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Xenotransplantation from pigs has the potential to resolve the growing shortage of human organ donors. Because of the extensive molecular incompatibilities between the donor and host, innate immunity plays a much greater role in xenograft rejection than in allograft rejection. CD47 is ubiquitously expressed and serves as a ligand of SIRPα, an inhibitory receptor on macrophages and DCs. During the current funding period, we demonstrated that the lack of cross-species interaction in CD47-SIRPα pathway largely accounts for macrophage-mediated rejection of hematopoietic and non-hematopoietic cellular xenografts. Transplantation of CD47-deficient cells induces rapid innate immune activation in syngeneic wild-type (WT) mice. Furthermore, CD47-SIRPα signal is required to repress recipient $CD11^{hi}$ DC activation and induce tolerance after donor-specific transfusion (DST). Based on these and other data presented in the application, we hypothesize that the interaction between donor CD47 and host SIRPα is essential for controlling activation of $SIRP\alpha^{+}$ macrophages and DCs, and that the absence of this interaction activates host macrophages and DCs, hence stimulating anti-donor T cell responses. Here, we propose 3 specific aims to test our hypothesis. Aim 1 is to elucidate the role of CD47-SIPRα signaling in the regulation of $SIRP\alpha^{+}$ innate immune cell activation after hepatocyte xenotransplantation. Aim 2 is to determine the role of “missing CD47”-induced innate immune cell activation in T cell xenoresponses after hepatocyte transplantation. Aim 3 is to determine the mechanisms by which CD47 on donor cells facilitates tolerance induction in DST plus costimulatory blockade-treated recipients. These studies are expected to provide significant insights into the mechanisms by which CD47 incompatibility activates innate and adaptive xenoimmune responses, and the potential of using human CD47 transgenic pigs as donors to facilitate xenotolerance induction and xenograft survival.