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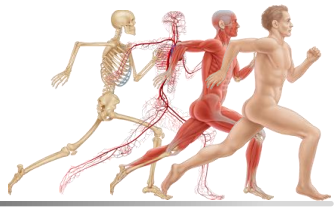
NEWSLETTER



12/2016

MARROW, BLOOD AND INFLAMMATION
The Healing Cascade

INTRODUCTION

When determining the optimal intervention, clinicians should consider a host of variables such as age, inflammatory profile, current medications, health history, and the biology of the micro-environment. Often one, or a combination of biologics, is considered to include PRP, bone marrow, fat or placental tissue. This paper summarizes the differences between PRP and marrow and highlights possible resulting clinical implications such as aspiration technique and centrifugation.

BACKGROUND: MARROW, BLOOD AND INFLAMMATION

Bone marrow cells reside deep inside bone cavities in the most protected part of the body and are redundant throughout the organism. (68) This preferential status reflects the primary role these cells play in the survival of the organism. Trauma initiates the inflammatory phase of the healing cascade and causes the up regulation of the cytokines SDF-1, ATP, and VEGF released from platelets and inflammatory peripheral blood cells that participate in the formation of and migrate into the clot. (17,18,25,29,31,50,55,57) These inflammatory cytokines are what primarily stimulate stem cell migration from marrow into the vasculature where these mobilized cells aggregate themselves into the recently damaged tissue (i.e vasculogenesis) (55,58,59,60) Tissue repair is a dynamic self-organizing process that relies on marrow stem cell and marrow complimentary cell mediated vasculogenesis, cell-to-cell contact between marrow cells, cell mobility and growth factor production. Trauma and the resulting tissue and cellular damage creates a hypoxic environment. (19) Unlike mature cells, immature marrow cells function and thrive in areas of hypoxia. (19,27,52) Once resident, marrow stem cells orchestrate the transition from the inflammatory phase of the healing cascade to the proliferation and remodeling phase. (19,27) Mobilization of stem cells from the marrow space through the process of vasculogenesis is positively correlated with better clinical outcomes. (53)

HEALING CASCADE

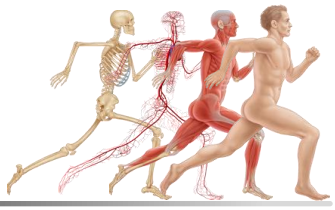
The combination of Scaffold, Cells, and Signals sets the Environment for the Healing Cascade

Aspire Medical Innovation GmbH
Prinzregentenhof
Einsteinstraße 167
D-81611 München

T: +49 (0)89 443844-10
F: +49 (0)89 443844-11
E: info@aspire-medical.eu
W: www.aspire-medical.eu

Geschäftsführer/CEO: Scott Shea
Amtsgericht München
HRB 220207
USt-Id Nr.: DE 302 148 636

Commerzbank AG, München
BLZ: 700 400 48 · Konto: 735096000
IBAN: DE12 7004 0048 0735 0960 00
BIC: COBADEFFXXX



Generally, a combination of a functional matrix, living cells, and growth factors produced by those living cells are required for tissue regeneration. The evolving types and amounts of growth factors produced by cells during the regeneration process drives the changing micro-environment during the healing cascade progression. (12,37)

Healing Cascade:

5-10 min post injury

HAEMOSTATSIS

- Flushing
- Vasoconstriction
- Platelet Aggregation
- Coagulation

48 hr post injury

INFLAMMATION

Early Phase

- Neutrophil arrival
- Pioneering

Late Phase

- Monocyte- macrophage

3-10 days post injury

PROLIFERATION

Re-epithelialisation

- Keratinocyte migration

Angiogenesis

- Sprouting
- Endothelial migration

Granulation tissue

- Fibroblast migration
- Fibrin-collagen GT
- Glycosaminoglycans
  Proteoglycans

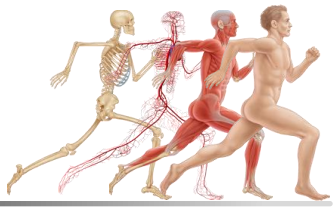
21 days post injury

REMODELLING

- Apoptosis
- Collagen III-I
- Matrix-metalloproteinase activity

Platelets and Cells from Peripheral Blood Initiate the Inflammatory Process of the Healing Cascade

