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Outside the Operating Room: Unlimited Directions in Research and Beyond

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ABSTRACT

The anesthesiologist's role often extends beyond the operating room and includes the realm of research. Recently, interest in investigating mesenchymal stem cells (MSCs) as therapy for myriad diseases has grown. MSCs are adult stem cells traditionally found in bone marrow that hone to damaged tissues and contribute to the tissues' repair by secreting chemokines, cytokines, and extracellular matrix proteins. Research has established a connection between the stimulation of specific Toll-like receptors and the immune-modulating responses of human MSCs, which allows for the polarization of MSCs into either a pro-inflammatory or an anti-inflammatory phenotype. It is anticipated that MSC-based therapies polarized into the anti-inflammatory phenotype will treat painful inflammatory diseases, such as diabetic peripheral neuropathy or rheumatoid arthritis. These new cell-based therapies will be another tool for anesthesiologists to employ while treating patients with chronic pain.

Anesthesiologists, whose first province is the operating room, are exploring new ways to apply their knowledge and expertise toward the advancement of healthcare. There are now Accreditation Council for Graduate Medical Education–accredited fellowships in critical care and pain management, as well as nonaccredited fellowships in perioperative care, research, informatics, and regional anesthesia. Strides are also being made in basic and clinical science, where the application of new therapies and techniques allows us to better care for our patients.

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Recently, interest in investigating mesenchymal stem cells (MSCs) as therapy for myriad diseases has grown. Mesenchymal stem cells are adult stem cells traditionally found in the bone marrow. However, MSCs can also be isolated from other tissues, including cord blood, peripheral blood, the fallopian tube, and fetal liver and lung. MSCs differentiate to form adipocytes, cartilage, bone, tendons, muscle, and skin under appropriate culture conditions.[1-4] They also offer the advantage that they are easily expanded and stored ex vivo and are considered to be immunoprivileged (once harvested, they can safely be infused into either autologous or allogeneic hosts owing to their lack of host immune reactivity).[2] These cells are prime targets for use in the development of new and innovative therapies for a wide variety of disease processes.

MSCs hone to damaged tissues and contribute to the tissues' repair by secreting chemokines, cytokines, and extracellular matrix proteins.[3,5] However, the precise molecular mechanisms governing stem cell fate, mobilization, and recruitment are not fully understood. Additionally, even though a clear clinical benefit is seen when MSCs have been used as therapeutic agents, few infused cells have been found at the target site.[2,6,7] This observation led to investigation of the local immune modulation capabilities of these cells as the source of the clinical benefits rather than differentiation or replacement of the damaged target tissue by the infused stem cells.

Recent research established a connection between the stimulation of specific Toll-like receptors (TLRs) and the immune-modulating responses of human MSCs.[8] Toll-like receptors, which are located on MSCs, recognize danger signals, and the activation of these receptors leads to profound cellular and systemic responses that mobilize innate and adaptive host immune cells.[9-13] The TLRs consist of a large family of evolutionarily conserved receptors (eg, TLR1-13). The danger signals that trigger TLRs are released after most tissue injuries. Exogenous danger signals typically released after microbial infections include endotoxin or lipopolysaccharide (LPS) shedding. Endogenous danger signals spilled into the circulation from aberrant or wounded cells are characterized by intracellular components like heat shock proteins or RNA. Typically, these danger signals that have been shed activate TLRs on sentinel innate immune cells

(eg, dendritic cells) and start an appropriate host response that reestablishes homeostasis.[9-12] Because danger signals recruit immune cells to injury sites, it was posited that MSCs might use the same mechanisms to find the tissues in need of repair.

