Molecular Pathways: Inflammation-associated nitric-oxide production as a cancer-supporting redox mechanism and a potential therapeutic target

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Abstract

It is widely accepted that many cancers express features of inflammation, driven by both microenvironmental cells and factors, and the intrinsic production of inflammation-associated mediators from malignant cells themselves. Inflammation results in intracellular oxidative stress, with the ultimate biochemical oxidants composed of reactive nitrogens and oxgens. Although the role of inflammation in carcinogenesis is well accepted, we now present data that inflammatory processes are also active in the maintenance phase of many aggressive forms of cancer. The oxidative stress of inflammation is proposed to drive a continuous process of DNA adducts and crosslinks, as well as posttranslational modifications to lipids and proteins that we argue support growth and survival. In this perspective we introduce data on the emerging science of inflammation-driven posttranslational modifications on proteins responsible for driving growth, angiogenesis, immunosuppression, and inhibition of apoptosis. Examples include data from human melanoma, breast, head and neck, lung, and colon cancers. Fortunately, numerous anti-oxidant agents are clinically available, and we further propose that the pharmacological attenuation of these inflammatory processes, particularly the reactive nitrogen species, will restore the cancer cells to an apoptosis-permissive and growth inhibitory state. Our mouse model data using an arginine antagonist that prevents enzymatic production of nitric oxide, directly supports this view. We contend that selected antioxidants be considered as part of the cancer treatment approach, as they are likely to provide a novel and mechanistically justified addition for therapeutic benefit.

Background

The most commonly recognized features of cancer-associated inflammation are those also expressed by the innate immune system, normally activated in response to stress or infection and which function teleologically during the initiation of wound control. The observed chronic inflammatory milieu in notable subsets of human cancers, and particularly in melanoma, is proposed to support tumor growth, plasticity, and resistance to therapy. Unfortunately, dysregulated persistent inflammation contributes to the chronic phase of many diseases, including maintenance of many cancers. It is accepted that inflammation drives development of some cancers which adapt to thrive in the oxidant-rich microenvironment as described initially in the review by Coussens and Werb, by “co-opting” expression of inflammatory mediators. From our view, this continues to provide a persistent and self-perpetuating oxidative stress composed of both Reactive Nitrogen Species (RNS) and Reactive Oxygen Species (ROS), and derived from pro-inflammatory interleukins, chemokines, NOSs (nitric oxide synthases) often via growth factor receptors. The critical oxidant sources are now realized to be more than reactive oxygen molecules, as the chronic production of another oxidant, NO (nitric oxide), also plays a major role in oxidative stress in melanoma and other cancers, and the aberrant constitutive RNS is argued here as possibly a more important source of oxidative stress in many cancers. In comparison to the oxygen radicals, NO is a more stable oxidant, easily crosses lipid bilayers, and generates several types of posttranslational modifications with known ability to alter protein function and stability; these modifications are dependent on both NO concentration and temporal availability,
resulting in a dynamic and reversible situation\textsuperscript{12}. A mathematical model of cutaneous melanoma predicted sufficient concentrations of NO at the periphery of a tumor to stimulate cell proliferation, lymphangiogenesis, and inhibit apoptosis \textsuperscript{13}.

\textit{Inflammation driven NO supports melanoma growth, and apoptosis resistance.}

In melanocytes, the precursor cell of melanoma, the pigment eumelanin provides a redox function supporting an antioxidant intracellular environment; however in melanoma, a pro-oxidant status develops\textsuperscript{8}. The enzymatic production of NO is cell type specific with cytokine-driven inducible NOS (iNOS) noted initially for the burst of higher levels as part of the pathogen defense system. Neuronal cells use nNOS (to produce NO for signaling, and as melanocytes are of neuroectoderm origin, it is not surprising to find nNOS also expressed. The third NOS, endothelial NOS, regulates NO production in endothelia and is responsible for vascular relaxation, and has also been reported to be expressed in melanoma \textsuperscript{14}.

