MINIREVIEW

This paper is available online at www.jbc.org

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 281, NO. 21, pp. 14529–14532, May 26, 2006


# Regulation of Ornithine Decarboxylase*

Published, JBC Papers in Press, February 3, 2006, DOI 10.1074/jbc.R500031200

**Anthony E. Pegg**[1]

*From the Department of Cellular and Molecular Physiology, Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033*

**Ornithine decarboxylase (ODC) initiates the polyamine biosynthetic pathway. The amount of ODC is altered in response to many growth factors, oncogenes, and tumor promoters and to changes in polyamine levels. Susceptibility to tumor development is increased in transgenic mice expressing high levels of ODC and is decreased in mice with reduced ODC due to loss of one *ODC* allele or elevated expression of antizyme, a protein that stimulates ODC degradation. This review describes key factors that contribute to the regulation of ODC levels, which can occur at the levels of transcription, translation, and protein turnover.**

L-Ornithine decarboxylase (ODC)[2] catalyzes the first step in the polyamine biosynthetic pathway forming putrescine, which is then converted into the polyamines spermidine and spermine (1–4) (Fig. 1). In some microorganisms and in plants, putrescine can also be made from arginine via an arginine decarboxylase and subsequent conversion of the agmatine to putrescine. However, evidence for a mammalian arginine decarboxylase is controversial (5), and ODC provides the only established route for polyamine synthesis *de novo*. Polyamine content plays important roles in both normal and neoplastic growth and alterations of polyamine synthesis via changes in ODC content occur in response to tumor promoters and carcinogens (2, 3).

ODC is very highly regulated, and ODC activity varies in response to many stimuli. These alterations in activity are brought about by changes in the amount of ODC protein, which turns over very rapidly. ODC degradation is controlled by a protein termed antizyme, which responds to polyamine concentration. ODC is also regulated at the level of transcription and the ODC gene is one of the targets of the Myc/Max transcription factor. A third level of regulation occurs in the translation of ODC mRNA. This brief review discusses these aspects of ODC and some relevant structural and comparative data focusing on relatively recent studies. Summaries of the vast literature describing earlier work on ODC, the myriad of factors altering its activity, and its value as a drug target are contained in previous reviews (2–4, 6).

## ODC Structure and Activity

ODC is a pyridoxal phosphate (PLP)-dependent amino acid decarboxylase. Biochemical studies showed that it is a homodimer with two active sites each made up of residues from both subunits (7). Crystallographic determination of the structures of mammalian and *Trypanosoma brucei* ODCs (8, 9) confirmed these observations. The structure of eukaryote ODC is that of a group IV decarboxylase, structurally homologous to the bacterial and plant arginine decarboxylases, bacterial diaminopimelic acid decarboxylase, and alanine racemase but unrelated to the bacterial ODCs.

Eukaryotic ODCs are, in general, highly specific for L-ornithine with a very weak activity on L-lysine and an even lower activity on L-arginine (10). However, a homolog was isolated from *Paramecium bursaria* chlorella virus. This protein has a key amino acid substitution (Glu for Asp) in a residue that forms an interaction with the δ-amino group of ornithine analogs in the x-ray structures of ODC and despite slight ODC activity is actually an arginine decarboxylase (11).

There are two domains in the ODC monomer, an $NH_2$-terminal domain forming a $\beta/\alpha$-barrel that binds the cofactor, and a COOH-terminal domain, which is predominantly a $\beta$-sheet structure. The active sites are formed at the dimer interface between the $NH_2$-terminal domain of one subunit and the COOH-terminal domain of the other (8, 9). One unusual property of ODC is that the association between two subunits is quite weak and the dimers are in rapid equilibrium with inactive monomers even under physiological conditions.

The PLP cofactor is bound in a Schiff base linkage to $Lys^{69}$ (7, 8, 12). It is likely that $Cys^{360}$ plays an essential role in ensuring correct protonation of the decarboxylated reaction intermediate at $C_\alpha$. If $Cys^{360}$ is mutated to Ser or Ala, there is a large reduction in activity (7), and the mutated enzyme becomes a decarboxylation-dependent transaminase due to frequent protonation of C-4′ of the intermediate (12). ODC is readily inactivated by nitric oxide due to the sensitivity of this Cys residue to nitrosylation (13). The most widely used pharmacological inhibitor of ODC is α-difluoromethylornithine (DFMO), a valuable antitrypanosomal agent that acts as an enzyme-activated irreversible inhibitor of ODC forming a covalent adduct with $Cys^{360}$ (6).

## Degradation of ODC

The rapid turnover of ODC is brought about by the 26 S proteasome, but ODC is highly unusual in that ubiquitination is not required for this degradation (Fig. 1). Instead, a non-covalent association with a protein termed antizyme directs ODC to the proteasome (14–17). Antizyme increases the degradation of ODC by enhancing its interaction with the proteasome but does not increase the rate of proteasomal processing (18). Breakdown of antizyme itself is not stimulated by ODC (19) and the antizyme released from the ODC-antizyme complex at the proteasome is able to bring about further degradation of ODC.

