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MINIREVIEW ARTICLE

Polyamine catabolism in carcinogenesis: potential targets for chemotherapy and chemoprevention

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Abstract Polyamines, including spermine, spermidine, and the precursor diamine, putrescine, are naturally occurring polycationic alkylamines that are required for eukaryotic cell growth, differentiation, and survival. This absolute requirement for polyamines and the need to maintain intracellular levels within specific ranges require a highly regulated metabolic pathway primed for rapid changes in response to cellular growth signals, environmental changes, and stress. Although the polyamine metabolic pathway is strictly regulated in normal cells, dysregulation of polyamine metabolism is a frequent event in cancer. Recent studies suggest that the polyamine catabolic pathway may be involved in the etiology of some epithelial cancers. The catabolism of spermine to spermidine utilizes either the one-step enzymatic reaction of spermine oxidase (SMO) or the two-step process of spermidine/spermine N^1-acetyltransferase (SSAT) coupled with the peroxisomal enzyme N^1-acetylpolyamine oxidase. Both catabolic pathways produce hydrogen peroxide and a reactive aldehyde that are capable of damaging DNA and other critical cellular components. The catabolic pathway also depletes the intracellular concentrations of spermidine and spermine, which are free radical scavengers. Consequently, the polyamine catabolic pathway in general and specifically SMO and SSAT provide exciting new targets for chemoprevention and/or chemotherapy.

Keywords Polyamines · Reactive oxygen species · Spermine · Spermidine · Spermine oxidase · Spermidine/spermine N^1-acetyltransferase

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Introduction

In eukaryotic cells, the polycationic polyamines putrescine, spermidine, and spermine are essential factors for embryonic development, differentiation, and cell proliferation. The total intracellular concentration of polyamines is typically in the millimolar range. However, the concentration of free polyamines in the cell is low and is carefully regulated by metabolic modulation and/or polyamine uptake, sequestration, and intermolecular associations (Casero and Marton 2007) (Fig. 1). The main roles of polyamines in the support of cell growth and survival are through association with nucleic acids, maintenance of chromatin conformation, regulation of specific gene expression, ion-channel regulation, maintenance of membrane stability, and free-radical scavenging (Igarashi and Kashiwagi 2010; Lopatin et al. 1994; Williams 1997; Ha et al. 1998; Kurata et al. 2006).

Diet is the major source of exogenous polyamines, some of which are also obtained from gastrointestinal bacteria (Atiya et al. 2011; Löser et al. 1999). The uptake of polyamines in mammalian cells is not yet completely

