Effects of induced pluripotent stem cell– and bone marrow–derived mesenchymal stem cells on cigarette smoke–induced lung damage in rats

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X Li[1], SC Yeung[1], YL Zhang[1], YM Liang[1], QZ Lian[1], HF Tse[1], MSM Ip[1], JCW Mak[1,2]
[1] Department of Medicine, The University of Hong Kong, Hong Kong
[2] Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Introduction: Cigarette smoking (CS) is the major cause of chronic obstructive pulmonary disease (COPD) which is the fourth leading cause of death and predicted to be the third by 2030. Administration of bone marrow–derived mesenchymal stem cells (BM-MSC) was reported to attenuate CS-induced emphysema in murine model. This study aimed to investigate the effects of induced pluripotent stem cell–derived MSC (IPSC-MSC) on CS-induced lung damage in comparison to BM-MSC treatment in rats.

Methods: Male Sprague-Dawley rats were randomly divided into four groups. The sham air (SA) group was exposed to fresh air while the other three groups to 4% cigarette smoke (CS) 1 hour per day for 56 days. During the second half of the smoking period, two doses of 3×10^6 of IPSC-MSC or BM-MSC cells were injected intravenously via tail vein to the two groups, ie IP/CS group or BM/CS group at day 29 and day 43. The SA and CS groups were injected with phosphate-buffered saline of the same volume. All rats were sacrificed 24 hours after the last CS exposure. Morphological changes were examined in paraffin-embedded lung sections. Levels of inflammatory markers were measured by ELISA.

Results: Both IPSC-MSC and BM-MSC were able to reside in the lung for as long as 14 days with significant higher density of resided IPSC-MSCs. Both treatments shared similar efficacy to attenuate CS-induced lung cell apoptosis to restore CS-induced reduction of lung IL-10 and to alleviate CS-induced elevation of systemic TGF-β1.

Conclusion: Our findings suggest that treatment of IPSC-MSC or BM-MSC might be able to slow down CS-induced disease progression, possibly through anti-oxidant, anti-inflammatory and anti-apoptotic properties.

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MDM2 inhibitor nutlin-3a impairs glucose homeostasis and insulin secretion in mice

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X Li[1], KK Cheng[1], C Chen[1], B Wang[1], KS Lam[1], A Xu[1,2]
[1] Department of Medicine, The University of Hong Kong, Hong Kong
[2] Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Introduction: Mdm2, an E3 ubiquitin ligase, regulates the tumour suppressor p53 by enhancing its proteasome-mediated degradation through the protein-protein interaction. A small molecule Nutlin-3a has been shown to disrupt the interaction between p53 and MDM2, thereby up-regulating expression of p53 in cancer cells. Therefore, this small molecular represents a promising therapeutic agent for cancer. However, the effect of nutlin-3a on glucose homeostasis has never been explored so far. In this study, we aimed to investigate whether nutlin-3a affects glucose metabolism using both in-vivo and in-vitro approaches.

Methods: Twelve-week male C57BL/6 mice were treated with nutlin-3 or DMSO (as a vehicle control) by oral gavage 2 hours before the experiment. Glucose tolerance and insulin sensitivity were assessed by intraperitoneal glucose tolerance test (GTT) or insulin tolerance test (ITT). Insulin secretion during GTT was examined. Effect of nutlin-3a on glucose or non-glucose secretagogues-stimulated insulin secretion was determined in mouse pancreatic islets and beta cell lines.

Results: The mice treated with nutlin-3 exhibited glucose intolerance which is accompanied with blunted insulin secretion, but similar insulin sensitivity compared to the DMSO control group. Further analysis revealed that beta cells treated with nutlin-3a exhibited impairment of glucose-stimulated insulin secretion (GSIS), which was associated with diminished ATP production and calcium influx. Furthermore, nutlin-3a treatment also suppresses insulin secretion induced by non-glucose secretagogues, including the mitochondria activators, the potassium channel blockers and the cell membrane depolarisation agents.

Conclusion: These findings demonstrated that disruption of the interaction between MDM2 and p53 by nutlin-3 leads to glucose intolerance, owing to defective insulin secretory capacity. Such inhibitory effects on insulin secretion may attribute to impaired glucose metabolism, mitochondria activation and/or calcium mobilisation.