

ORAL SESSIONS

Best Abstracts

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PLURIPOTENT STEM CELLS VARYING IN A SINGLE MINOR HISTOCOMPATIBILITY ANTIGEN ELICIT CELLULAR AND HUMORAL IMMUNE RESPONSES THAT CAN MEDIATE GRAFT REJECTION

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Pluripotent stem cells (PSCs), including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), hold great promises for regenerative medicine. They might be used to generate cells and tissues for new transplantation therapies to treat, e.g., heart failure or Parkinson's disease. Although it has been suggested that PSCs possess immunosuppressive properties, the risk of immune rejection remains a serious problem, since it is unlikely that autologous grafts can be produced for every individual patient despite improved iPSC technology. To clarify the immunogenicity of PSCs, we engineered mouse ESCs and iPSCs (129Sv, H2b) to express stably Ovalbumin (OVA) as a model of a single minor histocompatibility antigen for grafting into otherwise syngeneic recipients. The PSCs were able to suppress in vitro the activation of naïve OVA-specific CD4 and CD8-positive T cells from T cell receptor-transgenic OT-I and OT-II mice by exogenous antigen and they failed to process and present the endogenous OVA antigen. These findings suggest that PSCs indeed possess immunosuppressive and immunoprivileged properties. However, after subcutaneous transplantation into immunodeficient mice, PSCs induced proliferation of adoptively transferred naïve OVA-specific T cells. In immunocompetent 129Sv mice, the PSCs were rejected or resulting teratomas were significantly smaller than in immunodeficient mice. The 129Sv recipients developed OVA-specific IgM and IgG-antibodies and activated OVA-specific cytotoxic T lymphocytes were found especially in those recipients who rejected the graft. In established teratomas, OVA expression was lost or

significantly reduced compared to PSCs. The data clearly indicate that PSCs are immunogenic in vivo. The immune response can lead to graft rejection and suppression of teratoma growth. In conclusion, a single minor histocompatibility antigen can be sufficient to induce rejection of transplanted PSCs suggesting that therapies using grafts derived from major histocompatibility complex (MHC)-matched allogeneic PSCs will likely require immunosuppressive treatment.

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CIITA-DEPENDENT TRANSCRIPTIONAL DOWNREGULATION OF HLA CLASS II RESULTS IN LEUKEMIA IMMUNE ESCAPE AND RELAPSE AFTER ALLOGENEIC HSCT

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Disease relapse after allogeneic hematopoietic stem cell transplantation (HSCT) represents a major obstacle to the definitive cure of acute myeloid leukemia (AML). We demonstrated that a frequent mechanism of relapse after partially-incompatible HSCT is the genomic loss in leukemic cells of the HLA mismatched between patient and donor (Vago et al, NEJM, 2009). A currently unknown issue regards if and to what extent transcriptional alterations contribute to this process of leukemia immunoevasion. In the present study, we investigated this question by paired analysis of AML samples harvested from 9 patients at time of diagnosis and relapse after HSCT, using Illumina microarray-based gene expression profiling. Comparative enrichment analysis showed that most of the biological processes selectively and significantly deregulated at relapse were immune-related (18/29, 62%). We identified an immunological gene signature characteristic of post-transplantation relapse, which interestingly comprised significant and selective downregulation of HLA Class II antigens. HLA-DR, -DQ and -DP transcriptional downregulation at relapse was validated in 7 patients by qPCR and flow

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vs. 74%, $p=0.004$) when compared with patients with disappearing DSA. When preformed DSA disappeared during follow-up, patients had a graft survival and a risk of humoral rejection comparable to non-sensitized patients. A ROC curve showed that the threshold of MFI was 2,000 for prediction of the persistence of preformed DSA after grafting. We analyzed the potential of preformed DSA to bind C1q (C1qScreen, One Lambda®), all the six C1q+ DSA persisted after transplantation and led to graft failure in 4 patients. In conclusion: if the crossmatch by lymphocytotoxicity is negative, preformed DSA are only deleterious if they persist after transplantation. If their fluorescence on D0 is below 2,000 they tend to disappear without compromising the survival of the graft.