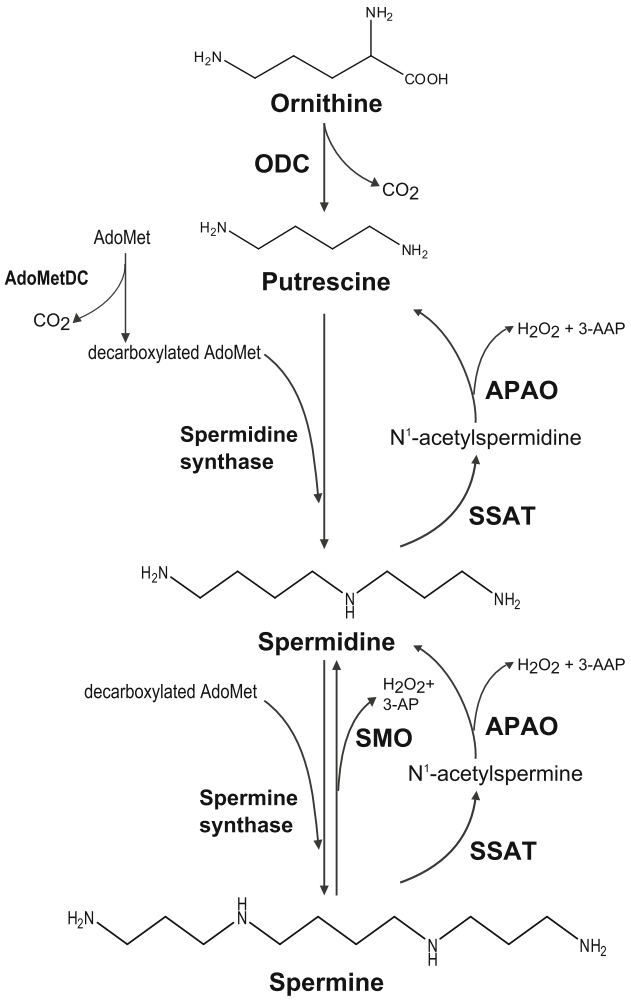

Fig. 1 Polyamine metabolism. Ornithine decarboxylase (ODC) is required for the first step in polyamine synthesis in which ornithine is decarboxylated to produce putrescine. The decarboxylation of *S*-adenosylmethionine (AdoMet) by AdoMet decarboxylase (AdoMetDC) yields decarboxylated AdoMet, which is then used as the aminopropyl donor for spermidine synthase and spermine synthase to produce the higher polyamines spermidine and spermine, respectively. The conversion to lower level polyamines is made in either two-steps by the spermidine/spermine N^1-acetyltransferase (SSAT)/N^1-acetylpolyamine oxidase (APAO) mechanism or directly from spermine to spermidine by spermine oxidase (SMO). The activities of both APAO and SMO lead to the production of H_2O_2 and the aldehydes 3-acetoaminopropanal (3-AAP) and 3-aminopropanal (3-AP), respectively

characterized, but there is evidence that it is energy dependent and could involve an endocytic caveolin-dependent mechanism or an unknown transporter (for a review on polyamine transport, see Poulin et al. 2012). Polyamines are bound by weak interactions, primarily hydrogen bonds, to various anions in the cell, including nucleic acids, proteins, and phospholipids. Consequently, most of the interactions in which polyamines are involved are readily reversible, thereby complicating the understanding of their molecular functions.

Recent findings have suggested possible links between polyamine catabolism and tumor development (for a review on polyamine catabolism and disease, see Casero and Pegg 2009). In particular, the polyamine catabolic enzymes spermine oxidase (SMO), spermidine/spermine N^1-acetyltransferase (SSAT), and N^1-acetylpolyamine oxidase (APAO) are thought to be potential sources of oxidative stress capable of damaging crucial cellular machinery or potentially contributing to oxidative DNA damage or chromatin instability. The purpose of this review is to provide an overview of the results suggesting a direct molecular link between polyamine catabolism and the early stages of cancer development.

Polyamine functions

Polyamines have numerous functions that affect growth and development. The total polyamine content increases rapidly in proliferating or differentiating cells and the depletion of polyamines is accompanied by a decrease in cell proliferation and, in specific cases, cell death (Luk et al. 1981, 1982; Casero et al. 1989). However, in other cell types, polyamine depletion may protect against the ability of some agents to induce apoptosis through a mitochondrial-mediated pathway (Yuan et al. 2002).

Most polyamines exist as a polyamine–RNA complex, and this influences protein synthesis. Indeed, the binding of polyamines to RNA causes structural changes leading to both the stimulation of and an increase in the efficiency of protein synthesis (Igarashi and Kashiwagi 2010). In bacteria, the "polyamine modulon" is a set of genes whose expression is increased by polyamines as a result of increased translation. These proteins are thought to be involved in stimulating the translation of transcription factors and kinases that can increase the expression of other proteins (Yoshida et al. 2004). Moreover, polyamines have been shown to regulate the synthesis of some proteins involved in eukaryotic translation. For example, the translation elongation factor eIF5A requires a posttranslational modification to form hypusine, and this reaction requires spermidine as a precursor (Park et al. 2010).

Interest in understanding the roles of polyamines in hyperproliferative and cancerous tissues has led to the development of specific inhibitors to every step of polyamine metabolism. For example, treatment with the ornithine decarboxylase (ODC) inhibitor alpha-difluoromethylornithine (DFMO) results in the depletion of polyamines and a delay in cell cycle progression and inhibition of DNA synthesis (Ray et al. 1999). Moreover, recently the overexpression of SSAT in HeLa cells was shown to cause polyamine depletion, total inhibition of protein synthesis, and growth arrest (Mandal et al. 2013).

