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Arginine pathways and the inflammatory response: Interregulation of nitric oxide and polyamines*: Review article

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Summary. An early response to an acute inflammatory insult, such as wound healing or experimental glomerulonephritis, is the conversion of arginine to the cytostatic molecule nitric oxide (NO). This 'anti-bacterial' phase is followed by the conversion of arginine to ornithine, which is the precursor for the pro-proliferative polyamines as well as proline for the production of extracellular matrix. This latter, pro-growth phase constitutes a 'repair' phase response. The temporal switch of arginine as a substrate for the cytostatic iNOS/NO axis to the pro-growth arginase/ornithine/polyamine and proline axis is subject to regulation by inflammatory cytokines as well as interregulation by the arginine metabolites themselves. Arginine is also the precursor for another biogenic amine, agmatine. Here we describe the capacity of these three arginine pathways to interregulate, and propose a model whereby agmatine has the potential to serve in the coordination of the early and repair phase pathways of arginine in the inflammatory response by acting as a gating mechanism at the transition from the iNOS/NO axis to the arginase/ODC/polyamine axis. Due to the pathophysiologic and therapeutic potential, we will further examine the antiproliferative effects of agmatine on the polyamine pathway.

Keywords: Agmatine – Arginine – Nitric oxide – Polyamines – Antizyme

Introduction

The structure of arginine was determined prior to the turn of the 20th century. However, it was the discovery of the urea cycle in 1932 that brought arginine to the forefront of physiology research (Krebs and Henseleit, 1932). In addition to its role as an amino acid for protein synthesis, arginine is also the precursor molecule for synthesis of urea, ornithine, nitric oxide (NO), polyamines, proline, creatine, glutamate and agmatine. The maintenance of plasma arginine levels is primarily dependent upon its synthesis in the kidney and dietary intake. Dietary arginine is not essential in healthy adult humans, demonstrating the utility of the kidney in this regard. However, it becomes 'essential' in conditions of starvation, injury or stress (Barbul, 1986). Arginine supplementation is therefore beneficial in pathophysiologic settings where systemic arginine levels decrease, such as in models of wound healing, lymphocyte responses and mitogenesis.

Two well-described pathways of arginine metabolism in inflammation include the conversion of arginine to NO, and the breakdown of arginine to urea and ornithine by arginase. These pathways are temporally regulated in acute inflammatory models such as wound healing and glomerulonephritis (Albina et al., 1990; Cook et al., 1994; Ketteler et al., 1994).

Nitric oxide

The early phase response to inflammatory insult is characterized by conversion of arginine by inducible nitric oxide synthase (iNOS) to produce high-output generation of NO in the millimolar range. Whereas low-output constitutive NOS (cNOS) generation of NO would expect to mediate its effects directly, for example by interactions with metal-containing proteins, such as heme groups, or

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interactions with free radicals (Wink and Mitchell, 1998), high-output NO generation would be expected to act indirectly via reactive nitrogen oxide species (RNOS). An interaction of NO with O_2 or O_2^- to generate RNOS NO_x or $ONOO^-$ is the first step of these effects. Although these reactions occur to a minor extent at normal physiologic conditions, the occurrence of high RNOS formation under pathological conditions where iNOS expression is induced can lead to chemical stress (Wink and Mitchell, 1998). There is a propensity of S-nitrosothiol (RS-NO) formation due to the prevalence of thiols over other biological nucleophiles. The thiols react with and quench NO_x, metal-NO and $ONOO^-$ species. Therefore, the potential for the 'indirect effects' mediated by RNOS are more likely to occur in settings of oxidative stress, i.e. pathologic conditions, where the thiol pool is depleted. High levels of RNOS can lead to lipid peroxidation, DNA damage, oxidation of thiols and nitration of tyrosine residues (Wink and Mitchell, 1998). Thus, high-output NO evokes protective actions in mammalian tissues due to its cytostatic/cytotoxic antimicrobial activity towards certain pathogens (De Groote and Fang, 1995; Stuehr and Nathan, 1989; Vincendeau and Daulouede, 1991).