Elegant experiments by Coffino and colleagues (20) have shown that proteasomes actually begin degradation of ODC at the COOH terminus. Rapid degradation of mammalian ODC requires a region located at the COOH terminus of the protein. This region is absent in *T. brucei* ODC, which is stable (21). Deletion of the 37 residues forming the COOH-terminal part of mammalian ODC renders this protein stable even in the presence of antizyme. Attachment of these residues to other stable proteins can cause their lability (18). $Cys^{441}$, which is located in this COOH-terminal sequence, appears to be a key residue (14). An isosteric alteration of $Cys^{441} \rightarrow$ Ser completely stabilizes ODC even in the presence of excess antizyme (18). Deletion of the 5 terminal residues (457–461; ARINV) also stabilizes ODC but to a lesser extent than removing the terminal 37 residues or mutation of $Cys^{441}$ (18). The structure of the COOH-terminal region needed for rapid degradation of ODC is not known; this region is absent from the *T. brucei* and truncated mouse ODC structures that have been solved and is disordered in the crystal structure of the human ODC (8, 9). Therefore, it is not clear what effect alterations such as $Cys^{441} \rightarrow$ Ser may have on the overall structure and to what extent this disorder or flexibility in this region may actually be involved in the degradation process.

Recently, a novel pathway has been described for ODC degradation during oxidative stress, which is regulated by NAD(P)H quinone oxidoreductase (NQO1) and does not require the COOH-terminal domain (17, 22). NQO1 binds to ODC and stabilizes it. If this interaction is disrupted with dicoumarol, it sensitizes ODC monomers to degradation by the 20 S proteasome in a manner independent of both antizyme and ubiquitin. The extent to which this pathway, which involves the 20 S proteasome that may only degrade unfolded proteins, contributes to ODC turnover in other physiological circumstances remains to be determined, but it could be involved in the turnover of nascent ODC chains.

## Antizyme and ODC Degradation

Antizyme was first recognized as a non-competitive inhibitor of ODC that was synthesized in response to an increase in polyamine content (23). This inhibition is due to the tight binding of the antizyme to the ODC monomer forming a heterodimer, which prevents enzymatic activity (Fig. 1). The relatively weak association between the ODC subunits may aid in the interaction

* This minireview will be reprinted in the 2006 Minireview Compendium, which will be available in January, 2007. Research on polyamines in the author's laboratory was supported in part by Grants CA-18138 and GM-26290 from the National Institutes of Health and a Tobacco Settlement Fund award from Pennsylvania State University.

[1] To whom correspondence should be addressed: Dept. of Cellular and Molecular Physiology, Pennsylvania State University College of Medicine, 500 University Dr., Hershey, PA 17033. Tel.: 717-531-8152; Fax: 717-531-5157; E-mail: aep1@psu.edu.

[2] The abbreviations used are: ODC, L-ornithine decarboxylase; PLP, pyridoxal phosphate; DFMO, α-difluoromethylornithine; NQO1, NAD(P)H quinone oxidoreductase; SSAT, spermidine/spermine $N^1$-acetyltransferase; ORF, open reading frame; UTR, untranslated region; IRES internal ribosome entry site; MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; ERK, extracellular signal-regulated kinase.

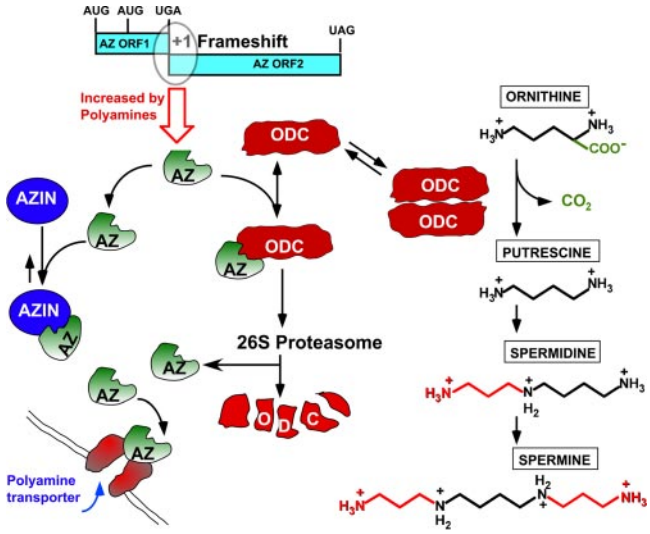


FIGURE 1. **Role of antizyme and ODC in polyamine metabolism.** The ODC dimer catalyzes the production of putrescine, which is then converted into the higher polyamines. Antizyme is synthesized via a +1 frameshift in translation of the mRNA fusing ORF1 and ORF2 in a manner stimulated by polyamines. Antizyme (*AZ*) can bind to ODC bringing about degradation by the 26 S proteasome or to antizyme inhibitor (*AZIN*).

with antizyme. Subsequent studies pioneered in the laboratory of Dr. S. Hayashi (24) showed that induction of antizyme leads to a loss of ODC protein and that this is due to an increase in ODC degradation (14–16).

