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Review

The impact of interferon-regulatory factors to macrophage differentiation and polarization into M1 and M2

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ABSTRACT

The mononuclear phagocytes control the body homeostasis through the involvement in resolving tissue injury and further wound healing. Indeed, local tissue microenvironmental changes can significantly influence the functional behavior of monocytes and macrophages. Such microenvironmental changes for example occur in an atherosclerotic plaque during all progression stages. In response to exogenous stimuli, macrophages show a great phenotypic plasticity and heterogeneity. Exposure of monocytes to inflammatory or anti-inflammatory conditions also induces predominant differentiation to proinflammatory (M1) or anti-inflammatory (M2) macrophage subsets and phenotype switch between macrophage subsets. The phenotype transition is accompanied with great changes in the macrophage transcriptome and regulatory networks. Interferon-regulatory factors (IRFs) play a key role in hematopoietic development of monocytes, their differentiation to macrophages, and regulating macrophage maturation, phenotypic polarization, phenotypic switch, and function. Of 9 IRFs, at least 3 (IRF-1, IRF-5, and IRF-8) are involved in the commitment of proinflammatory M1 whereas IRF-3 and IRF-4 control M2 polarization. The role of IRF-2 is context-dependent. The IRF impact on macrophage phenotype plasticity and heterogeneity is complex and involves activating and repressive function in triggering transcription of target genes.

1. Introduction

In homeostasis, monocytes circulate in the blood, bone marrow, and spleen (Auffray et al., 2009). The function of monocytes in homeostatic conditions is unclear but these cells likely to be involved in the removal of dead cells and toxic compounds and renewal of 'resident' macrophages and dendritic cells (DCs) (Geissmann et al., 2008). In inflammation, monocytes in response to proinflammatory stimuli move to inflamed sites and lymphoid tissues. Monocytes neutralize pathogens and toxic molecules, engulf dead, damaged, and exogenous cells, secrete cytokines and differentiate to macrophages and DCs (Woollard and Geissmann, 2010).

In atherosclerosis, a chronic inflammatory vascular disease, monocytes infiltrate intimal and subintimal regions of the arterial wall (Imhof and Aurrand-Lions, 2004). Interestingly, monocytes preferentially transmigrate through the endothelium in so-called athero-prone vascular regions located, for example, in arterial branches and characterized by disturbed/unstable bloodflow and local proinflammatory microenvironment (Davies et al., 2013).

Infiltrated monocytes differentiate to macrophages, which take up modified lipoproteins such as oxidized low density lipoproteins and convert to foam cells to form early intimal lesions defined as fatty streaks (Chistiakov et al., 2016).

In mice, there are two principal monocyte subsets. Circulating $Gr1^{+}/Ly6C^{high}CCR2^{+}CX3CR1^{low}$ cells are usually referred to as 'inflammatory monocytes' since they differentiate to inflammatory macrophages and DCs. Another subset ($Gr1^{-}/Ly6C^{low}CCR2^{-}$ $CX3CR1^{high}$) represents 'patrol monocytes' that scan the endothelium of small vessels (Geissmann et al., 2003). In Apolipoprotein (Apo)E-deficient mice, $Gr1^{+}/Ly6C^{high}$ monocytes were observed to attach to the endothelium,

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infiltrate plaques and transform to atherogenic M1 macrophages (Swirski et al., 2007). Gr1^{-}/Ly6C^{low} monocytes contribute to the formation of alternatively activated M2 macrophages (Tacke et al., 2007). M1 macrophages release inflammatory cytokines and proteases and perform phagocytosis. M2 macrophages are involved in phagocytosis, tissue repair and remodeling, and release chemokines and anti-inflammatory cytokines. Regarding foam cell formation, both M1 and M2 can contribute to their generation, with a putative preferential role of M2 because this subset up-regulates expression of scavenger receptors (SR) SR-A1 and CD36 while SR expression is reduced in M1 (Oh et al., 2012).

Proinflammatory M1 macrophages can be induced by proinflammatory stimuli such as bacterial products (lipopolysaccharides (LPS)) or cytokines like interferon-γ. These macrophages propagate and support the inflammatory reaction through secretion of inflammatory mediators (tumor necrosis factor-α (TNF-α), IL (interleukin)-1β, IL-6, IL-8, IL-12). However, prolonged activity of M1 macrophage eventually damages tissue. By contrast, M2 cells, which can be induced by IL-4/IL-13 and IL-10, liberate anti-inflammatory cytokines (transforming growth factor-β (TGF-β), IL-10) to resolve the immune response (Wolfs et al., 2011). Indeed, well-controlled M1/M2 balance is important to avoid pathology or acute reactions.

This control can be effectively achieved by macrophage phenotypic plasticity. In tissue injury, M1 macrophages come to the wounded place, kill pathogens, neutralize toxins, and clear dead cells and cell debris. M2 macrophages are then recruited to repair tissue and heal the wound (Lee et al., 2011). To avoid the mobilization of new monocytes/macrophages, M1 macrophages can switch the phenotype to M2 depending on the local microenvironment (Huen and Cantley, 2015). Indeed, in the model of ischemic kidney injury, a heterogeneity of macrophage phenotypes was observed (Lee et al., 2011). Similarly, a variety of macrophage phenotypes was detected in the atherosclerotic plaque (reviewed recently by Chistiakov et al., 2015a; Rojas et al., 2015; Tabas and Bornfeldt, 2016).

