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REVIEW

Monocyte and Macrophage Plasticity in Tissue Repair and Regeneration

Amitava Das, Mithun Sinha, Soma Datta, Motaz Abas, Scott Chaffee, Chandan K. Sen, and Sashwati Roy

From the Department of Surgery, Davis Heart and Lung Research Institute, Center for Regenerative Medicine and Cell Based Therapies and Comprehensive Wound Center, The Ohio State University Wexner Medical Center, Columbus, Ohio

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Address correspondence to Sashwati Roy, Ph.D., The Ohio State University Medical Center, 473 W 12th Ave, 511 Davis Heart and Lung Research Institute, Columbus, OH 43210. E-mail: sashwati.roy@osumc.edu.

Heterogeneity and high versatility are the characteristic features of the cells of monocyte-macrophage lineage. The mononuclear phagocyte system, derived from the bone marrow progenitor cells, is primarily composed of monocytes, macrophages, and dendritic cells. In regenerative tissues, a central role of monocyte-derived macrophages and paracrine factors secreted by these cells is indisputable. Macrophages are highly plastic cells. On the basis of environmental cues and molecular mediators, these cells differentiate to proinflammatory type I macrophage (M1) or anti-inflammatory or proreparative type II macrophage (M2) phenotypes and transdifferentiate into other cell types. Given a central role in tissue repair and regeneration, the review focuses on the heterogeneity of monocytes and macrophages with current known mechanisms of differentiation and plasticity, including microenvironmental cues and molecular mediators, such as noncoding RNAs. *(Am J Pathol 2015, 185: 2596–2606; http://dx.doi.org/10.1016/j.ajpath.2015.06.001)*

The concept of cell plasticity originated from the ability of adult stem cells to differentiate into multiple cell types. Heterogeneity and plasticity are the characteristic features of the cells of the monocyte-macrophage lineage.[1] In response to the cues from local milieu, these cells have the ability to undergo phenotypic/functional switch. In addition to switching between polarization states, these cells may transdifferentiate into endothelial or other cells *in vitro* and *in vivo*. In the current review, we focus on the heterogeneity and plasticity of monocytes and macrophages. The plasticity of macrophages plays a decisive role in tissue repair and regeneration. Herein, we discuss the current known mechanisms, including the roles of microenvironmental cues and molecular mediators, such as noncoding RNAs, underlying the plasticity and differentiation of macrophages in tissue repair and regeneration.

Mononuclear Phagocyte System

The mononuclear phagocyte system (MPS), originating from bone marrow progenitor cells, is composed of monocytes, macrophages, and dendritic cells (DCs), with phenotypic and functional overlaps between these cells.[2] These cells differentiate and enter the systemic circulation to form monocytes, and then infiltrate into tissues to become macrophages.[3] The other cells of the MPS (ie, DCs and macrophages) also have a remarkable heterogeneity related to their origin, phenotype, tissue localization, proliferative potential, and functions.[1,4] Cells of MPS display plasticity in their gene expression patterns, thus identification based upon surface markers is often challenging.[5] Activating the cells of the MPS by macrophage colony stimulating factor (MCSF)-1 and IL-34 results in proliferation as well as differentiation of these cells.[6] The differentiation of DCs from hematopoietic stem and progenitor cells may occur inside extramedullary tissues.[7]

Monocyte Origin, Function, and Heterogeneity

Monocytes correspond to 10% or 4% of leukocytes in human or murine blood, respectively. In addition to playing a critical

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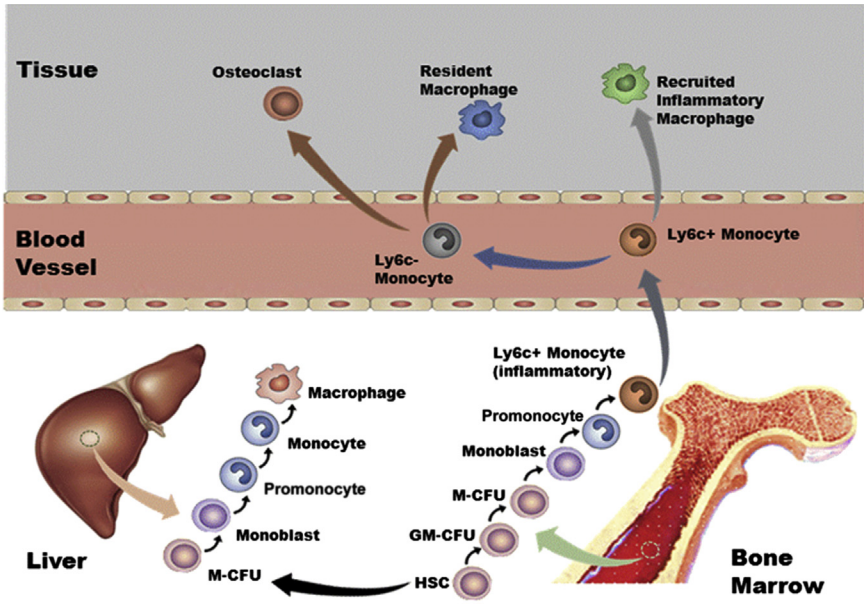