Normal physiologic wound healing undergoes three overlapping phases 1) hemostasis and inflammation, 2) proliferation and 3) remodelling. Trauma causes peripheral blood platelets, white cells, and granulocytes to migrate by chemotaxis to the injury, form a platelet fibrin clot to end bleeding, and start the beginning inflammatory stage of the healing cascade. (12,38) CD184, also known as CXCR4, is widely expressed on peripheral blood cells, including B and T cells, monocytes, macrophages, dendritic cells, granulocytes,



platelets, lymphoid, myeloid precursor cells, endothelial progenitor cells and mature endothelial cells. (12,31,77) Similar to marrow stem cells, CD184 is the receptor for CXC chemokine SDF-1. Granulocytes, which include neutrophils, are important inflammatory cells for fighting infection and removal of cellular debris. (12) Their activities in the wound bed can cause cell death. (12) Inflammatory blood cells release cytokines in response to the hypoxic condition of the wound (i.e. HIF-1) that act as a signal for marrow stem cells to migrate to the area. (12,27) Once resident, these stem cells drive the remodelling and regeneration phases of the healing cascade. (9,27,46)

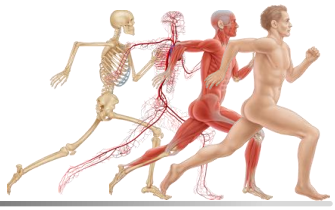
Immune System Stem Cells and the Transition of The Healing Cascade from the Inflammatory Phase to the Proliferation and Remodelling Phase.

At different stages of healing, immune system driven inflammatory and anti-inflammatory states are driven by cytokines that are variably expressed by resident and migratory cells. (11,12,34) A local increase in immune regulatory cells is required for suppression of the initial inflammatory response to begin the proliferation and remodelling phase. (14,22)

Regulatory immune cells at the site of injury are generated in response to contact with mesenchymal stem cells. (MSC's) (9,10,11,14) MSC's actively maintain a hypoimmunogenic state through the production of immunosuppressive paracrine factors or through direct cell-to-cell contact on immune cell populations, including t-cells and macrophages. (13,16,28,41,46) Such induced immune regulatory cells accumulate and converge their regulatory pathways to halt the inflammatory process. (15) MSC's impart immune tolerance through the early stages of remodelling and provide protection to the developing tissue by up-regulating t-regulatory cells (T-Regs) while suppressing inflammation. (20,83) T-Regs attenuate the accumulation of M1 pro inflammatory macrophages while up regulating the production of M2 anti-inflammatory macrophages along with tissue specific growth factors. (46,80)

CHRONIC CONDITIONS AND AGE

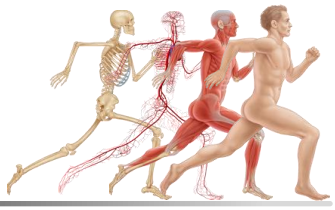
Successful repair after tissue injury requires resolution of the inflammatory response. (38) Different in-vitro and in-vivo studies have reported conflicting results regarding the use of blood sourced platelets and white cells for tissue regeneration. (32,63, 64, 67, 69,70) Controlling for platelet content of the biologic, certain research has demonstrated that leukocytes and their related growth factors contribute significantly to tissue regeneration while other research has documented the excess inflammation caused by the leukocytes hampered tissue regeneration. (32, 69) However, a consistent theme in the literature is the age-related increase in low-grade systemic inflammation defined as inflammation. (39,81,82) Blood monocyte changes with age result in a different survival profile and a shift towards a pro-inflammatory



phenotype and reduced function. (39,81) These age altered peripheral blood monocytes and macrophages from the innate immune system contribute significantly to inflammation through production of inflammatory cytokines and prolongation of the immune response to tissue injury. (39,46,81) The peripheral blood of older people has significantly larger proportion of inflammatory CD16+ cells than younger people. (82) Furthermore, the CD16+ population have increased adherence and migrate towards endothelial lesions via CX3CR1. (82)