Elevated levels of polyamines in tumor cells may also be crucial for understanding tumor biology as polyamines have been described as protective against the induction of

apoptosis. However, this effect requires further study since in some cell types, polyamines have been shown to enhance apoptosis (for a review on the controversial effect of polyamines in the induction of apoptosis, see Schipper et al. 2000). The protective effect could be attributable, at least in part, to the observation that polyamines, in particular spermine, act as reactive oxygen species (ROS) scavengers (Ha et al. 1998). Moreover, the higher polyamines, particularly spermine, have also been shown to reduce proinflammatory cytokine expression and other mediators of inflammatory damage (Zhang et al. 1997; ter Steege et al. 1999).

Eukaryotic polyamine biosynthesis

The precursor to the polyamines is ornithine, an amino acid intermediate of the urea cycle, which is derived from arginine by the action of arginase (EC 3.5.3.1). ODC, a pyridoxal phosphate-dependent enzyme (EC 4.1.1.17), is the first rate-limiting step in polyamine synthesis in which ornithine is decarboxylated to produce putrescine (Pegg 2006). ODC has a very short half-life and is regulated by ODC antizyme, a small protein induced by polyamines themselves; ODC antizyme can also regulate the polyamine transport system (Pegg 2006).

Another rate-limiting step in polyamine biosynthesis is the decarboxylation of S-adenosylmethionine (AdoMet) by AdoMetDC (EC 4.1.1.50), which yields decarboxylated AdoMet (Pegg 2009). The decarboxylated AdoMet then serves as an aminopropyl donor to form spermidine and spermine by two constitutively expressed aminopropyl transferases: spermidine synthase (EC 2.5.1.16) and spermine synthase (EC 2.5.1.22).

Polyamine catabolism

Spermidine/spermine N^1-acetyltransferase (SSAT)/N^1-acetylpolyamine oxidase (APAO)

SSAT (EC 2.3.1.57) is a propylamine acetyltransferase that catalyzes the formation of N^1-acetylspermine, N^1, N^{12}-diacetylspermine, and N^1-acetylspermidine by the transfer of an acetyl group from acetyl-CoA to the N^1 position of spermidine or spermine. The human gene for SSAT, *SAT1*, is present on the X chromosome at Xp22.1. The acetylated polyamines have two potential fates. First, acetylated polyamines can be exported from the cell. Second, acetylated spermidine and spermine are substrates for the FAD-dependent, peroxisomal APAO (EC 1.5.3.13). APAO produces spermidine or putrescine, depending on the starting substrate, 3-aceto-aminopropanal (3-AAP), and H_2O_2 (Fig. 1). SSAT is an inducible enzyme, while APAO is generally constitutively expressed and rate-limited by the availability of the acetylated substrate. The coupled responses of SSAT and APAO are responsible for preventing the over-accumulation of polyamines (for a review, see Pegg and Casero 2011).

Different stimuli, such as the natural polyamines, polyamine analogues, hormones and cytokines, drugs, and stress pathways, are able to induce SSAT expression (for a review, see Pegg 2008). Among them, tumor-necrosis factor-α (TNF-α), a key mediator of the inflammatory response, is capable of inducing SSAT through NF-kB in non-small cell lung cancer cells (Babbar et al. 2006a), and Nrf2 stimulates SSAT transcription in response to the addition of exogenous ROS such as H_2O_2 (Smirnova et al. 2012); both of these can be instrumental transcription factors in response to stress.

Spermine oxidase

As previously stated, another enzyme in polyamine catabolism is SMO (EC 1.5.3.16), an inducible FAD-dependent enzyme that catalyzes the breakdown of spermine, producing spermidine, H_2O_2, and the aldehyde 3-aminopropanal (3-AP) (Wang et al. 2001; Wang et al. 2003). The human gene for SMO (*SMOX*) is located on chromosome 20p13 and codes for several splice variants (Murray-Stewart et al. 2002, 2008). The predominant human splice variant, SMO1 (SMO/PAOh1), codes for a 61 kDa protein containing 555 amino acids. The purified recombinant protein demonstrated a K_m of 1.6 μM and a V_{max} of 7.7 μmol/mg protein/min for spermine (Wang et al. 2003). SMO is normally present at low levels, but its expression can be induced during cellular stress and is thought to be regulated at the transcriptional level and by mRNA stabilization (Wang et al. 2005).

