

STUDIES ON MESENCHYMAL STEM CELLS AS A POTENTIAL CELLULAR THERAPY FOR CANCER

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OBJECTIVE

Our past research works have shown that mesenchymal stem cells (MSC) profoundly inhibit the growth of various tumour cells. However there is insufficient data to elucidate the molecular mechanisms that mediate this anti-proliferative activity. Therefore, we have explored the inhibitory effect of MSC on cancer cell cycle status and their respective signalling pathways.

METHODOLOGY

Adult human bone marrow aspiration was utilised to generate MSC and their immunophenotype profile and mesodermal differentiation ability were confirmed by flow cytometry and differentiation assays respectively. Haematopoietic origin tumour cells BV173, K562, HL60 and Jurkat cell lines were purchased from ATCC and maintained in 10% foetal bovine serum supplemented RPMI media. Cell cycle analysis was performed using flow cytometry and western blotting.

RESULTS

In the presence of MSC, tumour cell proliferation was profoundly inhibited in dose dependent manner as measured by ³H-thymidine uptakes and quick cell proliferation assay. Transwell assays indicated that MSC mediated inhibition is mainly attributed to cell-to-cell contact. Furthermore, MSC did not induce apoptosis as their mode of anti-proliferation activity.

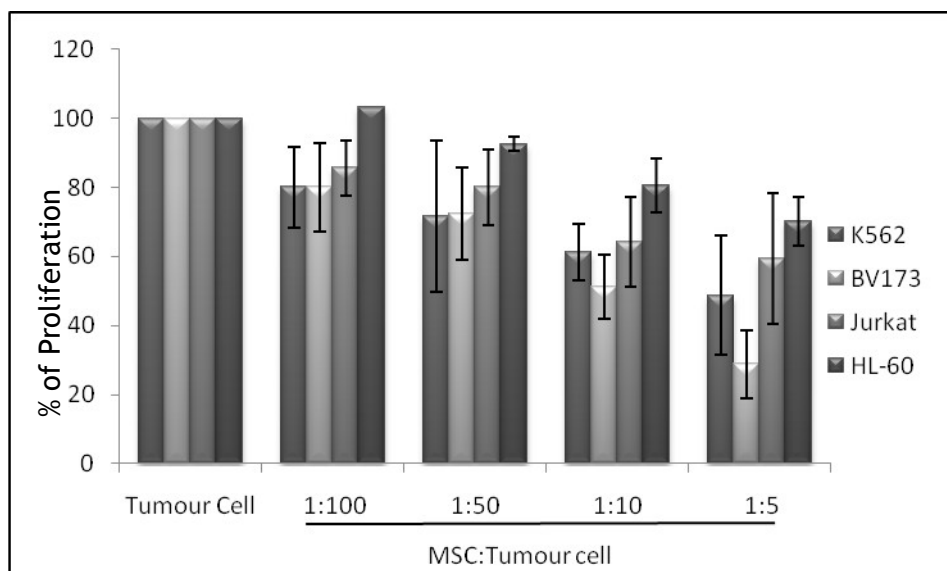


Figure 1. MSC inhibit tumour cells in dose dependent manner

Further investigation on tumour cell cycle revealed that MSC induce an arrest in G_0/G_1 phase of cell cycle of BV173 and Jurkat tumour cells. In the presence of MSC, tumour cells were prevented from entering S phase (DNA synthesis). However, MSC arrests the K562 tumour cells in S phase, thus preventing them from entering into G_2/M phase of cell cycle.