In melanoma tumors, we \textsuperscript{9,10,4,11} and others \textsuperscript{6,8} document expression of NOS, particularly \textit{iNOS and nNOS}. The iNOS protein was found \textit{in vivo} in the melanoma tumor cytoplasm of \textasciitilde60\% of advanced patients, and provided independent prognostic value by predicting decreased survival, so that the hazard ratio of iNOS positive patients was 4.6 by multivariate analysis\textsuperscript{9}. This was an unexpected finding as the anti-iNOS antibody was employed to identify activated macrophages, which were also often positive, but for which the positivity did not prove prognostic. Further evidence supporting intracellular NO production was by use of DAF-2DA staining \textsuperscript{4} as well as identification of irreversible protein nitration and the reversible thiol modifications known as “S-NO” (S-nitrosylation) \textsuperscript{4,9,10,11}. Using a human cell line model, \textit{in vitro} experiments were performed to scavenge endogenous NO which resulted in melanoma cell growth inhibition; the growth was restored with an RNS donor, providing data to support a pivotal functional role of NO in cell growth and proliferation \textsuperscript{15}. Therefore, molecular analysis supports the hypothesis that NO can drive proliferation as well as resistance to apoptosis, and the chemical quenching of NO resulted in G2 growth arrest followed by a gain of cisplatin-induced apoptosis, now confirmed in several reports \textsuperscript{15,11,16}.

As iNOS is downstream of Toll-like receptors, recently described in an earlier CCR Pathways \textsuperscript{17}, and results in NO production leading to a feed-forward loop and tumor progression,\textsuperscript{17} we asked whether we could identify a signature of the downstream common inflammatory markers. Although many markers have been noted in an extensive literature, in melanoma we have identified inflammatory cytokines IL-1\(\alpha\) and \(\beta\)\textsuperscript{18}, IL-6, and IL-8; and in a more recent study we have observed that an MIF-CD74 autocrine interaction upregulated by IFN-\(\gamma\), promoting the phosphorylation of AKT Ser473, and driving the expression of IL-6, IL-8, BCL-2 and BCL-xl (unpublished data). IFN\(\gamma\) also regulates iNOS gene expression via Interferon Regulatory Factors (IRFs). IRFs are nuclear transcription factors that respond to IFN-\(\gamma\) via the JAK-STAT signaling pathway \textsuperscript{19}. The importance of IRF-1 and STAT-1 for the induction of iNOS gene expression in response to IFN-\(\gamma\) has been well documented \textsuperscript{20,21}. Our earlier study showed that IL-24 (aka Melanoma Differentiation Antigen (MDA)-7) signaling modulates the IRF transcriptional system, to the extent that IL-24-treated melanoma cells exhibit a decline in IRF-1 and an increase in IRF-2 which blocks the IRF1 pathway. This alteration in the IRF balance predicts the result in inhibition of iNOS
expression. We have also employed gene array studies, followed by validation of protein in patient tumor samples, and identified iNOS, arginase, VEGFα, CXCL-10, IL-8, IL1α / β, and TNFSF9 as produced constitutively. Using melanoma patient’s tumors, recent results from our lab continue to support iNOS protein associating with NT, COX2, pSTAT3, and arginase, consistent with the report of Johansson et al., and with other recent studies. Figure 1 includes these cytokines and their hypothesized connections to either drive NOS, or result from iNOS, as well as growth and apoptosis signaling molecules modified by RNS.

**Biochemical and molecular mechanisms of NO-mediated dysregulation of cancer signaling**

NO in the presence of equimolar O2 forms ONOO⁻ (peroxynitrite), which under physiological conditions rapidly reacts with available tyrosine or thiol-containing proteins to form nitrotyrosine or reversible nitrosylation of thiol (S-nitrosylation aka S-NO). Nitration of tyrosines is considered a surrogate marker for higher but generally nontoxic μM concentrations of NO. Global analysis of melanoma patient samples for tyrosine nitration has been used by several groups as a biomarker of NO exposure in melanoma tumors as well as micro-environmental cells. This nitrotyrosine modification is considered irreversible in eukaryotes, and once modified nitrated proteins will continue to express altered function; also such modified proteins are also proposed in some cases to alter antigenicity. Due to the lower nM levels of NO functional in generating S-NO, this modification is considered more physiologic relevant. Studies on cardiovascular and neuronal signaling regulation by NO have identified numerous protein S-NO modifications, and their reversibility suggests a novel paradigm for attempting to restore dysregulated apoptotic pathways in the inflammation-driven tumors.