Polyamines

The conversion of arginine to ornithine and urea by arginase initiates the later repair phase of the inflammatory response. Ornithine is converted to the pro-proliferative polyamines via ornithine decarboxylase (ODC), and to proline, a constituent of extracellular matrix, via ornithine aminotransferase (OAT). Juxtaposed to the cytostatic effects of NO are the pro-proliferative effects of the polyamines. Polyamines (putrescine, spermidine, and spermine) are small ubiquitous cationic molecules required for cell growth and homeostasis (Pegg and McCann, 1982; Tabor and Tabor, 1984). ODC, one of the most highly regulated eukaryotic enzymes, is the first and rate-limiting enzyme of biosynthesis metabolizing ornithine to putrescine, the first polyamine. ODC overexpression results in the transformation of NIH/3T3 cells (Auvinen et al., 1992; Moshier et al., 1993), it enhances tumor development (Clifford et al., 1995) and invasiveness (Kubota et al., 1995), and is significantly elevated in virtually all animal tumors (Scalabrino and Ferioli, 1981; Scalabrino and Ferioli, 1982). A stepwise increase in ODC activity correlating with the progression from normal colon mucosa to adenocarcinoma suggests a role for ODC in multistage carcinogenesis (Luk and Baylin, 1984; Porter et al., 1987; Radford et al., 1990). ODC is a proto-oncogene. Conversely, the depletion of intracellular polyamines inhibits cell division. In addition, arginine, but not ornithine, deprivation induces compensatory polyamine transport (Bogle et al., 1994). This observation supports the position that arginine is at the crux of polyamine synthesis as well as NO generation. The production of ornithine and its metabolism to polyamines is a principal element of the repair phase.

The arginine switch

It is easy to see the necessity in regulating the transition between these arginine pathways in the inflammatory response. Induction of pro-proliferative polyamines in the early phase would offset the beneficial effects of NO in the eradication of pathogens; just as maintaining cytostatic NO production into the repair phase would suppress the positive growth effects mediated by polyamines. In both instances arginine would become limiting. However, the components and mechanisms that regulate this temporal switch are not well understood.

An indication of interregulation of these pathways was demonstrated in the model of experimental glomerulonephritis. NOS inhibition increased both the magnitude of, and decreased the 'lag' time for, ornithine production for the repair phase, suggesting suppression of the arginine/arginase pathway by NO (Cook et al., 1994). NOS could inhibit arginase by competing for substrate, or by the generation of an intermediate in the production of NO, N^G-hydroxy-L-arginine (NOHA) (Buga et al., 1998). There are numerous examples of arginase and NOS competing for arginine. However, in experimental glomerulonephritis the cells that employ arginine for NO generation (macrophage cells) are different than those that utilize arginine for the repair functions of polyamine and proline synthesis (mesangial cells) (Cook et al., 1994; Jansen et al., 1994), suggesting that competition for substrate alone is insufficient to explain these effects in this model. NOHA is a potent arginase inhibitor (Boucher et al., 1994). The effectiveness of NOHA in producing paracrine effects *in vivo*, such as required in the glomerulonephritis model, has also yet to be determined, although NOHA levels do increase in LPS-treated rats (Hecker et al., 1995). In addition, NOHA induces caspase-3 activity and apoptosis in a breast cancer cell line, whereas depletion of polyamines decreases caspase-3 activity and does not induce apoptosis (Singh et al., 2001). These results imply effects of NOHA beyond those of specifically suppressing the arginase/ODC/polyamine axis and require further investigation.

Can the NOS/NO pathway affect polyamine biosynthesis? NO can directly alter enzymatic activity by nitrosylation or nitration. ODC has a cysteine in its active site at the dimer interface that is an absolute requirement for full enzymatic activity (Coleman et al., 1993). Due to the rapid interchange of enzymatic subunits, this cysteine may be subject to attack by NO. We and others have shown NO can directly nitrosylate ODC and inhibit enzymatic activity (Bauer et al., 2001; Satriano et al., 1999). In the rat aortic smooth muscle model, inhibition of cellular proliferation by NO was attributed to inactivation of ODC activity (Ignarro et al., 2001). NO also inactivates S-adenosylmethionine decarboxylase (SAMDC), an essential enzyme for conversion of lower to higher order polyamines, via nitrosylation of the C82 residue of the enzyme (Hillary and Pegg, 2003). Nitrosylation, unlike nitration, is readily reversible and dependent upon the oxidative state of the cell. For example, high glutathione levels typical of unstressed cells could suppress or reverse nitrosylation, whereas oxidative stress would create an environment of low glutathione levels that would promote nitrosylation, and thus inactivation of ODC activity. In cell culture systems cytokine induction of NO demonstrated a component of ODC activity that was reactivated in the presence of dithiothreitol (DTT). This ODC component directly correlated with NO generation (Satriano et al., 1999), implying NO mediated ODC inhibition occurs in cells as an early event in the inflammatory response.

