Expression of ornithine decarboxylase in precancerous and cancerous gastric lesions

Xin-Pu Miao, Jian-Sheng Li, Hui-Yan Li, Shi-Ping Zeng, Ye Zhao, Jiang-Zheng Zeng

Xin-Pu Miao, Shi-ping Zeng, Department of Gastroenterology, the Affiliated Hospital of Hainan Medical College, Haikou 570102, Hainan Province, China
Jian-Sheng Li, Ye Zhao, Department of Gastroenterology, the First Affiliated Hospital of Zhengzhou University, Zhengzhou 450002, Henan Province, China
Hui-Yan Li, Department of Chemistry for Cancer, West China Hospital of Sichuan University, Chengdu 610041, Sichuan Province, China
Jiang-zheng Zeng, Department of Cancer, the Affiliated Hospital of Hainan Medical College, 31 Longhua Avenue, Haikou 570102, Hainan Province, China
Supported by Miao Pu Foundation of Hainan Medical College, No. 2004108 and Natural Science Foundation of Hainan Province, No. 80582
Correspondence to: Dr. Xin-Pu Miao, Department of Gastroenterology, West China Hospital of Sichuan University, 17 Renmin Avenue, Chengdu 610041, Sichuan Province, China. miaoxinpu@163.com
Telephone: +86-13438913825
Received: 2007-01-29 Accepted: 2007-02-14

Abstract
AIM: To investigate the expression of ornithine decarboxylase (ODC) in precancerous and cancerous gastric lesions.

METHODS: We studied the expression of ODC in gastric mucosa from patients with chronic superficial gastritis (CSG, n = 32), chronic atrophic gastritis [CAG, n = 43; 15 with and 28 without intestinal metaplasia (IM)], gastric dysplasia (DYS, n = 11) and gastric cancer (GC, n = 48) tissues using immunohistochemical staining. All 134 biopsy specimens of gastric mucosa were collected by gastroscopy.

METHODS: The positive rate of ODC expression was 34.4%, 42.9%, 73.3%, 81.8% and 91.7% in cases with CSG, CAG without IM, CAG with IM, DYS and GC, respectively (P < 0.01). The positive rate of ODC expression increased in the order of CSG < CAG (without IM) < CAG (with IM) < DYS and finally, GC. In addition, ODC positive immunostaining rate was lower in well-differentiated GC than in poorly-differentiated GC (P < 0.05).

CONCLUSION: The expression of ODC is positively correlated with the degree of malignity of gastric mucosa and development of gastric lesions. This finding indicates that ODC may be used as a good biomarker in the screening and diagnosis of precancerous lesions.

© 2007 The WJG Press. All rights reserved.

Key words: Ornithine decarboxylase; Gastric carcinoma; Precancerous lesions; Diagnosis; Immunohistochemistry

Miao XP, Li JS, Li HY, Zeng SP, Zhao Y, Zeng JZ. Expression of ornithine decarboxylase in precancerous and cancerous gastric lesions. World J Gastroenterol 2007; 13(20): 2867-2871

http://www.wjgnet.com/1007-9327/13/2867.asp

INTRODUCTION
Ornithine decarboxylase (ODC) is the first-rate limiting enzyme in the polyamine biosynthesis pathway[1]. ODC plays a critical role in cell proliferation[2], and it is implicated as an essential promoter in normal cell cycles. The activation of ODC is similarly related to tumor promotion and progression[3,4]. ODC activity appears to be directly coupled to the expression of ODC protein and increases with eukaryotic cell division in neoplasia and fetal development. Convincing evidence has confirmed that ODC plays an important role in the chemical carcinogenesis of mouse skin, and tumor formation can be blocked by the irreversible inhibitor of ODC, α-difluromethylornithine[5-7]. ODC is overexpressed in a variety of cancers. Elevated levels of ODC have been found in gastric cancer[8], gliomas[9], breast cancer[10,11], colon cancer[12], pancreatic cancer[13], lung cancer[14], and prostate cancer[15]. In addition, increased expression of ODC has been found associated with gastric atrophy[16].

Although ODC overexpression is clearly associated with cancer development, a definitive causal role for ODC overexpression in carcinogenesis has only been shown in NIH/3T3 fibroblast cells[17]. Overexpression of ODC is sufficient to transform fibroblast cells in vitro, causing increased frequency of skin tumors in a transgenic mouse model[17].

Although several studies have evaluated ODC expression in gastric cancer, to date, no one has investigated its associations with precancerous gastric lesions, namely, in chronic atrophic gastritis (CAG), intestinal metaplasia (IM) and gastric dysplasia (DYS). There is no information
presently available about the protein status of ODC in stomach mucosa collected by gastroscopy. A detailed study comparing the expression patterns of ODC in gastric carcinoma and precancerous tissues has not been conducted. Furthermore, whether overexpression of ODC is involved in the initiation or promotion of gastric cancer (GC) has not been established. Therefore, the aim of the present study was to investigate the expression of ornithine decarboxylase (ODC) in precancerous and cancerous gastric lesions.