In addition, the age of the actual cell in the blood impacts its inflammatory profile with aged neutrophils from peripheral blood having a significantly higher inflammatory profile than young neutrophils from marrow. (84,85) Neutrophils have been implicated in both driving tissue regeneration as well as mediating the tissue damage associated with a variety of chronic inflammatory diseases. (63,84,85) The abundant presence of neutrophils at the wound site corresponds to the elevated levels of proteolytic enzymes found in non-healing tissue. (86) Unbalanced proteolytic activity is a primary feature of non-healing wounds.(86) Mediators that are crucial for repair become targets of wound proteases that contribute to the overwhelming of local tissue protective mechanisms. (86) For example, growth factors pivotal for repair such as platelet-derived growth factor or vascular endothelial growth factor are targets of wound proteases, and they are inactivated by proteolytic cleavage. (86) The combination of a shift toward an inflammatory profile of blood monocytes combined with the action of neutrophils contributes to a diminishment of the body's tissue regeneration capability that correlates directly with age. (81,84,85,86) Autophagy is a cellular housekeeping mechanism that is responsible for the removal of neutrophils and dysfunctional intracellular proteins (for example, dead organelles, damaged scaffold proteins).

Efficient autophagy prevents excess stimulation of the inflammatory response by eliminating proteins that occur as a consequence of either tissue injury or necrosis. (76) Macrophages from older patients have significantly impaired autophagy capability that exacerbates the inflammation phase of the healing cascade. (40,81) However, marrow sourced macrophages retain their phagocytosis capability despite age which assists in removing neutrophils and inflammatory debris and transition the wound into the proliferation and re-modelling phase. (40,80) The above research suggests that in older patients, increasing the ratio of anti- inflammatory marrow cells to inflammatory peripheral blood cells in a treating biologic is desirable. Cells capable of forming a CFU-f or megakaryocytes are found in marrow but not peripheral blood. (71) Thus, a high CFU-f or megakaryocyte count to total nucleated cell count, often reported as the number of CFU-f per million cells, will be correlated to a higher ratio of marrow cells to peripheral blood cells. (66,78,79) This ratio may be more meaningful than the overall number of cells in a treating biologic.



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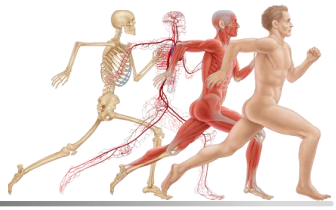

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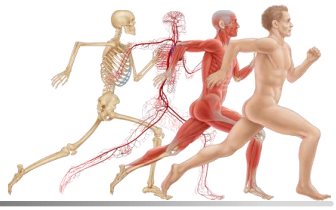

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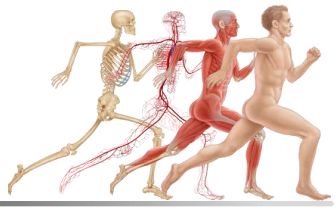
Aspire Medical Innovation GmbH
Prinzregentenhof
Einsteinstraße 167
D-81611 München

T: +49 (0)89 443844-10
F: +49 (0)89 443844-11
E: info@aspire-medical.eu
W: www.aspire-medical.eu

Geschäftsführer/CEO: Scott Shea
Amtsgericht München
HRB 220207
USt-Id Nr.: DE 302 148 636

Commerzbank AG, München
BLZ: 700 400 48 · Konto: 735096000
IBAN: DE12 7004 0048 0735 0960 00
BIC: COBADEFFXXX



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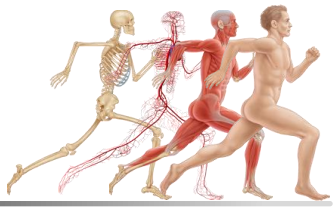
Aspire Medical Innovation GmbH
Prinzregentenhof
Einsteinstraße 167
D-81611 München

T: +49 (0)89 443844-10
F: +49 (0)89 443844-11
E: info@aspire-medical.eu
W: www.aspire-medical.eu

Geschäftsführer/CEO: Scott Shea
Amtsgericht München
HRB 220207
USt-Id Nr.: DE 302 148 636

Commerzbank AG, München
BLZ: 700 400 48 · Konto: 735096000
IBAN: DE12 7004 0048 0735 0960 00
BIC: COBADEFFXXX



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Address correspondence and reprint requests to: info@aspire-medical.eu