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Mesenchymal stem/stromal cell-based therapy: mechanism, systemic safety and biodistribution for precision clinical applications

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Abstract

Mesenchymal stem/stromal cells (MSCs) are a promising resource for cell-based therapy because of their high immunomodulation ability, tropism towards inflamed and injured tissues, and their easy access and isolation. Currently, there are more than 1200 registered MSC clinical trials globally. However, a lack of standardized methods to characterize cell safety, efficacy, and biodistribution dramatically hinders the progress of MSC utility in clinical practice. In this review, we summarize the current state of MSC-based cell therapy, focusing on the systemic safety and biodistribution of MSCs. MSC-associated risks of tumor initiation and promotion and the underlying mechanisms of these risks are discussed. In addition, MSC biodistribution methodology and the pharmacokinetics and pharmacodynamics of cell therapies are addressed. Better understanding of the systemic safety and biodistribution of MSCs will facilitate future clinical applications of precision medicine using stem cells.

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Mesenchymal Stromal Cell-derived Extracellular Vesicles in Preclinical Animal Models of Tumor Growth: Systematic Review and Meta-analysis

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Abstract

Background: Mesenchymal stromal cell derived extracellular vesicles (MSC-EVs) have been implicated in the regulation of tumor growth. Studies remain preclinical with effects ranging from inhibition of tumor growth to cancer progression. A systematic review and meta-analysis is needed to clarify the effect of MSC-EVs on tumor growth to facilitate potential translation to clinical trials.

Methods: A systematic search of the literature (MEDLINE, Embase, and BIOSIS databases to June 1, 2019) identified all pre-clinical controlled studies investigating the effect of MSC-EVs on tumor growth. Study selection and data extraction were performed in duplicate. Potential risk of bias was assessed using the SYRCLE tool. A random effects meta-analysis of reduction in tumor weight/volume (primary outcome) was performed.

Results: We identified 29 articles and 22 reported data on tumor responses that were included for meta-analysis. Studies were associated with unclear risk of bias in a large proportion of domains in accordance with the SYRCLE tool for determining risk of bias in preclinical studies. A high risk of bias was not identified in any study. MSC-EVs had a mixed response on tumor progression with some studies reporting inhibition of tumor growth and others reporting tumor progression. Overall, MSC-EVs exerted a non-significant reduction in tumor growth compared to controls (standardized mean difference (SMD) -0.80, 95 % CI -1.64 to 0.03, $p = 0.06$, $I^2 = 87$ %). Some studies reported increased tumor

growth which aligned with their stated hypothesis and some interrogated mechanisms in cancer biology. EVs isolated from MSCs that overexpressed anti-tumor RNAs were associated with significant tumor reduction in meta-analysis (SMD - 2.40, 95 % CI -3.36 to -1.44, $p < 0.001$). Heterogeneity between studies was observed and included aspects of study design such as enrichment of MSC-EVs with specific anti-tumor molecules, tissue source of MSCs, method of EV isolation, characterization of MSCs and EVs, dosage and administration schedules, and tissue type and source of tumor cells studied.

Conclusions: MSC-EVs are associated with mixed effects on tumor growth in animal models of cancer. In studies where anti-tumor RNAs are packaged in EVs, a significant reduction in tumor growth was observed. Reducing heterogeneity in study design may accelerate our understanding of the potential effects of MSC-EVs on cancer. [274 words] Forest plot of MSC-EV effect on tumor growth accordinggenetic modification of EVs in animal studies identified from a systematicreview of the literature. All cohorts from studies with multiple interventiongroups are presented separately with control groups divided equally among thegroups. M, modified; H, hypoxia.