High Glucose Stress Induces Mesenchymal Stem Cells Senescence through Up-regulating Autophagy

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Backgrounds: Mesenchymal stem cells (MSCs) show great promise for use in a variety of cell-based therapies. However, the expansion potential of MSC is limited and in vitro aging leads to loss of multipotency and replicative senescence. Stress induced by culture conditions, such as high glucose (HG), is likely to be a major cause of senescence. Materials and Methods: To confirm that HG induces senescence, we cultured BM-MSC in 25mM glucose and assessed senescence markers. Results: HG increased SA-β-Gal positive cells in a time-dependent manner. Correlated with increasing SA-β-Gal was progressive reduction of cumulative PD by HG. Since cellular senescence is controlled by autophagy, we determined whether HG suppresses autophagy thereby inducing premature senescence. Interestingly, BM-MSC cultured in HG medium exhibited enhancement of beclin-1 expression and LC-3II generation from LC-3 when compared to BM-MSC cultured in control medium. HG increased beclin-1 (Atg 6) mRNA as well as Atg 5, Atg 7 and Atg 12 mRNA when compared to control. HG also siginificantly increased autophagosomes over the control which was assessed by MDC stain. Furthermore, inhibition of autophagy with 3-MA reduces HG-induced BM-MSC senescence. Since it was suggested that HG induces cell stress via generation of reactive oxygen species (ROS), we therefore determined the role of ROS on HG-induced autophagy and senescence. We found that antioxidant such as NAC averts HG-induced autophagy and senescence. Conclusion: Our studies indicate that HG up-regulates the autophagosome formation and autophagy and this HG-induced autophagy promotes senescence.