Therefore, we now propose S-NO as not only a marker of nitrosative stress, but based on the specific molecule modified also serves functionally to activate oncogenes, inhibit apoptosis, drive growth and angiogenesis, and inhibit tumor suppressor functions. In a recent report by Switzer et al., oncogene activation include S-NO of Ras in ER-negative breast cancer. Using a model ER-negative breast cancer cell line, it was shown that NO not only induces S-nitrosylation of wild-type Ras, but led to phosphorylation and activation of Ets-1 through the Ras/MAPK/ERK pathway. Ets-1 is a key transcriptional mediator of oncogenic NO signaling, promoting the development of an aggressive disease phenotype in ER-breast cancer. S-NO-modified proteins involved in the apoptotic machinery include bcl-2 in lung carcinoma, the death receptor FAS in colon and breast cancer cells, and the associated FLICE inhibitory protein (FLIP), and caspase 9 in cholangiocarcinoma cells. Other early notable evidence supporting a role for NO in apoptosis resistance is the classic in vitro work of Mitchell and Marletta with caspase 3 inactivation by reversible S-NO modification. Earlier in vivo data also indicates the NO-driven inhibition of caspase3. Nitrosylation has also been shown to stabilize mitogen-activated protein kinase phosphatase-1 (MKP-1) in head and neck cancer, thus decreasing radiosensitivity by inhibiting apoptosis.

Tumor growth was also noted to be regulated by NO in a variety of tumor models via S-NO of Ras and S-NO of the epidermal growth factor receptor. Cellular migration in prostate cancer is enhanced by S-NO on the integrin alpha chain, and breast cancer invasiveness enhanced by nitrosylation of c-Src. In addition to the functional effects of nitrosylation of caspase 3 and 9, Ras, p53, PTEN, iNOS, COX2, AKT
referred above, other molecules that may have altered function as a result of S-NO as reported and include Bcl-2 \(^{41,42}\), HIF1\(\alpha\) \(^{43}\), PI3K \(^{44}\), NFkB and AP-1 \(^{45,46}\).

S-nitrosylation of a number of proteins can be linked to tumor proliferation. Many GTPases within the Ras superfamily contain redox-sensitive Cys residues that are susceptible to S-nitrosylation. Ras S-nitrosylation is associated with the initiation of tumorigenesis and maintenance of established tumors. In tumor cells, oncogenic K-Ras activates eNOS by PI3K-Akt-dependent phosphorylation of eNOS at S1117, which results in S-NO of wild-type N-and H-Ras; S1117-phosphorylated eNOS is elevated in tumors isolated from patients with pancreatic cancer, compared to matched and unmatched normal tissue controls from these patients. \(^{37}\).

Our additional data is consistent with the model that p53 in melanoma is inactivated by NO \(^{15}\) and the quenching of NO in melanoma led to cisplatin-mediated apoptosis, which was blocked with biochemical donation of NO indicating that this was not due to toxicity of the quencher. Tang further reported that the apoptosis was dependent on p53 via use of siRNA. In melanoma, p53 does not express the usual driver mutations and is considered as rarely mutated yet functionally inactivated, and the NO is somehow responsible for p53 inactivation \(^{15}\). We have preliminary data of S-NO modification of wt p53 (Qin, manuscript in preparation), which likely adds another major protein to the list above.

