CANCER

Oil for the cancer engine: The cross-talk between oncogenic signaling and polyamine metabolism

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The study of metabolism has provided remarkable information about the biological basis and therapeutic weaknesses of cancer cells. Classic biochemistry established the importance of metabolic alterations in tumor biology and revealed the importance of various metabolite families to the tumorigenic process. We have evidence of the central role of polyamines, small polycatonic metabolites, in cell proliferation and cancer growth from these studies. However, how cancer cells activate this metabolic pathway and the molecular cues behind the oncogenic action of polyamines has remained largely obscure. In contrast to the view of metabolites as fuel (anabolic intermediates) for cancer cells, polyamines are better defined as the oil that lubricates the cancer engine because they affect the activity of biological processes. Modern research has brought back to the limelight this metabolic pathway, providing a strong link between genetic, metabolic, and signaling events in cancer. In this review, we enumerate and discuss current views of the regulation and activity of polyamine metabolism in tumor cell biology.

INTRODUCTION

Cancer cells operate on the basis of distinct purposes compared to the vast majority of nontransformed counterparts in our organism, that is, to survive and proliferate in the niche where they arise (*1*). In this respect, driver mutations provide the basis for the functional divergence of cancer cells that rely on the acquisition of properties termed hallmarks of cancer (*1*). Whereas mutations are at the core of the disease etiology, multiple lines of evidence (emanating from observations from early 20th century) have demonstrated that changes in the metabolic landscape are instrumental for the cancer process (*2*). Much attention has been devoted to the reprogramming of metabolism in pathways related to the use of fuel and its conversion into anabolic intermediates, in support of the notion that cancer cells can modulate distinct means of nutrient uptake and metabolism to support the production of biomass (*3*). However, metabolic pathways provide intermediates and products that, without directly resulting in anabolic precursors, are central to the proliferative process. This property has been attributed to polyamines, which are the focus of this review. In an effort to provide an analogy, whereas glucose, amino acids, and lipids represent the primary fuel of cancer cells, polyamines serve as the oil for the cancer engine to function at optimal capacity. In turn, these metabolites are required for the cancer cell to build an anabolic signaling and metabolic program. These metabolites are found at higher abundance in various types of cancer and have been postulated as noninvasive biomarkers through their detection in biofluids (*4*).

Polyamines are small polycations that are produced from methionine and ornithine, and their levels are controlled by de novo synthesis and diet (Fig. 1). Putrescine, spermidine, and spermine comprise the major polyamines in mammals. Methionine is first metabolized by methionine adenosyltransferases (MAT1A, MAT2A, and MAT2B) to produce *S*-adenosylmethionine (SAM), the major methyl donor for cellular methylation (*5*). SAM has two predominant fates: (i) transmethylation through the action of methyltransferases (MTs) that transfer the methyl group to other molecules and (ii) decarboxylation through adenosylmethionine decarboxylase 1 (AMD1), resulting in the production of decarboxylated SAM (dcSAM) that is substrate for polyamine synthesis. On the other hand, ornithine is produced from arginine by arginases and metabolized by ornithine decarboxylase 1 [ODC1 (*6*)] to produce putrescine, which can be also generated to a lesser extent through an alternative pathway that starts from arginine and produces agmatine as an intermediate and that involves arginine decarboxylase and agmatinase (*7*). Spermidine synthase (SRS) produces methylthioadenosine (MTA) and spermidine from dcSAM and putrescine. Spermidine can react with a second dcSAM molecule through the action of spermine synthase to produce spermine and an additional MTA molecule. MTA is metabolized by MTA phosphorylase (MTAP) to produce adenine and methylthioribose 1 phosphate, which can be converted back to methionine through the salvage pathway. Polyamines are acetylated by spermidine/spermine N1-acetyltransferase 1 (SAT1) and excreted. Spermidine gives rise to an unusual amino acid (hypusine) through the action of deoxyhypusine synthase (DHPS) and deoxyhypusine hydroxylase (DOHH) that is conjugated exclusively to the translation regulator eIF5A (*8*). Hence, the components of this metabolic pathway are highly conserved throughout evolution and the route harbors multiple steps that are tightly controlled to provide a fine regulation of polyamine flux and correct pool sizes (*9*). To provide a few examples, polyamine abundance controls the +1 ribosomal frameshift of an ODC1 inhibitor, antizyme 1 (OAZ1) (*10*). AMD1 translation is also responsive to polyamine abundance, due to the existence of an upstream ORF (open reading frame) coding for the hexapeptide MAGDIS that induces ribosome stalling at its termination codon, hence preventing the ribosomal engagement of AMD1 coding sequence (*11*). The processing and catalytic activity of AMD1 is greatly stimulated by putrescine to coordinate the production of substrates for SRS (*9*), and polyamine catabolism is activated by polyamine production through the induction of SAT1 expression (*12*). A summary of polyamine biosynthesis pathway and key regulatory steps is illustrated in Fig. 1.

