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Mineralization by mesenchymal stromal cells is variously modulated depending on commercial platelet lysate preparations.

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Author information

Abstract

BACKGROUND AIMS:

Numerous cellular models have been developed to investigate calcification for regenerative medicine applications and for the identification of therapeutic targets in various complications associated with age-related diseases. However, results have often been contradictory due to specific culture conditions, cell type ontogeny and aging status. Human platelet lysate (hPL) has been recently investigated as valuable alternative to fetal bovine serum (FBS) in cell culture and bone regeneration. A parallel comparison of how all these multiple factors may converge to influence mineralization has yet to be reported.

METHODS:

To compare mineralization of human mesenchymal cell types known to differ in extracellular matrix calcification potency, bone marrow-derived mesenchymal stromal cells and dermal fibroblasts from neonatal and adult donors, at both low and high passages, were investigated in an ex vivo experimental model by supplementing the osteogenic induction medium with FBS or with hPL. Four commercial hPL preparations were profiled by liquid chromatography/electrospray ionization quadrupole time-of-flight spectrometry, and mineralization was visualized by von Kossa staining and quantified by morphometric evaluations after 9, 14 and 21 days of culture.

RESULTS:

Data demonstrate that (i) commercial hPL preparations differ according to mass spectra profiles, (ii) hPL variously influences mineral deposition depending on cell line and possibly on platelet product preparation methods, (iii) donor age modifies mineral deposition in the presence of the same hPL and (iv) reduced in vitro proliferative capacity affects osteogenic induction and response to hPL.

CONCLUSION:

Despite the standardized procedures applied to obtain commercial hPL, this study highlights the divergent effects of different preparations and emphasizes the importance of cellular ontology, donor age and cell proliferative capacity to optimize the osteogenic induction capabilities of mesenchymal stromal cells and design more effective cell-based therapeutic protocols.

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Mesenchymal stromal cells for tolerance induction in organ transplantation.

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Abstract

The primary challenge in organ transplantation continues to be the need to suppress the host immune system long-term to ensure prolonged allograft survival. Long-term non-specific immunosuppression can, however, result in life-threatening complications. Thus, efforts have been pursued to explore novel strategies that would allow minimization of maintenance immunosuppression, eventually leading to transplant tolerance. In this scenario, bone marrow-derived mesenchymal stromal cells (MSC), given their given unique immunomodulatory properties to skew the balance between regulatory and memory T cells, have emerged as potential candidates for cell-based therapy to promote immune tolerance. Here, we review our initial clinical experience with bone marrow-derived MSC in living-donor kidney transplant recipients and provide an overview of the available results of other clinical programs with MSC in kidney and liver transplantation, highlighting hurdles and successes of this innovative cell-based therapy.

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The inhibitory influence of adipose tissue-derived mesenchymal stem cell environment and Wnt antagonism on breast tumour cell lines.

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Abstract

Tumours exhibit a heterogeneous mix of cell types that reciprocally regulate their growth in the tumour stroma, considerably affecting the progression of the disease. Both adipose-derived mesenchymal stem cells and Wnt signalling pathway are vital in driving breast tumour growth. Hence, we examined the effect of secreted factors released by adipose-derived mesenchymal stem cells, and further explored the anti-tumour property of the Wnt antagonist secreted frizzled-related protein 4 (sFRP4) on MCF-7 and MDA-MB-231 breast tumour cells. We observed that conditioned medium and extracellular matrix derived from adipose-derived mesenchymal stem cells inhibited tumour viability. The inhibitory effect of the conditioned medium was retained within its low molecular weight and non-protein component. The conditioned medium also induced apoptosis accompanied by a decrease in the mitochondrial membrane potential in tumour cells, Furthermore, it downregulated the protein expression of active β-catenin and Cyclin D1, which are major target proteins of the Wnt signalling pathway, and reduced the expression of anti-apoptotic protein Bcl-xL. The combination of conditioned medium and sFRP4 further potentiated the effects, depending on the tumour cell line and experimental assay. We conclude that factors derived from conditioned medium of adipose-derived mesenchymal stem cells and sFRP4 significantly decreased the tumour cell viability and migration rates (MCF-7), accompanied with an

enhanced apoptotic activity through inhibition of canonical Wnt signalling. Besides giving an insight to possible paracrine interactions and influence of signalling pathways, reflective of a breast tumour microenvironment, this study emphasises the utilization of cell free-secreted factors and Wnt antagonists to improve conventional anti-cancer strategies.

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Exosome and mesenchymal stem cell cross-talk in the tumor microenvironment.

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Abstract

Mesenchymal stem cells (MSCs) are a major component of the tumor microenvironment (TME) and play a key role in promoting tumor progression. The tumor uses exosomes to co-opt MSCs and re-program their functional profile from normally trophic to pro-tumorigenic. These tumor-derived small vesicles called "TEX" carry and deliver a cargo rich in proteins and nucleic acids to MSCs. Upon interactions with surface receptors on MSCs and uptake of the exosome cargo by MSCs, molecular, transcriptional and translational changes occur that convert MSCs into producers of factors that are necessary for tumor growth and that also alter functions of non-tumor cells in the TME. The MSCs re-programmed by TEX become avid producers of their own exosomes that carry and deliver mRNA and miRNA species as well as molecular signals not only back to tumor cells, directly enhancing their growth, but also horizontally to fibroblasts, endothelial cells and immune cells in the TME, indirectly enhancing their pro-tumor functions. TEX-driven cross-talk of MSCs with immune cells blocks their anti-tumor activity and/or converts them into suppressor cells. MSCs re-programmed by TEX mediate pro-angiogenic activity and convert stromal cells into cancer-associated fibroblasts (CAFs). Although MSCs have a potential to exert anti-tumor activities, they largely provide service to the tumor using the multidirectional communication system established by exosomes in the TME. Future therapeutic options consider disruption of this complex vicious cycle by either molecular or gene-regulated silencing of pro-tumor effects mediated by MSCs in the TME.