Immunobiology 217 (2012) 1241–1249

Contents lists available at SciVerse ScienceDirect

Immunobiology

journal homepage: www.elsevier.com/locate/imbio

Dendritic cell reprogramming by the hypoxic environment

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ARTICLE INFO

Article history:
Received 23 April 2012
Received in revised form 6 July 2012
Accepted 19 July 2012

Keywords:
Chemokines/receptors
Dendritic cells
Gene regulation
Hypoxia
Immunoregulatory receptors
Inflammation

ABSTRACT

Myeloid dendritic cells (DCs) are professional antigen-presenting cells central to the orchestration of innate and acquired immunity and the maintenance of self-tolerance. The local microenvironment contributes to the regulation of DC development and functions, and deregulated DC responses may result in amplification of inflammation, loss of tolerance, or establishment of immune escape mechanisms. DC generation from monocytic precursors recruited at sites of inflammation, tissue damage, or neoplasia occurs under condition of low partial oxygen pressure (pO_2, hypoxia). We reviewed the literature addressing the phenotypic and functional changes triggered by hypoxia in monocyte-derived immature (i) and mature (m) DCs. The discussion will revolve around *in vitro* studies of gene expression profile, which give a comprehensive representation of the complexity of response of these cells to low pO_2. The gene expression pattern of hypoxic DC will be discussed to address the question of the relationship with a specific maturation stage. We will summarize data relative to the regulation of the chemotactic network, which points to a role for hypoxia in promoting a migratory phenotype in iDCs and a highly proinflammatory state in mDCs. Current knowledge of the strict regulatory control exerted by hypoxia on the expression of immune-related cell surface receptors will also be addressed, with a particular focus on a newly identified marker of hypoxic DCs endowed with proinflammatory properties. Furthermore, we discuss the literature on the transcription mechanisms underlying hypoxia-regulated gene expression in DCs, which support a major role for the HIF/HRE pathway. Finally, recent advances shedding light on the *in vivo* influence of the local hypoxic microenvironment on DCs infiltrating the inflamed joints of juvenile idiopathic arthritis patients are outlined.

Introduction

Hypoxia is defined as "a condition of decreased partial oxygen pressure (pO_2) relative to that present in the atmosphere at sea level (≈20% O_2)" and is an intrinsic component of both our physiology and our pathology. O_2 levels in the body are quite heterogeneous. Physiologic pO_2 in healthy tissues typically spans between 3% and 9% depending on vascularization, seldom below 2.5%, as in lymphoid organs. pO_2 varies within a tissue in relationship to the distance from the end of the nearest capillary (Caldwell et al. 2001; Semenza 2011; Sitkovsky and Lukashev 2008). "Pathologic hypoxia" always develops as an aberrant status in damaged or degenerated tissues as a result of a disorganized or dysfunctional vessel network, diminished blood supply, or insufficient neovascularization. In these situations, O_2 demand is not balanced by O_2 supply, and its concentration decreases below the levels of the corresponding healthy tissue, ranging from ≈5% to almost anoxic conditions of 0.1%. Pathologic hypoxia is a hallmark of malignant solid tumors, sites of ischemia, inflammatory lesions, healing wounds, and sites of bacterial infection (Beyer et al. 2009; Bjornheden et al. 1999; Bosco and Varesio 2010; Harris 2002; Imtiyaz and Simon 2010; Muz et al. 2009; Semenza 2011; Vaupel and Hockel 2003). A major role for hypoxia has been recognized in regulating development and biological functions of cells involved in innate and adaptive immunity (Bosco and Varesio 2010; Bosco et al. 2008b; Cramer et al. 2003; Imtiyaz and Simon 2010; Knowles and Harris 2007; Murdoch et al. 2004; Nizet and Johnson 2009; Peyssonnaux et al. 2005; Sica et al. 2011; Sitkovsky and Lukashev 2008). Furthermore, hypoxia can have both pro- and anti-apoptotic consequences depending on the cellular context (Sitkovsky and Lukashev 2008), inducing cell death (Carraro et al. 2007; Sun et al. 2010) or survival (Roiniotis et al. 2009) of distinct immune cell populations.