The relevance of polyamine production to cancer cell function has been known for decades. Polyamine biosynthesis is activated in tumors, and these metabolites are important for developmental and compensatory growth in response to systemic stimuli like hormones (growth hormones, corticosteroids, androgens, and estrogens). As a result, various strategies targeting polyamine biosynthetic enzymes have been brought

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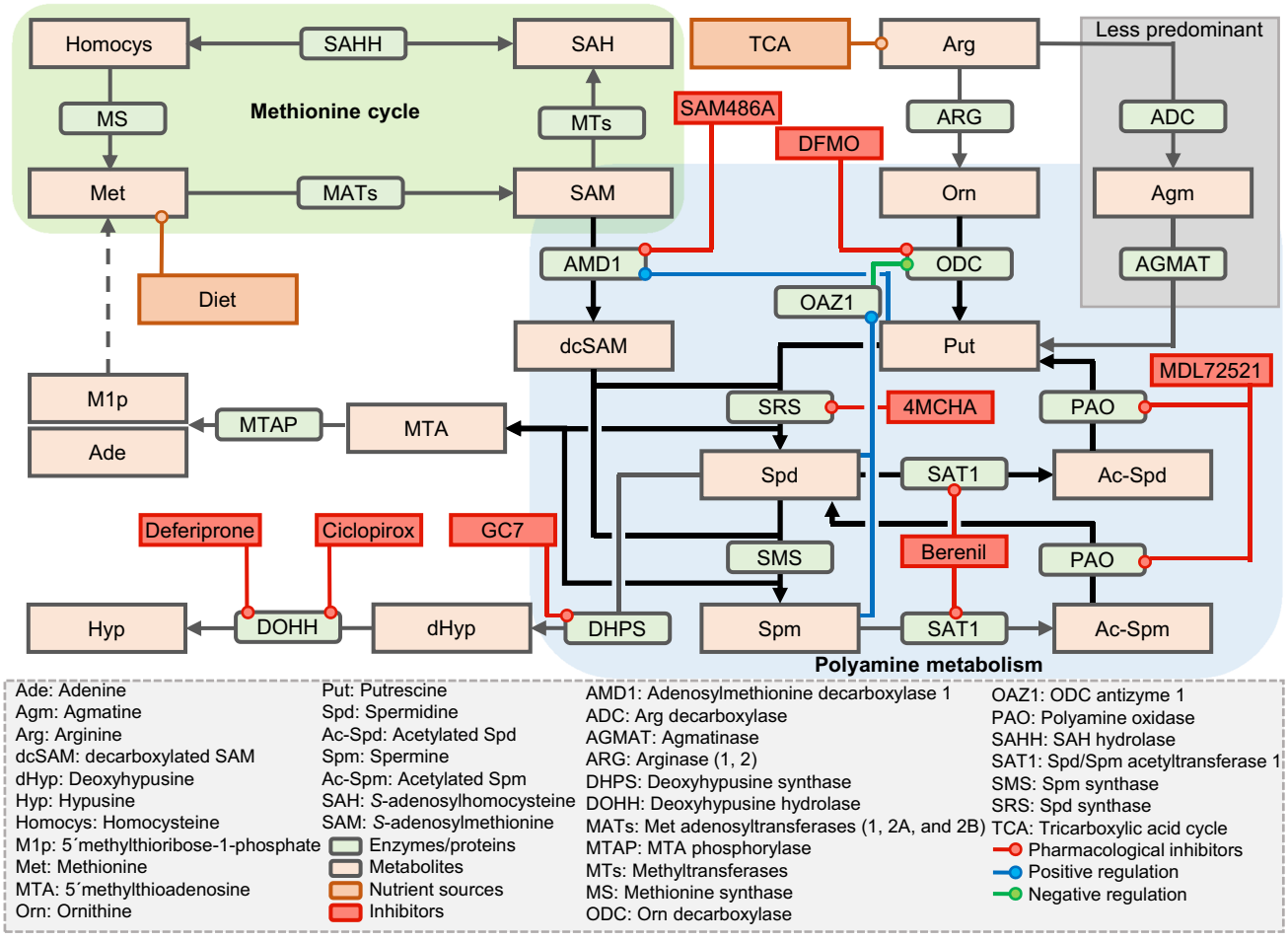

Fig. 1. Regulation and targeting of polyamine metabolism.

to the preclinical and clinical arena (Table 1). The major effort has been put in the enzymes involved in the initial steps of polyamine synthesis, namely, AMD1 and ODC1, although the use of inhibitors of SRS (*13*), SAT1 (*14*), and polyamine oxidase (*15*) has also been explored. Despite the initial excitement on the predicted anticancer potency of these compounds, the results have fallen behind the expectations that were based on preclinical cancer models. AMD1 inhibition can be achieved by the action of SAM486A (*16*), in turn, reducing dcSAM production and spermidine/spermine synthesis, with the consequent predicted accumulation of putrescine. SAM486A exhibits antitumor potency in vitro and in preclinical models. This compound exhibits minor signs of toxicity in mouse models (*17*), in both immunocompromised mice and the immune activation of immunocompetent animals. In clinical trials, SAM486A administration has been reported to cause several minor side effects in cancer patients. Dose-dependent neutropenia was the most commonly reported side effect, with associated fever in some of the most severe cases (*18*, *19*). The predominant pharmacological strategy to inhibit ODC1 is the use of difluoromethylornithine (DFMO), a competitive inhibitor of the enzyme. More than 30 years of research with this compound have provided extensive preclinical and clinical activity on its activity in cancer (*20*). On the basis of this research, we know now that DFMO is a promising chemopreventive agent with potential to be used in anticancer strategies in a combinatory regime.