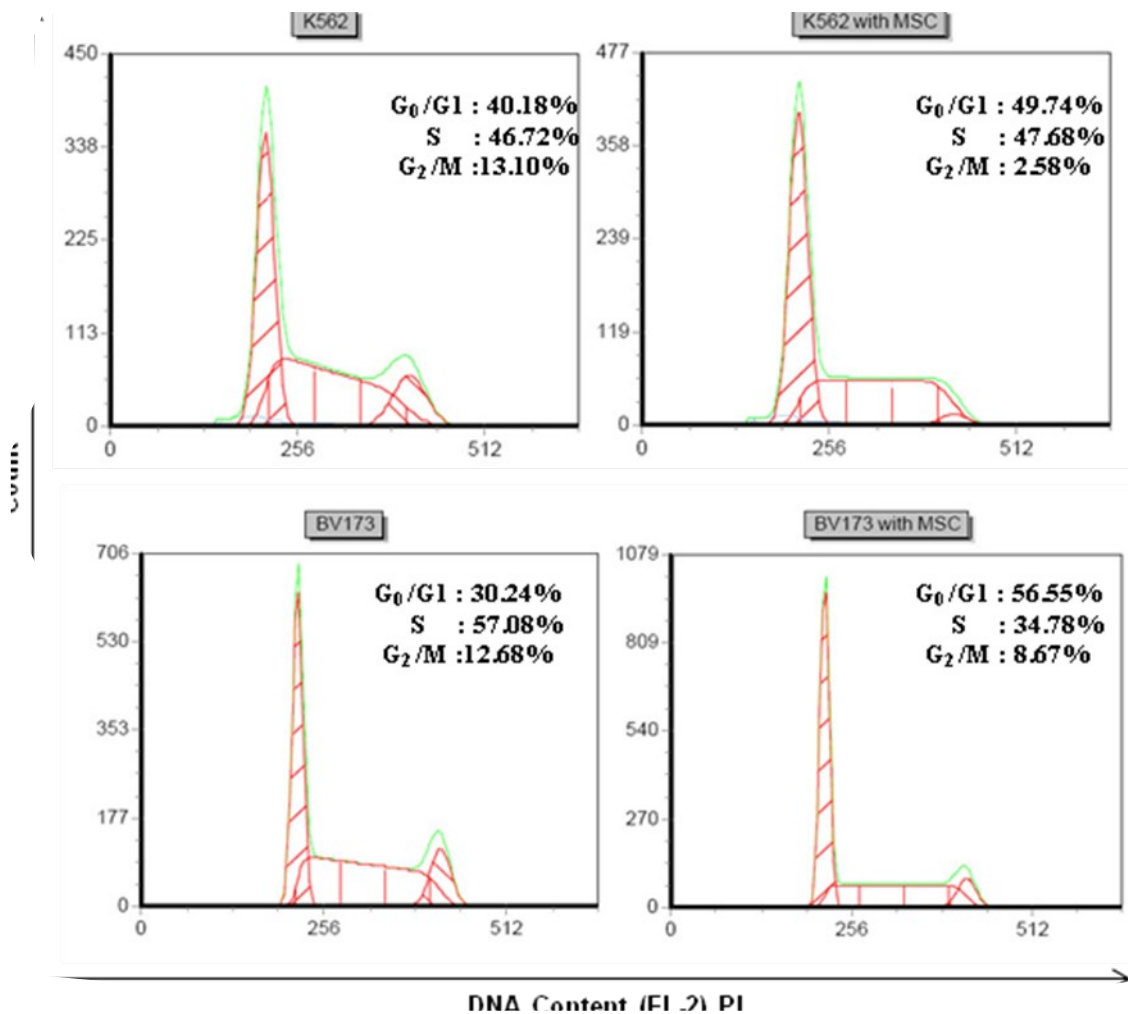


Figure 2. MSC induce cell cycle arrest of tumour cells

In order to dissect the cell cycle mechanism, cyclin molecules that govern cell cycle progress, their relevant kinases and kinase inhibitors have been investigated. The result showed a generalised pattern of inhibition exerted by MSC on all tumour cells. Mainly the expression of cyclin D1, D3, A, E, PCNA and ERK signalling molecules were significantly reduced in the presence of MSC. CDK4 enzymes that control transition of G_1 -S check point were reduced in BV173 and Jurkat cell line which is an indication of G_1 cell cycle arrest. However,

in K562 cells CDK2 is severely reduced and this is consistent with K562 growth arrest in G₂/M.

