Over the past 2 decades, many research laboratories have investigated monocyte/macrophage biology in relation to atherosclerosis and its complications.\textsuperscript{1–3} Atherosclerotic lesions contain a large number of inflammatory cells such as lipid-laden macrophages and dendritic cells, both of which are derived from monocytes.\textsuperscript{1–3} Recently, the diversity and plasticity of monocyte-macrophage-dendritic cell lineages have received much attention. In 1988, Ziegler-Heitbrock et al reported a population of monocytes that coexpressed CD14 and CD16 antigens.\textsuperscript{4} To date, monocytes have been divided into phenotypically distinct subsets, namely Ly-6C\textsuperscript{high} (Gr-1\textsuperscript{+}) and Ly-6C\textsuperscript{low} (Gr-1\textsuperscript{−}) monocytes in mice and classical (CD14\textsuperscript{high}CD16\textsuperscript{−}), intermediate (CD14\textsuperscript{+}CD16\textsuperscript{+}), and nonclassical (CD14\textsuperscript{dim}CD16\textsuperscript{+}) monocytes in humans. CCR, C-C motif chemokine receptor; CX3CR, C-X3-C motif chemokine receptor; MCP, monocyte chemotactic protein; IL, interleukin; TNF, tumor necrosis factor; RA, receptor antagonist.

**Figure.** Monocyte subsets in humans and mice. Monocytes have been divided into Ly-6C\textsuperscript{high} (Gr-1\textsuperscript{+}) and Ly-6C\textsuperscript{low} (Gr-1\textsuperscript{−}) monocytes as subsets in mice and classical (CD14\textsuperscript{high}CD16\textsuperscript{−}), intermediate (CD14\textsuperscript{+}CD16\textsuperscript{+}), and nonclassical (CD14\textsuperscript{dim}CD16\textsuperscript{+}) monocytes in humans. CCR, C-C motif chemokine receptor; CX3CR, C-X3-C motif chemokine receptor; MCP, monocyte chemotactic protein; IL, interleukin; TNF, tumor necrosis factor; RA, receptor antagonist.

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intermediate (CD14⁺CD16⁺), and nonclassical (CD14dimCD16⁺) monocytes in humans (Figure). The Ly-6C antigen is a glycosylphosphatidylinositol-anchored molecule expressed in monocytes, granulocytes, natural killer cells, and some dendritic cells. Ly-6Chigh monocytes adhere to the injured endothelium, migrate into the subendothelial space, and become macrophages in cholesterol-fed apolipoprotein E knockout mice. Because the phenotypes of Ly-6Chigh monocytes contain high levels of P-selectin glycoprotein ligand-1, they exhibit a high binding capacity to P-, E-, and L-selectin, as well as increased survival, continued proliferation, and impaired conversion from Ly-6Chigh to Ly-6Clow. In contrast, Ly-6Clow monocytes reside and exhibit a patrolling function in steady-state tissues, depending on CX3CR1 as a receptor of CX3CL1/fractalkine. These Ly-6Clow monocytes also have a reparative function because of their role in mediating healing after tissue injury.

The mechanism by which CD14⁺CD16⁺ monocyte counts are associated with the severity of coronary atherosclerosis and plaque instability remains unclear. Although it is known that CD14⁺CD16⁺ monocytes secrete high levels of tumor necrosis factor-α, interleukin (IL)-1β, and IL-6 after lipopolysaccharide stimulation, there are other unsolved issues. CD14⁺CD16⁺ monocytes produce not only inflammatory cytokines and chemokines such as IL-6, IL-8, and monocyte chemotactic protein-1, but also IL-10 as an anti-inflammatory cytokine. In addition, CD14⁺CD16⁺ monocytes produce IL-10. CD14⁺CD16⁺ monocytes also secrete IL-1 receptor antagonists as inhibitors of IL-1α and IL-1β activities (Figure). Moreover, flow cytometry analysis has demonstrated a continuous population, but not separate distribution, of each CD14⁺CD16⁺, CD14⁺CD16⁺, and CD14⁺CD16⁺ subset. These data suggest that each monocyte subgroup is both inflammatory and anti-inflammatory, and furthermore, they are a continuously growing population. Particular responses against different stimuli may be altered in each monocyte subset. A recent study demonstrated that CD14⁺CD16⁺CCR2⁺ monocytes in CD16⁺ populations have unique and functional characteristics, including cytokine production, in patients with AMI. In addition, a prospective study recently demonstrated that classical CD14⁺CD16⁺ monocytes, but not the CD16⁺ subset, predicted future cardiovascular events independently of conventional risk factors in the general population.

Atherosclerosis is an inflammatory and immune disease. The balance of M1/M2 macrophages and Th1/Th2 lymphocytes regulate and participate in the initiation and progression of atherosclerotic processes. The study by Ozaki et al. has raises a question about the delicate balance of monocyte subsets. The entire pathophysiology by which monocyte subgroups contribute to atherosclerosis and its complications remains unclear. A balance and dynamic equilibrium of monocyte subsets is possibly involved in all stages of the atherosclerotic process. The diversity and plasticity of monocyte/macrophage biology could be a promising target for future investigations aimed at decreasing the morbidity and mortality of patients with atherosclerotic diseases.

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