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Review

Phosphatase regulation of macrophage activation

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A B S T R A C T

Macrophages are innate immune cells that play critical roles in tissue homeostasis and the immune response to invading pathogens or tumor cells. A hallmark of macrophages is their "plasticity," that is, their ability to respond to cues in their local microenvironment and adapt their activation state or phenotype to mount an appropriate response. During the inflammatory response, macrophages may be required to mount a profound anti-bacterial or anti-tumor response, an anti-inflammatory response, an anti-parasitic response, or a wound healing response. To do so, macrophages express cell surface receptors for growth factors, chemokines and cytokines, as well pathogen and danger associated molecular patterns. Downstream of these cell surface receptors, cell signalling cascades are activated and deactivated by reversible and competing activities of lipid and protein kinases and phosphatases. While kinases drive the activation of cell signalling pathways critical for macrophage activation, the strength and duration of the signalling is regulated by phosphatases. Hence, gene knockout mouse models have revealed critical roles for lipid and protein phosphatases in macrophage activation. Herein, we describe our current understanding and the key roles of specific cellular phosphatases in the regulation of the quality of macrophage polarization as well as the quantity of cytokines produced by activated macrophages.

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1. Introduction

Macrophages are critical mediators of the immune response that initiate the innate immune response and direct the subsequent acquired immune response. Mature differentiated macrophages are found throughout the body, where they adapt to their local microenvironment and participate in tissue homeostasis [1]. During an inflammatory response, monocytes are recruited from the bloodstream to sites of inflammation, where they differentiate into mature macrophages and, in some instances; mature macrophages proliferate at sites of inflammation [2]. Macrophages play equally important roles in the three "Rs" of inflammation: recognition, response, and resolution [3,4]. To fulfill these multiple roles in the body, macrophages express cell surface receptors for growth factors, chemokines and cytokines, as well as pathogen and danger associated molecular patterns, which permit them to achieve appropriate activation states to perform their varied tasks.

Two of the best-described macrophage activation states are those induced by treatment with interferon gamma (IFNγ) or interleukin 4 (IL-4) (Fig. 1). IFNγ primes macrophages to promote an anti-microbial immune response to kill invading pathogens [3]. Thus, subsequent treatment with lipopolysaccharide (LPS), a constituent of the outer membrane of Gram-negative bacteria, causes macrophages to produce a robust pro-inflammatory cytokine response. IFNγ primed macrophages have been called classically activated or M1 macrophages, mirroring the T helper cell nomenclature. Due to the increasing complexity of macrophage activation and expanded use of the terms, M1 and classically activated macrophages, in the literature [5], it has been suggested that these macrophages be referred to as M(IFNγ), which is the nomenclature that we will adopt throughout this review [6]. Murine M(IFNγ+LPS) produce high levels of pro-inflammatory cytokines IL-12p40, TNF, and IL-6 [3]. In contrast, IL-4 or IL-13 treated macrophages, M(IL-4) or M(IL-13), have been referred to as M2 or alternatively activated macrophages [7]. M(IL-4) are critical for the host response to extracellular parasites and have been implicated in the resolution phase of inflammation. M(IL-4) express arginase 1, which inhibits inducible nitric oxide synthase (iNOS) production of nitric oxide (NO) by competition for their common substrate, L-arginine [8]. They also express the scavenger receptor, Mrc1, as well as FIZZ1 and Ym1 [6]. Like IFNγ, IL-4 primes macrophages and alters their ability to respond to cytokines and microbial associated molecular patterns, like LPS. Thus M(IL-4+LPS) express lower levels

