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T and B cell responses in xenotransplantation

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Postgraduate course 12 (Basic) Immunology of Xenotransplantation T and B Cell Responses in Xenotransplantation David K.C. Cooper MD, PhD, FRCS The major immunologic hurdle in pig-to-primate organ xenotransplantation is antibody-mediated rejection (AMR), primarily associated with primate antibodies directed to glycan antigens expressed on the pig vascular endothelial cells. However, when expression of the 3 known glycans is deleted by gene editing of the pigs (producing triple-knockout [TKO] pigs), AMR can still occur. This is presumably associated with the production of elicited antibodies against other porcine xenoantigens. The exact role of T and B cells in this antibody response remains uncertain but is probably related to inadequate suppression of the adaptive immune response in the recipient of the pig graft. The T and B cell responses depend on (i) the phenotype of the genetically-engineered pig source of the transplanted organ or cells, and (ii) the nature of the induction and maintenance immunosuppressive therapy administered to the recipient. For example, in nonhuman primates, the in vitro data are that the immune response to an organ from an α1,3-galactosyltransferase gene-knockout (GTKO) pig is significantly weaker than to one from a TKO pig, whereas the reverse is the case if the recipient is a human. However, the human T cell response to TKO pig cells in mixed lymphocyte reaction (MLR) is greater than against GTKO pig cells. Most immunosuppressive regimens used in xenotransplantation include induction therapy with (i) anti-thymocyte globulin (ATG) to reduce the T cell count, (ii) an anti-CD20mAb to reduce the B cell count, and (iii) a complement inhibitor, e.g., a C-1 esterase inhibitor, to reduce systemic complement activation. Maintenance therapy usually consists of an anti-CD154mAb or an anti-CD40mAb combined with a more conventional agent, such as rapamycin or mycophenolate mofetil (MMF), and corticosteroids. Using this regimen, we measured the T and B cell response to kidney grafts from GTKO pigs (with other gene edits, e.g., expression of one or more complement-regulatory proteins). In a study of 14 baboons, 4 survived >6 months, in 7 the graft failed in <6 months from AMR, and 3 failed early from non-immunologic causes. After induction therapy, total lymphocyte and T cell counts were reduced by 85%, but recovery to 30% of baseline occurred within days, but no further increase occurred. No B cells were seen in the blood for 2 months, after which recovery of B cell numbers to 30% of baseline occurred. Co-stimulation blockade therapy therefore

maintained depletion of T and B cells, potentially reducing donor-specific antibody production. However, T and B cells were not depleted from the lymph nodes. We could not determine any correlation between recovery of T or B cells and AMR. Of some concern was that, although naïve B cells provided the majority of the recovered B cells (which is beneficial), effector memory $CD8^+$ T cells increased to above baseline numbers, which might be a factor in the late development of AMR. We suggest that rapamycin may be the optimal agent to combine with CD40/CD154 co-stimulation blockade. Although it is not tolerated by all patients, it has several qualities that are important in xenotransplantation. It (i) suppresses T cell proliferation, (ii) is associated with an increase in the numbers of T regulatory cells, (iii) suppresses inflammatory gene expression, (iv) reduces pig organ growth, and has (vi) anti-viral and (vii) anti-cancer activity. We suggest that further gene editing of the organ-source pig will provide increased protection against the primate adaptive immune response, e.g., by reduction in expression of swine leukocyte antigens I and/or II and/or expression of PD-L1.