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Abstract:

Solid organ transplantation is limited by available donor allografts. Pig to human transplantation, xenotransplantation, could potentially solve this problem if physiologic and immunologic incompatibilities are overcome. Genetic modifications of pigs have proven valuable in the study of xenotransplantation by improving pig to human compatibility. More genetic targets must be identified for clinical success. First, this study examines platelet homeostasis incompatibilities leading to acute thrombocytopenia in liver xenotransplantation. Mechanisms for xenogeneic thrombocytopenia were evaluated using liver macrophages, Kupffer cells, leading to identification of CD18, beta-2 integrin, as a potential target for modification. When disruption of CD18 was accomplished, human platelet binding and clearance by pig Kupffer cells was inhibited. Further, human and pig platelet surface carbohydrates were examined demonstrating significant differences in carbohydrates known to be involved with platelet homeostasis. Carbohydrate recognition domains of receptors responsible for platelet clearance Macrophage antigen complex-1 (CD11b/CD18) and Asialoglycoprotein receptor 1 in pigs were found to be different from those in humans, further supporting the involvement of platelet surface carbohydrate differences in xenogeneic thrombocytopenia. Second, immunologic incompatibilities due to antibody recognition of antigens resulting in antibody-mediated rejection were studied. Identification of relevant targets was systematically approached through evaluation of a known xenoantigenic protein fibronectin from genetically modified pigs. N-Glycolylneuraminic acid, a sialic acid not found in humans, was expressed on pig fibronectin and was identified as an antigenic epitope recognized by human IgG. These studies have provided further insight into xenogeneic thrombocytopenia and antibody-mediated rejection, and have identified potential targets to improve pig to human transplant compatibility.

Description:

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