Antizyme interacts with ODC at the region encompassed by residues 117–140 located on the surface helices of the $\beta/\alpha$-barrel that binds the PLP cofactor (15). The region of antizyme interacting with ODC is contained in a section involving residues 106–212 in the COOH-terminal half of the antizyme molecule (15, 25). This region can inhibit ODC but is not sufficient to direct it to the proteasome. Proteasomal degradation of ODC also requires a region located between residues 55 and 105. The first 70 amino acids at the amino terminus of antizyme are not needed for stimulation of ODC degradation *in vitro* but may target antizyme to various locations.

The structure of a fragment of the antizyme protein (residues 87–227) was determined using NMR techniques (25). The protein has a novel arrangement of 8 $\beta$-strands and two $\alpha$-helices but, very interestingly, has a fold similar to some acetyltransferases including spermidine/spermine $N^1$-acetyltransferase (SSAT) (26). Antizyme and SSAT are the two major factors regulating polyamine homeostasis (2, 3). Like antizyme, SSAT is strongly induced by high levels of polyamines, although in the case of SSAT, this induction is brought about by increased transcription of the SSAT gene through polyamine-responsive elements and by a pronounced stabilization of the highly labile SSAT protein. The antizyme structure contains a group of conserved acidic amino acids ($Glu^{161}$, $Glu^{164}$, and $Glu^{165}$) on an external face that may interact with the binding element in ODC, which includes an electropositive surface (25).

Attachment of the $NH_2$-terminal region of antizyme (residues 1–97) to stable proteins renders them substrates for rapid degradation by the 26 S proteasome (15). Recently, a method for producing targeted destruction of selected proteins was described in which an ODC sequence was fused to the COOH terminus of a desired target protein. Induction of antizyme then led to its degradation (27).

## Synthesis and Degradation of Antizyme

Antizyme synthesis is regulated via a frameshifting event (14–16, 28) (Fig. 1). The antizyme mRNA contains two overlapping open reading frames (ORFs) comprised of a short ORF1 and a long ORF2. The latter, which is in the +1 frame relative to ORF1, does not have an initiation codon. Synthesis from ORF2 therefore requires the failure of the ribosome to terminate at the end of ORF1 and instead shift to the +1 reading frame. This frameshifting event is stimulated by polyamines so that synthesis of antizyme, which is made up of both ORF1 and ORF2, is increased when polyamine levels increase (Fig. 1). This is the major factor controlling antizyme synthesis, but there may also be a transcriptional regulation since polyamine depletion via DFMO led to a reduction of antizyme mRNA (29). Antizyme degradation requires ubiquitination, and this is inhibited by polyamines (17, 30). Thus, high levels of polyamines increase antizyme content by increasing synthesis and reducing degradation.

Spermidine and spermine are more effective than putrescine at stimulating translation of antizyme mRNA. A variety of polyamine analogs including agmatine and some synthetic (bis)ethylated compounds, which are powerfully antiproliferative and are in therapeutic trials as antitumor agents have also been shown to be effective inducers of antizyme presumably by stimulating the frameshifting event (31).

Frameshifting leading to antizyme production has been studied extensively using *in vitro* and *in vivo* systems and comparisons of the frameshifting site and flanking regions in a wide number of antizyme sequences from different species. The stop codon ending ORF1 is always UGA. There is a conserved element located 5′ to the shift site, which is needed for the polyamine effect. In mammals and many other species a second critical sequence occurs immediately following the shift site and this sequence forms a pseudoknot that stimulates the frameshifting (32, 33).

## Effect of Antizyme on Polyamine Transport

There is a cellular uptake system for polyamines, which is still not fully characterized in higher eukaryotes (34). Antizyme induction blocks polyamine transport by this system (14–16) (Fig. 1). This accounts for the increased rate of polyamine uptake in cells in which polyamine content is reduced by inhibitors such as DFMO, which may limit their usefulness for cancer therapy. It may also explain the rather paradoxical finding that there is no reduction in uptake of exogenous polyamines in cells, which greatly overproduce ODC. The excess ODC may sequester all the available antizyme and thus prevent the down-regulation of transport.

The uptake of polyamine analogs currently being tested as antitumor agents occurs via the polyamine transport system. Therefore, the induction of antizyme by such analogs described above (31) actually may limit the accumulation of these compounds (35). This may reduce their effectiveness but antizyme induction may mediate the therapeutic activity of such polyamine analogs by causing reduction in ODC.

