Cancer Letters 412 (2018) 236–242

Contents lists available at ScienceDirect

Cancer Letters

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

Original Article

The role of nitric oxide in metabolic regulation of Dendritic cell immune function

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ARTICLE INFO

Article history:
Received 12 July 2017
Received in revised form
30 September 2017
Accepted 22 October 2017

ABSTRACT

Dendritic cells (DCs) are canonical antigen presenting cells of the immune system and serve as a bridge between innate and adaptive immune responses. When DCs are activated by a stimulus through toll-like receptors (TLRs), DCs undergo a process of maturation defined by cytokine & chemokine secretion, co-stimulatory molecule expression, antigen processing and presentation, and the ability to activate T cells. DC maturation is coupled with an increase in biosynthetic demand, which is fulfilled by a TLR-driven upregulation in glycolytic metabolism. Up-regulation of glycolysis in activated DCs provides these cells with molecular building blocks and cellular energy required for DC activation, and inhibition of glycolysis during initial activation impairs both the survival and effector function of activated DCs. Evidence shows that DC glycolytic upregulation is controlled by two distinct pathways, an early burst of glycolysis that is nitric oxide (NO) −independent, and a sustained commitment to glycolysis in NO-producing DC subsets. This review will address the complex role of NO in regulating DC metabolism and effector function.

Introduction

Dendritic cells (DCs) are professional antigen presenting cells of the immune system and play a central role in coordinating both innate and adaptive immune responses [1]. In their unactivated state, DCs continuously sample the tissue microenvironment for foreign material and are equipped to react to inflammatory stimuli by expressing a wide variety of innate immune receptors including the Toll-like receptor (TLR) family [2–4]. These TLRs recognize multiple forms of pathogen-associated molecules, and recognition of cognate ligands via TLRs cause DCs to become highly activated. Activated DCs undergo a process of “maturation”, which is characterized by the upregulation of co-stimulatory molecule expression, the ability *in vivo* to migrate from the site of inflammation to secondary lymphoid organs, the synthesis and secretion of immune-modulating cytokines and chemokines, and the processing and presentation of antigens to T lymphocytes. In this manner, DCs play a fundamental role in initiating and maintaining both innate and adaptive immune responses [1,5,6]. A number of studies in recent years have identified that DC activation is accompanied by distinct metabolic changes, highlighted by significant upregulation of aerobic glycolysis, that regulates the survival and immune effector function of both human and mouse DCs [7–13]. The microbicidal gas nitric oxide (NO) is among the activation-induced compounds synthesized and secreted by activated DCs and plays a complicated role in regulating DC immune responses as well as their cellular metabolism. TLR-mediated glycolysis induction in DCs occurs in two distinct phases (modeled in Fig. 1, upper right panel). Shortly after activation, DCs experience an early phase of TLR-driven glycolytic burst that is NO-independent [8], which is subsequently followed by a sustained phase of glycolytic metabolism that is contingent upon NO production in subsets of these cells [8–10]. The focus of this review is to highlight and discuss the current understanding in the field regarding the role of NO in regulating DC immunometabolism and effector function.

NOS expression and NO production

Cellular production of NO is catalyzed by three distinct nitric oxide synthase (NOS) enzymes. Endothelial NOS (eNOS, NOS1) and neuronal NOS (nNOS, NOS3) are constitutively expressed and were originally named for their primary tissue distribution, although the

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https://doi.org/10.1016/j.canlet.2017.10.032
0304-3835/