Polyamine catabolism, inflammation, and cancer

Inflammation is a normal response to many kinds of damage and serves to recruit the appropriate actors to repair damaged tissues and/or eliminate infection. However, chronic inflammation has been shown to be associated with long-term damage and an increased risk for the development of cancer (e.g., gastritis, ulcerative colitis, Barrett's esophagus) (for a review, see Macarthur et al. 2004). However, the specific pathways related to this link between chronic inflammation and carcinogenesis are not well understood.

ROS at low levels are involved in different signaling pathways; for example, activation of the NF-kB, ERK1/2, and PI3K pathways is modulated by low ROS levels and

increases cell growth and proliferation (Schreck et al. 1991). By contrast, ROS at high levels may disrupt proper signaling in the cell and damage DNA and other crucial macromolecules in the cell, which in turn, may lead to DNA instability and, consequently, senescence or apoptosis. However, in cases of sustained elevated ROS levels, such as in chronic inflammation, some cells can escape the activation of the apoptotic pathways and potentially initiate the development of cancer (for reviews on inflammation and cancer, see Weinberg and Chandel 2009; Reuter et al. 2010). Indeed, it has been demonstrated that mice lacking the glutathione peroxidase genes *Gpx1* and *Gpx2* develop tumors in the digestive tract following an increase in inflammation in the tissues. This is evidence that tumors can be produced by a deficiency in antioxidant enzyme levels and, specifically, the consequent increase of the amount of H_2O_2 in the cells (Chu et al. 2004).

As mentioned, the pro-apoptotic cytokine TNF-α and other inflammatory stimuli induce the expression of both SSAT and SMO, and the resulting H_2O_2 has been demonstrated to result in DNA oxidation (Babbar et al. 2006a, b). Thus, the combination of the production of H_2O_2, the loss of the higher polyamines as ROS scavengers, and the general perturbation of the polyamine pool by SSAT/APAO and SMO is being investigated as a possible mechanistic link between inflammation and the development of cancer.

Prostate cancer is linked to chronic or recurrent inflammation (for a review, see Bardia et al. 2009). In particular, the initiation of prostate carcinomas appears to be associated with inflammation followed by a hyperproliferative state (De Marzo et al. 1999). In immunohistochemical (IHC) studies of prostate cancer tissue microarrays, SMO was shown to be associated with preneoplastic prostatic lesions (Goodwin et al. 2008). Tissue cores representing a range from normal to adenocarcinoma were scored for SMO staining. A small increase in SMO expression was observed in the precursor prostatic inflammatory atrophy (PIA) lesions, while a large increase in SMO staining was observed in the early prostatic intraepithelial neoplastic (PIN) lesions. Invasive prostate cancer also had increased SMO compared to normal tissues. However, in a transgenic model of prostate cancer (TRAMP mice), the overproduction of SSAT resulted in a significant reduction in aberrant growth of the mouse genitourinary tract, which is characteristic of these mice (Kee et al. 2004), suggesting that the induction of SSAT may be beneficial in the treatment of at-risk patients. These findings indicate that further studies are needed to understand the role of polyamine catabolism in prostatitis and prostate cancer.

SMO has also been associated with inflammation caused by pathogens. *Helicobacter pylori* is a bacterial pathogen that causes both chronic gastritis and peptic ulcer disease and is also strongly associated with gastric cancer. RAW 264.7 macrophages infected with *H. pylori* stimulate polyamine synthesis through ODC and also induce SMO, which was shown to be the source of H_2O_2 leading to mitochondrial depolarization and macrophage apoptosis (Chaturvedi et al. 2004). This increase in SMO activity in macrophages and the subsequent induction of their apoptosis may be a means by which *H. pylori* evades the innate immune system. When these same cells were treated with *N*,*N*′-bis(2,3-butadienyl)-1,4-butanediamine (MDL72527), an inhibitor of polyamine oxidases, or catalase, which catalyzes the decomposition of hydrogen peroxide, or by expression of siRNA against SMO, there was a significant decrease in H_2O_2 and an increase in cell survival. *H. pylori*-infected human gastric epithelial cells also exhibit a similar induction of SMO accompanied by an increase in DNA oxidation as assessed by 8-hydroxy-2′-deoxyguanosine and comet assays (Xu et al. 2004). Thus, SMO may provide a mechanistic link between *H. pylori* infection and the development of gastric cancer (Chaturvedi et al. 2012).