Despite the extensive research on the field of polyamines and cancer, their molecular activities to support oncogenicity and the means of regulation of this route by oncogenic events have only begun to emerge. These two major aspects are the focus of this review.

Biological activity of polyamines relevant to cancer

As mentioned above, polyamines are polycations, and therefore exhibit high binding affinity for nucleic acids. The ability of polyamines to bind RNA and DNA with high affinity is a cornerstone of their activity (*21*). The appropriate concentration of polyamines ensures key cellular processes related to the production or use of nucleic acids, and in turn, they control DNA replication, transcription, translation, and cell cycle progression (*22*–*26*). Whereas some of their best-studied activities relate to this property, the requirement of these metabolites for hypusine synthesis or the bulk of acetyl CoA that is required for their acetylation has been associated to novel and unexpected functions. Here, we summarize some of the best known or most exciting functions for cancer biology (Fig. 2).

Protein translation

Much attention has been placed on the molecular basis of the selective control of protein translation by these metabolites. The polyamine spermidine is the substrate for the production of a rare amino acid, hypusine (*27*, *28*), which is covalently bound to a single protein reported to date, eIF5A (*29*). eIF5A hypusination is highly conserved, and its biological

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Table 1. Table highlighting polyamine metabolism targeting inhibitors tested in preclinical and/or clinical studies. PA, polyamine.

Preclinical studies

Inhibitor	Target	Cancer	Reference
DFMO	ODC1	Prostate cancer	(*101*, *102*)
		Pancreatic cancer	(*103*)
		Breast cancer	(*104*, *105*)
		Colon cancer	(*106*)
		Neuroblastoma	(*107*, *108*)
		Live cancer	(*109*)
MGBCP	AMD1	Prostate cancer	(*102*)
		Leukemia	(*110*)
		Osteosarcoma	(*111*)
		Melanoma	(*112*)
SAM486A (CGP48664)	AMD1	Bladder cancer, melanoma	(*113*)
		Neuroblastoma	(*107*)
ORI 1202*	PA transporter	Breast cancer	(*105*)
		Prostate cancer	(*101*)
BENSpm/DENSpm# [N (1),N (11)bis(ethyl)norspermine]	PA analog	Breast cancer	(*114*)
PG11047/CGC-11047#	PA analog	Lung cancer	(*115*)
		Prostate and lung cancer	(*116*)
		Pediatric tumors	(*117*)
SL11144/ CGC-11144	PA analog	Breast cancer	(*118*)

Clinical trials

Inhibitor	Target	Cancer type	Reference
DFMO	ODC1	Prostate cancer	(*119*)
		Lung and colon cancer	(*120*)
MGBCP	AMD1	Prostate cancer	(*119*)
SAM486A (CGP48664)	AMD1	Solid tumors	(*18*, *19*, *121*, *122*)
		Non-Hodgkin's lymphoma	(*121*, *123*)
BENSpm/DENSpm# [N^1,N^{11}-bis(ethyl)norspermine]	PA analog	Solid tumors	(*124*)
		Non–small cell lung cancer	(*125*)
		Metastatic breast cancer	(*126*)
DEHSPM (N^1,N^{14}-diethyl homospermine)	PA analog	Solid tumors	(*127*)
PG11047/CGC-11047#	PA analog	Solid tumors	www.clinicaltrials.gov, NCT00705653
		Solid tumors and lymphoma	www.clinicaltrials.gov, NCT00705874

*In combination with other inhibitors. #As a single agent and in combination with chemotherapy.

relevance in cancer has progressively increased in the past decades. This posttranslational modification is closely related to tumor growth and aggressiveness, although some evidence of tumor-suppressive activity have also been reported (*30*). Hypusinated eIF5A is required for embryonic development and tumor growth, and the expression of eIF5A or the enzymes involved in hypusination (DHPS and DOHH) is elevated in multiple neoplastic settings (*31*–*34*). Mechanistically, hypusination of eIF5A results in the accumulation of proteins that promote cancer cell