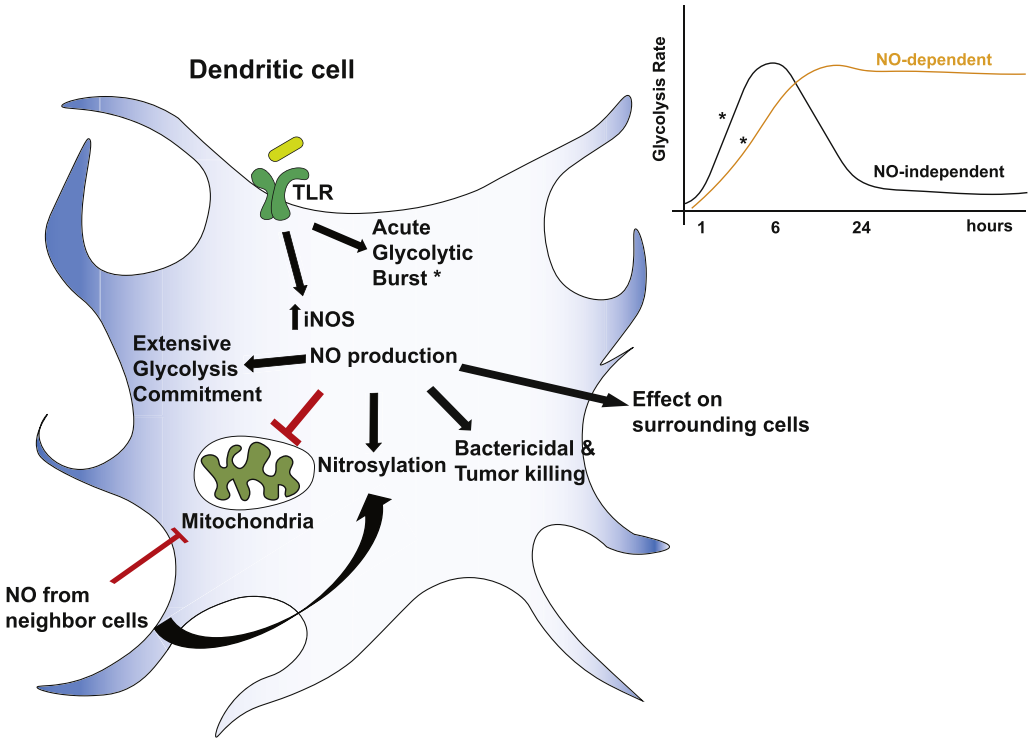

Fig. 1. Model of NO-mediated impacts on DC metabolism and function. Upper right panel, kinetics of NO-dependent and −independent glycolytic induction are illustrated. Main figure, the pleiotropic effects of NO on DC metabolism and function are modeled.

expression of these enzymes by a wide variety of cell types is now appreciated [14–17]. Of highest relevance to this review, inducible NOS (iNOS, NOS2) is the primary NO-synthesizing enzyme expressed by immune cells and is often not constitutively expressed but is potently induced during stimulation by inflammatory signals [18,19]. All NOS enzymes catalyze the reaction that converts substrates L-arginine, NADPH, and O_2 to L-citrulline, $NADP^+$, and NO [19]. As a membrane permeable volatile compound, NO participates in a variety of cellular processes that can extend beyond cell-intrinsic impacts on the cells that produce it [20–22]. The NO radical can influence cellular processes through a number of distinct mechanisms (reviewed in Ref. [20]), including: 1) the formation of toxic compounds such as superoxide (O_2^-) and peroxynitrite ($ONOO^-$) [23]; 2) S-nitrosylation of proteins leading to altered cellular activity [24,25]; 3) deamination of nucleic acids leading to genetic mutation [26].

Heterogeneity of DC subsets

DCs refer to a broadly heterogeneous family of immune cells that include cells derived from both myeloid and lymphoid lineage progenitors (reviewed in Ref. [27]). These cells are specialized in the their ability to acquire and process antigen, their expression of MHC-II antigen presentation machinery, their ability to travel to secondary lymphoid organs after activation, and their capacity to initiate antigen-specific T cell activation in these compartments [27]. So called “classical DCs” found in secondary lymphoid organs can be subdivided into two major subsets: $CD11b^+$ DCs, which are thought to specialize in cytokine production and $CD4^+$ T cell activation [28,29]; and $CD8^+$ DCs which specialize in cross-presentation of exogenous antigen and are potent activators of $CD8^+$ T cells [30–32]. In addition, there exist a number of non-classical DC subsets that play an important role in peripheral immune surveillance and infection response. These include the circulating and tissue-resident plasmacytoid DCs (pDCs) that are potent producers of Type I interferons [33,34], skin-resident Langerhans cells [35,36], and monocyte-derived “inflammatory DCs” (iDCs) [37–39]. With technological advances, different subsets of cDCs and pDCs in both mouse and human have been newly identified based on their tissue localization, surface markers, and ontogeny [40–42]. In the vast majority of *in vitro* −differentiated DC studies in both mouse and human systems, myeloid precursors (typically bone-marrow stem cells or circulating monocytes) are differentiated in the presence of the cytokine GM-CSF (with or without IL-4) to generate relatively pure populations of DC-like cells that are thought to most closely resemble iDCs both genetically and functionally [43,44].

Variability of iNOS expression in DC subsets

In evaluating the physiological role of NO in DC biology, it is important to note that iNOS is expressed only by specific subsets of DC populations, whether these be *in vivo* subsets or *in vitro* DC models, and that there exist notable differences in iNOS regulation between mice and humans DCs. Early studies determined that LPS and IFN-γ can induce iNOS expression in mouse GM-CSF −differentiated bone marrow-derived DCs (GM-DCs) [45]. In addition, mouse skin-derived DCs express iNOS and produce NO in response to LPS [46,47] and a role for NO production by thymic DCs in T cell differentiation has also been reported [48]. As originally defined, monocyte-derived iDCs (originally coined TNF-a/iNOS-producing-DCs, or “TipDCs”) express iNOS and are potent producers of NO that are required to control a number of different types of both bacterial and viral infections [39,49,50]. Nevertheless, unlike infection-associated iDCs and *in vitro* −cultivated GM-DCs, classical DC subsets in secondary lymphoid organs do not readily express iNOS nor produce detectable amounts of NO [9,51,52]. Conventional GM-