HUMAN ADIPOSE-DERIVED STEM CELLS ATTENUATE CIGARETTE SMOKE INDUCED BONE MARROW HYPOPLASIA VIA SECRETION OF ANTI-INFLAMMATORY CYTOKINE TSG-6

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Introduction We have previously observed bone marrow (BM) hypoplasia in a murine model of chronic smoking, which was ameliorated by murine adipose-derived stromal cells (ASC). This study was designed to test the hypothesis that ASC exert their marrow protective effects through key paracrine factors. **Methods** Mice (NSG or C57BL/6) were exposed to cigarette smoke (CS) for 1 day to 6 months. Human ASC or ASC conditioned media were administered through intravenous (i.v.) or intraperitoneal (i.p.) injections. Secretion of TSG-6 from ASC in response to TNF alpha and IL-1 beta were measured by ELISA. Expression of TSG-6 in ASC was knocked down by siRNA. BM hematopoietic progenitors were quantified by colony forming-unit assays. Possible engrafted human ASC in mouse BM were examined by anti-human nuclei staining. **Results** The myelossupressive effect of cigarette smoking occurred acutely (1 day: 65.6% of nonsmoking control, NSC, $p<0.01$) and worsened with prolonged exposure (3 days: 34.3% NSC, $p<0.01$). Such damage could be ameliorated with either ASC (111.0% NSC, $p>0.05$) or ASC conditioned media (105.7% NSC, $p>0.05$). Inflammatory cytokines (TNF alpha and IL-1 beta) elevated in smokers (Kuschner et al, 1996; de Maat et al, 2002) demonstrated strong cross-species stimulatory effects on secretions of an anti-inflammatory cytokine, TSG-6 from ASC (TNF alpha: 8.7 +/- 1.3 fold, IL-1 beta: 8.2 +/- 1.1 fold). Knocking down TSG-6 (>90%) abolished the marrow-protective effect of ASC. No human cells were detected in recipient mouse bone marrow. **Conclusions** The protective effects of ASC against smoking-induced myelosuppression are mediated by trophic factors rather than cell engraftment or differentiation. TSG-6 appears to play a significant role in the modulatory pathway: smoke--inflammatory cytokine release--TSG6 secretion from ASC--bone marrow protection.

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