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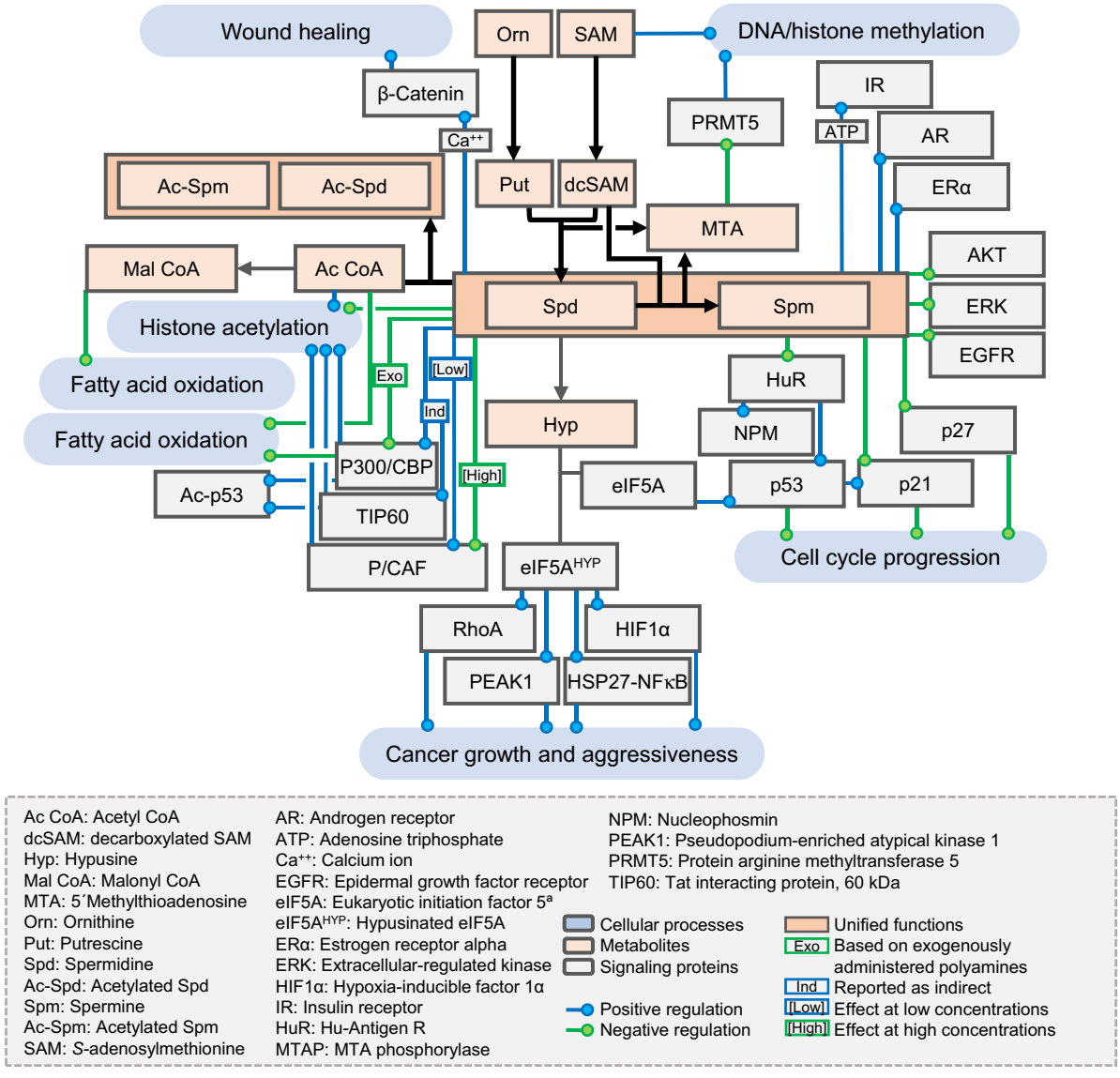

Fig. 2. Molecular and biological consequences of polyamines.

growth and aggressiveness, including (but not limited to) RhoA, PEAK1, and HSP27–nuclear factor κB (*31*–*33*). Note that therapeutic potential has been ascribed to targeting hypusination. For example, BCR-ABL–positive leukemia exhibit greater sensitivity to the inhibition of hypusinated eIF5A activity than those not harboring the translocation (*35*). Further understanding of the regulation of this post-translational modification and the impact of hypusinated eIF5A activity in cancer will be of great relevance for cancer research. In this regard, anecdotal evidence, such as a p53-regulatory tumor-suppressive activity of eIF5A (*36*) or the hypusination-independent activity of DHPS and DOHH inhibitors (*37*), exemplify the need to develop better molecular tools and experimental approaches to advance in this field.

Chromatin remodeling

In addition to the regulation of DNA replication, transcription, and translation, polyamine metabolism also affects the epigenome. Epigenome alterations frequently occur at the level of histones and DNA, by eliciting acetylation and/or methylation. Polyamine production stems from methionine metabolism, which is at the same time the source of SAM, the major methyl donor in the cells (Fig. 1). Therefore, the rate of polyamine production can dictate the availability of SAM for DNA and histone methylation versus its decarboxylation for polyamine synthesis (*38*). However, the impact of polyamine metabolism on histone acetylation has been more explored. Two major mechanisms for the modulation of histone acetylation have been reported. On the one hand, polyamines regulate the activity of various histone acetyltransferases (HATs) through direct and indirect means, including P300/CBP or P/CAF (*39*–*42*). Notably, in nontumoral settings, polyamine inhibition has been reported to increase H3K4 acetylation, which activates M1 differentiation of macrophages (*43*). On the other hand, polyamine catabolism limits the availability of free acetyl CoA. Polyamines are acetylated by SAT1, which constitutes a mechanism for clearance and excretion. SAT1 expression in prostate cancer depletes acetyl CoA pools and elicits an antitumoral response (*44*). SAT1 systemic overexpression elevated polyamine flux and excretion, whereas it reduced acetyl and

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malonyl CoA pools, resulting in a lean phenotype characterized by elevated glucose and fat oxidation. Conversely, deletion of SAT1 decreased polyamine flux and increased acetyl CoA availability, thus resulting in an obesogenic phenotype, which was largely dependent on the loss of SAT1 in the WAT (white adipose tissue) and a 5′ AMP–activated protein kinase (AMPK)–related molecular program (*45*, *46*). A polyamine-independent role for SAT1 in cancer has also been reported (*47*). SAT1 was identified in a glioblastoma screen for factors, which silencing sensitized to radiation. The elevated expression of the enzyme, in this tumor type, was associated to the poor outcome and resistance to radiation. This novel and paradoxical activity of SAT1 was not associated to polyamine regulation but rather to the acetylation of histone 3 which is necessary for BRCA1 gene expression. To which extent the control of chromatin remodeling downstream polyamine metabolism depends on changes in oxidative metabolism, polyamine balance, protein acetylation, or autophagy (see below) remains to be addressed.