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ASSOCIATION OF KIDNEY GRAFT LOSS WITH POSTTRANSPLANT PRESENCE OF HLA ANTIBODIES DETECTED BY SINGLE ANTIGEN TESTING

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The majority of studies on the impact of posttransplant donor-specific antibodies (DSA) suffer from a low number of cases with graft loss. We investigated in a series of kidney transplants with graft failure whether the posttransplant presence, de novo development, or post-transplant persistence of pre-existing DSA is associated with graft failure. As part of the CTS Serum Project, we studied a cohort of 64 patients with graft loss on whom a posttransplant serum obtained before graft failure was available. Recipients and donors were HLA typed for all 11 loci, which allowed the precise definition of DSA. Single Antigen Bead (SAB) assay-detected DSA and non-DSA antibodies were compared between patients with graft loss and matched control patients who had functioning grafts. At the 500 MFI cut-off, as many as 95% of patients with and 94% without graft loss showed evidence of SAB-detected HLA antibodies. The incidence of DSA in these patients was 44% and 36%, respectively ($P=n.s.$). With higher MFI cut-offs the difference between the two patient groups became more pronounced. At MFI >5,000, the patients with graft loss had a higher incidence of SAB-detected posttransplant antibodies than patients without graft loss (total antibodies: 59% vs. 36%; $P=0.013$; DSA: 19% vs. 9%, $P=0.20$; non-DSA: 56% vs. 33%, $P=0.013$). For 51 patients with graft loss a pretransplant serum was also available, which allowed the analysis of de novo antibody production after transplantation. Here, even the incidence of weak de novo antibodies (DSA or non-DSA) reactive at MFI >500 was higher in the graft loss group than in the non-rejector group (88% vs. 55%, $p=0.003$). Due to the low incidence of DSA, the

difference was significant only for non-DSA ($P=0.003$). Similar results were obtained at higher cut-offs. C1q-DSA was observed only in rejectors. Our data suggest that the posttransplant presence of strongly reactive HLA antibodies, especially if C1q-binding and/or de novo, is associated with graft loss, even if the antibodies are not specific for mismatched donor HLA.

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A PROPOSAL FOR A NEW KIDNEY ALLOCATION SYSTEM

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In light of the fact that deceased donor organs are a scarce resource, their distribution must be balanced in order to maximize utility and justice. It should take into account the relationship between supply and demand, hence seeking a balance between the higher net benefit of survival that can be provided by a particular organ and the transplant candidates' waiting time (as well as the probability of being transplanted). We propose a colour system classification for kidney allocation that will allow clinicians to know the position of a particular patient in the access to kidney transplantation from a deceased donor at all times. This colour system would prioritize candidates by colour ranging from red to green. Red will be attributed to all clinically urgent candidates. Orange would be allocated to candidates with values of calculated PRA (cPRA) >85% or their time on dialysis being higher than the third quartile of wait listed patients' time on dialysis to transplantation (i.e., how long it takes for 75% of wait-listed candidates to receive a transplant). Yellow would be given to candidates with cPRA >50% or time on dialysis being higher than the median of wait listed patients' time on dialysis to transplantation (i.e., how long it takes for 50% of wait-listed candidates to receive a transplant). Green will be for all of the remaining candidates. Within each colour group, the candidates' order will be determined taking into account the number of HLA compatibilities with the donor and, if a tie still persists, the decision is made by the time on dialysis.

This proposition for a new allocation system of kidney transplantation would be more transparent than existing point systems and advantageous for both doctor and patient; with it, clinicians can explain to the patient in a more intuitive manner how far they are from being transplanted. Also the realization that patients classified as green will likely wait too long for an organ, can easily sway them toward the solution of transplantation with a living donor. The discussion about access to kidney transplantation with deceased donors never comes to a close and is always in need of improvements; therefore, it must be done clearly and systematically in order to enable the best decisions at any given moment.