RESTORATION OF MESENCHYMAL STEM CELL FUNCTION USING PHARMACOLOGICAL AGENTS

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Introduction: The extensive characteristics of mesenchymal stem cells (MSCs), especially their capacity to replicate and differentiate into any type of fully developed cell make these cells suitable for use in cell therapy. These cells are clinically introduced into a tissue in an autologous or allogeneic manner for the treatment of inflammatory and degenerative diseases with or without gene therapy. There are however, some drawbacks related to the clinical use of MSCs, with one major limitation being that these cells tend to decrease in 'stemness' and quantity with increasing donor age and disease while the underlying mechanisms of stem cell ageing remain vague. An increased activity of the small RhoGTPase Cdc42 is thought to play a key modulatory role in MSC ageing. Cdc42 activity is known to partake in the regulation of numerous signaling pathways and also cause depolarization of planer cell polarity markers hence has been identified as a pharmacological target for improving MSC ageing. The aim of this study is to investigate the regulatory effect of small molecule on Cdc42 activity in MSCs.

Materials and methods: Three pharmacological agents in the form of small molecules: CASIN, ML141and ZCL278 were used as inhibitors of Cdc42 activity in MSCs isolated from differently-aged laboratory rats. The effects of these small molecules were assessed by monitoring Cdc42 activity, cell proliferation and β-galactosidase expression.

Results: Though Cdc42 activity increased in MSCs isolated from 6month old rats, it was seen to decrease in MSCs isolated from 1and 3month-aged rats. The highest Cdc42 activity was recorded in MSCs isolated from rats aged 24months. It was shown that Cdc42 inhibitors decreased Cdc42 activity in aged senescent cells with a subsequent increase in cell proliferation and decrease in β-galactosidase activity. Among the 3 small molecules used, CASIN and ZCL278 were shown to be more effective.

Conclusion: From the obtained results, it can be concluded that, the inhibitory effect of small molecules on Cdc42 activity substantially improves function characteristics of aged Mesenchymal stem cells.