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Review article

The heterogenic properties of monocytes/macrophages and neutrophils in inflammatory response in diabetes

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ABSTRACT

Inflammation is a complicated biological process in response to harmful stimuli, which involves the cooperation of immune system and vascular system. Upon pathogen invasion or tissue injury, resident innate immune cells such as macrophages and dendritic cells are activated and release inflammatory mediators, which result in the vasodilation and recruitment of leukocytes, mainly monocytes and neutrophils. As two of the most important inflammation-mediating immune cells, macrophages and neutrophils have long been regarded to have a pro-inflammatory effect. However, increasing evidences suggest the role of macrophage and neutrophil in inflammation is more complicated and diversified than we thought. Differently activated macrophages and neutrophils lead to diverse even opposite activities. Precise understanding of the role of different subpopulations is critical to achieve the effective treatment for inflammatory diseases. In this review, we discuss the two potentially distinct activation routes of macrophages and neutrophils in obesity and diabetes.

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Introduction

Constantly, human beings are assaulted by foreign bodies while our bodies defend against them through the immune system. One type of the immune responses is anti-inflammation, in which cells primarily from the monocyte and neutrophil cell lineages participate. Traditionally, inflammatory response is believed to start with neutrophils leaving vasculature toward an injured location as the initial responders (Henderson et al., 2003; Petrofsky and Bermudez, 1999). After neutrophils are recruited to that area, these cells actively kill or phagocytose foreign bodies and release cytokines (Petrofsky and Bermudez, 1999). It is also believed that as the inflammatory response continues, monocytes would then be recruited following neutrophils to the site of injury and differentiate into macrophages (Henderson et al., 2003). After neutrophils and monocytes enter that area, various cytokines are released to aid either pro-inflammatory or anti-inflammatory responses (Henderson et al., 2003; Duffield, 2003).

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Thus, neutrophils were originally thought to be intimately related with acute inflammation while monocytes/macrophages to be with chronic inflammation. However, in 2003, monocytes were found to travel independently of neutrophils toward injured sites (Henderson et al., 2003). This finding has been supported by several other studies, and now points toward neutrophils and monocytes act freely during injury responses (Henderson et al., 2003; Duffield, 2003). Nevertheless, there are still conflicting findings that point one way or another (Soehnlein et al., 2008a,b,c). Here, we summarize the two potentially distinct properties of monocytes/macrophages and neutrophils in inflammatory responses.

Monocyte differentiation

Monocytes are known to originate in the bone marrow from myeloid progenitor cells and then released into the peripheral blood (Fig. 1) (Volkman and Gowans, 1965). Monocytes have a relatively short lifetime in the blood circulation. They only stay for an average of 10 to 20 h in the blood and then enter into the tissues so as to be activated and differentiated into macrophages (Sunderkotter et al., 2004). As early as 1939, monocytes were reported to be able to emigrate from the blood and differentiate into macrophages in the tissues (Ebert and Florey, 1939). The recruitment of monocytes to the peripheral was found to be enhanced by inflammatory stimuli (Van Furth et al., 1973).

As one of the first lines in immune defense, macrophages are essential to antigen recognition, initiation of inflammatory response and tissue repair (Laskin et al., 2011). Macrophages reside in almost every tissue and are responsible for monitoring signs of tissue injury and infection. They also coordinate with adaptive immune responses to clear pathogens and participate in tissue homeostasis (Rosenberger and Finlay, 2003). By using a transgenic mouse model in which depletion of macrophage can be induced by the administration of diphtheria toxin, Goren and coworkers proved that depletion of macrophages severely impaired wound inflammation, angiogenesis and tissue remodeling (Goren et al., 2009).

Human subpopulations of monocytes can be identified by the expression of various levels of CD14, CD16 or CD64 (Sunderkotter et al., 2004; Gordon and Taylor, 2005). While murine monocytes do not have an exclusive marker, they can be identified based on high Ly-6C expression and low CD31 expression (Sunderkotter et al., 2004).

Monocytes vary in size and have different degrees of granularity and varied nuclear morphology. They are capable of differentiating into dendritic cells or macrophages. Due to the heterogeneity of the monocytes, macrophages are also highly heterogenous (Gordon and Taylor, 2005). Monocytes express distinct chemokine receptors and adhesion molecules. They are preferentially recruited into different tissues and differentiated into distinct subtype of macrophages. For instance, monocytes that emigrated into the liver differentiate into Kupffer cells in the liver, microglia in the brain and spinal cord, and alveolar macrophages in the lung.

Monocyte/macrophages in tissue injury: promoting tissue repair or enhancing tissue destruction?

