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Short Review

Short Review on Immune Response to Allogeneic Equine Mesenchymal Stromal Cells

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Our research investigated the interaction of the cell-mediated and innate arms of the immune system with allogeneic Mesenchymal Stromal Cells (MSCs). This study monitored population changes and activation of Equine Leukocyte Antigen (ELA) - mismatched leukocytes in direct co-culture with MSCs. Cytotoxic T cells, helper T cells, regulatory T cells, B cells and neutrophils were identified using flow cytometry. Gene expression from MSCs and lymphocytes were evaluated over time in co-culture. Lymphocyte proliferation was monitored with a tritiated thymidine inclusion test.

Donor MSCs from 10 horses aged 2-21 years were used. The MSCs from these 10 horses were grouped into three types including: MHC II- low expressing MSCs, MHC II-high MSCs, and those MSCs from equine blood donor type horses (Aa, Ca, and Qa negative). No correlation between erythrocyte antigens and MSC antigens has been seen in previous literature [1]. Haplotyping revealed that the leukocytes utilized were ELA-mismatched from each of the allogenic MSCs. All animals were heterozygotes. MSCs were plated on 48 or 96-well plates dependent on the assay. MSCs were plated using non-xenogeneic media 48 hours prior to the addition of leukocytes to the culture wells. Lymphocyte testing was performed after 3 and 5 days in co-culture. Neutrophil testing was performed at 6 and 12 hours post co-culture. Ratios of 1:1, 1:10, and 1:100 MSC:PBMC or MSC:Neutrophil were utilized.

Assessment of MHC I and II expression was completed prior to culture with leukocytes and at day 3 and day 5 in co-culture with lymphocytes. Prior to co-culture, blood donor MSCs showed low levels of MHC II expression consistent with those levels expressed by the samples in the MHC II-low MSC group. MHC II expression increased significantly in the blood donor and MHC II-low MSCs in co-culture with lymphocytes as compared to same day controls at both day 3 and day 5. MHC I expression was high in all groups. The median value of MHC I expression was greater than 90% for each of the sample groups prior to co-culture and at day 3 and 5 of co-culture

Lymphocyte proliferation upon interaction with MSCs was assessed using thymidine incorporation assays. No significant lymphocyte proliferation occurred in the MHC II-low MSC co-cultures at day 3 nor day 5. The MHC II-high co-cultures caused lymphocyte proliferation at day 3.

Our results found that helper T and cytotoxic T cell populations showed little variation from autologous to allogeneic co-cultures. On flow cytometry, activation rates of CD4 and CD8 lymphocytes in allogeneic co-cultures were consistent with those co-cultured with autologous cells. The only exception to this was the universal blood donor MSC group which caused greater activation of CD4 lymphocytes at some MSC:lymphocyte ratios.

In our study, Tregs cells were consistently increased in co-cultures at low MSC:PBMC ratios. In these ratios, MSCs would potentially have the greatest interaction with lymphocytes. Blood donor MSCs caused a significant increase in Tregs as compared to other MSC groups at both Days 3 and 5, and MHC II-low MSCs showed an increase in Tregs, though this was not significant. The increase in Tregs when cultured with MSCs is consistent with previously published human studies [2,3].

B lymphocyte numbers were not consistently increased in the face of co-culture with allogeneic MSCs. B lymphocyte numbers increased over time when PBMCs were cultured alone, but this was not seen in any of the co-cultures. All MSCs were capable of B lymphocyte immunosuppression. Antibody production is a common concern for successive allogeneic MSC treatments [4], and it is well known that B cells create antibodies against ELA mismatched allogeneic MSCs which leads to their destruction [5,6]. The lack of B lymphocyte proliferation may be an indication of B lymphocyte suppression by MSCs that would provide MSCs with some degree of immunopriviledge as compared to other types of alloantigens.

Neutrophil co-cultures showed some increased activation when plated with allogeneic MSCs as compared to autologous MSCs, though this was not true for all three types of allogeneic MSCs. At the 6 hour time point, median levels of activation were low for all groups with a median percent of neutrophils activated at less than 6% for all groups. But at this 6 hour time point, both the blood donor and the MHC II-high MSC groups showed significant increases in neutrophil activation over autologous co-cultures at one of the MSC: Neutrophil ratios.

All assays showed high MSC viability throughout co-culture. No decrease in viability was seen when MSCs were co-cultured with neutrophils.

Gene expression over time was then examined for both the autologous and allogeneic MSCs in co-culture with lymphocytes. MSCs are known to deliver anabolic factors such as TGF-β1, FGF, and G-CSF;

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anti-inflammatory factors such as IL-1RA and IDO1; and immunomodulating factors such as CXCLB/IL8 and IFN- γ [7-9]. Two groups of MSCs, the blood donor and the MSC II-low groups, increased their gene expression of these anabolic genes when co-cultured with lymphocytes. MHC class II-low MSCs had significantly greater gene expression than autologous and MHC II-high MSCs for the genes encoding CD59, FGF-2, HGF, IDO, IL-10, IL-RA, IL-2, SOX2, and TGF-β1. MHC class II-low MSC gene expression was significantly higher than autologous MSCs for some inflammatory or immunomodulating genes. MHC class II-low MSCs showed increased expression of ADAMSTS-4, CCL2, CXCLB/IL-8, IL-1b, and TNFα. MHC class II-low MSC showed significantly decreased expression ADAMSTS-5 and MMP-13. Genes that showed no significant difference between autologous and MHC II-low allogeneic co-cultures included SOX2, VEGF, IFNγ, IL-6, and COX2.

Our research reached several important conclusions. First, donor MHC II-low MSCs caused no increased lymphocyte activation nor proliferation when compared autologous MSCs. No neutrophil activation was seen in MHC II-low co-cultures. Furthermore, MHC II-low MSCs had a significant increase in their gene expression for most genes when compared to autologous MSCs. When ELA-mismatched MHC II-low MSCs were placed in culture with allogeneic leukocytes, no significant activation of the innate immune system occurred. Although the MHC II expression increased when the MHC II-low MSCs were placed in co-culture with allogeneic leukocytes, MHC II-low MSCs behaved considerably differently, and preferentially, as compared to MHC II-high MSCs.

In summary, MHC II-low MSCs should be utilized for future MSC donor studies in equine regenerative medicine. Innate immune reactions to allogeneic equine MSCs are unlikely to cause significant MSC cytotoxicity nor significant immune reactions when placed in a naïve environment.

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