## Multiple Forms of Antizyme

The above description refers to antizyme-1, the best characterized member of the mammalian antizyme family, which is widely distributed in many different cell types. However, there are multiple antizyme genes with at least four members. All members inhibit ODC activity (16). Antizyme-3 has a very limited distribution being expressed only in the haploid spermatids where it may play a role in spermatogenesis (36, 37). Antizyme-2 is similar to antizyme-1 in distribution but less abundant. It is unclear if antizyme-2 causes ODC degradation *in vivo*. It did not lead to degradation of ODC in an *in vitro* 26 S proteasomal system (38). This difference was mapped to the presence of 2 Asp residues, which replace amino acids $Arg^{131}$ and $Ala^{135}$ in antizyme-1 (38).

There are also multiple forms of antizyme-1 due to the presence of two potential start codons and to post-translational modifications such as phosphorylation. These alterations may affect the compartmentation of antizyme as well as its function. Antizyme-1 contains two potential nuclear export signals, one located in the first 12 amino acids at the amino terminus and the other at residues 114–134. Exposure to the nuclear export inhibitor leptomycin caused antizyme to accumulate in the nucleus (39). Translocation of antizyme-1 to the nucleus occurs during mouse development (40). Antizyme-1 was found in the nucleus co-localized with ODC after treatment of carcinoma cells with polyamines or polyamine analogs (41). It was suggested on the basis of these experiments, which utilized an ODC fused to green fluorescent protein, that antizyme may be involved in nucleocytoplasmic shuttling of ODC (41). Antizyme and ODC accumulated in the nucleus after treatment with a proteasome inhibitor (40), which would also be consistent with a nuclear degradation of ODC.

Initiation of antizyme-1 at two potential start sites can result in 29- and 24.5-kDa forms. Use of the second start site, which is in a better sequence context for initiation, predominates, and the 24.5-kDa form, which lacks one of the putative nuclear export signals, is synthesized in larger amounts (42–44). The additional 33 amino acids in the 29-kDa form also include a mitochondrial targeting sequence and only this form was found in mitochondria (43, 44). However, antizyme did not affect uptake of spermine by mitochondria (44).

Antizyme genes have been found in many eukaryotes, and more than 100 such sequences are known in species including mammals, worms, insects, other invertebrates, and fungi (16, 32, 45). The pseudoknot identified in some invertebrates differs from that in mammals and some invertebrate sequences may lack the pseudoknot sequence (45), but it is not known how this affects their responsiveness to polyamines. Species in which antizyme mediates the reduction of ODC in response to increased polyamine content include *Saccharomyces cerevisiae* (30,

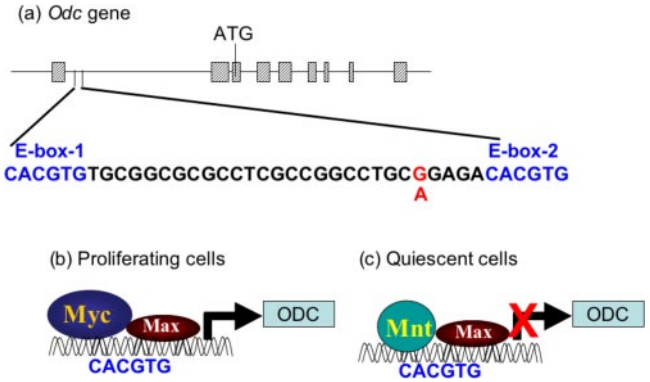


FIGURE 2. **Role of Myc in transcription of ODC.** *a* shows a schematic of the *ODC* gene with an expanded version of the region including the 2 E-boxes, which are shown in *blue*. The G/A polymorphism located in intron 1 in this region is shown in *red*. *b* shows the shows the stimulated synthesis of ODC in proliferating cells under the influence of Myc/Max. *c* shows the shows the inhibited synthesis of ODC in quiescent cells under the influence of Mnt/Max (54, 55).

46), which had previously been reported to lack antizyme, although a clear and functional homolog was present in *Schizosaccharomyces pombe*.

## Antizyme Inhibitor

A protein that blocks the effects of antizyme on ODC was discovered by Drs. S. Hayashi and colleagues. This protein, termed antizyme inhibitor, has substantial similarity to ODC itself but has no ODC activity (47). It binds to antizyme more tightly than ODC and thus releases ODC from the antizyme-ODC complex (47, 48) (Fig. 1). Recent studies have shown that antizyme inhibitor is able to disrupt the interaction between all four forms of mammalian antizyme and ODC (49).

Although the physiological importance of antizyme inhibitor is not yet fully established, a strong case can be made for it to be included as a component of the polyamine pathway. Down-regulation of antizyme inhibitor by small interfering RNA in A549 lung cancer cells reduced ODC levels and polyamine content and led to growth inhibition (50). The mRNA for antizyme inhibitor increases very rapidly when growth is induced supporting the hypothesis that this protein may play a physiological role in regulating ODC levels (48). Finally antizyme inhibitor turns over rapidly ($t_{1/2}$ of $<$30 min) and is degraded by the 26 S proteasome after ubiquitination. Binding of antizyme stabilizes the antizyme inhibitor by preventing ubiquitination (51). These properties would be consistent with a physiological role in maintaining polyamine levels.