Can the arginase pathway effect the NOS/NO axis? As stated above, arginase can inhibit NOS activity by competing for substrate, arginine. Yet direct competition would be insufficient means alone to explain the temporal arginine switch in the model of glomerulonephritis where NOS and arginase activities are observed in different cell types. However, cytokines and hormones can influence the balance of the arginine switch in inflammation. For example, whereas T helper 1 (Th1) cells generate interferon-γ and induction of iNOS, Th2 cells generate IL-4 and IL-10 with resultant induction of arginase and suppression of iNOS (Munder et al., 1999).

Agmatine

Arginine decarboxylase (ADC) converts arginine to agmatine. Although well described in some bacteria and plants, this is the most recent arginine pathway demonstrated in mammals (Li et al., 1994). The kidney and liver, sites of high arginine synthesis, maintain high constitutive ADC activity (Lortie et al., 1996; Morrissey et al., 1995). The intracellular concentration of agmatine in the kidney was reported by HPLC analysis approximating 430 μM with plasma concentrations of 2.8 μM (Lortie et al., 2000). Due to the lability of agmatine in the derivatization process, values reported in the literature may be underestimated. Agmatine has been shown at concentrations several fold higher than the kidney in several organs that do not demonstrate ADC activity (Lortie et al., 1996; Raasch et al., 1995), suggesting circulating agmatine could have paracrine and endocrine effects. Interestingly, many of the organs that maintain high agmatine levels are prone to environmental stress.

We believe that the principal function of agmatine has evolved from the precursor of polyamines in bacteria and plants to that of a regulatory role in mammals. Agmatine can effect both the generation of NO as well as the intracellular concentrations of polyamines. We will describe both of these events and formulate a model whereby these effects coordinate the transition of arginine from the iNOS/NO axis to the arginase/ODC/polyamine axis in the inflammatory response.

Early studies on the effects of agmatine on NO generation yielded contradictory results. Several laboratories, including ours, demonstrated vasodilatory effects of agmatine that are attenuated in the presence of NOS inhibitors (Gao et al., 1995; Ishikawa et al., 1995; Lortie et al., 1996). In endothelial cells this induction of NO was purportedly due to an increase in intracellular calcium transients, which in turn activate cNOS (Morrissey and Klahr, 1997). These studies demonstrate that activation of cNOS is a downstream component of agmatine-mediated vasodilation, although other NO independent effects of agmatine may also contribute to this outcome (Blantz et al., 2000). Conversely, other laboratories utilizing cell culture or *ex vivo* models have observed suppression of NO generation with agmatine administration (Auguet et al., 1995; Feng et al., 2002; Galea et al., 1996). However, studies using highly purified enzyme preparations have demonstrated that agmatine itself is neither a substrate for, nor inhibitor of, NOS (Komori et al., 1994; Yokoi et al., 1994). Our findings indicate the aldehyde metabolite of agmatine, guanidinobutyraldehyde, but not agmatine itself, is the NOS inhibitory moiety (Satriano et al., 2001b). That it is not agmatine, but agmatine aldehyde that inhibits NOS would explain why agmatine was not able to inhibit NOS in purified enzyme systems but could inhibit NOS in cell culture and *ex vivo* experiments where it could be metabolized to an aldehyde by endogenous amine oxidases. The conversion of agmatine to an aldehyde for iNOS inhibition is fundamental to the proposed model system (Fig. 1).

