Natural Killer Cells in Xenotransplantation and Establishment of a Target Cell Line Producing Porcine Endogenous Retrovirus

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Technology description

Summary

The worldwide shortage of human organs and tissues for allotransplantation combined with recent advances in transplantation immunobiology, surgery and medicine, have sparked renewed interest in the clinical use of xenotransplantation, the use of living nonhuman animal materials for the treatment of human diseases. In addition to whole organ transplants, cellular implants and ex vivo use of living material from animal sources have been suggested for treatment of disease in human patients. For a variety of reasons, the pig is currently the source animal of choice for xenotransplantation in humans, but there are two major obstacles to successful pig to human xenotransplantation. These are the immune response, responsible for rejecting xenotransplants, and the risk of transmission of infection including porcine endogenous retrovirus, which, at least at the present time, cannot be removed from the xenotransplantation porcine source. Natural killer (NK) cells play an important role in the delayed rejection of xenotransplants, and have been shown to infiltrate rejecting grafts.
Current efforts in the Laboratory of Immunology and Virology, Division of Cellular and Gene Therapies, Center for Biologics Evaluation and Research, FDA, are aimed at understanding the human NK cell response to porcine target cells. Findings suggest that NK cells have the capacity to participate in early stages (hyperacute or acute rejection) of xenograft rejection as well as later stages (delayed rejection). In addition, human NK cell activity against porcine cells as measured by lysis and proliferation, is regulated by certain cytokines such as interleukin (IL)-2, IL-12, and IL-15, but not by IL-18 and IL-8. Moreover, the human NK cell response to porcine endothelial cells is regulated by the combination of redox status and nitric oxide (NO) availability, such that under conditions of oxidative stress, lysis of porcine endothelial cells is inhibited by NO through a nuclear factor-kappa B-dependent pathway. Finally, in the process of carrying out these investigations, a new porcine cell line, MS-PBMC-J2 (J2), was established from the peripheral blood of a NIH miniswine. J2 constitutively produces infectious porcine endogenous retrovirus. J2 expresses porcine CD2, CD8, CD16, CD31, and MHC class I and class II but does not express CD3 or CD4. Phenotypically it resembles NK cells, but does not mediate NK-like activity. Further studies into the regulation of human NK cell anti-porcine cytotoxicity are underway, and other experiments using J2 as a model of PERV production are planned.

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