Regulation of Ornithine Decarboxylase*

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Anthony E. Pegg1
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 recently published 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 (2–6).

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 Paramaecium bursaria chlorella virus. This protein has a key amino acid substitution (Glu for Asp) in a residue that forms an interaction with the 8-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 NH2-terminal domain forming a β/α-barrel that binds the cofactor, and a COOH-terminal domain, which is predominantly a β-sheet structure. The active sites are formed at the dimer interface between the NH2-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 Lys69 (7, 8, 12). It is likely that Cys360 plays an essential role in ensuring correct protonation of the decarboxylated reaction intermediate at Cys360. If Cys360 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′–C′′ of the intermediate (12). ODC is rapidly inactivated by nitric oxide due to the sensitivity of this Cys residue to nitrosylation (13). The most widely used pharmacological inhibitor of ODC is an α-fluoromethylornithine (DFMO), a valuable antitrypanosomal agent that acts as an enzyme-activated irreversible inhibitor of ODC forming a covalent adduct with Cys360 (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). Cys441, which is located in this COOH-terminal sequence, appears to be a key residue (14). An isosteric alteration of Cys441 → 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 Cys441 (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 Cys441 → 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 26 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

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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-fluoromethylornithine; NQO1, NAD(P)H quinone oxidoreductase; SSAT, spermidine/spermine N1-acetyltransferase; ORF, open reading frame; UTR, untranslated region; IRES internal ribosome entry site; MEK, mitogen-activated protein kinase/extracellular signal-regulated 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 fusion 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 βα-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 vivo 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 β-strands and two α-helices but, very interestingly, has a fold similar to some actetyltransferases including spermidine/spermine N1-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 (Glu161, Glu164, and Glu165) on an external face that may interact with the proteasome. Proxosomal degradation of ODC also requires a region involved in 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 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 but 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 Arg153 and Ala154 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). 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.

**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.

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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).

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**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),
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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 (t1/2 of <30 min) and is degraded by the 26S 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 CAGGTG 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 CAGGTG 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 3'-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 over-expressing 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 antagonize 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 NQO1-regulated 20 S proteasome-mediated degradation of ODC monomers described above.

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).

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 vivo. Antizyme-agonists was blocked in the latter mice, but translation representing another level of control of polyamine content.

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, 38) show the effect of increased antizyme on ODC and polyamine content that is needed for neoplastic development.
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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−/− mice.

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