Abbreviations: DC, dendritic cells; pO_2, partial oxygen pressure; MP, mononuclear phagocytes; BM, bone marrow; MDPs, common macrophage/DC precursors; CDPs, common DC precursors; pre-DCs, DC-restricted precursors; pDCs, plasmacytoid DCs; H-iDCs, hypoxic immature DCs; H-mDCs, hypoxic mature DCs; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; IRS, immunoregulatory Ig-like signaling; TREM-1, triggerering receptor expresse on myeloid cells; JIA, juvenile idiopathic arthritis; HIF, hypoxia-inducible factor; HRE, hypoxia-responsive element; NF-κB, nuclear factor-κB.

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0171-2985/$ – see front matter © 2012 Elsevier GmbH. All rights reserved.
http://dx.doi.org/10.1016/j.imbio.2012.07.023

Myeloid dendritic cells (DCs) represent a prominent component of the leukocyte infiltrate in damaged and inflammatory tissues (Crowther et al. 2001; Knowles and Harris 2007; Lin et al. 2006; Murdoch et al. 2004; Ueno et al. 2007). They belong to the mononuclear phagocyte (MP) system, deriving from a common committed bone marrow (BM) progenitor, and are found in every organ of the body at sites of potential entry of "dangerous factors" (Allavena et al. 2000; Bosco et al. 2008b; Cavanagh and Von Andrian 2002; Cramer et al. 2003; Geissmann et al. 2010; Hume 2008; Murdoch et al. 2004; Shortman and Naik 2007; Ueno et al. 2007). Whether there is a genuine functional distinction between DCs and other MPs has been extensively debated (Geissmann et al. 2010; Hume 2008). DCs are commonly considered as professional antigen-presenting cells, functioning as sentinels of the immune system and tailoring adaptive immune responses to match environmental cues, thereby serving as a bridge between innate and acquired immunity. They are central in both the orchestration of protective immunity against invading pathogens and the maintenance of tolerance to self-antigens. DC immunostimulatory properties reside in the capacity to migrate and patrol from non-lymphoid peripheral tissues, where they recognize pathogens and danger signals, to T cell areas of secondary lymphoid organs, where they present antigens to naive T cells and trigger T-cell responses (Rossi and Young 2005; Steinman and Banchereau 2007; Ueno et al. 2007). Deregulated DCs responses may result in amplification of inflammation, loss of tolerance, or establishment of immune escape mechanisms (Granucci et al. 2008; Rossi and Young 2005; Shortman and Naik 2007; Steinman and Banchereau 2007; Ueno et al. 2007). DC development and functions are acquired during a complex differentiation and maturation process tightly regulated by a network of inhibitory and activating signals present in the local microenvironment (Allavena et al. 2000; Bosco et al. 2008b; Cavanagh and Von Andrian 2002; de Jong et al. 2005; Lanzavecchia and Sallusto 2001; Lin et al. 2010; Rama et al. 2008; Sozzani 2005; Ueno et al. 2007). These cells may experience low pO_2 both during differentiation/maturation in pathologic tissues (Beyer et al. 2009; Bjornheden et al. 1999; Muz et al. 2009; Semenza 2011; Sitkovsky and Lukashev 2008; Vaupel and Hockel 2003) and upon migration to secondary lymphoid organs (Caldwell et al. 2001; Sitkovsky and Lukashev 2008), thus raising the question of the contribution of reduced oxygenation to DC development and acquisition of immunogenic or tolerogenic properties.

Review criteria

We focus on recent studies addressing the functional reprogramming of monocyte-derived DCs when generated in, or exposed to, a hypoxic environment. We will refer to scholar reviews with regard to DC differentiation/maturation process and expression of immunogenic/tolerogenic properties. We used as a criterium for MEDLINE search: "Hypoxia and dendritic cells (title/abstract)". Current knowledge of the regulatory control exerted by low pO_2 on primary monocyte recruitment and functional responses in diseased tissues, as well as on their terminal differentiation into inflammatory or tumor associated macrophages has been extensively reviewed (Bosco et al. 2008b; Crowther et al. 2001; Imtiyaz and Simon 2010; Knowles and Harris 2007; Murdoch et al. 2004; Sica et al. 2011) and will not be further addressed here. The discussion will revolve around studies of gene expression profiling that give a global view of DC biology (Foti et al. 2007; Robbins et al. 2008; Tang and Saltzaman 2004), including the complexity of response to hypoxia. Finally, we discuss the involvement of hypoxic DCs in chronic inflammatory synovitis in Juvenile Idiopathic Arthritis patients.

