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Review Article

Monocyte: Truly a Multi-purpose Magical Cell

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Abstract

Monocytes are classically defined as circulating blood cells that constitute approximately 10% of peripheral leukocytes in humans. Monocytes are progenitor cells that lead the inflammatory cascade reaction responsible for guiding revascularization and regeneration of tissue at injury sites. They do this by secreting inductive cytokines responsible for endothelial cell migration. When released into the peripheral blood, monocytes enter tissues and become macrophages. Monocytes also trigger the body's defense mechanism against microbial invasion by lysing and removing cell debris and dead tissue.

Key words: Monocytes, Macrophages, Progenitor cells

Introduction

Monocytes constitute 5% to 10% of the white blood cells in the peripheral blood.[1] In the blood, individual monocytes typically remain viable for 1 to 3 days.[2] Within the bone marrow, monocytes make up approximately 2% of the mononuclear cells and are the largest of the phagocytic cells, ranging in size between 12 and 20 µm.

Monocytes derive from undifferentiated pluripotent progenitor stem cells found in bone marrow that are positive for CD34+ markers. These stem cells give rise to cells with a lymphoid or myeloid progenitor lineage. Lymphoid cells differentiate to T and B cells. Myeloid progenitor cells differentiate to monoblasts and promonocytes.[3]

By the action of granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and interleukin-3, monoblasts

differentiate to monocytes circulating in the blood. Circulating monocytes can enter into tissues to become macro- phages, which can survive for months.

Macrophages have 2 main functions: [4–7]

1. They replenish tissue-resident macrophages and dendritic cells.

2. In response to inflammation signals, they move quickly (within 8-12 hours) to infected sites. They migrate to inflamed tissue after the incursion of neutrophils (polymorphic nucleated cells).

The large kidney-shaped nuclei of monocytes contain 2 to 3 nucleoli and can fuse together to form multinucleated giant cells that engulf large foreign bodies during the process of endocytosis. Macrophages have the ability to adapt to local environments through phenotypic alterations. They assume tissue-specific properties that affect their functions, transforming, for example, into alveolar macrophages in lungs, Kupffer cells in the liver, peritoneal macrophages, synovial type A cells in joints, Langerhans cells in skin, microglia in the central nervous system, and multinucleated giant cells (osteoclasts) in bone. All of these cells are components of the reticulo-endothelial system.[8] In their immature state, they can differentiate to smooth muscle cells, fibroblasts, and osteoblasts.[9-11]

The ability of monocytes and macrophages functionally to change their phenotype and cellular expression and adapt to alternative microenvironments makes them available to respond to tissue damage, hypoxia, and/or infection. Their plasticity is initiated by exposure to various factors such as cytokines, chemokines, and hormones. In contrast, well-differentiated cells such as mature osteoblasts and mature dendritic cells lack the ability to alter their phenotype expression.[12,13]

Monocytes and macrophages are involved in tissue healing and regeneration by contributing to the following biologic functions:

Wound healing

The presence of monocytes and macrophages is crucial and mandatory for undisturbed wound healing as they play a key role in reducing inflammation of ischemic tissue, chronic inflammation, and tumor growth.[14,15]

Tissue injury and hypoxia (decreased oxygen tension) are the signals that attract monocytes to injury sites.[16] The decreased oxygen gradient stimulates them to move toward the hypoxic area.[17,18] In the early phases of inflammation, monocytes are recruited to the inflamed tissue from the blood through the orchestrated sequential interactions between them and GM-CSF chemokine, a small protein produced by endothelial cells, leukocytes, or stromal cells. Monocytes then extravagate through the wall of the blood vessel into the tissue to become macrophages.[19,20]

Phagocytosis

Monocytes and macrophages within tissues produce cytokines that lead to early inflammation, cell lyses, and phagocytosis of the debris.[21-23] They are programmed to defend against invading microorganisms by microbial control (cytotoxicity). They look for and ingest foreign substances in the extracellular matrix between cells, and digest the debris of damaged or dead cells. They perform phagocytosis by first using opsonizing proteins that coat the pathogens. They are also capable of killing infected host cells by antibody-mediated cellular cytotoxicity. Once activated by an antigen, they travel to the lymph nodes where they activate T and B cells to initiate and shape the adaptive immune response.

Angiogenesis

Monocyte activation promotes angiogenesis and arteriogenesis, a requirement for ischemic tissue repair.[18,24-31] Cytokines such as vascular endothelial growth factor[32], angiopoietin[33] and GM- CSF[28,34,35] initiate this process and mobilize endothelial and other cells. The new blood vessels then deliver cells, nutrients,

and oxygen to the site and remove noxious substrates. Angiogenesis occurs when new capillaries are formed from existing blood vessels.

Immunologic activity

Macrophages are the primary players in the immune response to injury. They arrive quickly at injury sites, removing toxic debris, and releasing cytokines that induce the recruitment of more lymphocytes. In addition to becoming macrophages when they leave the circulation, monocytes also become myeloid dendritic cells in the tissue. Dendritic cells are potent in stimulating, initiating, and shaping the adaptive immune response. The activated dendrites and lymphocytes secrete more cytokines and growth factors, amplifying effects on tissue survival and regeneration.[36] Interferon-γ, the main cytokine secreted by activated T cells, plays a central role in the antigen-presenting cells' amplification effect.