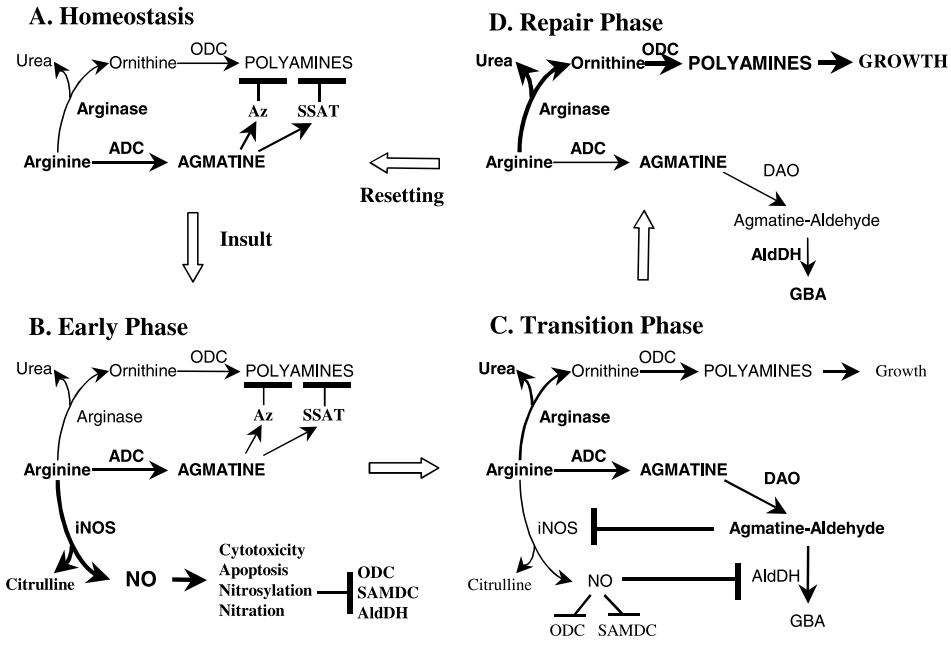

Fig. 1. Proposed interregulation of arginine pathways by ADC metabolites. In inflammatory models, arginine to NO production is an early phase response whereas the production of ornithine and polyamines is a later repair phase response. **A** Agmatine, in part by adding to the free polyamine pool, can induce antizyme and/or SSAT to aid in the regulation of intracellular polyamine levels in normal cell homeostasis. **B** The early phase of an acute inflammatory response: induction of iNOS and NO mediated events. **C** Suppression of iNOS via agmatine aldehyde comprises the transition phase: AO induction metabolizes agmatine to an aldehyde. Nitrosylation by NO inhibits AldDH activity and suppresses the further metabolism of agmatine aldehyde. Suppression of iNOS can occur by several other factors released during inflammation, such as cytokines. **D** The metabolism of agmatine shifts its repression away from the polyamines. This shift is permissive for growth and supports the repair phase. Activation of AldDH occurs after suppression of iNOS allowing metabolism of the aldehydes. Resetting to (**A**) occurs when AO returns to normal levels. Bars represent negative regulation. *ODC*, ornithine decarboxylase; *ADC*, arginine decarboxylase; *NO*, nitric oxide; *iNOS*, inducible nitric oxide synthase; *DAO*, diamine oxidase; *AldDH*, aldehyde dehydrogenase; *GBA*, guanidinobutyric acid

Agmatine is shown to affect intracellular polyamine levels by induction of antizyme (Satriano et al., 1998) and/or by induction of spermine/spermidine N-acyltransferase (SSAT) activity (Vargiu et al., 1999), an enzyme in the back conversion from higher to lower order polyamines (spermine → spermidine → putrescine). There are at least three isoforms of antizyme to date. Agmatine induces antizyme-1 and is the only endogenous molecule exclusive of the canonical polyamines themselves with this capacity. The effects of agmatine on the other isoforms of antizyme have not been evaluated. In this discussion antizyme will signify the antizyme-1 isoform. Antizyme expression increases in response to high intracellular polyamine levels. Antizyme, in turn, inhibits polyamine biosynthesis and polyamine import (Mitchell et al., 1994; Suzuki et al., 1994) while increasing polyamine export (Sakata et al., 2000). This is a rapid response system as the cell maintains antizyme mRNA that is translated to full length, active antizyme by a programmed +1 translational frameshift in response to high polyamine levels (Matsufuji et al., 1995). Antizyme inhibits polyamine biosynthesis by binding and inhibiting ODC, and promoting its degradation by the 26S proteasome in an ubiquitin independent fashion. It is then recycled to bind and inhibit another ODC monomer. Antizyme is a tumor suppressor. Several studies support antizyme as a promising means of attenuating neoplastic growth (Feith et al., 2001; Iwata et al., 1999; Koike et al., 1999; Pegg et al., 2003).

In accord with these observations, agmatine administration markedly reduced both intracellular polyamine levels, and cellular proliferation in a transformed kidney proximal tubule cell line (MCT) (Satriano et al., 1998). We found that agmatine suppressed ODC activity and proliferation in all immortalized and transformed cell lines examined (unpublished data and (Satriano et al., 1998)). Agmatine can also reduce intracellular polyamines by upregulation of SSAT (Vargiu et al., 1999). The resultant lower order and acetyl polyamines are more readily exported from the cell.