DC biology

Heterogeneity and roles in immunity and tolerance

The DC population in the body is highly heterogeneous in phenotype and function, associated with a typical anatomical and tissue distribution (Allavena et al. 2000; Bobryshev 2010; Cavanagh and Von Andrian 2002; Hume 2008; Lin et al. 2006; Shortman and Naik 2007; Ueno et al. 2007). DC generation involves three functionally and phenotypically distinct stages for which the terms "precursors", "immature" and "mature" are commonly used (Bobryshev 2010; Granucci et al. 2008; Shortman and Naik 2007; Ueno et al. 2007). DCs originate from hematopoietic stem cells in the BM *via* committed intermediate progenitors, such as the common macrophage/DC precursors (MDPs), which give rise to both the common DC precursors (CDPs) and blood monocytes. CDPs differentiate into DC-restricted precursors (pre-DCs) and plasmacytoid (p)DCs, although pDCs can also arise from the common lymphoid progenitors (CLPs) (Shortman and Naik 2007; Geissmann et al. 2010). In the steady-state, pre-DCs leave the BM to circulate *via* the bloodstream to reach non-lymphoid and lymphoid peripheral tissues, where they give rise to migratory and lymphoid-tissue-resident conventional (c)DCs, respectively. In many cases, pre-DCs differentiate into inflammatory DCs as a consequence of infection or inflammation (Shortman and Naik 2007). Peripheral blood monocytes recruited from the circulation to peripheral tissues can also serve as cDC precursors in the steady state, but they mostly give rise to inflammatory DCs in response to microbial or inflammatory stimuli (Allavena et al. 2000; Bosco et al. 2008b; Cavanagh and Von Andrian 2002; Cramer et al. 2003; Hume 2008; Murdoch et al. 2004; Shortman and Naik 2007; Ueno et al. 2007). Immature (i)DCs are specialized for antigen capture and processing and have a low T-cell stimulatory activity (Rossi and Young 2005; Steinman and Banchereau 2007). Under steady-state conditions, iDCs mostly reside at sites of potential pathogen entry within interface tissues, such as the skin and the respiratory or gastrointestinal mucosa, and in lymphoid tissues, where they play crucial roles in maintaining tolerance, not only to self antigens, but also to harmless environmental antigens and commensal organisms (Cavanagh and Von Andrian 2002; Ueno et al. 2007). However, they continuously scan the surroundings for the presence of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), which they recognize through a defined repertoire of pattern-recognition (PRRs) and scavenger cell surface receptors (Colonna et al. 2000; Lin et al. 2010; Schakel 2009).

Upon antigen uptake and activation by proinflammatory cytokines and DAMPs released in the context of tissue injury or PAMPs, iDCs undergo phenotypic and functional changes that culminate in their maturation into mature (m)DCs, which have a reduced potential for antigen uptake, but a higher capacity for antigen presentation and T-cell priming (Rossi and Young 2005; Ueno et al. 2007). mDCs upregulate the expression of MHC antigens, maturation markers and co-stimulatory molecules (such as CD83, CD80, CD86, and CD40), decreasing that of phagocytic/endocytic receptors, and switch their chemokine receptor repertoire, down-regulating receptors for inflammatory chemokines (*e.g.* CCR1, CCR2, CCR5, CCR6, and CXCR1) and upregulating those for homeostatic chemokines required for homing to secondary lymphoid organs, namely CCR7 and CXCR4, where they prime naive T cells triggering specific immune responses (Allavena et al. 2000; Cavanagh and Von Andrian 2002; Sozzani 2005). DC maturation is also associated with profound changes in the expression profile of both homeostatic (CCL17, CCL22, CCL19, and CCL18) and pro-inflammatory (CCL2, CCL3, CCL5, CCL20, CXCL8, CX3CL1, CXCL10, and CXCL16) chemokines, and distinct mDC populations and activation states can produce different sets of T cell-polarizing