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REVIEW

Monocytes and dendritic cells in a hypoxic environment: Spotlights on chemotaxis and migration

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Abstract

A common denominator of several pathological conditions, such as solid tumors and inflammatory lesions, is represented by low partial oxygen pressure (pO_2)[2]. Mononuclear phagocytes are recruited in large numbers as primary monocytes from the circulation to diseased tissues, where they accumulate within ischemic/hypoxic sites terminally differentiating into inflammatory and tumor-associated macrophages or myeloid dendritic cells (DCs). Thus, mononuclear phagocyte responses that ensue at pathological sites begin in the setting of reduced pO_2. In the last years, extensive work from several groups has been carried out to characterize hypoxia-mediated changes in mononuclear phagocyte gene expression and functional properties under different pathologic situations, demonstrating that oxygen availability is a critical regulator of their functional behavior. However, the majority of reports are focused on the characterization of differentiated macrophages, in particular tumor-infiltrating macrophages (TAM), whereas limited evidence is available for what concerns the responses of peripheral blood monocytes or DCs to the local hypoxic environment.

This brief review provides an overview of the phenotypic and functional changes triggered by hypoxia in primary monocytes and DCs. A major focus is given to the chemotactic activity and migratory behavior of these cells when exposed to levels of hypoxia similar to those present in ischemic tissues. Specifically, we discuss the influence of the local hypoxic microenvironment on the expression profile of genes involved in cell motility/migration. Experimental evidence demonstrating that hypoxia modulates in primary monocytes the expression of a selected cluster of

Abbreviations: ADM, adrenomedullin; Ang-2, angiopoietin-2; Arg-1, arginase-1; ARNT2, aryl hydrocarbon receptor nuclear translocator-2; C/EBPα/β, CCAAT/enhancer binding protein-α/β; AP-1, activator-protein-1; CBP, CREB-binding protein; CTSC, cathepsin C; DCs, dendritic cells; ECGF1, endothelial cell growth factor-1; ECM, extracellular matrix; EGLN1, EGL-nine homolog-1; Egr-1, early growth response-1; EMAPII, endothelial monocyte-activating polypeptide II; ENPP2, autotoxin; ET, endothelin; F3, coagulation factor III; FGF1, acid fibroblast growth factor 1; FLT1, VEGF receptor-1; FosB, Fos homolog B; FRA2, Fos-like antigen 2; GLUT1, glucose transporter-1; Hi-DCs, hypoxic iDCs; HIF, hypoxia-inducible factor; Hm-DCs, hypoxic mDCs; hMDM, human monocyte-derived macrophages; HRE, hypoxia-responsive element; hTNF, human tumor necrosis factor; iDCs, immature dendritic cells; IL-18BP, IL-18-binding protein; iNOS, inducible nitric oxide synthase; mDCs, mature DCs; MIF, macrophage migration inhibitory factor; MITF, microphthalmia-associated transcription factor; MKP-1, MAPK phosphatase 1; MMP, matrix metalloproteinases; NCOA1, nuclear receptor co-activator 1; NF-κB, nuclear factor-κB; OASE, oligoadenylate synthetase; P4HA1, A2, proline 4-hydroxylases-AI, II; PA-1, plasminogen activator inhibitor-1; pO_2, partial oxygen pressure; pVHL, von Hippel Lindau tumor suppressor protein; RGS1, regulator of G-protein signaling 1; SPP1, osteopontin; TAM, tumor-infiltrating macrophages; TFPI1, 2, tissue factor pathway inhibitors 1 and 2; TIMP1, tissue inhibitor of metalloproteinase 1; TLR, toll-like receptor; VEGF, vascular endothelial growth factor; ZNF197, zinc finger protein 197.

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chemokine genes with a characteristic dichotomy resulting in the up-regulation of those active on neutrophils and the inhibition of those predominantly active on monocytes, macrophages, T lymphocytes, NK cells, basophils and/or DCs is reported. We also review the findings suggestive of a negative regulatory role of hypoxia on monocyte migration, which is exerted through several alternative or complementary mechanisms and results in monocyte "trapping" within ischemic/hypoxic sites of diseased tissues. Furthermore, we summarize data relative to the ability of hypoxia to differentially regulate in immature DCs (iDCs) the expression profile of genes coding for chemokines and chemokine receptors, the former being down-regulated and the latter up-regulated, thus promoting the switch from a proinflammatory to a migratory phenotype of iDCs by, respectively, reducing their capacity to recruit other inflammatory leukocytes and increasing their sensitivity to chemoattractants.

Similarities and differences between the gene expression pattern induced by hypoxia in primary monocytes and that reported in differentiated macrophages are also outlined in this review, to attempt to establish which gene clusters representative of the hypoxic transcriptome of mononuclear phagocytes are specific for a certain stage of differentiation. In particular, we discuss the partial overlap existing among mononuclear phagocytes at various differentiation stages in the expression of a cluster of hypoxia-responsive genes coding for regulators of angiogenesis, proinflammatory cytokines/receptors, and inflammatory mediators and implicated in tissue neo-vascularization and cell activation.

Finally, we review studies on the transcription pathways underlying hypoxia-regulated gene expression in monocytic lineage cells, which support a major role for the hypoxia-inducible factor-1 (HIF-1)/hypoxia responsive element (HRE) pathway in monocyte extravasation and migration to hypoxic sites and in the activation of monocyte/macrophage proinflammatory and immunoregulatory responses by hypoxia both *in vitro* and *in vivo*. Recent experimental evidence suggesting the requirement of additional transcription factors, such as nuclear factor-κB (NF-κB), Ets-1, CCAAT/enhancer binding protein-α/β (C/EBPα/β), activator-protein-1 (AP-1), and early growth response-1 (Egr-1), for hypoxic regulation of gene transcription in primary human monocytes and differentiated macrophages and indicative of the existence of both a positive and a negative O_2-driven HIF-1-dependent feedback regulatory mechanism of hypoxia transcriptional response in primary monocytes, are also reported.
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Keywords: Chemokines/receptors; Dendritic cells; Hypoxia; Migration; Monocytes; Transcription

Contents

Introduction

Hypoxia is defined as a condition of reduced oxygen tension (pO_2) relative to that present in the atmosphere and is an intrinsic component not only of our pathology but also of our physiology (Semenza, 2001; Sitkovsky and Lukashev, 2008). Life on earth evolved in a hypoxic environment. The first fossil bacteria dates back 2.8 billions of years and originated in the absence of oxygen. Following the development of photosynthetic organisms (about 2 billion years ago), oxygen was released in the atmosphere but most of it was trapped by the abundant iron. Oxygen "rusted" earth and did not build up to a sufficient level to reverse the hypoxic nature of the environment, which conditioned the evolution of the primordial eukaryotic organisms until 600 millions years ago when the oxygen concentration reached what we define now as a "normoxic "atmosphere containing about 20% oxygen (154 mmHg). This time coincided with the beginning of the great evolutionary explosion leading to the exuberant biodiversity that we now experience. Evolution in a hypoxic environment left a mark in the biology of the modern cell that can cope with fluctuation in the oxygen tension and exploit

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