Presentation Abstract

Presentation Title:	High glucose stress induces mesenchymal stromal cell senescence through up-regulating autophagy
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Abstract: Diabetic hyperglycemia was reported to induce impairment of human bone marrow (BM) hematopoietic function and cause niche dysfunction. As multi-potent mesenchymal stromal cells (MSC) are a key constituent of BM hematopoietic niche, we determined the influence of high glucose (HG) on cultured MSCs. MSCs were cultured in medium containing 5.5 mM glucose (low glucose, LG) or 25 mM glucose (HG) for up to 28 days and cell proliferation and morphology were analyzed. MSCs cultured under HG exhibited reduced cumulative population doubling and BrdU incorporation and increased p16 and p21 in a time-dependent manner. Senescence-associated β-galactosidase (SA-β-Gal) positive cells and interleukin-6 (IL-6) production were increased. Cells underwent morphological changes consistent with senescence. Since cellular senescence is controlled by autophagy, we determined whether HG suppresses autophagy thereby inducing premature senescence. Interestingly, MSC cultured in HG medium exhibited enhancement of beclin-1 expression and LC3-II generation when compared to MSC cultured in LG. HG increased beclin-1 (Atg 6) as well as Atg 5, Atg 7, and Atg 12 mRNA when compared to LG. HG also significantly increased autophagosome formation. To elucidate the relationship between autophagy and senescence, we treated MSCs with 3-methyladenine (3-MA), an inhibitor of autophagy and analyzed changes in senescence. 3-MA prevented growth arrest and p21 elevation and abrogated SA-β-Gal and IL-6 expressions. These results indicate that HG induces senescence through activation of autophagy. It was reported that HG induces cell injury via generation of reactive oxygen species (ROS). We evaluated the effect of N-acetylcysteine (NAC), an antioxidant, on MSC autophagy and senescence. NAC reduced Atg expressions, LC3-II generation and autophagosome formation accompanied by preventing senescence. DPI, an inhibitor of NADPH oxidase, exerted a comparable effect as NAC.
These findings indicate that HG induces premature senescence by ROS-mediated

autophagy upregulation. MSC senescence contributes to niche dysfunction and bone marrow inflammation.

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