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Beneficial effects of transgenic expression of human CD200 on top of quadruple-knockout/double-knockin (CD46/thrombomodulin) pigs on kidney xenograft survival in nonhuman primates.

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Introduction: CD200 suppresses xenogeneic immune responses of macrophages similarly as CD47. Moreover, CD200 can suppress other immune cells, such as T cells. Previous studies demonstrated that overexpression of hCD200 in pig endothelial cells successfully suppressed vascular xenograft rejection to greater extent than that of human CD47 in humanized mice. This study aimed to explore beneficial effects of hCD200-TG pigs on pig to nonhuman primate kidney xenotransplantation.

Methods: The first group included triple knockout (KO) (GGTA1, B4galNT2, CMAH) or quadruple KO (triple + iGb3S) pigs [TKO+QKO, N=5]; the second group included a triple KO/double knockin (DKI) (human CD46, human thrombomodulin) pig [TKO/DKI, N=1]; the third group included a QKO/DKI/hCD200-TG pig [QKO/DKI/CD200, N=1]. The cynomolgus monkeys in three groups received pig kidney xenografts under the same immunosuppressive regimen that consisted of thymoglobulin, rituximab, anti-CD154, sirolimus, and corticosteroid.

Results: The survival time of kidney xenografts were 36, 49, 77, 79, and 114 days for the TKO+QKO group, 136 days for the TKO/DKI group, and 139 days for the QKO/DKI/CD200 group, respectively. Spot urine protein/creatinine ratio had been kept low through the entire observation period in the QKO/DKI/CD200 group, whereas transient or persistent heavy proteinuria occurred in the other groups. Titers of donor-specific antibodies (DSA) in the TKO+QKO group increased during the first month, whereas rise of the DSA titers in the TKO/DKI group and QKO/DKI/CD200 group was delayed. TNF-alpha levels in the TKO+QKO group markedly increased during the first week after xenotransplantation, while there was only mild increase in the TKO/DKI and QKO/DKI/CD200 groups.

Conclusion: The hCD200-TG on top of QKO/DKI (CD46/TBM) pigs successfully suppressed proteinuria and delayed DSA development in pig-to-nonhuman primate kidney xenotransplantation, leading a good kidney xenograft survival compared to TKO or QKO pigs. These results suggest CD200 as a promising new target molecule to optimize genetically-modified pigs for kidney xenotransplantation.