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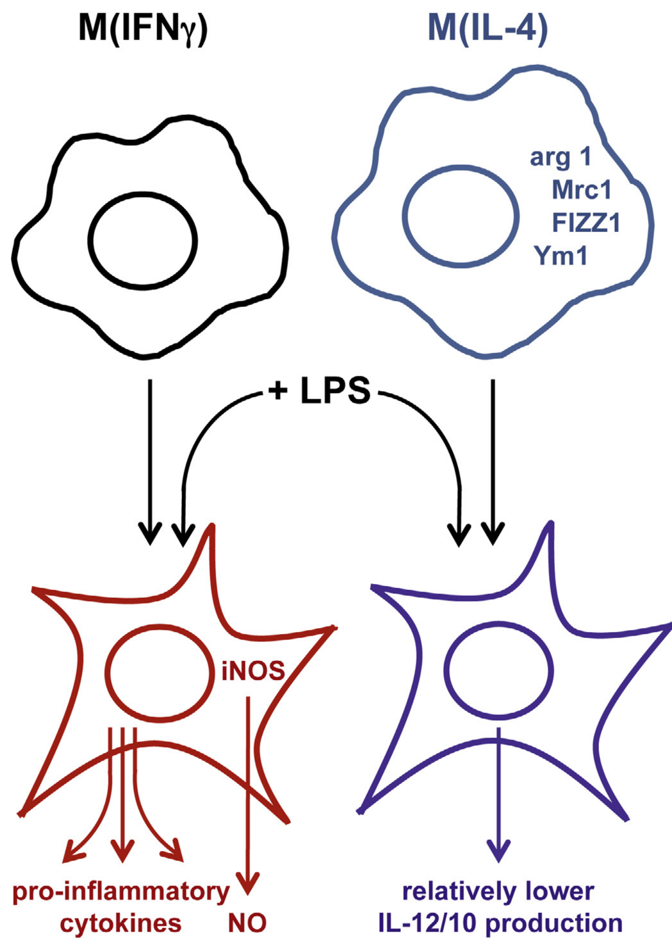

Fig. 1. Macrophage activation by IFNγ and IL-4. Macrophages are primed by treatment with IFNγ (left). In response to lipopolysaccharide (LPS), M(IFNγ) produce high levels of pro-inflammatory cytokines, and murine M(IFNγ) make nitric oxide (NO) via the enzyme, inducible nitric oxide synthase (iNOS). Macrophages primed by treatment with IL-4, M(IL-4) (right), express arginase 1 (arg 1), Mrc1, FIZZ1, and Ym1. Upon treatment with LPS, M(IL-4) make relatively lower levels of pro-inflammatory cytokines and more IL-10 than M(IFNγ). Murine M(IL-4) do not make NO because arg 1 outcompetes iNOS for their common substrate, L-arginine.

of pro-inflammatory cytokines and a higher ratio of IL-10/IL-12p40 compared to macrophages that are unprimed or primed with IFNγ [8]. Macrophages from mice deficient in receptors for IFNγ or IL-4 are unable to acquire these specialized macrophage phenotypes [9].

Ligation of cell surface receptors on macrophages initiates cell signalling cascades, which drive distinct transcriptional profiles and enable macrophage activation [10]. IFNγ binds to the IFNγ receptor that associates with Janus kinases (Jaks), which in turn phosphorylate and activate the STAT1 driven transcription of IFNγ responsive genes as well as STAT1 independent pathways (reviewed in [11]) (Fig. 2a). IL-4 binds to the IL-4 receptor, which activates Jak-STAT6 driven transcription of IL-4 responsive genes (Fig. 2b). IRS-2 also binds and recruits phosphatidylinositol 3-kinase (PI3K) to the activated IL-4R, which enhances transcription of some IL-4-responsive genes [12]. LPS binds to Toll-like receptor 4 (TLR4) on the cell surface ultimately leading to activation of the transcription factor NFκB. This pathway is finely tuned by cross-talk with the map kinase (MAPK) and PI3K pathways (Fig. 3) [13]. Each of the cell signalling pathways involved in macrophage activation is driven by kinases, which phosphorylate and predominantly activate cell signalling proteins. However, these cell signalling cascades and their outcomes are regulated by phosphatases that determine the length and strength of the resulting signal. Recent evidence,

