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Grant Title: Targeting the stem cell hyaluronan microenvironment for regenerative medicine

Abstract

Human umbilical cord mesenchymal stem cells (hUMSCs) present great regenerative capabilities and plasticity, and have recently been shown to present unique immunosuppressive properties which prevent xenograft rejection, making these cells extremely attractive for cell therapy. Our previous work demonstrated that hUMSCs secrete a rich glycocalyx composed of hyaluronan (HA), heavy chains (HCs), tumor necrosis factor stimulated gene 6 (TSG6), versican and pentraxin 3 (PTX3), which is anchored to the hUMSCs by the HA binding receptor CD44. This HA glycocalyx regulates inflammatory cells, inhibiting M1 macrophage maturation and promoting M2 macrophage and T-regulatory cell activation, which enables hUMSCs to survive xenograft rejection. Our unpublished findings suggest that the glycocalyx extracted from hUMSCs successfully regulates the immune response, inhibiting inflammatory cell adhesion and M1 polarization. The aim of this proposal was to characterize how HA, TSG-6, HCs, PTX3 and versican assemble into a specialized HA/HC/TSG-6/PTX3/versican glycocalyx, and exactly how this glycocalyx modulates inflammatory cells. For such we aimed to characterize the role of individual components (HA, HCs, TSG-6, PTX3, versican) in hUMSC glycocalyx assembly and in regulating the immune response using CRIPSR/CAS9 technology to knock-out out each component individually. The overarching goal of the proposal was to promote the expression of a highly specialized HA/HC/TSG6/PTX3/versican glycocalyx by hUMSCs and human bone marrow mesenchymal stem cells (hBMSCs), thereby increasing their anti-inflammatory properties and transplantation success. Treating hBMSCs with IαI leads to the production of a specialized glycocalyx that rapidly attenuates the inflammatory response. Moreover, treating hUMSCs with IαI increases the deposition of the specialized glycocalyx increasing their anti-inflammatory properties. Thereafter, we established the optimal technique to extract the glycocalyx from hUMSCs and hBMSCs while retaining its immunosuppressive properties. The extracted glycocalyx retained anti-inflammatory properties and promoted wound healing using an in vivo debridement model. Our findings suggest the HA specific glycocalyx can be extracted from hUMSCs and hBMSCs for treating diseases that result from immune dysfunctions. Use of the extracted glycocalyx, as opposed to the UMSCs themselves, is more ethically viable and shows great potential for expedited clinical trials.