Agmatine enters mammalian cells via the polyamine transporter (Cabella et al., 2001; Satriano et al., 2001a).

As polyamine transport is positively correlated with proliferation rate (Bogle et al., 1994; Moulinoux et al., 1991; Pegg, 1988), we examined the effects of agmatine on several mammalian cell lines. We observed an increased sensitivity of transformed cell lines, relative to their non-transformed counter-parts, to the antiproliferative effects of agmatine due, in part, to preferential import and accumulation of the molecule (manuscript in preparation). We find the decreased growth response by agmatine is attributed to an active G1 arrest of the cell cycle, and is independent from apoptotic attrition in an H-ras transformed NIH/3T3 cell line (Ras/3T3). Ras/3T3 cells administered agmatine display temporal increases in antizyme and cyclin kinase inhibitor (CKI) expression with concurrent decreases in retinoblastoma protein (Rb) phosphorylation and cyclin A expression (unpublished data). Rb is a tumor suppressor protein considered the guardian of the G1 restriction site, and thus the transition from the G1 to S phase of the cell cycle. Rb must be inactivated by cyclin/cyclin dependent kinase mediated hyperphosphorylation to allow this G1 to S phase transition. CKI can act by suppressing the hyperphosphorylation of Rb, allowing it to remain active and inhibiting G1 to S transition.

Inhibition of proliferation by agmatine also occurs in cell lines in which these CKI are suppressed or deficient, suggesting a redundant mechanism of arrest by agmatine in addition to the temporal CKI mediated G1 arrest observed in Ras/3T3 cells. The mechanism(s) of arrest is currently under investigation. In primary rat hepatocytes where agmatine significantly increases SSAT activity an increase in apoptosis is observed (Gardini et al., 2001; Vargiu et al., 1999). Antiproliferative effects of agmatine have been observed in *in vivo* models as well (Dudkowska et al., 2003; Ishizuka et al., 2000).

Hypothesis: The agmatine pendulum

In this paradigm we propose agmatine would act as a guardian against aberrant proliferation in the normal, unstressed physiologic state. In this regard intracellular agmatine levels would be complimentary, or additive, to the endogenous polyamine pool in their ability to bring about the induction of antizyme in the regulation of intracellular polyamines. This would effectively lower the threshold levels of 'free' intracellular polyamine required for antizyme induction. Other means, such as increasing SSAT activity (Vargiu et al., 1999) or mechanisms yet unresolved, could also be employed by agmatine to aid in this protective antiproliferative function. As such, agmatine has the capacity to defend against increased intracellular polyamine levels required for growth (Fig. 1A) (Satriano et al., 1998).

The onset of the inflammatory response is marked by a transient upregulation of iNOS and generation of high NO levels. NO would promote cytostatic/bactericidal effects, as well as the nitrosylation and nitration of several proteins and enzymes (Fig. 1B). Nitrosylation of ODC and SAMDC by NO can inhibit both polyamine biosynthesis and conversion to higher order polyamines (putrescine → spermidine → spermine), respectively (Bauer et al., 2001; Hillary and Pegg, 2003; Satriano et al., 1999). Another enzyme inactivated by NO mediated nitrosylation that is pertinent to this discussion is aldehyde dehydrogenase (AldDH) (McDonald and Moss, 1993).

In this model we propose that the transition from the NO phase to the advent of the repair phase would be marked by increased amine oxidase activity, such as diamine oxidase (DAO) which metabolizes agmatine to agmatine aldehyde (Holt and Baker, 1995) (Fig. 1C). However, it is unknown whether induction of DAO, or another amine oxidase with this capacity, occurs in pathological settings in cells that do not normally express the enzyme. The precedent for such an enzyme response is iNOS, which is markedly induced by inflammatory cytokines in all cell types. The difference is that iNOS is induced early and robustly in the response whereas a lag phase would be necessary prior to the induction of DAO, if our hypothesis is correct. However, DAO levels decrease in viral hepatitis (Gang et al., 1976), inflamed appendix (Menningen et al., 1986), Crohn's disease (Schmidt et al., 1990) and ulcerative colitis (Mennigen et al., 1990). Although DAO does increase in partial small bowel resection (Kusche et al., 1988) and in the Arthus reaction (Tachibana et al., 1986), this occurs early, with decreasing DAO levels reported as the disease progresses. Opposite to what we would expect for our model. Also, several lines of evidence demonstrate polyamines can induce DAO expression, suggesting a protective feedback loop (D'Agostino et al., 1990; Daniele and Quaroni, 1991; Perin et al., 1986). In accord with this idea DAO increases in some cancers, such as experimentally induced gliomas (Sessa et al., 1993) and hepatocarcinoma (Sessa et al., 1990), whereas the potentiation of other cancers, such as colorectal cancer (Linsalata et al., 1993) and large bowel tumors (Mennigen et al., 1988) may be attributed to a decrease in DAO, and thus a decrease in polyamine degradation leading to transformation (Quash et al., 1979). Alternatively, DAO activity could be a function of the invading inflammatory cells. Indeed, human eosinophils (Herman, 1982; Zeiger et al., 1976) and neutrophils