Surprisingly, researchers have found that specific TLR agonist engagement drastically affects the capability of MSCs to migrate, invade, and secrete immune-modulating factors. In particular, TLR3 stimulation by polyinosinic:polycytidylic acid (poly I:C) leads to the secretion of factors with mostly immune-suppressive properties, while stimulation of TLR4 with LPS resulted in the secretion of more proinflammatory factors.[8] Further studies on TLRs and immune modulation by MSCs lent support to these concepts and built on initial observations that low-level, short-term stimulation with specific TLR3 and TLR4 agonists (poly I:C and LPS, respectively) mediates distinct immune-modulating responses by MSCs.[14]

Stimulation of monocytes with known cytokines or agonists to their TLRs, such as interferon-c and endotoxin (LPS, TLR4 agonist), polarizes them into a classical M1 phenotype that participates in early proinflammatory responses, while interleukin-4 treatment of monocytes yields the alternate M2 phenotype associated with later anti-inflammatory resolution responses.[15] A new aspect of MSC biology suggests that MSCs, like monocytes, are polarized by downstream TLR signaling into 2 homogenously acting phenotypes classified as MSC1 and MSC2, following the monocyte nomenclature. It has also been suggested that MSC polarization provides a convenient way to render these heterogeneous preparations of MSCs more uniform while introducing a new facet to study and also provides an important aspect to consider for the improvement of current stem cell–based therapies.[14] Therefore, the next step in research will be to examine the efficacy of polarized MSCs in inflammatory diseases.

Many human diseases are caused or exacerbated by inappropriate inflammation that is refractory to most current treatment protocols. Such diseases include arthritis, lupus, fibromyalgia, and diabetic peripheral neuropathy (DPN). As a cause of disability, inflammation affects more people than back pain, heart and lung conditions, diabetes, or cancer.[16] According to the Arthritis Foundation, inflammation is responsible for 427 million days of restricted activity, 156 million days in bed, and 45 million days lost from work each year. The economic impact is dramatic and costs the US economy at least $128 billion per year in medical care and lost wages. A recent report from the Centers for Disease Control and Prevention containing data from 2007-2009 showed that 22% of the adult population in our country has arthritis and 9% of the adult population has arthritis and arthritis-attributable activity limitations. These numbers are in line with previous predictions that arthritis cases would rise with the aging of the population.[17]

DPN is a complication of diabetes, estimated to be present in approximately 50% of the diabetic population. It costs the United States between $4.6 and $13.7 billion a year.[18] In patients with diabetes, it has been shown that low-grade inflammatory reactions are triggered secondary to the oxidative stress caused by the generation of reactive oxygen species.[19] Additionally, inflammatory markers are increased by the high levels of glucose, pointing to a chronic, low-grade inflammatory state in patients with the disease.[20-22]

Recently, stem cell–based therapies for inflammatory diseases have received significant attention. However, current methods for adult stem cell therapy use whole stem cell populations that may or may not behave in the manner intended by a physician. For example, because current methodologies infuse a mixed and undefined cell population into patients, the potential exists that some patients will receive a population of cells that has undergone differentiation cues and is only capable to fill in where bone cells are needed, while another patient may be infused with a mix of cells that solely directs anti-inflammatory behaviors or fat deposition. Thus, the problem is an inability to predict what behavior the infused mix of cells will have in the patient. As such, current stem cell therapies are used blindly.

Future research aims to establish new stem cell–based therapies that allow on-site repair of the aberrant inflammation in a manner that has not been possible previously. The idea that polarized MSC2 will quell overactive inflammation in DPN and rheumatoid arthritis, 2 chronic diseases that often require pain management, is currently being pursued. By transforming heterogeneous MSC preparations into uniform MSC preparations, MSCs will be programmed to repair inflammation as needed and restore the targeted diseased sites.[23] It is anticipated that polarized MSC-based therapies will readily treat both acute and chronic inflammatory diseases. Furthermore, because the treatments involve cells and not single agents, resistant diseases will not develop after multiple or long-term treatments. As mentioned above, MSCs are immunoprivileged and are not known or expected to elicit immune rejection mechanisms after multiple treatments. Finally, manipulation of TLRs is believed to be safe, as several US Food and Drug Administration–approved biologicals that target or manipulate TLRs have been used for many years without clinical consequence.

Research, whether basic or clinical, is a valuable endeavor for any physician. For anesthesiologists,

research presents an additional way to impact patient care that extends beyond the operating room.

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