Cell signaling

Polyamines exert an important impact on the signaling of cancer cells. Various pathways have been reported to be a target of these metabolites, whereas their molecular regulatory mechanism is not completely understood. In line with the tumor-promoting nature of polyamines, activation of oncogenic pathways has been demonstrated in cancerous and noncancerous settings. Cumulative evidence points at the role of polyamines in the control of hormone signaling. In prostate cancer, ODC1 was found to be overexpressed in tumor samples (*48*). Ectopic ODC1 expression promoted malignant transformation of benign immortalized prostate epithelial cells, whereas its silencing reduced the activation of androgen receptor (AR) signaling in AR-dependent cells. Similar evidence has been provided in breast cancer, where inhibition of polyamine synthesis by means of polyamine analogs or ODC1 targeting reduces estrogen receptor α expression and activity (*49*).

Insulin-regulated pathways are also affected by polyamines. The regulation of insulin receptor activity by these metabolites might be associated to a broader activity of polyamines in the regulation of phosphorylation reactions, frequently enhancing the phosphorylation of cellular proteins (*50*). The activity of various kinases, including the insulin receptor, is exacerbated by the addition of these polycations (*51*), which could depend on the ability of polyamines to interact with adenosine 5′-triphosphate (ATP) and favor the phosphotransfer reaction by the kinase (*21*, *52*). To which extent the affinity of polyamines for ATP (or potentially other energetic nucleotides relevant to cell signaling, such as guanosine 5′-triphosphate) is central to the regulation of cell signaling by these molecules remains to be clarified.

Polyamines favor the activation of β-catenin (*53*, *54*). Polyamine supplementation activates this pathway in adipose-derived stem cells, resulting in their differentiation to osteoblasts (*53*). In epithelial cells, polyamines are required for wound healing and migration, a process that is dependent on increased calcium influx and activation of β-catenin (*54*). Because activation of polyamine production is observed in murine models of colorectal cancer induced by aberrant β-catenin activation (*55*), it is plausible that these metabolites are important players in tumors that depend on this oncogenic pathway. In line with this notion, a recent report in hepatocellular carcinoma provides evidence of the tumor-suppressive role of polyamine clearance by SAT1 expression, which negatively affects, among others, the nuclear translocation and activity of β-catenin (*56*). Note that the negative regulation of oncogenic signaling pathways by polyamines has also been reported, relating to epidermal growth factor receptor, mitogen-activated protein kinase (MAPK), or AKT signaling (*57*, *58*).

Inhibition of tumor-suppressive pathways

Since the realization of the relevance of polyamines for cellular homeostasis, targeting this pathway has been of the utmost interest in cancer research. In this sense, the use of DFMO as a general polyamine synthesis-inhibitor has boosted the molecular deconstruction of polyamine-regulated pathways. DFMO treatment elicits a tumor-suppressive response that has been widely associated to the accumulation of tumor suppressors. There is consensus on the fact that polyamine depletion elicits a cytostatic response and does not trigger apoptosis (*59*–*62*). The antiproliferative activity of DFMO in this context is associated to the induction of p21, p27, and p53, which in the latter depends on the cytoplasmic accumulation of the RNA-binding protein HuR (*59*, *60*, *62*–*64*).

Autophagy

The control of autophagy is an emerging aspect of polyamine function. Autophagy is a tightly regulated process that is often ascribed to the generation of autophagosomes in macroautophagy (*65*). Autophagosomes engulf intracellular organelles and macromolecules through a sequence of signaling steps that involve recognition of cargo and targeting to these double-membrane structures, for their ultimate degradation upon formation of the autolysosome (the fusion of autophagosomes with lysosomes). Polyamines activate the autophagic process, and several systemic benefits have been reported related to this activity, whereas its impact in tumor cells remains largely unexplored. Systemic polyamine administration in yeast, flies, worms, and mammals has a variety of effects related to the extension of life span and healthy aging. These include cardioprotection, neuroprotection, impairment of memory loss, and myopathy (*66*–*70*), although it reduces liver tumorigenesis and promotes anticancer immunosurveillance (*71*, *72*). There is high coherence around the molecular cues behind these beneficial effects. Although antiapoptotic effects of these polycations have also been reported (*70*), the primary effect of polyamine supplementation is the activation of autophagy through the regulation of acetylation processes, in line with the notion that acetyl CoA is a potent inhibitor of autophagy (*73*, *74*). Supplementation of spermidine inhibits the activity of HATs, specifically EP300, to trigger autophagy (*41*, *75*). With regards to cancer, it is difficult to anticipate the contribution of a potential autophagy-inducing activity of polyamines because this self-digesting process has been associated to both tumor promotion and tumor suppression (*76*).