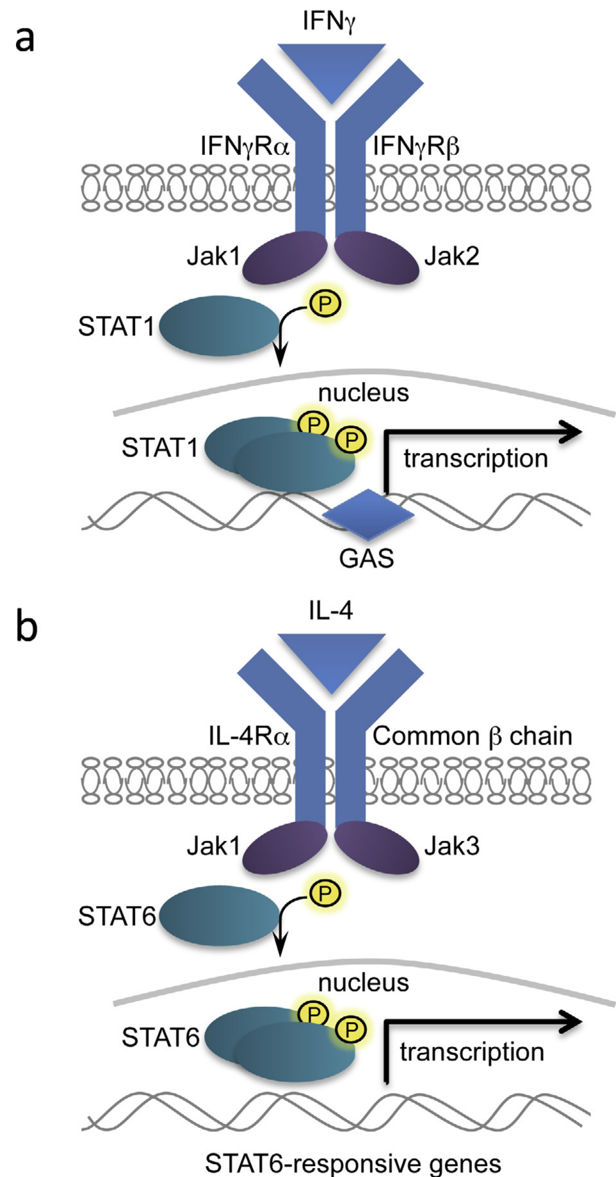

Fig. 2. IFNγ and IL-4 signal through the Jak-STAT pathway. (a) IFNγ binds to the heterodimeric IFNγ receptor, which recruits Jak1 and Jak2. Jak1 and Jak2 phosphorylate STAT1 leading to its dimerization, translocation to the nucleus, binding to gamma interferon activation sites (GAS), and transcription of IFNγ-responsive genes. (b) IL-4 binds to the type I or type II IL-4 receptor (type I receptor is shown), which recruits Jak1 and Jak3. Jak1 and Jak3 phosphorylate STAT6 leading to its dimerization, translocation to the nucleus, and transcription of IL-4-responsive genes.

primarily generated from knockout mouse models, has shed light on a critical role for both lipid and protein phosphatases in regulating macrophage activation.

2. Lipid phosphatases

Phosphatidylinositol 3-kinases (PI3Ks) are a family of enzymes involved in cell growth differentiation, motility, survival, and immune responses (reviewed in [14] and [15]). These enzymes phosphorylate the 3′ hydroxyl group in the inositol ring of phosphatidylinositol. PI3Ks are subdivided into three classes based on their substrate preferences, Class I, Class II, and Class III. Class I PI3Ks are further subdivided into Class IA PI3Ks, which are activated downstream of receptor tyrosine kinases, growth factor, cytokine, and Toll-like receptors, and Class IB PI3K, which is activated

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