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Selective Depletion of ABO-Specific B Cells by T Cell-Engaging Bispecific Antibody Conjugates for ABO-Incompatible Kidney Transplantation

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Objectives : ABO-incompatible (ABOi) transplantation, developed to expand the donor pool, presents significant clinical challenges of anti-ABO antibody-mediated rejection. Current therapies employing broad B-cell depletion, effectively reduce antibody-mediated rejection but increase infection risks. Therefore, novel strategies to selectively deplete ABO-specific B cells are warranted.
Methods : We developed a novel bispecific antibody-ligand conjugate (BiALC) platform designed to selectively target A-specific B cells. Utilizing synthetic trisaccharide A antigens conjugated to T-cell-recruiting Fab fragments, we optimized BiALC as hexameric construct, (A3-peg)2-anti-(mouse or human) CD3. Mouse or human B cells were cocultured with T cells in the presence of phosphate-buffered saline (PBS), anti-CD20 antibodies, or BiALC to assess selective cytotoxic effects of BiALC. To investigate the in vivo depleting effects of BiALC on A-specific B cells, BALB/c mice sensitized to A antigen, received PBS, anti-CD20 antibodies, or BiALC with or without kidney transplantation from blood group A-transgenic B6 mice.
Results : Mouse BiALC enhanced in vitro affinity and cytotoxicity specifically against A antigen-responsive mouse B cells. Similarly, the human BiALC effectively and selectively depleted A-specific human B cells, with potency comparable to rituximab, while sparing total antibody-secreting cells. In parallel, BiALC decreased anti-A IgM and IgG levels in culture supernatant, without affecting total IgM and IgG levels. In murine sensitization models, BiALC selectively depleted A-specific B cells without broadly affecting total B cell populations, preserving overall immune competence. BiALC also decreased serum levels of anti-A IgM and IgG to similar extent as anti-CD20 antibodies. Furthermore, BiALC decreased serum levels of anti-A IgM and IgG after mouse ABOi kidney transplantation. BiALC also suppressed histologic injury scores in kidney allografts to similar extent as anti-CD20 antibodies.
Conclusions : Overall, the BiALC strategy offers a promising antigen-specific approach to reduce rejection risks in ABOi transplantation without inducing broad immunosuppression through nonspecific pan-B cell depletion, supporting its potential for clinical translation.

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