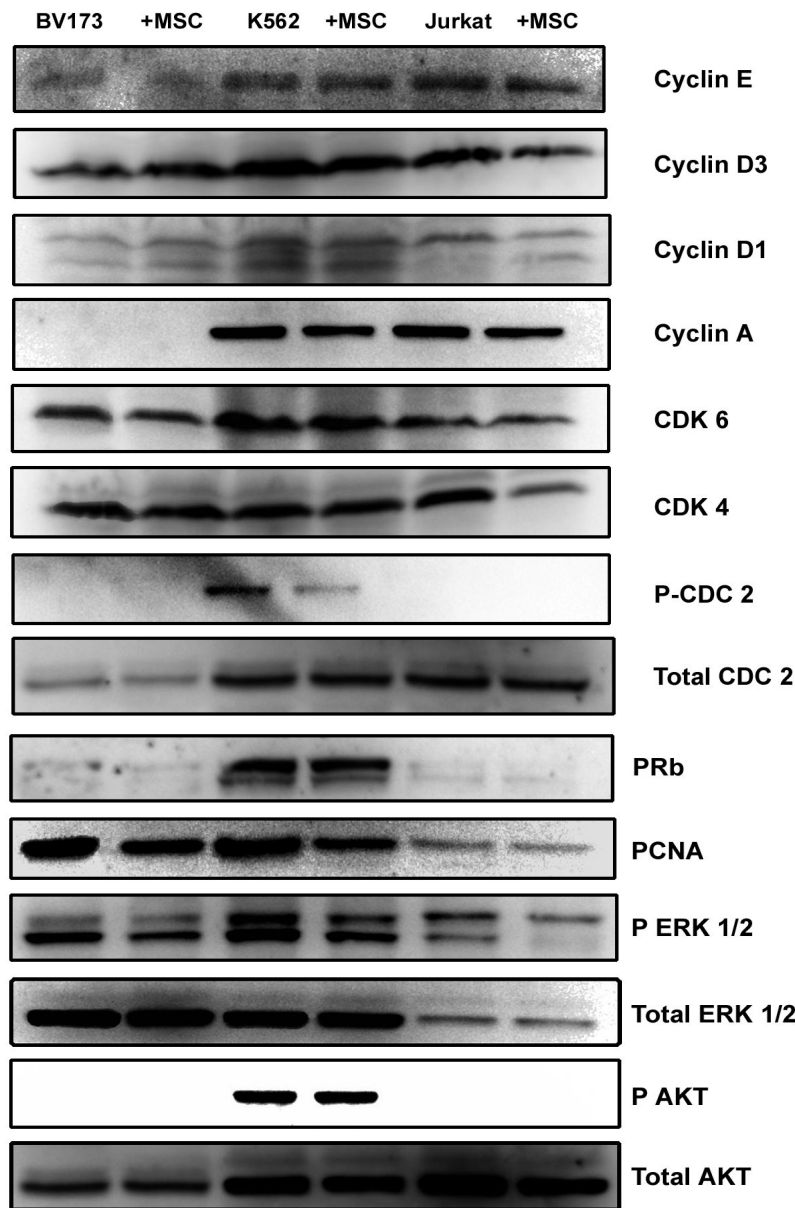


Figure 3. MSC target different signalling pathways and cell cycle check points to exert their inhibition

CONCLUSION

Our results showed that MSC exerted anti-proliferative effects specifically targeting the cell cycle and it could be confined to any cell cycle check points. The generalised tumour cell inhibition by MSC could be potentially exploited to treat various tumours. However, this anti-proliferative activity needs to be tested and verified with primary tumour cells for better understanding.