From the molecular view, we hypothesize that endogenous NO in the presence of stoichiometric availability of O2- chemically nitrosylates accessible thiols to activate oncogenes, inhibit multiple apoptosis and growth pathway proteins, and support enhanced growth. Local production of NO as a plausible mechanism for tumor resistance to therapy was elegantly presented by Dedon and Tannenbaum \(^{47}\) almost a decade ago, and while still accepted to be provided by microenvironmental macrophages as in that first report, we now extend this understanding that NO is produced by tumor cells including melanoma. Although studies of S-NO modifications were performed initially by redox chemists, more accessible methods are becoming available to cancer biologists, such as the biotin-switch method for direct S-NO protein characterization \(^{48}\), and even more recently the mass-spect/peptide sequencing methods for biochemical validation of the specific site and protein verification such as the SNO-Flo \(^{49,50,51}\). The S-NO modifications are dynamic, can be identified biochemically, and can be reversed with various antioxidant approaches, some of which may prove useful in melanoma for inhibition of growth and restoration of apoptosis pathway function.

A second mechanism resulting in S-NO on signaling proteins in cancers is called trans-nitrosation, as reported with NO transferred from PTEN to AKT \(^{52}\), or from iNOS to COX2 \(^{53}\), as iNOS and PTEN are both themselves reported to have S-NO as well in those reports; the actual transfer of NO is based on differential nucleophilic profiles of the cysteine donor and receptor sites on each molecule. Therefore, after NO is generated and proteins are S-NO modified, the transfer of NO radicals can also regulate the dynamic and reversible post-translational modifications.

Currently there is no evidence that inflammation is uniquely linked to a specific driver mutation in melanoma; however in some recent data testing melanoma tumors containing mutated BRAF, it was reported that the mutation may actually support expression of IL-1\(\beta\) expression \(^{54}\), and in another report
antisense BRAF inhibited iNOS expression\textsuperscript{55}. More analysis is needed to understand the driving forces for NO production and associated effects.

Inflammation-associated molecules drive formation of the pro-tumor cancer microenvironment and tumor-mediated immunosuppression.

By upregulating key inflammatory molecules, including iNOS, COX2, and proinflammatory cytokines and chemokines, tumor cells invoke a chronic inflammatory state that also induces tumor-supporting myeloid cells such as tumor-associated macrophages and myeloid-derived suppressor cells (MDSC), and drives their infiltration of the tumor microenvironment\textsuperscript{56,57}. While many host cell types including T cells are involved in creating an inflammatory pro-tumor microenvironment, in this Pathway, we focus on inflammation-directed recruitment of MDSC and macrophage polarization. As tumors progress, the macrophage population is thought to switch from a tumoricidal M1 to a pro-tumor M2 phenotype, under the influence of IL-4, IL-10, IL-13 and TGFβ. M2 macrophages are associated with immunosuppression via arginase expression, the release of TGFβ and IL-10\textsuperscript{58} and Treg recruitment\textsuperscript{59}. M2 macrophages also contribute to formation of the pro-tumor microenvironment and tumor progression by promoting angiogenesis\textsuperscript{60}.

MDSC are a myeloid cell type shown to play a critical role in establishing a cancer-supporting microenvironment\textsuperscript{61} and implicated in suppression of anti-tumor immune responses\textsuperscript{62}. The role of MDSC has been the focus of a recent Molecular Pathways by Lu and Gabriolvich\textsuperscript{27} describing MDSC producing NO and ONOO- leading to protein modifications in vivo and vitro. A recent paper by us also identified a pivotal role for iNOS and ROS as mediators of MDSC recruitment and cancer-mediated immunosuppression, as in vivo melanoma tumor-expressed iNOS regulated MDSC induction by modulating VEGF release, and that pharmacologic iNOS inhibition depletes intratumoral MDSC and unmasks anti-tumor immunity\textsuperscript{63}. We have further investigated the role of iNOS in orchestrating MDSC migration in response to iNOS or NO inhibition, leading to upregulation of CXCL-10\textsuperscript{23}, as well as that iNOS inhibition blocks release of a number of inflammatory mediators by melanoma cells, including VEGF, which we subsequently showed to be required for accumulation and functional activation of MDSC\textsuperscript{63}. Another interesting paper shows in several preclinical cancer models that nitration of the chemokine CCL2 abolished intratumoral infiltration of anti-tumor CD8+ T cells, and in clinical specimens that tumor-infiltrating T cells are depleted in NO-expressing tumors\textsuperscript{64,65}. COX2 can also play a role in MDSC induction, via the direct MDSC-stimulating effects of its enzymatic product PGE2\textsuperscript{66,67,68}. Nagaraj et al also showed that pharmacologic modulation of ROS with an antioxidant CDDO-Me triterpenoid compound resulted in dramatic reduction of ONOO- and suppressed MDSC function and boosted immunity in tumor-bearing mice and in cancer patients receiving the drug in a clinical trial\textsuperscript{69}. Each of these papers suggests potential therapeutic strategies for reversing tumor-mediated immunosuppression by blocking inflammation-induced MDSC, particularly involving NO regulation.

