BBA - Reviews on Cancer 1868 (2017) 500–509

Contents lists available at ScienceDirect

BBA - Reviews on Cancer

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

Review

The role of nitric oxide in melanoma

Keerthi Yarlagadda, John Hassani, Isaac P. Foote, Joseph Markowitz*

Department of Cutaneous Oncology, Moffitt Cancer Center Tampa, FL 33612, United States

ARTICLE INFO

Keywords:
Nitric oxide
Melanoma

ABSTRACT

Nitric oxide (NO) is a small gaseous signaling molecule that mediates its effects in melanoma through free radical formation and enzymatic processes. Investigations have demonstrated multiple roles for NO in melanoma pathology via immune surveillance, apoptosis, angiogenesis, melanogenesis, and on the melanoma cell itself. In general, elevated levels of NO prognosticate a poor outcome for melanoma patients. However, there are processes where the relative concentration of NO in different environments may also serve to limit melanoma proliferation. This review serves to outline the roles of NO in melanoma development and proliferation. As demonstrated by multiple in vivo murine models and observations from human tissue, NO may promote melanoma formation and proliferation through its interaction via inhibitory immune cells, inhibition of apoptosis, stimulation of pro-tumorigenic cytokines, activation of tumor associated macrophages, alteration of angiogenic processes, and stimulation of melanoma formation itself.

1. Mechanisms of nitric oxide production in melanoma

Nitric oxide (NO) is a free radical inorganic signaling molecule that is generated via multiple mechanisms (Fig. 1). One of these mechanisms catalyzed by nitric oxide synthase (NOS) is the oxidation reaction of L-arginine and oxygen with a NADPH co-substrate to produce L-citrulline and NO [1]. There are 3 isotypes of NOS in humans: neuronal NOS (nNOS or NOS1), inducible NOS (iNOS or NOS2) and endothelial NOS (eNOS or NOS3). iNOS is transcriptionally induced by immunologic stimuli produced by various cells in the immune system (e.g. macrophages) in a calcium independent manner [2,3]. The eNOS and nNOS isoforms have been collectively grouped as constitutively active NOS (cNOS). These cNOS isoforms are constitutively expressed and their activity has classically been thought to be dependent on prior calcium influx that enables the isoforms to bind to calmodulin. Normal melanocytes express both cNOS and iNOS [4].

Another source of NO is the conversion of nitrate into NO in a two-step process. First nitrate is reduced to nitrite and then nitrite is reduced to nitric oxide. For example, oral bacteria reduce dietary inorganic nitrate into nitrite and then in an acidic environment such as the stomach nitrite is then reduced to NO via non-enzymatic disproportionation [5–7]. Therefore, it is not surprising that the major sources of nitrate and nitrite are the diet, products of the endogenous NOS pathway, and products of the oxidation and reduction by commensal organisms [1,7]. A similar mechanism occurs in the skin where nitrate present in the sweat is reduced to nitrite with subsequent conversion to NO in the presence of the acidic skin surface [8]. Nitrite may also be converted into NO enzymatically via the xanthine oxidoreductase or proteins containing the iron porphyrin moiety (e.g. cytochrome *c*, deoxyhemoglobin, mitochondrial electron transport chain) [2,9]. In normal human skin, photolabile compounds (e.g. nitrate, nitrite and the S-nitroso compounds such as S-nitrosothiols, S-nitrosoalbumin, S-