During host defense, the infiltration of monocytes into inflammatory site usually helps the clearance of foreign antigens and tissue repair. By releasing pro-inflammatory, angiogenic, fibrogenic or mitogenic cytokines, macrophages cooperate with other immune and progenitor cells to limit tissue injury and repair tissue damage (Laskin and Pendino, 1995). When recruited to injured tissue, macrophages remove debris by phagocytosis and release various cytokines to attract fibroblasts, lymphocytes and endothelial cells to repair the tissue damage (Crowther et al., 2001; Danenberg et al., 2002; Greenburg and Hunt, 1978; Moldovan et al., 2000; Polverini et al., 1977). The infiltration of

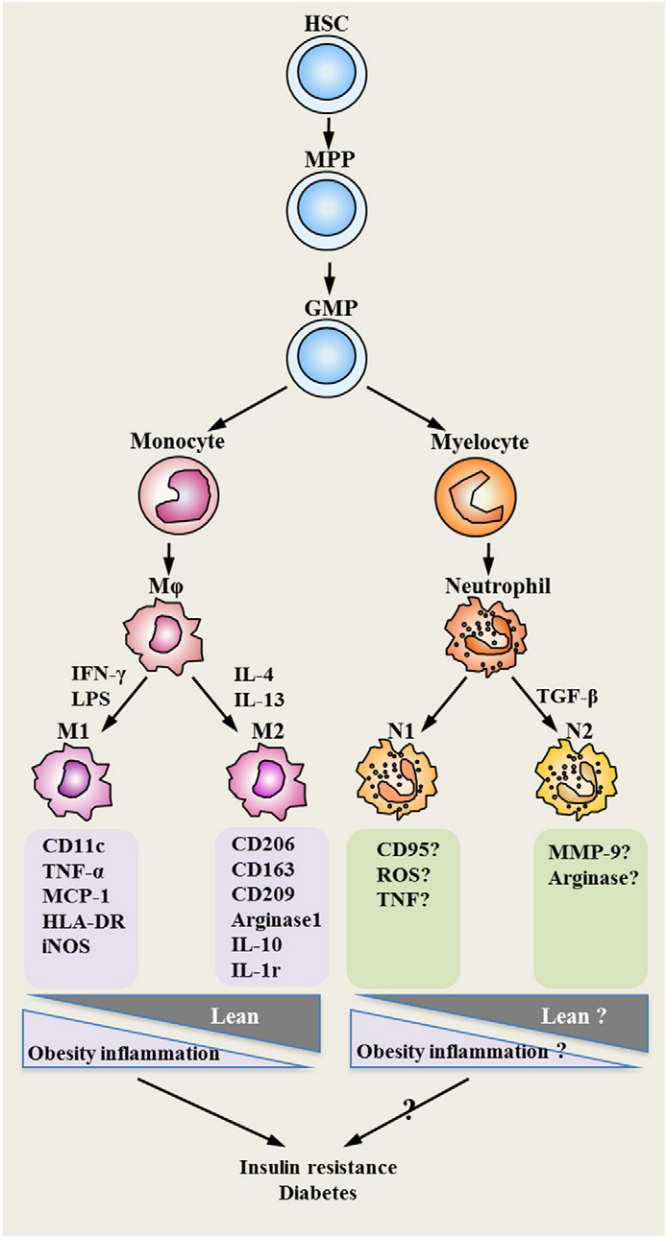

Fig. 1. Heterogeneity of monocyte/macrophage and neutrophil. Monocyte and neutrophil are originated from the same progenitor cell (GMP) that is differentiated from hematopoietic stem cell (HSC). GMP is able to differentiate into monocyte or myelocyte. When enter into tissues, monocytes become macrophages. Macrophages acquire distinct features when activated through different ways. "Classically" activated macrophages (M1) express CD11c, HLA-DR, and iNOS, secret TNF-α and MCP-1, while "alternatively" activated macrophages (M2) express CD206, CD163, CD209, IL-1r, arginase 1 and IL-10. In obesity/diabetes, polarization of macrophages skews towards to "M1", which contributes to the maintenance of chronic inflammation and insulin resistance in various tissues. Similar to macrophages, neutrophils differentiated from myelocytes display different phenotype when activated in different environment. "N1" possesses a pro-inflammatory or anti-tumor phenotype, whereas "N2" driven by TGF-β displays anti-inflammatory or pro-tumor phenotype. Increased levels of CD95, TNF and ROS are responsible for the anti-tumor phenotype of "N1", while higher levels of MMP-9 and arginase might contribute to the pro-tumor phenotype of "N2". However, as the classification of "N1" and "N2" was not proposed until recently, it requires further studies to identify the "N1"- or "N2"-specific protein expression profile and their functional role in obesity/diabetes. Abbreviations: HSC: hematopoietic stem cell; GMP: granulocyte-monocyte progenitor; MPP: multiple potent progenitor; TNF: tumor necrosis factor; ROS: reactive oxygen species; MMP-9: matrix metallopeptidase 9; HLD-DR: human leukocyte antigens; iNOS: inducible nitric oxide synthase; MCP-1: monocyte chemoattractant protein-1; IL-1r: interleukin-1 receptor; IL-10: interleukin-10.