Mesenchymal Stem Cells as a Source of Repair Cytokines: Mesenchymal Stem Cells as the Conductor

Martin J. Stoddart, PhD

Ever since the first description of mesenchymal stem, or stromal, cells (MSCs) in the 1960s, the focus of research has been on their potential to differentiate into multiple tissues, such as cartilage, bone, and adipose.[1] This has led to a vast body of work dedicated to their potential for tissue engineering or regenerative medicine in musculoskeletal applications. However, more recently a greater emphasis is being placed on the molecules they secrete, rather than their functional differentiation. A major question in MSC therapy revolves around how many cells actually survive implantation and become a functional part of the tissue. The survival of implanted cells is viewed with increasing doubt, and yet a benefit of cellular implantation is often seen. Over time it has become progressively clearer that the alternative mechanisms of MSC biology, such as the potential to regulate the immune system and to secrete soluble molecules that direct the behavior of resident endogenous cells, play a major role in the repair response generated. In these roles, the MSC can be more likened to the conductor, rather than the orchestra itself. This has led to Caplan and Correa[2] coining the phrase "medicinal stem cell," a cell that effectively acts like a growth factor factory or drugstore.

Evidence is growing that the cell secretome may actually be the main mechanism of action during cell-based therapies. The implanted cells produce several soluble mediators that initiate or enhance the healing response. The exact growth factors and cytokines being expressed by the cells have largely been unexplored, and the interest in determining which factors are produced is increasing dramatically.[3] Although the expression levels of the various factors are donor dependent, it has been shown that general levels of expression are greater than those of control fibroblasts.[4]

Recruitment factors, such as stem cell–derived factor-1, play an active role in attracting endogenous cells to the healing environment.[5] As the recruitment factors infiltrate the hematoma, MSCs are also able to modulate the immune response. Regulation of the immune system and control of inflammation by modulating macrophage phenotype are increasing in importance.[6] It is well accepted that an acute inflammation at the time of injury is required to initiate a healing response. However, the initial acute inflammation needs to recede to allow for the healing response to develop because chronic inflammation is inhibitory to healing. Anti-inflammatory factors, such as interleukin-10, are then secreted by the infiltrating cells.

The changing face of MSC biology offers new avenues for potential therapies. By enhancing the expression of cytokines that enhance the wound healing response, MSCs could be used to boost the endogenous response. It is interesting to note that different sources of MSCs have been shown to have different expression profiles, and this may influence the results obtained.[7] Using MSCs as a source of paracrine factors is also likely to require

From the AO Research Institute Davos, Davos, Switzerland.

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fewer cells than those strategies that implant MSCs as a source of potential new tissue-specific cells. To establish such therapies, newer culture models are needed to allow the study of naïve MSCs that would be present during a natural healing response rather than monolayer expanded cells, which behave differently.[8]

The intrinsic MSC secretome has been shown to be modified by inflammatory cytokines, such as interleukin-1β,[4] and this modification can be initiated after a relatively short, 2-hour stimulation, which is clinically relevant.[9] This finding offers potential mechanisms by which cell behavior can be tailored for specific healing environments by enhancing the secretory profile of the cells. Considering the regulatory requirements of minimally manipulative methods for using autologous cells, it remains to be seen whether ex vivo cell stimulation will be acceptable to the regulatory authorities. Because of the rapidly changing nature of the autologous cell field regulations, the onus should be on the research community to actively approach the regulators to devise a safety testing protocol that may finally allow such manipulations to be performed intraoperatively.

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References printed in **bold type** are those published within the past 5 years.

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