(Baenziger et al., 1994) can generate DAO activity in inflammatory states. Interestingly, partial hepatectomy (Sessa et al., 1981) or nephrectomy (Desiderio et al., 1982) maximally increase DAO activity at delayed time points that could correspond to the repair phase of our model.

ADC is a mitochondrial bound enzyme whose product, agmatine, has been shown to bind imadazoline (I_2) receptors. Both monoamine oxidase (MAO) and semicarbazide-sensitive amine oxidase (SSAO) activities have been localized to the mitochondria (Senatori and Nicotra, 1988), and may also co-localize with I_2 binding sites (Marti et al., 1998), making them attractive candidates for agmatine regulation. Although changes in both MAO and SSAO were associated with malignancy in experimentally induced breast cancer (Lizcano et al., 1990), LPS/ IFN-γ administration had little effect on MAO activity in astrocytes (Mazzio et al., 2003). However, SSAO activity is associated with inflammatory conditions and number of pathophysiological conditions such as diabetes, heart and vascular diseases, cirrhotic liver inflammation, atherogenesis, and some cancers (for review see (Boomsma et al., 2003; Yu et al., 2003)). SSAO is present in a wide variety of tissues, yet its source, regulation of expression and functional role has not been well resolved. Another protein, vascular adhesion protein-1 (VAP-1), has a high degree of sequence identity to SSAO and demonstrates SSAO activity. It is expressed in multiple tissues and cell types and is upregulated at sites of inflammation (Salmi et al., 1993). As an adhesion molecule VAP-1 also supports adhesion of lymphocytes to, and transmigration across, endothelial cells (Lalor et al., 2002). Furthermore, the soluble form of VAP-1 may be the primary soluble SSAO in man (Kurkijarvi et al., 2000). Thus, further investigation is required to delineate the amine oxidase responsible for metabolizing agmatine to an aldehyde in inflammatory settings (depicted as DAO in Fig. 1).

In the LPS model of sepsis we observed beneficial effects of agmatine that were indistinguishable from those of a selective iNOS inhibitor (Satriano et al., 2001b; Schwartz et al., 1997). To inhibit iNOS agmatine needs first to be converted to an aldehyde (Satriano et al., 2001b), implying conversion by an amine oxidase under these conditions. The amine oxidase induced in response to LPS has yet to be delineated. That agmatine is neuroprotective in ischemic neuronal injury may also be attributed to similar effects on the arginine pathways (Fairbanks et al., 2000; Feng et al., 2002; Gilad and Gilad, 2000; Yu et al., 2000).

Metabolism of agmatine to an aldehyde by an amine oxidase would shift the effects of agmatine away from polyamine regulation, and thus be permissive for growth. As NO inactivates AldDH, the enzyme that converts the aldehyde into a stable acid, the aldehyde form of agmatine would be sustained. Increased levels of agmatine aldehyde could aid in the suppression of NO generation (Fig. 1C). As such agmatine aldehyde could exert beneficial constraining influences on iNOS in an inflammatory setting. Lower NO relieves inhibition of ODC and SAMDC promoting growth, and of AldDH allowing metabolism of agmatine aldehyde to continue to guanidinobutyrate (GBA) (Fig. 1D). Resetting occurs with DAO returning to normal levels. We thus envision this potential feedback loop to work in a pendulum-like manner with agmatine alternately regulating intracellular polyamine levels, then iNOS, and finally back to polyamines after resetting (Fig. 1).

In summary, the products of a third arginine metabolic pathway, via ADC, pose the potential to coordinate regulation of both the antiproliferative NO and pro-proliferative polyamine repair phase pathways of arginine in the inflammatory response.

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