Clinical-Translational Advances:

Based on the contention that a cancer’s “inflammatory niche” drives alterations in critical protein function via identifiable S-NO post translational modifications as proposed above, two clinical-
translational advances are in progress. The first is development of a marker set or predictive signature of inflammation that would prove useful for targeting. This work is active currently with a clinically useful melanoma protein signature around iNOS, IL-1s, IL-6, MIF, pSTAT3 and at a global level of total nitrated tyrosines and total S-NO at both the cellular and microenvironmental levels still being resolved. As our detection methods become more sensitive and specific, it is likely the modified proteins such as SNO-PTEN or AKT will also be useful markers. Another important complimentary marker in the tumor microenvironment was MIF itself also from both melanoma cells and infiltrating immune cells, for which its presence negatively associated with CD74 expression. Our work in progress as well as that of others continues to support the growing evidence that “an inflammatory protein signature” is likely to continue as a consideration of an independent prediction model for clinical outcome, still to be validated. A large set of markers is undergoing analysis on both blinded patient tumor samples, and prospective testing on tumor samples from ongoing clinical trials. Ideally, a blood test and specific anti S-NO-protein epitope is envisioned, and underway using a new method named the SNO-Flo system49. Direct measurements of SNOed proteins and their loss of this adduct after use of an anti-inflammatory agent is currently a view considered as a future consideration as a set of predictive markers.

A second advance we view is the development of clinically useful pharmacologic approaches with carefully selected anti-oxidants and/or small molecule inhibitors of RNS, possibly combined with inhibitors of other pro-oxidant enzymes to permit the restoration of susceptibility to immune or targeted therapy in melanoma patients. The known reversibility of SNO post-translational modifications suggests a novel paradigm for attempting to restore the apoptotic pathway in the inflammatory-driven tumors of patients for therapeutic goals. We now propose pharmacologic approaches with carefully selected anti-oxidants which will inhibit the reactive nitrogen species of oxidants to permit the restoration of susceptibility to immune or targeted therapy in melanoma patients, possibly predicted by reversal of SNO on selected markers, for which much research is currently underway.

Although NSAIDs have been popularized and continue to be assessed for prevention of cancers, their application to inhibiting inflammation supporting metastatic disease remains to be considered. The in vivo use of other classes of antioxidants in treatment of established cancers has been explored. As one of the most investigated antioxidant, Resveratrol, shown to be protective against DNA damage by inhibiting hydro peroxidases and scavenging free-radicals 70. In melanoma, Resveratrol has been shown to inhibit growth and induce apoptosis in cell lines, potentially by regulating p53 expression, CDKs, and COX-2 71, 72. Another much studied agent, Curcumin (Curcuma longa), has been shown by many groups, including us, as an apoptosis inducer in human melanoma cells, most known pathways is through the inhibition of NK-kb which drives iNOS 73, 74. Other approaches include clinically applicable arginine antagonists, such as L-NIL which was developed for treating asthma and used in our recent mouse model 11 and for which an entire class of agents is currently available. Other drugs with anti-cancer potential known to downregulate iNOS include WP-760 75 which was found to inhibit iNOS production, and also localize to the mitochondria and activate caspase 3. As aberrant expression of inflammatory molecules is common to many cancers, it stands to reason that therapeutic approaches targeting these molecules have the potential for anti-tumor efficacy across a broad range of tumor types. In fact, much of the preclinical literature describing these approaches uses targeted inhibition of inflammatory
molecules to simultaneously prove their relevance to cancer, and invoke therapeutic efficacy. As discussed above, we have shown that pharmacologic inhibition of iNOS has anti-tumor effects in various melanoma models which may be directly related to tumor cell-intrinsic growth and survival pathways\textsuperscript{11};\textsuperscript{15} or indirect and mediated by effects on the tumor-promoting microenvironment including vascular\textsuperscript{11} or immunoregulatory cells\textsuperscript{63}. The role of MDSCs is particularly relevant here as Nagaraj et al also showed that an antioxidant triterpenoid compound can suppress MDSC function and boost immunity in tumor-bearing mice and in cancer patients receiving the drug in a clinical trial\textsuperscript{69}.