## Transcriptional Regulation of ODC mRNA

ODC is transcriptionally regulated, and many factors have been shown to increase the synthesis of ODC mRNA. The *Odc* gene promoter region contains multiple sequences that allow response to hormones, growth factors, and tumor promoters including a cAMP response element, CAAT and LSF motifs, AP-1 and AP-2 sites, GC-rich Sp1 binding sites, and a TATA box (52, 53). It is well established that *Odc* is a target of the oncogene c-*myc* and that increased activity of the Myc/Max transcription complex leads to an increase in ODC (54, 55) (Fig. 2). The promoter region of the *Odc* gene contains two E boxes with CACGTG sequences conforming to the canonical CAYGTG sequence that binds the Myc/Max transcription factor and is activated when c-Myc levels are increased. These sites are occupied by the inactive Mnt/Max complex in quiescent cells (Fig. 2), and *Odc* transcription is very low (54, 55).

There is an interesting single nucleotide polymorphism in the human *Odc* gene, which occurs in intron 1 where there is an A/G variation at position +317 relative to the transcription start site (56, 57). This position is located between the two E boxes five nucleotides 5′ from the second CACGTG sequence (Fig. 2). Such flanking sequences can affect Myc/Max binding, and analysis showed that the ODC promoter with the minor A allele (about 24% in Caucasians) was more active than that containing the major G allele (about 76%). Thus, individuals may differ in their ability to increase ODC response to stimuli that increase Myc expression. Such differences may influence susceptibility to prostate and colon cancer (58).

## Translational Regulation of ODC Synthesis

There is also translational regulation of ODC synthesis (59, 60). The ODC mRNA has a long 5′-untranslated region (UTR) (275–313 nucleotides in mammals) that has extensive predicted secondary structure. Translation is therefore greatly enhanced by high levels of active eIF-4E (59), and cells overexpressing eIF-4E have an elevated content of ODC, which may contribute to their transformed phenotype (61). The 5′-UTR also contains a short internal ORF located about 150 nucleotides 5′ to the initiation codon and a GC-rich sequence located in the first 130 nucleotides at its 5′ end. These sequences are strongly inhibitory *in vitro* and *in vivo* to translation of either ODC itself or reporter genes to which the 5′-UTR is attached. It is possible that the 3′-UTR of ODC may partially ameliorate this inhibition (62). There is very limited other experimental data on the role of the long (about 300 nucleotides) and conserved 3′-UTR region, but it is also known that the increase in ODC mRNA translation in response to hypotonic shock requires the 3′-UTR sequence (63).

Numerous, but not all studies, have indicated that translation of ODC mRNA is reduced by polyamines. Ribosomal protein synthesis in general requires polyamines but is inhibited by their excess. However, ODC is more sensitive to excess polyamines. The mechanism underlying this effect is not clear. Although polyamine-responsive elements in the 5′-UTR and proteins binding to it have been described (reviewed in Ref. 59), other studies suggest that the effect is independent of both the 5′- and 3′-UTRs (63). It is possible that some of the apparent effects of polyamines on ODC translation are due to alterations in the very rapid degradation of nascent ODC protein due to antizyme induction or the NQOI-regulated 20 S proteasome-mediated degradation of ODC monomers described above.

It is noteworthy that ODC is not only under the control of the oncogene c-*myc* but is also downstream from another oncogene of widespread importance, *ras*. Activation of the Ras pathway has stimulatory effects on both ODC mRNA content and translation (64). Increased *Odc* transcription occurs via Raf/MEK/ERK activation. The major effect of Ras is on translation and this may be mediated through changes in phosphorylation of eIF-4E and its binding protein eIF-4E-BP1 via phosphoinositide 3-kinase and Raf/MEK/ERK signaling (64).

ODC translation may also occur in a cap-independent manner using an internal ribosome entry site (IRES) (60). ODC mRNA 5′-UTR contains a sequence similar to that found in picornavirus IRES sequences. Evidence that it does indeed act as an IRES was obtained by using a reporter gene construct and by showing cap-independent and rapamycin-insensitive translation of ODC during the $G_2$/M phase of the cell cycle of HeLa cells (60). Alternate splicing of ODC mRNA detected in rat pancreatic tumor cell RNA can lead to sequences that showed enhanced IRES activity and increased sensitivity to cell cycle-dependent changes in ODC synthesis in HeLa cells (65). The generality of these findings remains to be established, but in view of the importance of maintaining polyamine concentrations for normal growth and passage through the cell cycle, it seems likely that both cap-dependent and -independent ODC mRNA translation represent another level of control of polyamine content.