Polyamine catabolism, in particular SMO, has also been linked to the effects of another pathogen, enterotoxigenic *Bacteroides fragilis* (ETBF), which produces an enterotoxin (*B. fragilis* toxin, BFT) causing acute diarrheal diseases in humans and animals. It has been demonstrated that in culture, BFT upregulates SMO in human colonic epithelial cells with consequent H_2O_2 generation (Goodwin et al. 2011). In a multiple intestinal neoplasia ($Min^{Apc\Delta 716}$) model of tumorigenesis utilizing ETBF-induced inflammation of the distal colon to cause the formation of numerous polyps, the administration of the polyamine oxidase inhibitor MDL72527 reduced the number of polyps in infected $Min^{Apc\Delta 716}$ mice. Studies are ongoing to determine the relationship between ETBF induction of polyamine catabolism and tumorigenesis. One potential link may involve the recruitment of epigenetic chromatin modifiers to the site of oxidative DNA damage; such a response has been observed in the ETBF-inflammation model mentioned above (O'Hagan et al. 2011).

Ulcerative colitis (UC) is a chronic, relapsing inflammatory disease of the gastrointestinal tract that increases the risk for colorectal cancer as much as 20–30 fold (Riddell et al. 1983). Previously, it was determined that the cellular spermine level decreases and spermidine level increases during active UC (and returns to normal after the inflammatory episode). However, the small increase in SSAT observed was not sufficient to explain the extent of spermine catabolism (Kobayashi et al. 1992; Obayashi et al. 1992; Weiss et al. 2004). In a study of 69 UC patients, colon biopsies were analyzed for both SMO protein (IHC) and mRNA expression (Hong et al. 2010). IHC scoring determined that in these patients, there was an increase in SMO in the mononuclear inflammatory cells and *SMOX*

mRNA was increased in the tissue biopsies obtained from diseased versus normal patients. As with the prostate cancer study described above, this study of UC indicates a correlation of SMO expression in early inflammatory diseases linked to cancers.

To evaluate the role of SSAT expression on intestinal tumorigenesis, transgenic mice bearing multiple copies of the *Sat1* gene, such that SSAT is elevated in the majority of tissues including the intestine, were crossed with mice bearing a truncation in the tumor suppressor gene *adenomatous polyposis coli* (*Apc*), which causes a multiple intestinal neoplasia (Min) phenotype. In Min mice overexpressing SSAT, there was a significant increase in polyps in both the small intestine and the colon, suggesting that polyamine catabolism through SSAT may increase the initiation of disease. Further, when Min mice were crossed with SSAT knockout mice, there was a significant reduction in the number of tumors in the intestine (Tucker et al. 2005).

Other mouse models have also implicated the importance of SSAT in the induction or severity of disease. In a mouse model of renal ischemia-reperfusion injury (IRI), *Sat1* and *Smox* expression was induced in the kidney 12–24 h after IRI (Zahedi et al. 2003). In IRI, tissue undergoes oxidative damage when there is a temporary loss of blood flow followed by the restoration of blood flow. IRI is associated with stroke, myocardial infarction, and acute tubular necrosis associated with native and allograft kidney disease. Further, SSAT knockout mice exhibited significant protection from tissue damage in hepatic and renal models of IRI (Zahedi et al. 2009) as well had attenuated liver damage in a carbon tetrachloride hepatotoxicity model (Zahedi et al. 2012). Similarly, in a model of endotoxin-induced acute kidney injury, both *Sat1* and *Smox* expression were elevated in lipopolysaccharide-treated mice and SSAT knockout mice had less severe kidney damage than did wild-type mice treated with polyamine oxidase inhibitor MDL72527 (Zahedi et al. 2010a). The oxidation of glutathione, as measured by GSSG/GSH ratios was also reduced in SSAT knockout and MDL72527 wild-type mice implicating polyamine catabolism as an important source of oxidative damage in this model of inflammation.

