Enhanced Mucosal Immunity and SIV Suppression After Mesenchymal Stem Cell Transfer

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BACKGROUND

Despite the presence of HIV-specific cellular and humoral responses, HIV reservoirs persist in HIV-infected individuals and pose obstacles for HIV cure. Early pathogenic effects of HIV infection in secondary lymphoid tissues including the gut contribute to chronic inflammation, tissue damage and ineffective anti-viral immunity, which are not repaired by ART in a timely manner. We investigated the potential of mesenchymal stem/stromal cells (MSC) on enhancing anti-viral mucosal immunity and viral suppression in the SIV model of AIDS. MSC secrete immuno-modulatory molecules and have beneficial effects in clinical and preclinical studies.

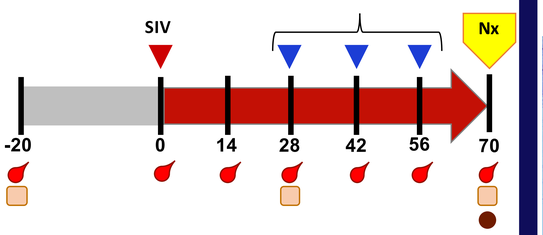
HYPOTHESIS

Systemic allogeneic MSC administration will modulate antigen presentation and enhance anti-viral immunity at mucosal sites and lead to better viral suppression and increased immune recovery.

MSC transfer enhances virus-specific cellular and humoral immune responses by corralling virus to the lymphoid follicles which improves antigen presentation and antiviral response.

METHODS



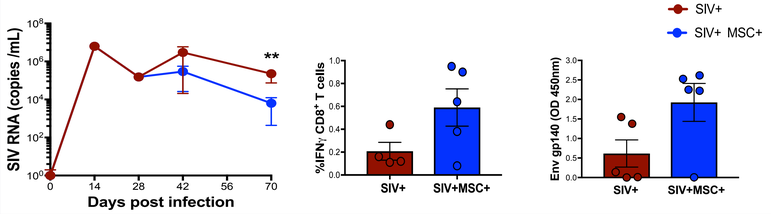


Ten rhesus macaques were intravenously infected with SIV at day 0. Five animals received three MSC infusions at days 28, 42 and 56 post infection while the control group received saline. Animals were necropsy at 70 days post-SIV infection.

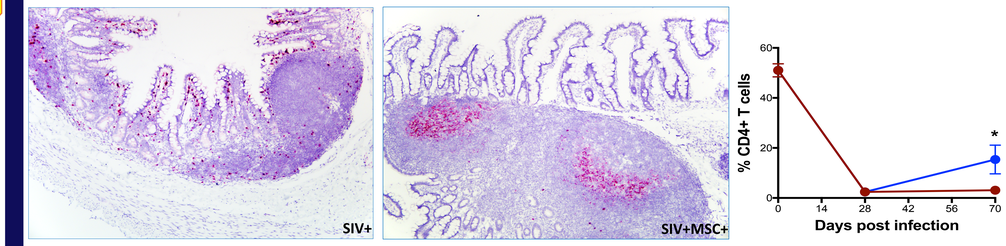
- Plasma SIV RNA loads (RtPCR)
- Virus localization in tissue (RNAscope)
- Imunophenotyping and T cell specific response (Flow cytometry)
- Humoral response (ELISA)
- Gene expression analysis (RNA seq)
- Gut microbiota (16s sequencing)
- Metabolomic profilling