## Role of ODC and Antizyme in Carcinogenesis

In a transgenic mouse model, a large increase in ODC expression targeted to the skin resulted from a construct in which a COOH-terminally truncated form of ODC was expressed from a keratin promoter. Tumor development was increased in these mice after a variety of stimuli including chemical carcinogens, UV radiation, and an activated Ras (66–68). Conversely, expression of antizyme-1 using a keratin promoter-driven cDNA construct with a T205 single nucleotide deletion to remove the requirement for polyamine-stimulated frameshifting in translation greatly reduced carcinogenesis in mouse skin. Tumor incidence was lowered after treatment with a two-stage initiation-promotion protocol, exposure to UV radiation, or after breeding with mice having activated oncogenes or reduced tumor suppressor genes (66, 69). Formation of tumors after exposure to chemical carcinogens was also reduced in other epithelial cells from transgenic mice that expressed antizyme from keratin promoters including tongue, esophagus, and forestomach (70).[3]

There was no obvious toxic effect of the increased antizyme in these transgenic mice or in transgenic mice expressing very large amounts of antizyme in the heart from a construct driven by the $\alpha$-myosin heavy chain promoter (71). Induction of cardiac ODC by $\beta$-agonists was blocked in the latter mice, but basal levels of ODC activity were not completely reduced suggesting that there may be a small pool of ODC that is impervious to antizyme.

The most probable explanation of the antitumor effect of antizyme expression is that it acts via reducing an increase in ODC and polyamine content that is needed for neoplastic development. Other mechanisms explaining the role of antizyme in reducing tumor development cannot be ruled out, particularly if reports (15, 37,

[3] D. F. Feith, L. Y. Fong, and A. E. Pegg, unpublished data.

72, 73) that antizyme affects the turnover of other proteins can be confirmed, but the hypothesis that the effect is mediated via polyamines is supported by recent studies using ODC knock-out mice. The $Odc^{-/-}$ genotype is embryonic lethal but $Odc^{+/-}$ is viable. Cells and tissues derived from these mice have a reduction in polyamine content and a 50% reduction in ODC activity (74, 75). These changes are in line with the reduced gene copy number but are remarkable in view of the detailed regulation of ODC activity. The $Odc^{+/-}$ mice had less epidermal ODC enzyme activity and polyamine accumulation following treatment with a tumor promoter and substantially fewer skin papillomas than $Odc^{+/+}$ littermates. Similarly, Myc-induced lymphoma development was strongly retarded in E$\mu$-*Myc* transgenic $Odc^{+/-}$ mice (75). These results confirm that even modest reductions in ODC activity can lead to marked resistance to tumor development. Finally, many of the effects of antizyme expression or ODC haploinsufficiency are mimicked by exposure to DFMO. Thus, there is a convincing case that ODC is a viable target for chemoprevention. Increased antizyme content may have an additional benefit over ODC inhibitors such as DFMO in reducing polyamine uptake, but at present there are no clear feasible ways to increase antizyme content except for the use of polyamine analogs.

*Acknowledgments—I thank Drs. J. L. Cleveland, D. J. Feith, L. M. Shantz, and T. G. O'Brien for helpful discussion and comments. I apologize to the many contributors to this field whose work is not cited due to space constraints.*