An increase in polyamine catabolism may also be associated with brain injury, neuroinflammation, and neuronal cell death. In a mouse model of traumatic brain injury, SSAT expression increases in neuronal tissues in the early stages while SMO was elevated in late stages (Zahedi et al. 2010b). Moreover, the activity of amine oxidases, particularly SMO, has also been connected to oxidative damage during stroke by way of acrolein, a toxic byproduct of 3-aminopropanal metabolism. Measurement of protein-conjugated acrolein and polyamine oxidase activity is considered as good biochemical markers of stroke, even in the early stages of injury (for a review, see Igarashi and Kashiwagi 2011).

The overexpression of SSAT has also been linked with other inflammatory processes. For example, transgenic rats expressing a metallothionein promoter-driven *SSAT* gene develop severe acute pancreatitis with a non-toxic dose of zinc, leading to the activation of polyamine catabolism. In this model, an increase in oxidative stress was observed and pretreatment with the metabolically stable polyamine analogue bismethylspermine (Me_2Spm) prevented pancreatitis and partially prevented the activation of NF-κB. The serum levels of some cytokines, among them TNF-α, was increased during the course of polyamine catabolism-induced pancreatitis, and this increase was also prevented by pretreatment with Me_2Spm (Merentie et al. 2007).

SSAT overexpression has also been connected with an increase in skin carcinogenesis in a two-step skin carcinogenesis model, possibly by the activation of APAO activity and the subsequent increase in ROS production. Indeed, treatment with the polyamine oxidase inhibitor MDL72527 reduced the number of skin tumors (Wang et al. 2007).

That polyamines may have a role in inflammatory disease is also borne out by the response of polyamine enzymes to anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are currently considered some of the most promising strategies for the chemoprevention of cancers such as colorectal and ovarian cancer. In animal models of genetic or chemical carcinogenesis as well as in patients with familial adenomatous polyposis coli (FAP), NSAIDs have been shown to reduce the growth of tumors or increase apoptosis in human cancer cell lines (for a review, see Burn et al. 2013). However, the classical activities of NSAIDS, inhibition of COX-2 and PGE_2 synthase-mediated inflammation, do not explain the entirety of their anti-tumor potential since some cells that respond positively lack COX-2 (Goel et al. 2003; Ruschoff et al. 1998).

NSAIDs have been shown to induce SSAT transcription and activity, suppress ODC, and deplete cellular polyamine levels (Turchanowa et al. 2001; Hughes et al. 2003; Babbar et al. 2006a, c). In a Min mouse model of intestinal tumorigenesis, SSAT activity was significantly induced upon treatment with the NSAID sulindac, followed by the expected decrease in polyps. Further confirming the importance of the change in polyamine pools was the finding that adding dietary putrescine to the sulindac-treated mice increased the number of high-grade adenomas and also moderately restored polyp numbers (Ignatenko et al. 2006). Thus, there is growing interest in developing chemopreventive combination treatments that would synergize the response of NSAIDs with other drugs that induce SSAT/polyamine catabolism. Recently, Xie et al. (2011)

combined the NSAID celecoxib with the SSAT-inducing polyamine naphthalimide conjugate NPC-16, and their data further supported the findings that the combination of a COX-2 independent NSAID and SSAT induction induces cell death in human cancer cell lines.

Indeed, human trials in which the common NSAID sulindac is combined with the polyamine synthesis inhibitor DFMO to investigate the chemopreventive potential of this combination in patients at risk for or diagnosed with colorectal cancers are underway (Zell et al. 2010; Raj et al. 2013). These trials have shown significant promise for the targeted treatment of at-risk patients. Further studies of the contribution of polyamine catabolic enzymes, SSAT, APAO and SMO, to these chemotherapeutic strategies are warranted given the multiple mechanisms through which these enzymes may contribute to early disease, such as enzyme induction by inflammatory stimuli, ROS scavenger reduction due to the depletion of the higher polyamines, and H_2O_2 and reactive aldehyde generation.

