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Cell-Mediated Pathologies in Traumatic Orthopaedic Injuries

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Physical trauma is one of the most common mechanisms leading to orthopaedic injury. The trauma and associated inflammatory response initiates the process of tissue regeneration and repair, which includes the recruitment and induction of multipotential cells to participate in the process. Too much inflammation can overwhelm this response to cause scarring. Although stem cells have been extensively studied as therapy for regenerating functional tissues, concerns of ethics, availability, and ease of clinical utility call for investigation into an alternative source of multipotential cells for potential therapeutic use. Here, we describe trauma-derived mesenchymal progenitor cells (MPCs). These cells are morphologically and functionally similar to bone marrow-derived mesenchymal stems cells. MPCs, which are not present in large numbers in untraumatized tissue, but are abundant in injured muscle tissue and after isolation have the potential for clinical application in regenerative medicine. MPCs appear to be activated by injury, enhancing their capability of differentiating into multiple cell lines, generating trophic factors, and producing functional tissue. This cell lineage is now thought to be involved in the pathologic process of heterotopic ossification, whereby inflammation and scarring dominates the local tissue response to injury. The utility of MPCs as a therapeutic arm for regenerative medicine can be further realized when the microenvironment commands that trigger these cells to activate are elucidated. This in turn can create patient-specific resource of nongenetically modified induced multipotent cells for regenerative therapy after orthopaedic injury.
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Introduction

The musculoskeletal system has an amazing ability to undergo an intense regenerative process in response to injury. Orthopaedic surgeons have capitalized on this regenerative potential and focus much of their efforts on restoring the physical and structural relationships of bone, tendon, ligaments, cartilage, and muscle so that the body can regenerate normal, functional tissues (Fig. 1). Central to this strategy is trauma, whereby normal tissue must be disrupted for a regenerative response to be triggered. The regenerative response first starts with an inflammatory cascade that accomplishes several key functions such as removal of injured tissue, recruitment or activation of regenerative progenitor cells, and production of trophic factors, both physical and biochemical that assist in the regenerative response.[1]

Although inflammation is a salient feature in the response to injury, it must be modulated so that it does not overwhelm the regenerative sequence. One of the key functions the recruited or activated progenitor cells is to modulate this inflammatory response, a critical step for normal tissue repair.[2] These cells also have the potential to provide trophic signals for tissue regeneration as well as terminally differentiate into the desired

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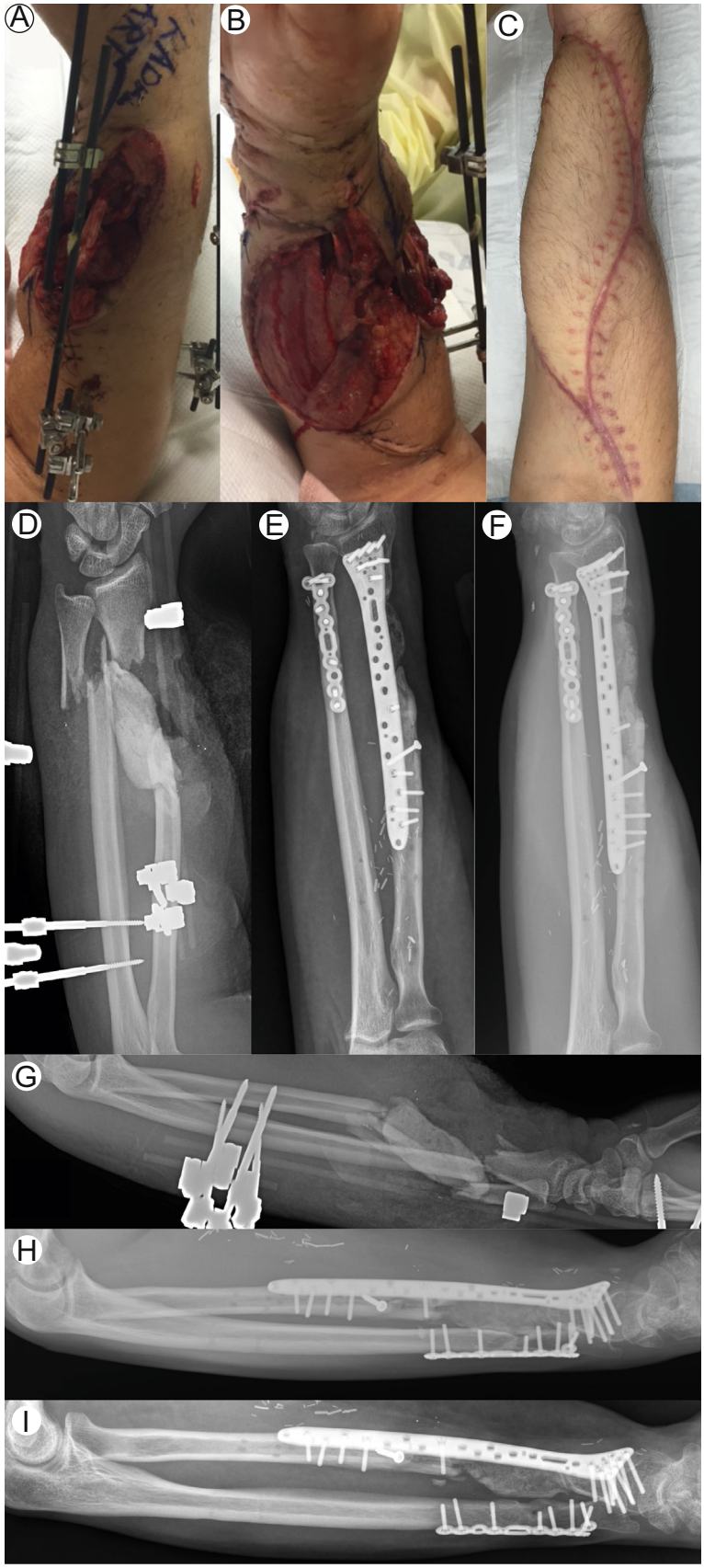

Figure 1 Orthopaedic trauma often encompasses a wide zone of injury that crosses many different tissue planes. This patient sustained a ballistic injury to the forearm with significant bone (D and G—segmental radius and ulna fractures) and soft tissue loss (A and B—segmental artery, nerve, muscle tendon, and skin loss). After revascularization, skeletal stabilization (E, F, H, and I), nerve grafting, and free flap coverage (C) the patient has demonstrated a remarkable amount of tissue regeneration and repair.