Figure 1 Origin and development of the mononuclear phagocyte system. Hematopoietic stem cells (HSCs) in fetal liver or adult bone marrow develop into a progenitor of both macrophages and granulocytes. The granulocyte-macrophage colony-forming unit (GM-CFU) population can commit to the macrophage colony-forming unit (M-CFU) or the granulocyte CFU group of cells. Before becoming macrophages, the M-CFU differentiates into monoblasts, promonocytes, and mature monocytes. This process requires the growth factor colony-stimulating factor-1. In mice, Ly6C is a marker for an inflammatory population of monocytes. In humans, the corresponding marker is CD16.

role in development, homeostasis, and inflammation, they are also responsible for the removal of apoptotic and necrotic cells.[8] The monocytes originate from hematopoietic stem cell (HSC) monoblasts that differentiate to promonocytes and then to mature monocytes. (Figure 1).[9] A clear understanding of monocyte heterogeneity is lacking, but it is suggested that monocytes mature in the blood and then get recruited to injury sites. The point at which these cells start their journey from blood may define their functions.[10]

In mice, two populations of monocytes have been identified and named as inflammatory and patrolling monocytes, depending on the time they spend in the blood before migrating to tissues.[11] The Nomeclature Committee of the International Union of Immunologic Societies (Berlin, Germany) has recently approved a new nomenclature of monocytes in humans. According to this new system, the monocyte population has been divided into three subsets: i) the major, or classical, population of human monocytes (90%) with high CD14 but no CD16 expression ($CD14^+CD16^-$); ii) the intermediate subset ($CD14^+CD16^+$), and iii) the low CD14- but high CD16-expressing or nonclassical subset ($CD14^{dim}CD16^+$).[12] Human classical and intermediate monocyte subsets that display inflammatory properties are referred to as inflammatory monocytes whereas the nonclassical monocyte subset demonstrates crawling or patrolling behavior along blood vessel walls. These cells are known to respond to viral infection. The plasticity of the inflammatory monocytes enables them to alter their phenotype based on the environment and/or the immune responses elicited after exposure to a particular pathogen.[13]

Although contentious, inflammatory monocytes have been reported to produce patrolling monocytes in the blood or bone marrow.[13] A rare subset of monocytes is known to express TIE2, the receptor for angiopoietins, and is therefore termed TIE2-expressing monocytes.[14] The TIE2-expressing monocytes and intermediate ($CD14^+CD16^+$) subsets of monocytes with high angiogenic potential have been associated with liver regeneration.[14] Another example of involvement of monocytes in tissue regeneration is based on the observation that the osteoclasts of the regenerating salamander limb form by fusion of monocytes.[15] These studies suggest involvement of specific subsets of monocytes in the tissue regeneration process.

DC Origin, Function, and Heterogeneity

DCs are essential mediators of innate and adaptive immune responses.[16] The function and phenotypes of dendritic cells subsets remains to be elucidated.[16] Relative to other cells of the MPS, our understanding of the molecular mechanisms that regulate the development of DCs is limited. DCs are composed of distinct subsets for which precise functions and interrelationships remain to be elucidated. The advances in establishing classic DCs as a distinct lineage among myeloid cells and their function *in vivo* have been recently reviewed.[16] Because of relative rarity and phenotypic similarity to other cells of the MPS, their role in wound healing is not well described. Among DCs, the plasmacytoid DCs, which are normally not found in healthy skin, have been shown to rapidly infiltrate skin wounds with quick kinetics, similar to that of neutrophils.[17] Whether such infiltration of plasmacytoid DCs into wounds is a general occurrence or is associated with conditions such as infection, remains to be tested. Plasmacytoid DCs, a rare population of circulating cells, produce high quantities of type I interferons (IFN) when exposed to viral infections.[18]

Macrophages

Origin, Functions, and Steady-State Tissue Distribution

Considered to be important immune effector cells of the innate immune system, macrophages not only provide the