Future directions

The studies discussed herein highlight the correlation between an increase in the activity of polyamine catabolism, various inflammatory stimuli, and the presence of these activated enzymes during the early stages of inflammation-related carcinogenesis. Further, considering

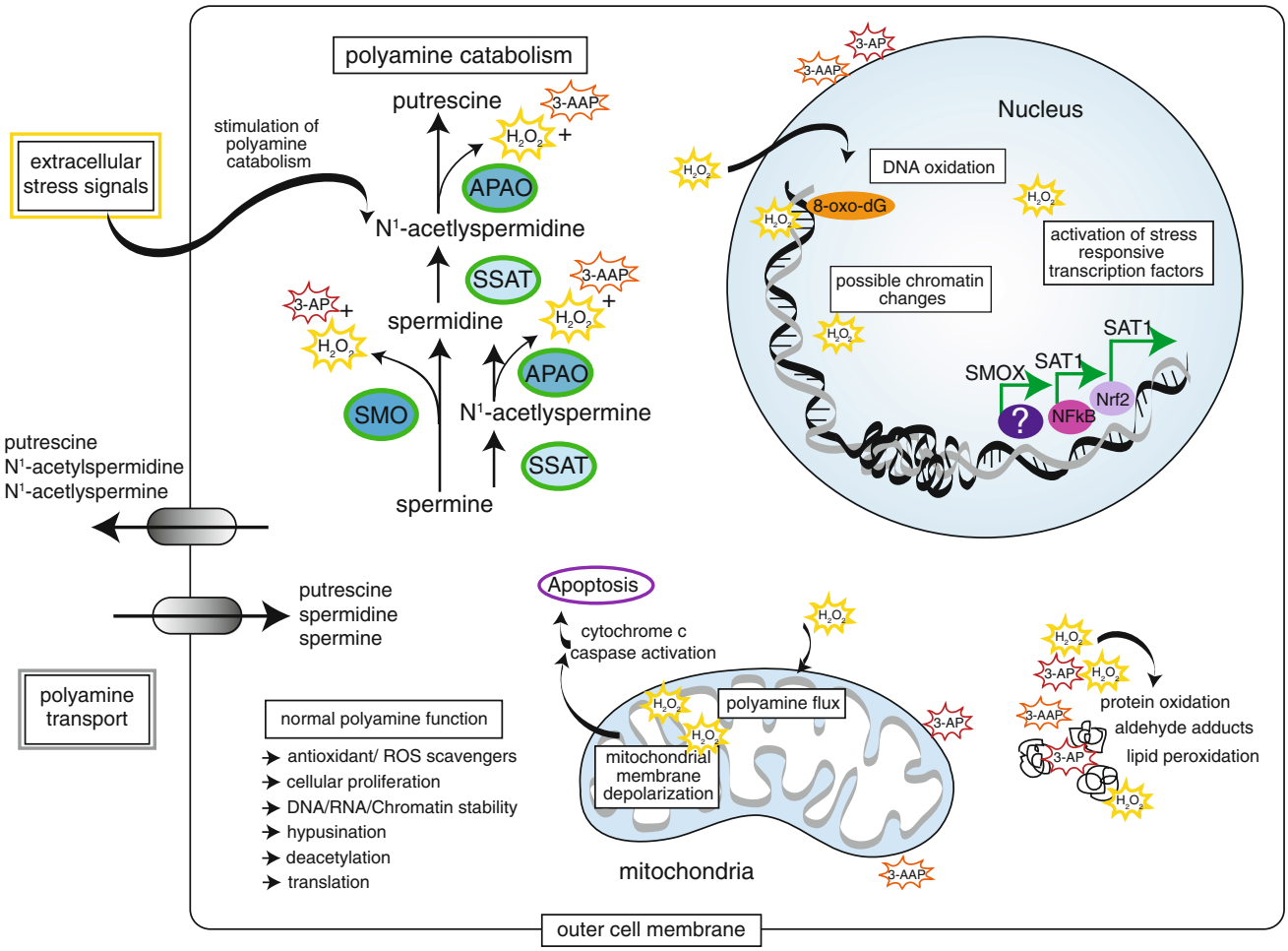

Fig. 2 Potential contributions of polyamine catabolism to cell damage. Polyamine catabolism can be stimulated by various stressors, and transcription of the catabolic enzymes is targeted by transcription factors known to be crucial to stress response such as NFkB and Nrf2. Spermine is catabolized by spermine oxidase (SMO) to produce spermidine, 3-aminopropanal (3-AP), and H_2O_2. Spermine and spermidine can both be catabolized by spermidine/spermine N^1-acetyltransferase (SSAT) to produce N^1-acetylspermine and N^1-acetylspermidine, which can then serve as substrates for N^1-acetylpolyamine oxidase (APAO), which produces either spermidine or putrescine, respectively, along with 3-acetoaminopropanal (3-AAP) and H_2O_2. These reactive aldehydes and H_2O_2 are capable of damaging cellular machinery, lipids, and DNA, leading to cellular dysfunction, apoptosis, or damage that may lead to carcinogenesis. Polyamines have many crucial roles in the cell and perturbance of the polyamine pool and loss of the higher polyamines through catabolism or export can also disrupt normal function and may contribute to the progression of disease

the ability of SSAT, SMO, and APAO to reduce the cellular concentrations of the free-radical scavenging higher polyamines, temper inflammatory cytokine responses, as well as produce a reactive aldehyde and H_2O_2 that could result in mutagenic DNA damage or chromatin changes, we suggest that polyamine catabolism represents a promising target for chemoprevention or chemotherapy. For a schematic of potential contributions of polyamine catabolism to cell damage, see Fig. 2.

In order to interrogate the specific roles of SMO and APAO in both polyamine homeostasis and the development of disease, it is necessary to develop more specific inhibitors. One of the most powerful inhibitors of polyamine oxidation, MDL72527, is known to inhibit both SMO and APAO. MDL72527 competitively and irreversibly inhibits murine SMO-catalyzed spermine oxidation ($K_i = 6.3 \times 10^{-5}$ M) and murine APAO oxidation of N^1-acetylspermine ($K_i = 2.1 \times 10^{-5}$ M) and N^1-acetylspermidine ($K_i = 1.1 \times 10^{-6}$ M) (Bianchi et al. 2006; Wu et al. 2005). Thus, studies utilizing MDL72527 are useful for understanding the role