COMMENTARY

Ornithine Decarboxylase: A Promising and Exploratory Candidate Target for Natural Products in Cancer Chemoprevention

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Abstract

Ornithine decarboxylase (ODC), the first enzyme in the polyamine biosynthesis, plays an important role in tumor progression, cell proliferation and differentiation. In recent years, ODC has been the subject of intense study among researchers, as a target for anti-cancer therapy and specific inhibitory agents, have the potential to suppress carcinogenesis and find applications in clinical therapy. In particular, it is suggested that ODC is a promising candidate target for natural products in cancer chemoprevention. Future exploration of ornithine decarboxylase inhibitors present in nature may offer great hope for finding new cancer chemopreventive agents.

Keywords: Ornithine decarboxylase - molecular target - natural products - cancer chemoprevention

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Introduction

In the validation and selection of molecular targets for therapeutic intervention in cancer, the frequency with which a particular target undergoes mutation or deregulation is a valuable indicator of its importance in the malignancy process and of the potential uses of a drug that acts on that target. Polyamines (putrescine, spermidine, spermine), a group of cell components, have been implicated in the transformation of cell, tumor development, regulation of cell proliferation, cell differentiation and apoptosis. High levels of polyamines are frequently seen in a variety of human malignancies (LaMuraglia et al., 1986; Luk and Casero, 1987; Paz et al., 2011; Soda, 2011). Ornithine decarboxylase (ODC), the first and rate-limiting enzyme in polyamine biosynthesis, and one of the promising candidate target, plays an important role in tumor progression, cell proliferation and differentiation (Coffino, 2001; Criss, 2003). It is one of the most highly regulated enzymes in eukaryotic organisms stimulated by a number of factors including hormones, tumor promoters and growth factors (McCann and Pegg, 1992; Verma, 1992). It is thought that ODC plays role in tumor promotion stage of carcinogenesis, transformation and metastasis of tissues, resulting in increased level of polyamines not only in humans but also in rodents (Verma, 1990; Kubota et al., 1997; Peralta Soler et al., 1998; Shantz and Pegg, 1998; Hurta, 2000; Hardin et al., 2002). The activity of ODC is controlled by a combinatorial effect of transcription, translation and enzyme degradation. In addition, the activity is specifically inhibited by antizyme protein feed-back regulation by polyamines. Depletion in polyamine pools has been shown to provoke pro-apoptotic activity in cancer cells and even prevent metastasis (Pezzuto et al., 2005; Shantz and Levin, 2007). So, inhibiting ODC activity should not only prevent tumor growth but also stops metastatic progression even in the event of cells escaping environment of the primary tumor. Therefore, ODC has been identified as a potential target in chemotherapy of cancer and parasitic diseases (Pegg et al., 1995).

Information Retrieval

Exploration of fundamental information was attained from international journals of repute, book chapters, books, reports, abstract, summary available at google (www.google.co.in), SciFinder (https://scifinder.cas.org/), PubMed (www.ncbi.nlm.nih.gov/pubmed/), Science Direct (http://www.sciencedirect.com/) search engines using keywords 'ornithine decarboxylase', 'natural products', 'cancer chemoprevention', 'molecular targets'. Information collected were compiled and arbitrarily used for preparing the commentary.

ODC Inhibitors

Difluoromethylomithine (DFMO), an inhibitor of ODC, has been found effective in essentially all animal models studied (Meyskens and Gerner, 1999) and has been the subject of clinical trials for colon, breast, prostate, skin, esophagus and cervical cancer (Lee and Pezzuto, 1999). Despite this potential, to the best of my knowledge very few ornithine decarboxylase inhibitors

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are in development or on the market and only 2-3 among them is being investigated for the treatment of cancer. This exciting target thus deserves further pharmaceutical attention to search for new ODC inhibitors. To accomplish this, natural products especially from plants receive much attention these days as lead molecule followed by chemical modification with improved activity. Some of the most interesting inhibitors belonging to rotenoids, flavonoids, lignans, retinoids, thiols, thiones and diterpene class of compounds were shown to have potent activity by regulating ODC (Table 1; Sharma et al., 1994; Gerhauser et al., 1995). Some examples like deguelin, tephrosin, hydroxydeguelin, hydroxytephrosin (rotenoids), munetone and mundulone (isoflavones), and mundulinol (flavanol), (+)-7-oxo-l3-epipimara-14,15-dien-18-oic acid, (+)-7-oxo-13-epipimara-8,15-dien-18-oic acid, and (+)-isopimaric acid (diterpenes), (1S,2S,3R)-(+)-isopicrodeoxypodophyllotoxin, (-)-deoxypodophyllotoxin, (-)-deoxypodorhizone, sulforaphane, resveratrol, curcumin, tea catechins and quercetin were found to have strong inhibitory activity against TPA-induced ODC activity (Kato et al., 1983; Lee et al., 1999a; Lee et al., 1999b) whereas zapotin and 5, 6, 2'-trimethoxyflavone exhibited moderate activity (Ito et al., 1998). Most potent deguelin and sulphoraphane were also found to be active in mouse skin carcinogenesis and rat mammary tumor models (Gerhauser et al., 1997; Udeani et al., 1997). Mechanistic studies revealed that deguelin affects TPA-induced transcriptional increase of the ODC gene and TPA-independent c-myc-induced ODC activity in BALB/c c-MycER cells. Deguelin and tephrosin were also found to affect mitochondrial oxidative phosphorylation by inhibiting NADH dehydrogenase activity. It is likely possible that a disturbance of cellular ATP may be the mechanism through which these rotenoids influence tumor promoter-induced signaling mechanisms (Lee et al., 1999b). Thus, ODC is the subject of intense study among researchers, as a target for anti-cancer therapy and agents that inhibit ODC activity, have the potential to suppress carcinogenesis and have therapeutic potential. It has been anticipated that less than 10% of higher plant species have been screened for biological activity so far, suggesting that nature is a fundamentally untapped rich source for the discovery of new natural product based chemopreventive agents.High diversity of chemicals, structural complexity, and easy access, inexpensive, less toxic, pleiotropic modes of action, low chemo-resistance are some of the major advantages of natural products over rationally designed synthetic drugs. Thus, it is suggested that ODC is a promising exploratory candidate target for natural products in cancer chemoprevention and future exploration of natural products as ornithine decarboxylase inhibitors may offer great hope for finding new cancer chemopreventive agents.