Abbreviations: AMG, Aminoguanidine; APE/Ref-1, Apurinic/apyrimidinic endonuclease-1/redox factor-1; ARG1, Arginine 1; BCL2, B-cell lymphoma 2 gene; BRAF, B- Rapidly Accelerated Fibrosarcoma; cGMP, Cyclic guanosine monophosphate; cNOS, constitutional nitric oxide synthase; COX-2, cyclooxygenase-2; c-PITO, 2-4-carboxyphenyl-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide; CTL, cytotoxic T lymphocytes; CXCL10, chemokine (C-X-C motif) ligand 10; DAF-FM, 4-Amino-5-methylamino-2′,7′-difluorofluorescein (Diaminofluorescein); DC-HIL, dendritic cell-associated, heparan sulfate proteoglycans-dependent integrin ligand; DR4, antigen D related 4; eNOS, endothelial NOS; GM-CSF, Granulocyte macrophage colony stimulating factor; HIF-1, hypoxia inducible factor-1; IFN-α, Interferon-alpha; IFN-γ, Interferon-gamma; iNOS, inducible NOS; JAK/STAT, Janus kinase/Signal Transducer and Activator of Transcription proteins; JunD, JunD is the transcription fractor protein product of the JUND gene; L-NAME, L-NG-Nitroarginine methyl ester; L-NIL, L-N6-(1-Iminoethyl)lysine; L-NMMA, NG-monomethyl L-arginine; LPS, Lipopolysaccharide; MAPK, Mitogen-activated protein kinases; MDSC, Myeloid derived stem cells; MHY966, 2-bromo-4-(5-chloro-benzol[*d*]thiazol-2-yl; MMP-1, Metalloproteinase-1; NAPDH, Nicotinamide adenine dinucleotide phosphate (Reduced); nNOS, neuronal NOS; NO, Nitric oxide; NONOate, diethylaminedinitric oxide; NOS, Nitric oxide synthase; NOS1, neuronal NOS; NOS2, inducible NOS; NOS3, endothelial NOS; ONOO, Peroxynitrite; PAPA NO, (Z)-1- [N-(3-ammonio-propyl)-N-(n-propyl)amino]diazen-1-ium- 1,2diolate; PDE-5, phosphodiesterase type 5; PD-L1, Programmed cell death ligand 1; pO2, Partial pressure of oxygen; pSTAT1, phosphorylated Signal transducer and activator of transcription 1 (STAT1); RET, rearranged during transfection gene; ROS, reactive oxygen species; SNAP, s-nitroso-*n*-acetyl-dl-penicilamine; SNP, Single nucleotide polymorphisms; TAM, tumor associated macrophage; TGFβ1, Transforming growth factor beta 1; VCAM-1, Vascular cellular adhesion molecule-1; VEGF, Vascular endothelial growth factor

* Corresponding author.
E-mail address: joseph.markowitz@moffitt.org (J. Markowitz).

http://dx.doi.org/10.1016/j.bbcan.2017.09.005
Received 9 July 2017; Received in revised form 24 September 2017; Accepted 25 September 2017
Available online 27 September 2017
0304-419X/

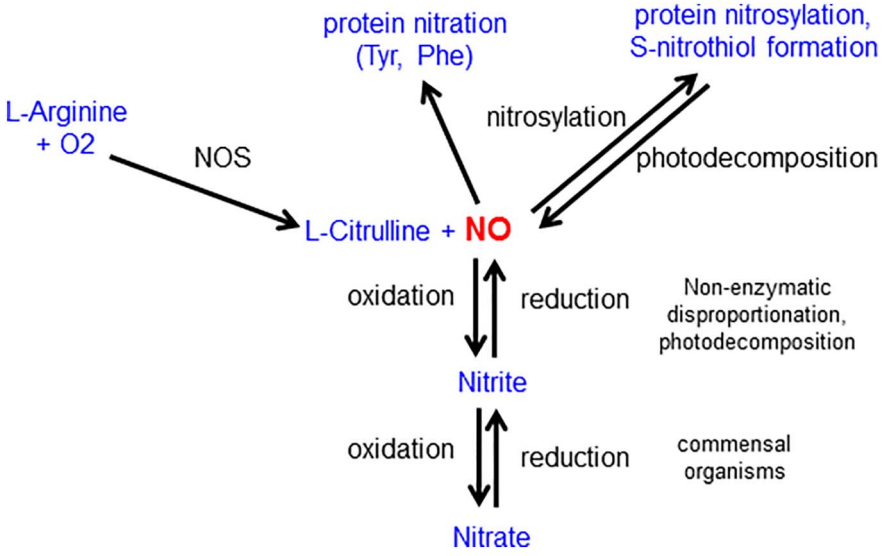

Fig. 1. NO biochemistry. NO is produced by various biochemical processes and is involved in post-translational modifications of proteins.

nitrosoglutathione or S-nitrosocysteine) generated NO via photodecomposition after exposure to ultraviolet A (UVA) or blue light. In the presence of blue light, photolabile NO derivatives photodecompose to NO via a copper (Cu^{1+}) dependent mechanism. In the presence of UVA radiation, nitrite decomposed to NO and subsequent electron transfer reactions generated highly toxic nitrogen dioxide ($NO_2\cdot$), which in turn initiated a lipid peroxidation chain reaction [10,11]. It is not surprising with these interdependent processes nitrite can also serve as the substrate to form s-nitrosothiols in vivo [12]. NO and metabolites of NO such as nitrite may be measured via colorimetric dyes such as the Griess reagent, fluorescent dyes such as DAF-FM, and in vivo via electron paramagnetic resonance spectroscopy [13–15]. Generally, NO may be derived enzymatically (NOS, xanthine oxidoreductase, or iron porphyrin containing proteins) or non-enzymatically (UVA or blue light photochemistry or low pH induced disproportionation).