Cell Regulation

The immediate reaction to a tissue injury such as an incision, reflection of a mucoperiosteal flap, or bone-site preparation or to other stimulation by bacteria, viruses, fungi, mechanical injury, toxic inducers, or hypoxia is an influx of neutrophils and migration of monocytes that serve as a source of a multitude of cytokines. [37,38]

The interplay between cytokines, growth factors, and other factors will dictate the lineage committed and the apoptosis of the target cells.[39-66]

Granulocyte and granulocyte macrophage colony stimulating factor (G-CSF and GM-CSF)

It is secreted by monocytes and macrophages and their target cells are endothelial cells, hematopoietic stem cells (HSC), monocytes, macrophages and Neutrophils. G-CSF and GM-CSF regulate a lot of biological functions like:

- Angiogenic activities
- Hematopoietic effect
- Mobilization of Hematopoietic stem cells
- Activation of quiescent Hematopoietic stem cells
- Acts as a mitogen, morphogen
- Enhancing the survival of endothelial cells
- Maintain steady state of neutrophils

Transforming growth factor-α (TGF-α and β)

It is secreted by activated macrophages and target cells are endothelial cells, mesenchymal stem cells, osteoblasts and osteoclasts. Biological effects of TGF-α and β includes:

- Mitogen for endothelial cells
- Angiogenic effect: Mesenchymal Stem Cell differentiation
- Increase in Bone formation.
- Increase in Woven bone formation and matrix synthesis.
- Chemotaxis for osteoblasts stimulates angiogenesis.
- Increase in Endothelial cell mobilization
- Decrease in Osteoclast effect

Insulin-like growth factor I

It is secreted by activated macrophages and target cells for this growth factor are endothelial cells. Biological effects include enhancement of chemotaxis and angiogenesis. It also plays an important role in enhancing the vessel formation.

Platelets derived growth factor (PDGF)

It is secreted by activated monocytes and target cells include endothelial cells, mesenchymal stem cells and

macrophages or hematopoietic stem cells. It acts directly on endothelial cells enhancing capillary formation. It also acts as a chemo attractant and mitogen for mesenchymal stem cells. It also plays an important role in activating macrophages and increasing the proliferation and migration of stem cells.

Vascular endothelial growth factor (VEGF)

It is secreted by activated macrophages and target cells are endothelial cells. It induces Angiogenic effect and act as a mitogen for endothelial cells. Permeability of vasculature is increased by action of VEGF.

Interleukin- 1, 3, 6, 8 (IL-1, 3, 6, 8)

These cytokines are secreted by activated macrophages and mainly acting on endothelial cells. They play an important role in chemotaxis and induce proliferation of endothelial cells. It increases differentiation of cells to osteoclasts and proliferation of hematopoietic stem cells.

Substance P

It is secreted by activated macrophages and target cells are endothelial cells. Substance P stimulates migration and proliferation of endothelial cells. It also helps in inducing neovascularization during tissue repair.

Macrophage-derived Angiogenic factors

It is secreted by activated macrophages and target cells are endothelial cells. It acts as a chemotactic agent and mitogen changes in the extracellular matrix.

Prostaglandins

Prostaglandins are secreted from activated monocytes and macrophages and act on endothelial cells. Major role of prostaglandins include inducing angiogenesis and neovascularization.

Monocyte chemotactic protein-1 (MCP-1)

Macrophages and endothelial cells secrete MCP-1 and target cells are monocytes. It helps in recruiting monocytes to inflammation site by attachment to endothelial cells and they also create inflammatory reaction to build arterioles.

Tissue regeneration

Tissue regeneration is the goal and end result of inflammation, and neovascularization is part of that process. Two of the cell types that are most important for new vessel formation are endothelial cells and pericytes. Monocytes and macrophages can transdifferentiate into endothelial cells to form blood vessels directly or they can become pericytes.[21,23,26,67-70] Endothelial cells initiate new vessel- tube formation. Pericytes may arise from endothelial cells or bone marrow [71,72] and are present adjacent to endothelial cells in basal lamina on the abluminal surface of newly formed blood vessels. They encircle blood vessels in tissue and periosteum.

Conclusion

Monocytes seem to be the super cells that are involved throughout the process of bone regeneration. They may remain at injury sites for days or years, constantly secreting growth factors necessary for regeneration. This contrasts with current regenerative approaches that use short-lived growth factors such as platelets-derived growth factors or bone morphogenetic proteins obtained from various technologies. From the first few hours of grafting, when the hypoxic environment causes them to migrate to the site, monocytes kill bacteria, remove debris, activate the immune system to amplify their effects, secrete growth factors such as PDGF and GM-CSF to induce blood-vessel formation, and cause the release of stem cells from the bone marrow that

come to the site to regenerate bone. In bone, monocytes can fuse to form osteoclasts that resorb debris and remodel the bone.

As monocytes and macrophages are abundant and easily harvested from autologous or allogenic sources, they provoke no legal or ethical concerns, unlike embryonic stem cells. They thus are an attractive source for cell-based therapy and research.

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