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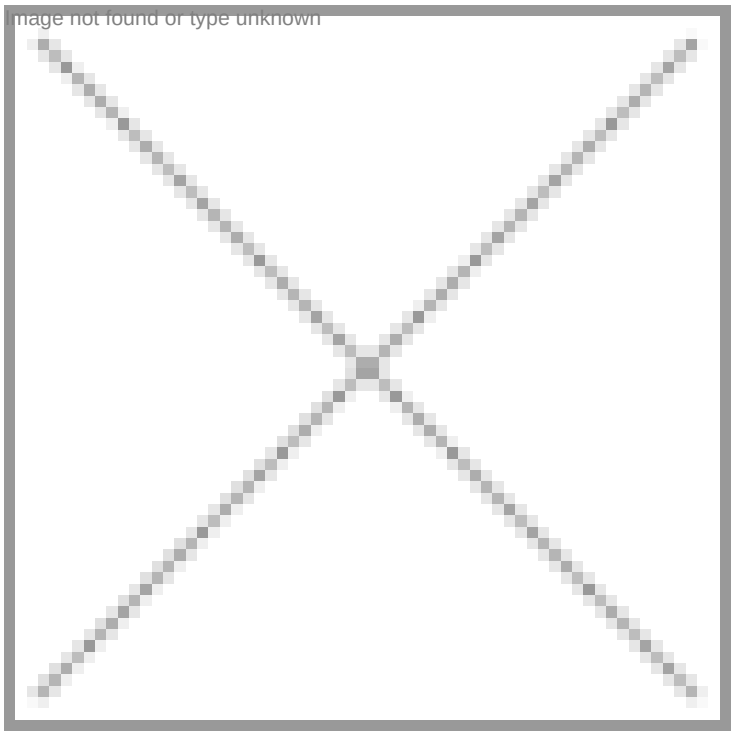
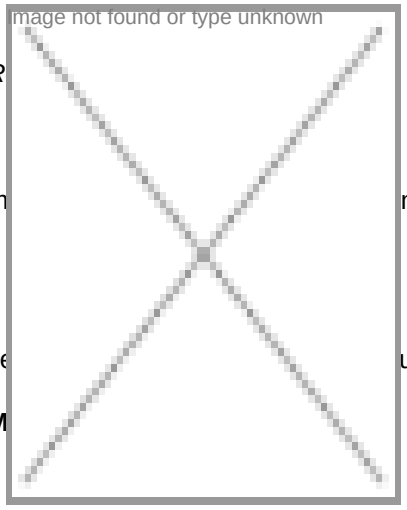


Mesenchymal Stem Cells, a Promising Tool for Regenerative Medicine



-Dr. Chandra Viswanathan, senior vice president, Regenerative Medicine Group, R

m ng the patient to health.

Regenerative medicine is a new way of treating diseases using human stem cell-based therapies. Unlike most molecular medicines for chronic conditions, regenerative

Stem cells are unspecialized 'master' cells in the human body having a unique capacity to multiply and differentiate into many types of specialized cells and tissues. Stem cells exist at all stages of human development from early embryos to fetuses to adults. In general, there are three types of stem cells: embryonic, fetal and adult. Embryonic stem

ce ue to face ethics related controversies.

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Mesenchymal stem cells (MSCs) are classically defined as CD34 negative, CD45 negative, SH2 and SH4 positive, and Thy-1 (CD90) positive cells. These are adult stem cells traditionally isolated from bone marrow (BM) aspirates. These are spindle-shaped, and during culture, adhere to plastic. These can be expanded in culture while maintaining their 'stemness'. These have the capacity to differentiate into a wide variety of mesenchymal tissues and also cross lineage boundaries. MSCs qualify to serve as a broadly applicable stem cell source for regenerative medicine, repopulating injured tissues and clinically ablated diseased tissues with healthy, terminally differentiated and tissue-specific cells. Thus, so far, several hundred patients have

received systemically and locally infused MSCs for various indications, and there are good observations made from those.
MSCs have the capacity to differentiate into mature cells and populate the resident tissue, giving them a therapeutic potential for regenerative medicine; secrete cytokines or other soluble mediators and serve as a vehicle for delivery of proteins i.e. gene therapy may be tried through one or more routes using different dosages.
Since the mid 1990s, the safety of MSCs has been established, after which there has been an effort to show that co-infusion of MSC could hasten the time for hematopoietic stem cell engraftment, since they could possibly rebuild the marrow micro-environment. More recently, the immunosuppressive capacity of MSC has taken center stage, but the mechanism is still under debate.
Literature review suggests that soluble factors released by the MSC are key elements in their mechanism of action for most, if not all, of the systemic effects. MSC secrete stromal derived factor-1 (SDF-1), which plays a critical role in the homing of haematopoietic stem cells to the marrow niche. In vitro, MSCs constitutively secrete several interleukins, macrophage colony-stimulating factor (M-CSF), Flt-3 ligand and stem cell factor. Upon IL-1? stimulation, MSC are induced to express further IL-1?, leukemia inhibitory factory (LIF), granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF) and several chemokine ligands.
MSCs are also thought to secrete biochemical mediators unrelated to the lymphohematopoietic system like the brain-derived neurotropic factor (BDNF) and nerve growth factor (?-NGF). Currently, the search for indescribed mediators generated by MSCs from several non-traditional sources like placenta, umbilical cord, fat tissue and so on is an active area of investigation and will probably reveal a new array of important signaling secreted molecules.
The isolation, culture expansion conditions and the tissue source of stem cells may significantly affect gene expression and therefore the bioactivity of the cells. Such conditions include the seeding density, culture media, serum supplementation, extent of ex vivo expansion etc. Furthermore, bioreactors in contrast to conventional plastic culture flasks may affect gene expression. These observations suggest that the cell-processing protocols can modify expression of specific genes to optimize the cytokine profile for a given clinical indication.

Observations so far

These observations suggest a new paradigm for the therapeutic application of MSCs. Systemically infused MSC exert a therapeutic effect primarily through the release of soluble mediators that act on local and possibly distant target tissues. Rather than serving as stem cells to repair tissues, they serve as cellular factories secreting mediators to stimulate the repair of tissues or modulate the local microenvironment to foster requisite beneficial effects. In the future, the lack of human leukocyte antigen (HLA) expression in certain MSC types may also allow allogenic usage applications.
MSCs can also serve as progenitors. For local therapy, such as in spinal cord injury, non-healing fractures etc. MSCs seem to differentiate into nerve, bone and muscle tissue to foster healing. They have also been reported to reduce the risk of graft failure after haplo-identical transplant. Similarly, pre-clinical models of MSC-based cell therapy for acute myocardial infarction, neuronal disease, injury such as stroke and autoimmune disorders appear very promising.

Summary

Secretion of soluble mediators seems to be the predominant mechanism of action of MSCs. We must demonstrate precise processing protocols that could generate populations of MSC especially suited for specific clinical indications from specific sources.
Another intriguing prospect for the future is the use of MSCs to create ‘off-the-shelf’ MSC banks. To fully harness the potential of these cells, future studies should be directed to ascertain their cellular and molecular characteristics for optimal identification, isolation and expansion, and to understand the natural, endogenous role(s) of MSCs in normal and abnormal tissue functions.
In this way, we will continue to move the field forward and, hopefully, the promise of MSCs to address unmet medical needs can be fully
realized.