## REFERENCES


1. Tabor, C. W., and Tabor, H. (1976) *Annu. Rev. Biochem.* **45,** 285–306
2. Pegg, A. E. (1988) *Cancer Res.* **48,** 759–774
3. Gerner, E. W., and Meyskens, F. L., Jr. (2004) *Nat. Rev. Cancer* **4,** 781–792
4. Cohen, S. S. (1998) *A Guide to the Polyamines*, pp. 231–259, Oxford University Press, New York
5. Coleman, C. S., Hu, G., and Pegg, A. E. (2004) *Biochem. J.* **379,** 849–855
6. McCann, P. P., and Pegg, A. E. (1992) *Pharmacol. Ther.* **54,** 195–215
7. Coleman, C. S., Stanley, B. A., Viswanath, R., and Pegg, A. E. (1994) *J. Biol. Chem.* **269,** 3155–3158
8. Almrud, J. J., Oliveira, M. A., Kern, A. D., Grishin, N. V., Phillips, M. A., and Hackert, M. L. (2000) *J. Mol. Biol.* **295,** 7–16
9. Jackson, L. K., Baldwin, J., Akella, R., Goldsmith, E. J., and Phillips, M. A. (2004) *Biochemistry* **43,** 12990–12999
10. Osterman, A., Kinch, L. N., Grishin, N. V., and Phillips, M. A. (1995) *J. Biol. Chem.* **270,** 11797–11802
11. Shah, R., Coleman, C. S., Mir, K., Baldwin, J., Van Etten, J. L., Grishin, N. V., Pegg, A. E., Stanley, B. A., and Phillips, M. A. (2004) *J. Biol. Chem.* **279,** 35760–35767
12. Jackson, L. K., Brooks, H. B., Myers, D. P., and Phillips, M. A. (2003) *Biochemistry* **42,** 2933–2940
13. Bauer, P. M., Buga, G. M., Fukuto, J. M., Pegg, A. E., and Ignarro, L. J. (2001) *J. Biol. Chem.* **276,** 34458–34464
14. Hayashi, S., and Murakami, Y. (1995) *Biochem. J.* **306,** 1–10
15. Coffino, P. (2001) *Nat. Rev. Mol. Cell Biol.* **2,** 188–194
16. Mangold, U. (2005) *IUBMB Life* **57,** 671–676
17. Kahana, C., Asher, G., and Shaul, Y. (2005) *Cell Cycle* **4,** 1461–1464
18. Zhang, M., Pickart, C. M., and Coffino, P. (2003) *EMBO J.* **22,** 1488–1496
19. Gandre, S., Bercovich, Z., and Kahana, C. (2002) *Eur. J. Biochem.* **269,** 1316–1322
20. Zhang, M., MacDonald, A. I., Hoyt, M. A., and Coffino, P. (2004) *J. Biol. Chem.* **279,** 20959–20965
21. Persson, L., Jeppsson, A., and Nasizadeh, S. (2003) *Biochem. Soc. Trans.* **31,** 411–414
22. Asher, G., Bercovich, Z., Tsvetkov, P., Shaul, Y., and Kahana, C. (2005) *Mol. Cell* **17,** 645–655
23. Heller, J. S., Fong, W. F., and Canellakis, E. S. (1976) *Proc. Natl. Acad. Sci. U. S. A.* **73,** 1858–1862
24. Murakami, Y., and Hayashi, S. (1985) *Biochem. J.* **226,** 893–896
25. Hoffman, D. W., Carroll, D., Martinez, N., and Hackert, M. L. (2005) *Biochemistry* **44,** 11777–11785
26. Bewley, M. C., Graziano, V., Jiang, J., Matz, E., Studier, F. W., Pegg, A. E., Coleman, C. S., and Flanagan, J. S. (2006) *Proc. Natl. Acad. Sci. U. S. A.* **103,** 2063–2068
27. Matsuzawa, S., Cuddy, M., Fukushima, T., and Reed, J. C. (2005) *Proc. Natl. Acad. Sci. U. S. A.* **102,** 14982–14987
28. Ivanov, I. P., Gesteland, R. F., and Atkins, J. F. (2000) *Nucleic Acids Res.* **28,** 3185–3196
29. Nilsson, J., Koskiniemi, S., Persson, K., Grahn, B., and Holm, I. (1997) *Eur. J. Biochem.* **250,** 223–231
30. Palanimurugan, R., Scheel, H., Hofmann, K., and Dohmen, R. J. (2004) *EMBO J.* **23,** 4857–4867
31. Mitchell, J. L., Leyser, A., Holtorff, M. S., Bates, J. S., Frydman, B., Valasinas, A., Reddy, V. K., and Marton, L. J. (2002) *Biochem. J.* **366,** 663–671
32. Ivanov, I. P., Matsufuji, S., Murakami, Y., Gesteland, R. F., and Atkins, J. F. (2000) *EMBO J.* **19,** 1907–1917
33. Petros, L. M., Howard, M. T., Gesteland, R. F., and Atkins, J. F. (2005) *Biochem. Biophys. Res. Commun.* **338,** 1478–1489
34. Soulet, D., Gagnon, B., Rivest, S., Audette, M., and Poulin, R. (2004) *J. Biol. Chem.* **279,** 49355–49366
35. Mitchell, J. L., Simkus, C. L., Thane, T. K., Tokarz, P., Bonar, M. M., Frydman, B., Valasinas, A. L., Reddy, V. K., and Marton, L. J. (2004) *Biochem. J.* **384,** 271–279
36. Ike, A., Ohta, H., Onishi, M., Iguchi, N., Nishimune, Y., and Nozaki, M. (2004) *FEBS Lett.* **559,** 159–164
37. Zhang, J., Wang, Y., Zhou, Y., Cao, Z., Huang, P., and Lu, B. (2005) *FEBS Lett.* **579,** 559–566
38. Chen, H., MacDonald, A., and Coffino, P. (2002) *J. Biol. Chem.* **277,** 45957–45961