Oncogenic signaling upstream polyamine metabolism

As described above, polyamine biosynthesis is tightly regulated. Considering that cancer cells present a high demand for polyamines to support growth, the molecular changes underlying the transformation process would require the active deregulation of this metabolic route. Surprisingly, despite the multiple lines of evidence supporting the need of polyamines for cancer cells, the molecular control of the pathway by oncogenes and oncogenic pathways has been marginally explored. Only recently have we started gathering conclusive data on this important mode of regulation in tumors (Fig. 3).

Genomic alterations in polyamine metabolism enzymes are rare. The most studied gene in this regard is MTAP, which is encoded by a gene located in 9p21. This locus is frequently deleted in tumors, and its relevance to cancer has been ascribed to the concomitant loss of CDKN2A at that genomic position. MTAP was found to be co-deleted with CDKN2A in multiple cancer samples and was reported to exhibit tumor-suppressive activity (*77*). Recent studies have uncovered the vulnerabilities derived from MTAP deletions and the alteration in polyamine metabolism. Various groups reported that MTAP loss elicits enhanced susceptibility to the inhibition of the protein arginine

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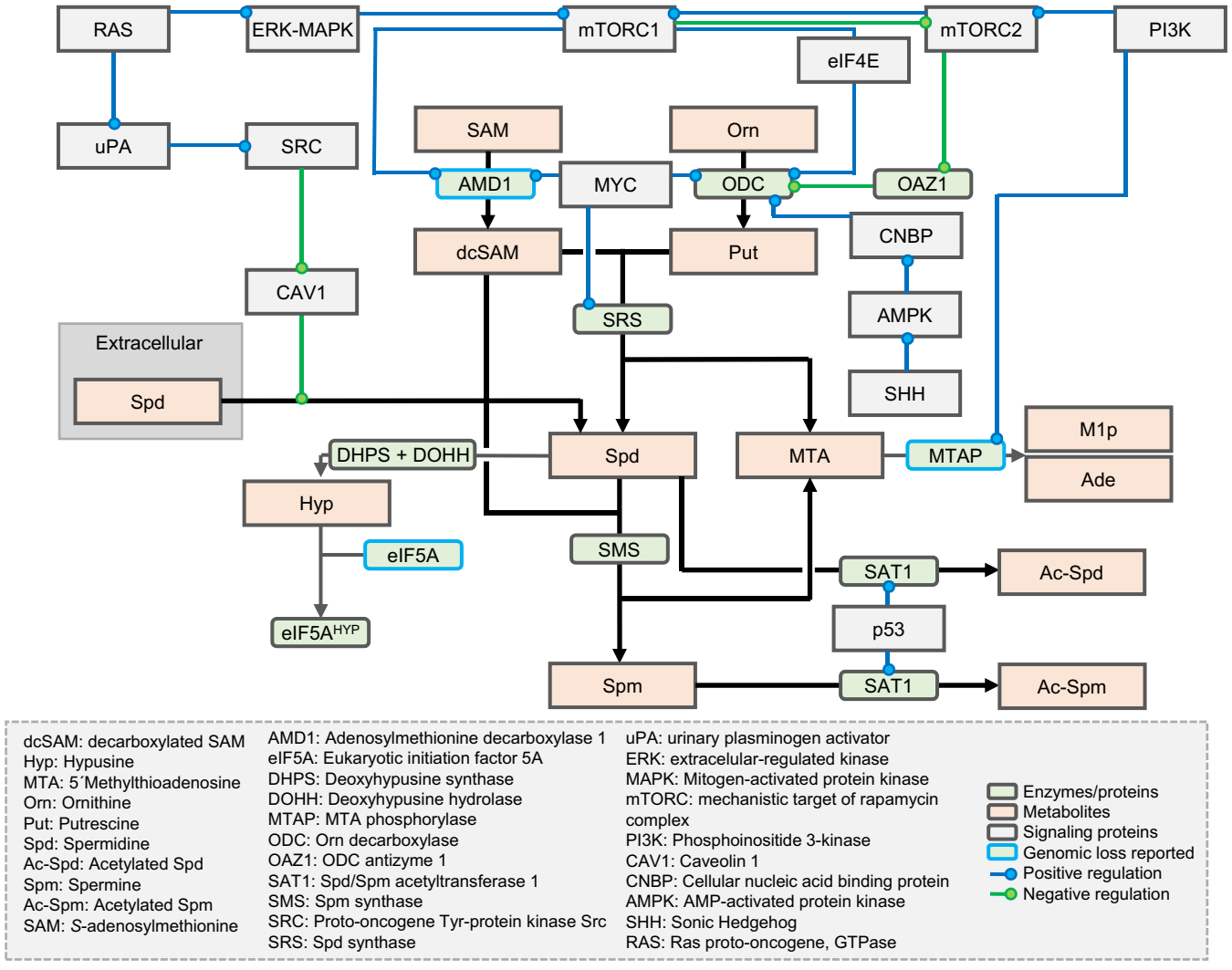

Fig. 3. Oncogenic signaling regulating polyamine metabolism.

methyltransferase PRMT5 (*78*–*80*). The molecular mechanism underlying this biological effect relies on the ability of accumulated MTA to inhibit PRMT5. In these settings, pharmacological PRMT5 inhibition results in greater antitumoral activity, probably by achieving lower basal enzyme activity in MTAP-deleted cells. A second puzzling genomic event in polyamine biosynthesis-coding enzymes was found in AMD1. In an elegant screen of putative lymphoma suppressors, AMD1 and eIF5A were identified as negative regulators of lymphomagenesis (*30*). The paradoxical tumor-suppressive activity of polyamines was associated to the production of hypusine, and the robust interference of the pathway was sufficient to trigger lymphomagenesis in mice, which was coherent with combined loss of AMD1 and eIF5A in human specimens. Because of the restricted literature on the tumor-suppressive activity of AMD1 and hypusination, we lack a good understanding of the dichotomous nature of the molecules and the biological context in which a tumor-suppressive activity could be predominant. Because hypusinated eIF5A controls the translation of specific mRNAs, it is plausible that the set of regulated proteins differs based on tumor type or microenvironment, leading to the opposing biological consequences described above. The potential existence of additional examples of a double-edged activity of this metabolic pathway in tumorigenesis warrants further investigation.

