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B CELL TOLERANCE

STALling B cell responses

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A recent study published in *The Journal of Clinical Investigation* describes an elegant new strategy to eliminate undesired antibody responses, such as those that arise in autoimmunity, after transplantation and against biological agents. The approach uses antigenic liposomes that display ligands for the inhibitory B cell co-receptor CD22 and that effectively induce B cell tolerance to T cell-dependent antigens.

CD22 — a member of the SIGLEC (sialic acid-binding immunoglobulin-like lectin) family — has an inhibitory effect on B cell activation when it is localized with the B cell receptor (BCR). So, the authors forced the localization of CD22 with a BCR using liposomal nanoparticles containing a high affinity SIGLEC ligand and an antigen; these were referred to as STALs (SIGLEC-engaging tolerance-inducing antigenic liposomes).

In initial experiments, mice were injected with STALs bearing different antigens and this prevented the B cell response to challenge with the corresponding antigen, which occurred in mice injected with liposomes displaying the antigen alone (immunogenic liposomes). The antigen-specific inhibitory effect of STALs was shown to be CD22 dependent, as it did not occur in immunized CD22-deficient mice.

Next, the authors investigated the mechanism by which STALs induced tolerance. STALs completely abrogated the activation of antigen-specific B cells *in vitro*, as measured by calcium influx, by the upregulation of CD86 expression and by cell proliferation. Moreover, using annexin V staining, the authors noticed a time-dependent decrease in the number of live B cells following their incubation with STALs. Indeed, antigen-specific B cells that were adoptively transferred into mice following immunization with STALs proliferated much less and their numbers were considerably reduced compared to B cells that were transferred to mice that had been immunized with control liposomes.

Analysis of BCR signalling showed STALs, but not immunogenic liposomes, to strongly inhibit the phosphorylation of proximal and distal BCR signalling components. Of note forkhead box protein O1 (FOXO1) and FOXO3A, which are known to be involved in cell-cycle inhibition and apoptosis in B cells, were hypophosphorylated and localized to the nucleus. Taken together, these observations suggest that STALs induce a tolerogenic mechanism involving apoptosis.

Consistent with the possible application of this approach in a therapeutic setting, the authors showed that STALs containing various T cell-dependent antigens (such as ovalbumin, factor VIII (FVIII) and myelin oligodendrocyte glycoprotein) induced tolerance to these antigens, as measured by low specific antibody responses following subsequent challenge with the corresponding antigen. Importantly, using FVIII-deficient mice, which are a mouse model of haemophilia A, the authors showed that immunization with STALs displaying FVIII prevented the formation of inhibitory antibodies against infused recombinant FVIII, which protected the mice from bleeding following a tail cut.

Given that 20–30% of patients with haemophilia A develop inhibitory antibodies shortly after initiation of FVIII therapy, which renders them unresponsive to the therapy, the possible application of STALs in this setting is a promising prospect.

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ORIGINAL RESEARCH PAPER Macauley, M. S. *et al.* Antigenic liposomes displaying CD22 ligands induce antigen-specific B cell apoptosis. *J. Clin. Invest.* **123**, 3074–3083 (2013).