RESULTS

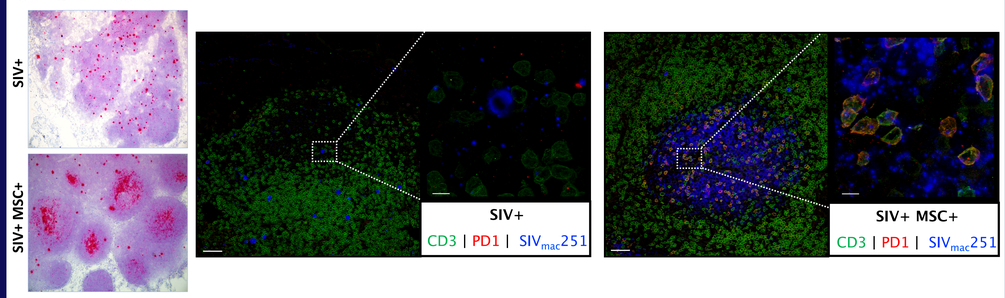
Significant viral suppression and increased levels of SIV-specific cellular and humoral responses in peripheral blood of MSC treated animals compared to controls



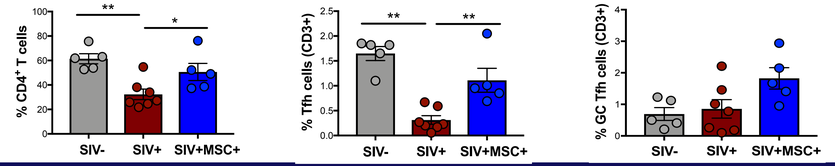
Corralling of the virus into the germinal centers and increased prevalence of CD4+ T cells in the gut mucosa of MSC treated animals



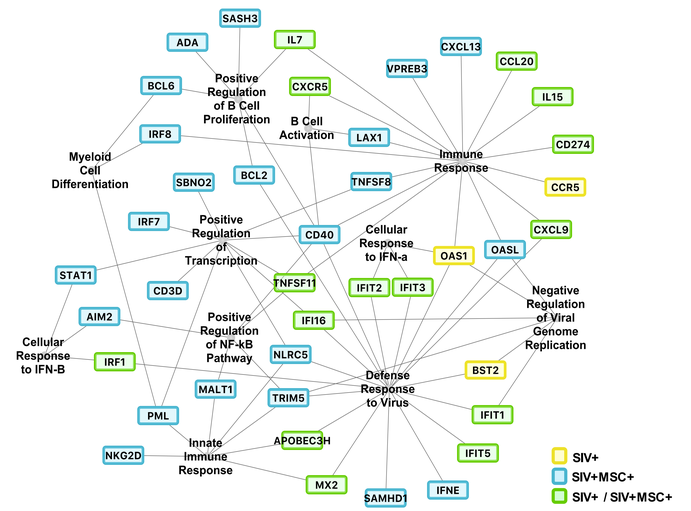
Revival of mesenteric lymph node micro-architecture following MSC treatment and co-localization of the virus on PD-1⁺ T cells

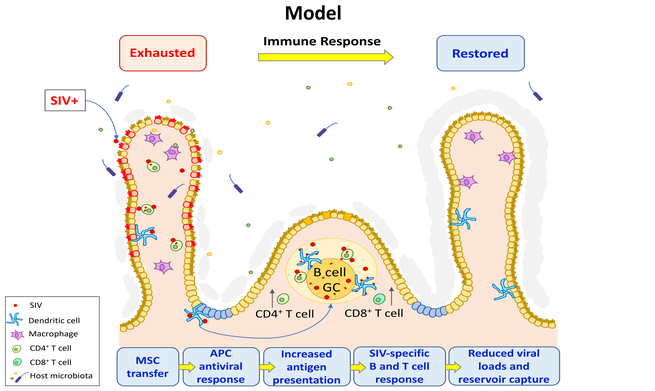


Restoration of the frequency of CD4+ T cells and Tfh cells in the mesenteric lymph node of MSC treated animals



A unique gut mucosal transcriptomic signature of enhanced anti-viral immunity





CONCLUSION

•MSC administration enhances SIV-specific antibody production and cytotoxic T cell response as well as increased mucosal immunity, decreasing viral loads in the blood.

•MSC transfer presents a unique mechanism for corralling SIV into the germinal center, enhancing antigen presentation and antiviral response.

•MSC can be used for reviving mucosal immunity in SIV infection for virus clearance.

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