Oncogenic pathways

Beyond the genomic regulation of metabolic enzymes, which is infrequent, polyamine metabolism is regulated by signaling cues in cancer. Activation of oncogenic signaling pathways is a direct consequence of many prevalent mutations in cancer, including RAS, phosphoinositide 3-kinase (PI3K), and MYC among others. Recent studies have shed light on the control of polyamine metabolism downstream these aberrantly activated pathways.

RAS-MAPK

Mutations in RAS exhibit high prevalence in cancer and promote cell proliferation among other biological effects. Activation of RAS-dependent signaling converges in the production of polyamines, which is supported by mechanistic and observational studies. Colorectal tumors (CRC) frequently harbor mutations in RAS and β-catenin pathways. A study oriented to the characterization of metabolic changes in CRC revealed an association between polyamine synthesis and tumorigenesis. Taking a mouse model of CRC and tumor biopsies as basis for the study, the group identified polyamines among the most altered metabolic pathways in this disease, which could be also observed in premalignant polyps (*55*). Accumulation of polyamines in the form of acetylated spermidine and spermine was evident also in the urine of mice bearing tumors. This notion is corroborated by an earlier study

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were tumor biopsies and surrounding nontumoral tissue was analyzed and stratified on the basis of the underlying metabolic alterations (*81*). Polyamines were also consistently up-regulated in tumor tissue from this cohort. The authors found a significant association between mutations in K-RAS (valine 12) and the accumulation of these metabolites, independent of the status of the tumor suppressor *TP53*. Mechanistically, activation of RAS has been shown to control both polyamine biosynthesis and uptake. Mutant RAS increases ODC1 activity in vitro, which is coherent with the aforementioned mutational association studies. Through molecular deconstruction of RAS-governed pathways and the use of RAS mutants lacking specific downstream target regulation capacity, MAPK and PI3K activation was shown to be at the core of ODC1 regulation. MAPK regulates ODC1 transcription, whereas both pathways promote its translation through internal ribosome entry site–mediated translation downstream eIF4E, thus enabling full enzyme activity (*82*, *83*). These data are in agreement with the cooperativity observed between ODC1 expression and RAS effector pathways in malignant transformation (*84*).

Note that polyamines are secreted to the extracellular environment and can therefore be uptaken by neighboring cells. In this regard, it has been demonstrated that these metabolites are incorporated to cancer cells through the endocytic pathway, thus providing an alternative source of polyamines to support cell growth. The fact that caveolin-1 (a negative regulator of this endocytic uptake mechanism) inhibits the incorporation of polyamines led to the discovery of oncogenic RAS mutations as regulators of this uptake strategy through the inhibitory phosphorylation of caveolin-1 (*85*). This activity of mutant RAS is consistent with other molecular strategies elicited by the oncogene that maximize the uptake of fuel from the extracellular milieu (*86*).

MYC

The MYC family of transcription factors is amplified, overexpressed, or activated through multiple means in cancer. cMYC, the most widely studied member of this family, is central to cell proliferation, survival, and differentiation, and hence, it has been a major target of anticancer drug development. Polyamine synthesis is heavily regulated by MYC at multiple levels. This transcription factor controls the expression of ODC1, which harbors canonical MYC-binding sites (E-boxes) in its promoter. Less studied but equally relevant is the regulation of other polyamine synthesis genes, including SRS and AMD1 by this oncogene (*87*, *88*). In turn, the requirement of polyamine metabolism to unleash full tumorigenic potential of oncogenic signals has been considered very relevant in the context of MYC. Murine models have provided conclusive evidence on the relevance of this signaling-metabolic cross-talk. cMyc and nMyc require active polyamine synthesis to give rise to lymphoma and neuroblastoma, respectively (*89*, *90*). The use of ODC1 heterozygous mice [the knockout is embryonic lethal (*91*)] revealed the requirement of this gene for Myc-induced lymphomagenesis in the eμ-Myc mouse model. The preventive/therapeutic activity of a partial decrease in ODC1 is particularly relevant because it better represents the therapeutic reality of inhibiting an enzyme with small molecules in vivo, which was achieved in the neuroblastoma model of *nMyc* with DFMO (*89*). Despite these evidence, we lack specific information about the potential of MYC activation in cancer as an stratification marker that could inform about the therapeutic efficacy of ODC1 inhibition or the potential therapeutic benefit of combining these compounds (for example, DFMO) with recently unraveled inhibitors of MYC function [for example, bromodomain inhibitors (*92*)].

