}$ mice had lower body weights and shorter survival times than $Terc^{-/-}Wrn^{+/+}$ mice. Although healthy in early life, by 12–16 weeks of age many of the $Terc^{-/-}Wrn^{-/-}$ mice had features of premature ageing, including Werner-syndrome-related diseases. Increased apoptosis in gastrointestinal crypt cells and increased numbers of fused chromosomes in bone-marrow cells were seen in successive generations of $Terc^{-/-}Wrn^{-/-}$ mice. This reinforced a link between genomic instability due to WRN loss and telomere dysfunction.

So, how did these genotypes affect the cancer phenotype of these mice? The prematurely aged late-generation $Terc^{-/-}Wrn^{-/-}$ mice were

IMMUNOLOGY

Receptors and effectors

Effective therapies for non-Hodgkin's B-cell lymphoma aim to deplete the B-cell population in patients. However, the precise mechanism by which the humanized immunoglobulin G1 (IgG1) antibody therapy rituximab kills B cells was previously unknown. Jungi Uchida *et al.* now reveal the mechanism involved.

Rituximab, which targets a B-cell-specific antigen called CD20, could affect many aspects of the immune response, including antibody, effector-cell-(macrophage and natural killer cell) and complement-dependent cytoxicity; the disruption of CD20 signalling pathways; and the induction of apoptosis. Previous studies have looked at the mechanisms *in vitro* or in circulating human B cells only. So, the authors developed a mouse model for anti-CD20 immunotherapy using 12 mouse anti-mouse CD20 monoclonal antibodies (mAbs) to study each of the possible mechanisms. All these antibodies bound to B cells in the CD20 wild-type mice and depleted both the circulating and splenic B-cell compartments. The effectiveness of mAb-induced B-cell depletion correlated closely with mAb isotype — a single injection of an IgG2a mAb (MB20-11) depleted more than 95% of blood B cells and more than 93% of splenic B cells. None of the antibodies had any effect in $Cd20^{-/-}$ mice.

Immune effector cells express three different Fc receptor classes for IgG. FcγRI is the highest-affinity receptor and binding of IgG to it triggers phagocytosis by macrophages and cytotoxicity by natural killer cells. Although treatment of mice deficient in either FcγRI or FcγRIII with MB20-11 did deplete B cells, treatment of mice deficient in both FcγRI and FcγRIII did not deplete B cells. This shows that binding to one of these receptors is important for efficacy of anti-CD20 mAbs. Next, the authors looked at complement-deficient mice to assess the role of complement in B-cell depletion by anti-CD20 mAbs. *In vitro*, the antibodies caused B-cell lysis and apoptosis only in the presence of complement. However, *in vivo*, there was no difference in the ability of any mAb to induce B-cell killing in the wild-type or complement-knockout mice.

So, Fc receptors are crucial for the efficiency of anti-CD20 mAbs; but what are the effectors of this response? When mice lacking T cells or natural killer cells were treated with MB20-11, more than 96% of B cells were depleted. However, similar treatment of macrophage-deficient mice did not cause significant depletion of circulating or splenic B cells.

The authors conclude that a likely mechanism of B-cell depletion by anti-CD20 mAbs is FcγR-mediated phagocytosis of mAb-coated B cells by macrophages. This knowledge should help to understand the response and resistance to rituximab therapy and the development of effective methods to enhance the benefits of therapies for non-Hodgkin's lymphoma.

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References and links

ORIGINAL RESEARCH PAPER Uchida, J. *et al*. The innate mononuclear phagocyte network depletes B lymphocytes through Fc receptor-dependent mechanisms during anti-CD20 antibody immunotherapy. *J. Exp. Med*. **199**, 1659–1669 (2004)