1.1. Nitric oxide biochemistry

NO exerts its effects through two major signaling pathways, the cGMP dependent pathway and the cGMP independent pathway (Fig. 2) [16]. In the cGMP dependent pathway, NO synthesized from NOS diffuses across the plasma membrane and cytoplasm, reacts with the active site of soluble guanylate cyclase and produces cGMP. cGMP then phosphorylates the cGMP dependent protein kinase G, which in-turn phosphorylates and activates cGMP dependent gated ion channels and phosphodiesterase. As describes above, NO and its derivatives may be involved in redox chemistry with other small molecules and metal complexes on proteins [6,17]. The cGMP independent pathway occurs commonly through modification of proteins through S-nitrosylation of cysteine residues [16,18]. Nitrosation or nitrosylation (biological term for nitrosation) is the incorporation of NO onto another molecule with an alkene bond between the N and O. Such post translational modifications affect transcriptional activity by alteration of DNA-protein interactions [16,19] (see Fig. 3).

The derivatives of NO are responsible for multiple post-translational modifications resulting in altered functional properties of proteins [2]. NO can react with superoxide anions to yield peroxynitrite, which in turn serves as a nitrating and nitrosylating agent. Peroxynitrite interacts with amino acids, generating nitrotyrosine and reversible thiol nitrosylation [20]. In fact, there are known motifs in proteins that have been shown to be preferentially nitrosylated [18]. A literature review of 233 S-nitrosylated proteins revealed that S-nitrosylation sites were found in alpha helices, solvent accessible areas, and structural motifs with charged amino acids within 6 Å [21]. S-nitrosylated proteins are also involved in the reactions of energy metabolism such as mitochondrial respiration/proliferation and reactions of glucose

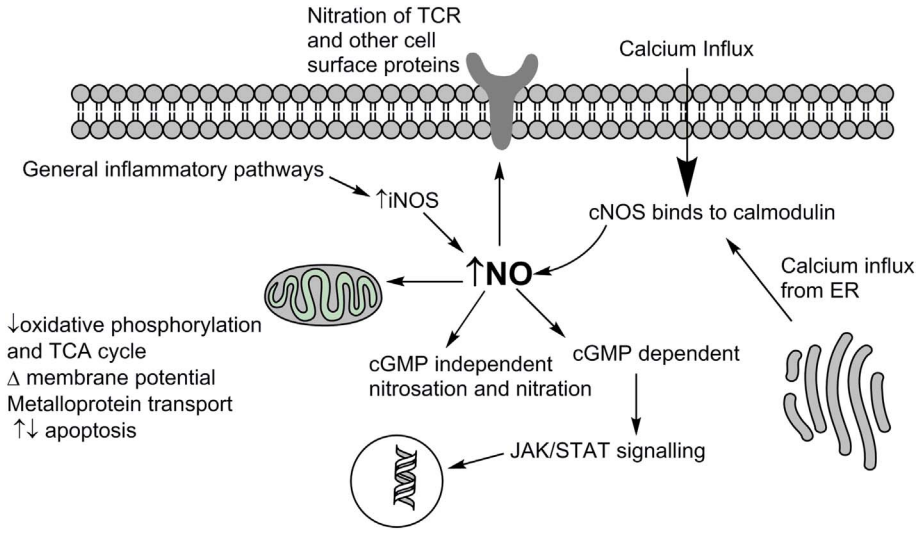

Fig. 2. NO general cellular function. NO is involved in cGMP dependent and independent cell processes. It is involved in regulating mitochondrial function, apoptotic processes and multiple other pathways such interferon response pathways and production of chemokines/cytokines. This figure has been generated utilizing the tools provided in the ChemDraw program (PerkinElmer, Waltham, MA, USA).