PI3K-mTORC1

Alterations in the PI3K pathway are frequent in tumors. Cancer cells exhibit aberrant activation of this pathway as a result of multiple mutations, including, but not limited to, PTEN, P110α (a catalytic subunit of PI3K), AKT, and TSC2. Deregulated activation of the PI3K pathway promotes a "growth factor–rich" state, where the signaling alterations mimic the scenario of the extracellular signaling encoding for growth and proliferation. Cells with activated PI3K pathway will in turn activate anabolic pathways, including lipid, protein, and nucleotide synthesis. Recent studies suggest that polyamine metabolism is also induced in conditions of PI3K activation. The study of isogenic PI3K wild-type and mutant (E545K) CRC cells revealed alterations in polyamine biosynthesis in the mutants, with a predominant increase in putrescine, spermidine, and MTA (*58*). The increase in MTA was consistent with the elevated levels of MTAP in mutant cells, which could be due to substrate availability–dependent feed-forward loop. MTA and spermidine are the result of the reaction catalyzed by SRS, which uses as substrate dcSAM and putrescine. Complementary to this study, mTORC1 (mechanistic target of rapamycin complex 1) has been recently shown to activate the production of dcSAM and putrescine through the regulation of AMD1 and ODC1, respectively. On the one hand, in vivo PI3K activation in prostate epithelial cells by means of *Pten* deletion elicited changes in the metabolome from which the accumulation of polyamines and intermediates of its biosynthesis were predominant. Further molecular studies revealed that mTORC1 promotes the stability of AMD1 proenzyme and, in turn, favors the production of mature AMD1 and dcSAM synthesis (*17*). On the other hand, mTORC1 promotes ODC1 mRNA stability, in turn supporting elevated enzyme levels (*93*). This is complemented with additional evidence showing that mTORC1 activity blocks the production of OAZ1 through the negative regulation of mTORC2 [which is an activator of OAZ1 production (*94*)]. These studies translated the molecular evidence to therapeutic applications, by demonstrating that polyamine synthesis inhibitors (targeting ODC1 or AMD1) would exhibit anticancer properties. As elaborated with MYC, this new information has yet to be translated in therapeutic strategies directed at targeting tumors driven by PI3K overactivation.

Other pathways

Beyond the implication of the major oncogenic signaling pathways in the production of polyamines, other cascades also affect the activity of this metabolic route. In line with the predominant regulation of ODC1 by oncogenic pathways, sonic hedgehog (SHH) signaling regulates the translation of this enzyme, which is central to neuronal and medulloblastoma growth (*95*). In this scenario, SHH promotes noncanonical AMPK activation, which leads to stabilization of CNBP (CCHC-type zinc finger nucleic acid binding protein), an upstream positive regulator of ODC1 translation. In turn, targeting polyamine production hampers SHH-induced medulloblastoma growth.

Tumor suppressor pathways

On the basis of the requirement of polyamines for proliferation and oncogenesis, it is tempting to speculate that tumor suppressor pathways would negatively regulate the pathway. A few examples have emerged in the recent years that support this notion. Activation of p53 induces multiple antitumoral programs (*96*). Ferroptosis is a form of programmed cell death characterized by dysfunctional condensate mitochondria and elevated iron chelator-sensitive reactive oxygen species (ROS) production. It has been recently shown that p53 activation elicits a ferroptotic response, which partially requires the modulation of polyamine metabolism (*97*). SAT1 is a target of p53, and its accumulation results in deacetylation of acetylated polyamines and the conversion of spermidine and spermine to putrescine. Surprisingly, SAT1 was partly required for the ferroptotic response elicited by p53 by contributing to the accumulation of ROS. The tumor-suppressive activity

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of SAT1 in this context was supported by its decreased abundance in cancer, suggesting that counteracting polyamine metabolism by SAT1 could be at the core of tumor suppression.

Despite the existence of multiple reports demonstrating the tight regulation of polyamine metabolism downstream the action of oncogenes and tumor suppressors, this field is in its infancy. In addition, the physiological regulation of polyamine dynamics, such as their control by circadian rhythms (*98*), could feed the cancer research field with new and unexpected regulatory modes. The availability of new and well-annotated genomic and transcriptomic cancer-specific studies is an invaluable source for the better understanding of the molecular means underlying the regulation of this metabolic route in cancer. This, in turn, will allow us to fine tune the therapeutic approaches aimed at inhibiting polyamine production in cancer.

Concluding remarks

Polyamines are fascinating molecules, because despite their pleiotropic effects, they have consistently been shown to be essential in cancer cell biology. The last 50 years of research have provided solid evidence on their contribution to tumor growth and aggressiveness and more recently to the healthy aging of living organisms. From yeast to plants and mammals, polyamine synthesis is essential for embryonic development (*99*) and needs to be exquisitely controlled, and the fact that cells retain a large fraction of polyamines inert and vesiculated (*100*) implies that there is a need for a quick turnover and release as free bioactive molecules. However, the use of polyamine metabolism-targeting drugs in the clinic and their efficacy to curb cancer is below initial expectations, probably owing to the little molecular information that we have around their mechanism of action and regulation. Therefore, we can foresee that deepening our understanding of the role of polyamine metabolism in cancer will lead to better patient stratification and polyamine inhibitors–based combinatorial therapies that maximize the efficacy of this antimetabolic strategy.

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