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PLATELET RICH PLASMA vs. MARROW CELL COMPOSITION Growth Factor Strategy vs. Cell Driven Therapy

PRP—A GROWTH FACTOR DRIVEN THERAPY

Platelet Rich Plasma (PRP) is a general term used for a biologic that is made from centrifuging venous whole blood to volume reduce plasma and red blood cells and thereby enriching the treating composition for platelets and white blood cells. The therapy targets the inflammatory phase of the healing cascade. (69) In younger patients with healthy red marrow, or in cases where the injury is minor, adding additional peripheral blood platelets and white blood cells to the clot, (PRP) and the resulting growth factors, beyond what aggregates at the wound bed naturally, can amplify the vasculogenic response. (54, 57, 74) The number of platelets and white blood cells in peripheral blood and their ability to home to sites of tissue damage and form a platelet fibrin clot does not diminish with age. The ability of one's body to mobilize marrow cells to the site of trauma in response to the cytokines released by blood cells in the wound diminishes greatly over time. (42, 44) In addition, age impacts the number of stem cells and the function of both peripheral blood mature cells and immature marrow cells. (42, 44)

In a stalled partially healed situation, starting a new healing cascade by introducing PRP into micro-wounds created by the PRP delivery needle, is often sufficient to create a corresponding vasculogenic response to complete the healing cascade. (45, 69, 74) Thus, PRP is a white blood cell and platelet dependent strategy. The additional growth factors from the exogenously added platelets and white cells, beyond what would naturally be present from cells that aggregate at the wound site, causes greater stem cell migration with a resulting transition from the inflammatory phase to the proliferation and remodelling phase of the healing cascade. (54, 57, 69) The 1) heightened age dependent inflammatory profile of blood sourced monocytes, macrophages, and neutrophils and their deleterious impact on the micro-environment of the wound bed and 2) the age dependent diminished vasculogenic capability of marrow, suggests that PRP may be a strategy better suited for healthy older patients with minor defects or younger patients. (39, 50, 56, 61, 69, 71, 81, 86, 88) Also, leukocyte depleted PRP (often referred to as pure PRP), may be better suited for patients that are older or otherwise have a heightened immune profile associated with such co-morbidities as obesity or diabetes. (32, 43, 45, 54, 61, 67, 70, 71)



TREATING COMPOSITIONS SOURCED FROM MARROW ASPIRATE—A CELL DRIVEN THERAPY

Marrow is a Cell Driven Strategy

Properly aspirating and appropriately administering marrow cells is significantly enhancing and exactly mimicking the body's natural healing process. In a hind limb ischemia animal model using aged animals of diminished vasculogenic capacity, mechanically mimicking the natural healing response through autologous transplantation has shown to have a statistically significant clinical benefit. (35, 42) Through cytokine release and cell-to-cell contact, bone marrow stem cells orchestrate the transition from inflammation to proliferation and remodelling. (9, 10, 13, 15, 16) Marrow based treating compositions are cell dose dependent and take advantage of marrow stem cells and complimentary cells ability to alter the type and function of local cells to create an immune driven cascade to transition and amplify the cellular inventory needed to complete the remodelling phase of the healing cascade. (50, 68, 78, 79, 80, 83)

Mechanically sourcing and placing the cells responsible for transitioning from the inflammatory to the proliferation phase, is often sufficient to complete the healing process. (66, 78, 79)

Dose Response of Marrow Cells

Critical to successful healing are adequate numbers of immature stem cells and complimentary cells that have migratory capability and whose growth factor profile can influence migrating and resident cells to move into a tissue proliferation and regeneration profile. (23, 24, 50, 78, 79) The growth factor profile of a biologic that has a greater proportion of cells from marrow is different from PRP that is made entirely from peripheral blood cells and platelets. (21) Hernigou et al in non-union and osteonecrosis demonstrated that clinical results were linked to the stem cell content of the graft as measured by CFU-f. (66, 78, 79) This correlation between the CFU-f content of the biologic and outcomes has been repeated by other groups. (5) Interestingly, in the Hernigou work, CFU-f was the only measured variable that rose to statistical significance; not total nucleated cells or platelets. (66, 78) This is consistent with bone marrow rescue therapy in oncology where the stem cell content of the graft, not the number of nucleated cells, is the driver of clinical success.

Through Cytokine Release and Cell-to-Cell Contact, Bone Marrow Stem Cells are the Quarterbacks of the Injury Site

The growth factor profile of cells from marrow is different than that produced by blood cells. (21, 33, 36, 80) Paracrine signalling to create synergistic interactions between cells in wound healing requires a coordinated interplay among cells, growth factors, and extracellular matrix proteins. (9, 10, 13, 14, 15, 16, 28, 46) MSC's have a substantial involvement in the initial stage of healing by controlling the fate of inflammation. (38, 39) By responding to changes in their environment, and using complex growth factor mediated signalling circuitry, MSC's organize site-specific regenerative responses. (9, 10, 13, 14, 15, 16, 28,



46, 80) Mature resident cells, under the influence of migrating stem cells, demonstrate a plasticity that allows them to make a significant contribution to the healing cascade. (46, 80) For example, MSCs modulate the phenotype of macrophages by inducing a shift from inflammatory M1 macrophages to anti-inflammatory M2 macrophages, thereby transitioning the wound healing cascade from inflammatory to proliferation and remodelling.

Complimentary Cells from Marrow

A diverse group of complimentary cells other than stem cells migrate to the source of hypoxia caused by trauma. Removing BMSC's (bone marrow stem cells) from their normal environment of complimentary cells reduces their capacity and that to achieve their maximal potential, BMSC's require direct physical contact with accessory cells. (26, 50) In a clinical setting, the bone forming capability of a full complement of cells was demonstrated to be superior to single cell suspensions of MSC alone. (57)



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