The M1/M2 balance is dynamic and controlled by activity of intracellular signaling mediators activated by exogenous stimuli. A prevalence of nuclear factor-kB (NF-kB) and signal transducer and activator of transcription-1 (STAT-1) activity stimulates M1 polarization while predominance of STAT-3 and STAT-6-dependent signaling activated by IL-4, IL-10 or IL-13 induces M2 macrophage polarization (Wang et al., 2014). An existence of a new M3 'switch' phenotype, which responds to proinflammatory signals with reprogramming towards the M2 phenotype or, contrarily, to anti-inflammatory stimuli with reprogramming towards the M1 phenotype, was hypothesized (Malyshev and Malyshev, 2015). Indeed, the presence of M3 updates the existing concept of macrophage plasticity. However, direct proofs for the occurrence of M3 should be mined.

2. Macrophage differentiation factors in lesions

Macrophage and granulocyte-macrophage stimulating factors (M-CSF and GM-CSF) are principal hemapoietic growth factors that control differentiation of monocytes to macrophages. In the presence of GM-CSF, bone marrow cells differentiate to macrophages with antigen-presenting abilities, which in turn can give rise to DCs (in the presence of IL-4) (Hiasa et al., 2009). M-CSF drives transformation of bone marrow cells to macrophages with advanced phagocytic properties (Hamilton, 2008). Macrophages obtained with the M-CSF or GM-CSF treatments demonstrate different inflammatory properties. In GM-CSF macrophages, Toll-like receptor (TLR-4)/myeloid differentiation primary response gene 88 (Myd88)-dependent mechanism is up-regulated mediating production of inflammatory cytokines TNF-α, IL-12, and IL-23. M-CSF macrophages release IL-10 through up-regulated type I IFN signaling (Fleetwood et al., 2007a).

In summary, in humans and mice, GM-CSF promotes differentiation to M1 whereas M-CSF induces generation of M2-like phenotype in macrophages (Table 1) (Sierra-Filardi et al., 2010; Jaguin et al., 2013).

Table 1
Characteristics of macrophage subpopulations induced by M-CSF and GM-CSF stimulation of monocytes.

Differentiation factor	GM-CSF (M1-like)	M-CSF (M2-like)
Signaling mechanisms	TLR/MyD88-dependent	TLR/MyD88-independent
Key transcription factors		STAT-1, STAT-2, IRF-3
Surface markers	CD14^{low}	CD14^{high}, CD163
Cytokines released	TNF-α, IL-23, IL-10^{low}	IL-10^{high}, INF-β
Lipid metabolism	ABCA1↑ ABCG1↑ ApoE↑	ABCG↓ SR-A1↑ CD36↑

Abbreviations: ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; ApoE, apolipoprotein E; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; INF-β, interferon-β, IRF-3, interferon-regulatory factor 3; M-CSF, macrophage colony-stimulating factor; MyD88, myeloid differentiation primary response gene 88; SR-A1, scavenger receptor A1; STAT, signal transducer and activator of transcription; TNF-α, tumor necrosis factor-α.

The basal expression of M-CSF was observed in the endothelium, smooth muscle cells (SMCs), macrophages, and fibroblasts (Filonzi et al., 1993). In physiological conditions, expression of GM-CSF in vascular cells and macrophages is very low but can be significantly stimulated by inflammatory signals such as oxLDL, IL-1β, and TNF-α (Zoellner et al., 1992; Filonzi et al., 1993; Sakai et al., 1999). M-CSF expression is also activated by inflammatory mediators (oxLDL, TNF-α, IFN-γ) (Liao et al., 1991). While M-CSF is constitutively expressed in both normal and diseased vessels (Brochériou et al., 2011), GM-CSF expression is greatly up-regulated in atherosclerotic vessels (Plenz et al., 1997).

Since intraplaque expression of M-CSF and GM-CSF is stimulated by proinflammatory signals, both growth factors can contribute to the differentiation of infiltrated monocytes to lesional macrophages. Due to the up-regulation of GM-CSF in the plaques, this factor can contribute to the predominance of proinflammatory M1 macrophages in lesions (Khallou-Laschet et al., 2010). Recently, Huen and Cantley, showed the ability of GM-CSF expressed by mouse proximal tubular cells to induce the phenotype switch in macrophages after renal ischemia/reperfusion injury to promote tissue repair. GM-CSF-induced phenotype transition was mediated by STAT-3 and STAT-5 but not STAT-6 (Huen and Cantley, 2015). It would be interesting to know whether GM-CSF can mediate similar phenotypic changes in proinflammatory macrophages that infiltrate atherosclerotic plaques.

Transcriptome analysis of M-CSF-differentiated macrophages revealed significant changes in expression of 868 genes compared to monocytes (Martinez et al., 2006). These genes formed three major nodes clustered around cyclin-dependent kinase 1 (CDK1), chemokine (CC motif) ligand 2 (CCL2) and Bcl-2-like protein 11 (BCL2L11) and one cluster associated with the down-regulation of human leucocyte antigen (HLA) genes. Indeed, activation of cell cycle-related genes suggest for proliferation potential of macrophages associated with increased migratory properties and suppressed antigen-presenting function. Martinez et al. (2006) also found a second cluster enriched with genes responsible for maintaining macrophage-specific features and resistant to polarization. Notably, functional analysis showed significant up-regulation of genes involved in lipid handling, a characteristic of mature macrophages (Chistiakov et al., 2015b). Indeed, macrophage differentiation is associated with significant transcriptome changes including down-regulation or activation of certain transcriptional regulators essential in this developmental stage.

3. A family of interferon-regulatory factors

Interferon-regulatory factors (IRFs) are crucially involved in differentiation and polarization of macrophages. These factors were found due to their ability to bind to the virus-responsive elements in the promoter region of type I IFN genes. All IRFs are able to activate expression of IFN-α whereas IRF-3 in cooperation with NF-kB prime