of polyamine catabolism in general, but not for isolating the roles of the different catabolic players SMO, SSAT, and APAO. As discussed, rodent models for both SSAT overexpression and SSAT knockout exist and have been useful in elucidating the critical interplay of this enzyme in multiple systems. Future studies combining these models with SMO and APAO knockouts and overexpression models will be informative in dissecting the role of each of the individual enzymes involved in polyamine catabolism. Such models will be particularly useful in determining the precise involvement of polyamine catabolism in carcinogenesis.

Another method to assist our understanding of the role of SMO in disease has recently been suggested by Yao et al. (2012). Here, the authors suggest the use of SMO autoantibodies, which are present in the sera of lung cancer patients, as potential biomarkers for the early diagnosis of non-small cell lung cancer. Although additional work will be required to validate these studies and determine their actual clinical utility, they do emphasize the importance of gaining a better understanding of the role of polyamine catabolism in disease.

Alternatively, considering the increase in polyamine content in tumor cells, the pharmaceutical induction of polyamine catabolism to trigger cell death or cell growth arrest by the depletion of cellular polyamine pools and the consequent ROS production also provides chemotherapeutic potential that should be further investigated. Indeed, several polyamine analogues have been described to induce the expression of both SSAT and SMO to trigger cancer cell death or decrease cell proliferation, demonstrating a potential for chemotherapy that has not yet been fully exploited. For example, the polyamine analogue N^1, N^{11}-bis(ethyl)norspermine (BENSpm) is able to induce the expression of both SSAT and SMO and has been used in combination with standard chemotherapeutic agents in breast cancer cell lines to cause increased antiproliferative effects (Pledgie-Tracy et al. 2010).

While there has been much promise with existing analogues and current models, there are still many unanswered questions. Greater understanding of the links between polyamine catabolism and the inflammatory pathways and other vital cellular processes will be important in understanding their roles in tumorigenesis and how they can be therapeutically exploited.

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Conflict of interest The authors declare that they have no conflicts of interest.

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