Table 1. Ornithine Decarboxylase Inhibitory Activity of Reported Chemopreventive Agents

Chemopreventive Agent (s)	Cell Line (s)	IC_{50} (μM)	Reference (s)
Zapotin	ME308	0.580	Pezzuto et al., 2005; Maiti et al., 2007
	T24	3.400	Kondratyuk et al., 2011
Deguelin	ME308	0.001	Pezzuto et al., 2005
	T24	0.100	Kondratyuk et al., 2011
	MCF-7	0.110	Fang & Casida, 1998
(13R)-hydroxydegeulin	ME308	0.010	Pezzuto et al., 2005
Tephrosin	ME308	0.005	Pezzuto et al., 2005
	MCF-7	0.147	Fang & Casida, 1998
(13R)-hydroxytephrosin	ME308	0.050	Pezzuto et al., 2005
N-(4-Hydroxyphenyl) retinamide (4-HPR)			
	ME308	5.000	Lee & Pezzuto, 1999
BASF 47343 (4-HPR Derivative			
	ME308	4.300	Lee & Pezzuto, 1999
Munetone	ME308	0.110	Pezzuto et al., 2005;
	c-MycER	0.072	Lee et al., 1999a
Mundulone	ME308	0.070	Pezzuto et al., 2005
Mundulinol	ME308	0.008	Pezzuto et al., 2005
Benzyl isothiocyanate	ME308	4.000	Lee & Pezzuto, 1999
Blumenol A	ME308	30.700	Lee & Pezzuto, 1999
(-)-deoxypodophyllotoxin	ME308	0.080	Pezzuto et al., 2005
(-)-deoxypodorhizone	ME308	6.500	Pezzuto et al., 2005
Sulforaphane	HL60	6.800	Gerhauser et al 1997; Lee et al., 1999b
	ME308	6.800	Lee & Pezzuto, 1999
5,6,2-trimethoxyflavone	ME308	0.960	Pezzuto et al., 2005
Carbenoxolone	ME308	17.600	Lee and Pezzuto, 1999
Curcumin	ME308	4.000	Lee and Pezzuto, 1999
Quercetin	HepG2	11.920	Ramirez-M et al., 2004
Diallyl sulfide	ME308	3.500	Lee & Pezzuto, 1999
Phenyl ethyl isothiocyanate	ME308	6.100	Lee & Pezzuto, 1999;
(+)-7 –oxo-13-epi-pimara-14,15-dien-18-oic-acid			Kato et al., 1983
	ME308	0.500	Pezzuto et al., 2005
(+)-7-oxo-13-epi-pimara-8,15-dien-oic acid			
	ME308	0.980	Pezzuto et al., 2005
(+)-isopimaric acid	ME308	0.860	Pezzuto et al., 2005
(1S,2S,3R)-(+)-isopicrodeoxy-podophyllotoxin			
	ME308	0.550	Pezzuto et al., 2005
Morusin	ME308	6.700	Lee & Pezzuto, 1999
Miconazole	ME308	4.100	Lee & Pezzuto, 1999
Rotenone	MCF-7	0.008	Fang & Casida, 1998
Rotenolone	MCF-7	0.091	Fang & Casida, 1998
Apigenin	T24	6.000	Wei et al., 1990; Kondratyuk et al., 2011
Menadione	T24	8.300	Kondratyuk et al., 2011
	ME308	5.000	Lee & Pezzuto, 1999
Verapamil	ME308	12.000	Lee & Pezzuto, 1999
Resveratrol 4' Sulfate	T24	0.700	Kondratyuk et al., 2011
Substituted Stillbene 5'	T24	1.300	Kondratyuk et al., 2011
Nordihydroguaiaretic acid	ME308	6.300	Lee & Pezzuto, 1999
α-difluoromethylornithine	ME308	20.000	Lee & Pezzuto, 1999
All trans retinoic acid	ME308	2.500	Lee & Pezzuto, 1999
13-cis retinoic acid	ME308	1.200	Lee & Pezzuto, 1999

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