In conclusion, many human cancers express inflammatory molecules that lead to an intrinsic pro-oxidant environment in the cancer cell, as well as potentiate a microenvironment that drives immune escape and resistance to apoptosis. We contend that by attenuating the NO production resulting from this inflammation, possibly by repurposing currently available agents, that the prospects for cancer control will be greatly increased. Our data and that of others provides an emerging molecular model by which the RNS drive growth, immunosuppression, angiogenesis, and apoptosis resistance by specifically altering the function of signaling molecules by nitration and/or nitrosylation. We propose that the NO-contributed oxidants and the pathways that drive them may be useful targets as part of a therapeutic consideration which may be useful when combined as part of targeted and immune therapy approaches.

References


**Figure Legend:**

Simplified examples of molecular pathways known to induce NO production in cancer cells, and examples of proteins directly modified by reactive nitrogens.

Numerous mediators of chronic inflammation are produced by melanoma and microenvironment cells including growth factors (GF), transcription factors, adhesion molecules, signaling molecules and Extracellular Matrix (ECM) proteins. Melanoma tumor cells also are known to produce NO from NOS and each of the four major NOS-inducing pathways are shown in different colors (green, purple, blue, and white). Once produced, NO combines chemically with oxygen radicals to form ONOO- (peroxynitrite) resulting in direct nitrosylation/nitrosation or nitration on many important signaling proteins (in red with *) in the tumor cells. The concentration of NO also influences the anti-tumor immune response, as shown in the box on left, with increased NO associated with immune suppression. Immune system cells are functionally affected including the recruitment of activate myeloid-derived suppressor cells (MDSC), regulatory T cells (Treg), Tumor Associated Macrophages (TAM), and Th2 lymphocytes. Once activated, MDSCs also produce high amounts of NO in the tumor microenvironment, which further contributes to the inhibition of antitumor responses and nitrosative stress.
* Posttranslational confirmation of nitration or nitrosylation affecting function of each protein consistent with supporting growth, inhibiting apoptosis and/or driving angiogenesis and growth.
Tumor microenvironment

ECM proteins
Adhesion molecules

Signaling molecules
- MAPK
- Ras/Raf
- Cox2
- PI3K
- PTEN
- AKT

Growth factors/Cytokines
- VEGFs/VEGFRs
- PDGF/PDGFRs
- FGF/FGFRs
- Chemokines/Chemokine receptors
  - CXCL-8, CXCL-12, CCL2, CXCL10, CXCR4
  - IL-1α/β, IFN-γ, TNF-α, IL6, IL8

MIF

Th1
MDSC
TAM
Th2
MDSC
Th1
CTL
MDSC

Melanoma cell

Growth factors/Cytokines
- VEGFs/VEGFRs
- PDGF/PDGFRs
- FGF/FGFRs

Chemokines/Chemokine receptors
- CXCL-8, CXCL-12, CCL2, CXCL10, CXCR4

IL-1α/β, IFN-γ, TNF-α, IL6, IL8

TLR 1-6
JAK

nRAS*
bRAF
PI3K*
AKT*
mTOR
NFkB*
Ras*
p53*
Casp-3*
Cox2

ONOO-

NO

NOS
L-Arginine

iNOS

AP-1
HIF-1α
IFN-γ

STAT1
STAT1a

M1
M2
TAM
CTL
Th2
Th1
Treg
MDSC

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