**ABSTRACTS - Cardiac Function and Heart Failure**

**1051-127 Molecular Pathways of Cardiac Allograft Dysfunction Independent of Acute Cellular Rejection**


**Background:** The biology of allograft dysfunction independent of cellular rejection remains poorly understood. B-type natriuretic peptide (BNP) can serve as a sensitive marker of graft dysfunction despite normal systolic function. This investigation was designed to evaluate gene expression (GE) patterns associated with graft dysfunction and to identify underlying molecular pathways independent of cellular rejection.

**Methods:** Cardiac allograft recipients were prospectively enrolled as part of The Cardiac Allograft Rejection Gene Expression Observational (CARGO) multi-center study. Subjects were followed at each post-transplant visit with biopsy (read by 3 pathologists blinded to clinical data), whole blood BNP, echocardiography and hemodynamics. GE profiles of circulating cells were evaluated using microarray microarrays with > 8,000 genes and validated with real-time PCR (RT-PCR).

**Results:** 42 subjects were followed for two years. For 342 encounters the median BNP was 190 pg/ml. Levels differed significantly as a function of gender and ethnicity (n=324 vs. n=48, p<0.003). The genes were associated with granulocyte and monocyte lineages and included elastases, adherence receptors, metalloproteinases and cytokine receptors. They were distinct from genes correlated to acute cellular rejection using microarrays and RT-PCR in the multi-center study. For 35 patients, BNP levels were compared to quantitative results of a clinically validated 14 gene RT-PCR test for acute cellular rejection. No correlation was found.

**Conclusions:** Peripheral immune cell molecular pathways indicative of allograft dysfunction are associated with elements of innate immunity distinct from cellular immunity pathways. GE assays for acute rejection and assessment of graft function by BNP may be complementary for detection of the quiescent state in cardiac allograft recipients.

**1051-128 Inhibition of p38 Mitogen Activated Protein Kinase to those with lower levels (< 10%) had HLA sensitization was detected using Panel Reactive Antibody screening tests (PRA) and VE-Cadherin were determined in 3 groups and compared using the Kruskal-Wallis test. Mann-Whitney U test was used when comparing between 2 groups. P values <0.05 were considered to indicate significant statistical differences.

**Results:** The results showed that MIP-1β and VE-Cadherin were differentially expressed between the 3 groups (p=0.01 and p=0.009 respectively) as observed in the macroarray data and IHC staining. The relative amount of MIP-1β was significantly increased in allografts compared to isografts and NT (p=0.01 and p=0.02 respectively). The relative amount of VE-Cadherin was significantly decreased in allografts compared to isografts and NT hearts (p=0.05 and p=0.02 respectively).

**Conclusions:** We have identified 2 genes (MIP-1β and VE-Cadherin) as markers of acute rejection after HT in a murine model. Several lines of evidence, obtained by macroarray and IHC, have shown that MIP-1β was over expressed and that VE-Cadherin was under expressed in the acute rejection group (allografts). To validate the macroarray and immunohistochemical results, the mRNA copy numbers for MIP-1β and VE-Cadherin were determined in 3 groups and compared using the Mann-Whitney U test.

**1051-130 Inhibition of p38 Mitogen Activated Protein Kinase Mediates Endothelial Cell Survival During Cardiac Transplantation**

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**Background:** The hypothermic ischemic preservation required for cardiac transplantation exposes the donor heart to myocardial ischemia/reperfusion (I/R) injury upon implantation. p38 mitogen-activated protein kinase (MAPK) has been directly linked to increased apoptosis in models of myocardial I/R injury and its inhibition has significantly improved post-ischemic myocardial function in in vivo models. However, the intracellular signaling pathways responsible for these changes are not well determined. Additionally, the inhibition of p38 MAPK inhibitors into myocardial preservation solutions has yet to be examined. Here we hypothesize that the incorporation of the p38 MAPK inhibitor, SB239063, into University of Wisconsin (UW) preservation solution results in effective inhibition of TNF-α-induced p38 MAPK activation. The inhibition of p38 MAPK may play a key role in mediating endothelial cell survival through the activation of the pro-survival signals, AKT and ERK.

**Methods:** Mature human umbilical vein endothelial cells (HUVEC) at 37°C are pre-incubated in cold (4°C) UW solution at 4°C with or without SB239063 (50 µM, 4°C, 12h). Cells are warmed and activated with TNF-α. Lysates are analyzed for p38, AKT, and ERK1/2 activities by Western blotting.

**Results:** 1) UW solution with SB239063 successfully inhibited TNF-α-induced p38 MAPK activation (n=3). 2) Inhibition of p38 MAPK produced an average upregulation of AKT activity of 42% and an average upregulation of ERK1/2 activity of 148% (n=3).

**Conclusion:** The p38 inhibitor, SB239063, has been effectively incorporated into UW solution to inhibit TNF-α-induced p38 MAPK activation in HUVEC. Inhibition of p38 MAPK upregulates the activities of the anti-apoptotic signals AKT and ERK1/2. These data suggest that p38 MAPK is a pro-apoptotic signal whose inhibition may represent a novel method to mitigate apoptosis and improve myocardial performance following cardiac transplantation.