39. Murai, N., Murakami, Y., and Matsufuji, S. (2003) *J. Biol. Chem.* **278,** 44791–44798
40. Gritli-Linde, A., Nilsson, J., Bohlooly-y, M., Heby, O., and Linde, A. (2001) *Dev. Dyn.* **220,** 259–275
41. Schipper, R. G., Cuijpers, V. M., De Groot, L. H., Thio, M., and Verhofstad, A. A. (2004) *J. Histochem. Cytochem.* **52,** 1259–1266
42. Feith, D. J., Shantz, L. M., and Pegg, A. E. (2001) *Cancer Res.* **61,** 6073–6081
43. Gandre, S., Bercovich, Z., and Kahana, C. (2003) *Mitochondrion* **2,** 245–256
44. Hoshino, K., Momiyama, E., Yoshida, K., Nishimura, K., Sakai, S., Toida, T., Kashiwagi, K., and Igarashi, K. (2005) *J. Biol. Chem.* **280,** 42801–42808
45. Ivanov, I. P., Anderson, C. B., Gesteland, R. F., and Atkins, J. F. (2004) *J. Mol. Biol.* **339,** 495–504
46. Chattopadhyay, M. K., Tabor, C. W., and Tabor, H. (2005) *Proc. Natl. Acad. Sci. U. S. A.* **102,** 16158–16163
47. Murakami, Y., Ichiba, T., Matsufuji, S., and Hayashi, S. (1996) *J. Biol. Chem.* **271,** 3340–3342
48. Nilsson, J., Grahn, B., and Heby, O. (2000) *Biochem. J.* **346,** 699–704
49. Mangold, U., and Leberer, E. (2005) *Biochem. J.* **385,** 21–28
50. Choi, K. S., Suh, Y. H., Kim, W. H., Lee, T. H., and Jung, M. H. (2005) *Biochem. Biophys. Res. Commun.* **328,** 206–212
51. Bercovich, Z., and Kahana, C. (2004) *J. Biol. Chem.* **279,** 54097–54102
52. Zhao, B. W., and Butler, A. P. (2001) *Mol. Carcinog.* **32,** 92–99
53. Qin, C., Samudio, I., Ngwenya, S., and Safe, S. (2004) *Mol. Carcinog.* **40,** 160–170
54. Packham, G., and Cleveland, J. L. (1997) *Oncogene* **15,** 1219–1232
55. Nilsson, J. A., Maclean, K. H., Keller, U. B., Pendeville, H., Baudino, T. A., and Cleveland, J. L. (2004) *Mol. Cell Biol.* **24,** 1560–1569
56. Guo, Y., Harris, R. B., Rosson, D., Boorman, D., and O'Brien, T. G. (2000) *Cancer Res.* **60,** 6314–6317
57. O'Brien, T. G., Guo, Y., Visvanathan, K., Sciulli, J., McLaine, M., Helzlsouer, K. J., and Watkins-Bruner, D. (2004) *Mol. Carcinog.* **41,** 120–123
58. Martinez, M. E., O'Brien, T. G., Fultz, K. E., Babbar, N., Yerushalmi, H., Qu, N., Guo, Y., Boorman, D., Einspahr, J., Alberts, D. S., and Gerner, E. W. (2003) *Proc. Natl. Acad. Sci. U. S. A.* **100,** 7859–7864
59. Shantz, L. M., and Pegg, A. E. (1999) *Int. J. Biochem. Cell Biol.* **31,** 107–122
60. Pyronnet, S., Pradayrol, L., and Sonenberg, N. (2000) *Mol. Cell* **5,** 607–616
61. Shantz, L. M., Hu, R.-H., and Pegg, A. E. (1996) *Cancer Res.* **56,** 3265–3269
62. Grens, A., and Scheffler, I. E. (1990) *J. Biol. Chem.* **265,** 11810–11816
63. Lövkvist Wallström, E., Takao, K., Wendt, A., Vargiu, C., Yin, H., and Persson, L. (2001) *Biochem. J.* **356,** 627–634
64. Shantz, L. M. (2004) *Biochem. J.* **377,** 257–264
65. Pyronnet, S., Pradayrol, L., and Sonenberg, N. (2005) *Cell. Mol. Life Sci.* **62,** 1267–1274
66. Pegg, A. E., Feith, D. J., Fong, L. Y. Y., Coleman, C. S., O'Brien, T. G., and Shantz, L. M. (2003) *Biochem. Soc. Trans.* **31,** 356–360
67. Hayes, C. S., Defeo, K., Lan, L., Paul, B., Sell, C., and Gilmour, S. K. (2006) *Oncogene*, in press
68. George, K., Iacobucci, I. A., Uitto, J., and O'Brien, T. (2005) *Mol. Carcinog.* 212–218
69. Tang, X., Kim, A. L., Feith, D. J., Pegg, A. E., Russo, J., Zhang, H., Aszterbaum, M., Kopelovich, L., Epstein, E. H., Jr., Bickers, D. R., and Athar, M. (2004) *J. Clin. Invest.* **113,** 867–875
70. Fong, L. Y., Feith, D. J., and Pegg, A. E. (2003) *Cancer Res.* **63,** 3945–3954
71. Mackintosh, C. A., Feith, D. J., Shantz, L. M., and Pegg, A. E. (2000) *Biochem. J.* **350,** 645–653
72. Gruendler, C., Lin, Y., Farley, J., and Wang, T. (2001) *J. Biol. Chem.* **276,** 46533–46543
73. Newman, R. M., Mobascher, A., Mangold, U., Koike, C., Diah, S., Schmidt, M., Finley, D., and Zetter, B. R. (2004) *J. Biol. Chem.* **279,** 41504–41511
74. Guo, Y., Cleveland, J. L., and O'Brien, T. G. (2005) *Cancer Res.* **65,** 1146–1149
75. Nilsson, J. A., Keller, U. B., Baudino, T. A., Yang, C., Norton, S., Old, J. A., Nilsson, L. M., Neale, G., Kramer, D. L., Porter, C. W., and Cleveland, J. L. (2005) *Cancer Cell* **7,** 433–444