MATERIALS AND METHODS

Tissue samples
We collected gastric mucosal specimens from 134 patients including 32 with chronic superficial gastritis (CSG), 43 with CAG (15 with and 28 without IM), 11 with DYS and 48 with antral GC, during gastroscopy. These specimens were obtained from symptom-free subjects who volunteered to participate in gastroscopic screening for gastric cancer in the Department of Gastroenterology of the First Affiliated Hospital of Zhengzhou University. The 48 GC patients had not received any radiation therapy or chemotherapy. GC tissues could be further separated on the basis of differentiation grade. Histopathologically, all the 48 gastric specimens were confirmed as adenocarcinoma. All of the biopsies were taken from gastric antrum. The tumors were histologically graded as well-differentiated (17 patients, 35%), moderately-differentiated (10 patients, 21%) and poorly-differentiated (21 patients, 44%). The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University.

Immunohistochemical staining for anti-ODC antibody
Tissues were fixed in 96% ethanol for 6 h at 4°C, embedded in paraffin, and cut into 5-mm thick sections. For Immunohistochemical (IHC) analysis, endogenous peroxidase activity was neutralized by treating the section in 1% hydrogen peroxide in phosphate-buffered saline for 20 min. For the microwave antigen retrieval procedure, slides were immersed in 10 mmol/L citrate buffer (pH 6.0) in a clean polyethylene chamber and placed inside a full-powered microwave, then heated for 10 min at 95°C to repair antigens, and subsequently cooled for 10-20 min. After being washed 3 times with phosphate-buffered saline, the sections were blocked in 10% mouse serum for 30-60 min to suppress nonspecific binding of IgG. Each tissue section was then incubated with primary mouse antihuman ODC monoclonal antibody (1:1000, Westbury, NY) for 2 h at room temperature. The slides were washed 3 times with phosphate-buffered saline and incubated with anti-mouse biotinylated secondary antibody (Vector, Burlingame, CA). The slides were colorized by DAB Reagent (Vectastain) and counterstained with hematoxylin. Negative controls were established by replacing the primary antibody with PBS supplemented with normal mouse or rabbit serum.

The staining results were evaluated according to the immunodetection of stain intensity and positive cells by two pathologists (Z Tan and L H Jiao), who discussed each case until they reached a consensus. Stain intensity is up to the standard of the relative stain intensity of most cells. The stain intensity could be from 0 to 3 (0, no staining; 1, shallow brown; 2, brown; 3, dark brown); and the positive cells in the observed stomach mucous cells ranged from 0 to 3 in percentage (0, no staining; 1, < 30%; 2, 30%-70%; and 3 > 70%). The samples were scored by their summation: 0-1 (-); 2-3 (+); 4 (++); 5-6 (+++). Any staining score ≥ 2 (+) was considered as positive expression.

Histopathological diagnosis for gastric epithelia was made according to the cellular morphological changes and tissue architecture using previously established criteria[18,19]. In brief, SCG, an inflammation manifested by mild lymphocyte and plasma-cell infiltration; CAG, glandular morphology disappeared partially or completely absent in the mucosa and replaced by connective tissues, inter-glandular space was infiltrated mainly by plasma cells and lymphocytes; IM, confirmed by the presence of goblet cells in gastric mucosa; and DYS, characterized by nuclear atypia with or without architectural abnormalities in the gastric epithelium without invasion. GC is characterized by invasion of neoplastic gastric cells through the basement membrane. Carcinomas were classified according to the histological classification of WHO and the Japanese Gastric Cancer Association[20,21].

Statistical analysis
The χ² test was used for the percentage of samples with positive staining among lesions of different severities. SPSS 12.0 was used for statistical analyses. P < 0.05 was considered statistically significant.

RESULTS

Positive immunostaining for ODC was observed in the gastric epithelial cells and cancer cells with different rates in the lesions of CSG, CAG (without IM), CAG (with IM), DYS and GC. To estimate the difference, staining for ODC was carried out on whole sections. The positive immunostaining rate for ODC was 34.4% (11 of 32), 42.9% (12 of 28), 73.3% (11 of 15), 81.8% (9 of 11), and 91.7% (44 of 48), respectively (P < 0.001) (Table 1). ODC

| Histological grade | ODC protein expression (a) | Total | Positive rate (%) |
|--------------------|-----------------------------|-------|------------------|
|                    | -   | +   | ++  | +++ | |                    |
| CSG                | 21  | 9   | 2   | 0   | 32 | 34.4% |
| CAG (without IM)   | 16  | 9   | 1   | 2   | 28 | 42.9% |
| CAG (with IM)      | 4   | 2   | 6   | 3   | 15 | 73.3% |
| DYS                | 2   | 1   | 4   | 4   | 11 | 81.8% |
| GC                 | 4   | 4   | 23  | 17  | 48 | 91.7% |

*P < 0.01, by trend; **P < 0.01, CSG vs CAG (with IM), CSG vs DYS, CSG vs GC, CAG (without IM) vs DYS and CAG (without IM) vs GC; and ***P < 0.05, CAG (without IM) vs CAG (with IM). CSG: chronic superficial gastritis; CAG: chronic atrophic gastritis; IM: intestinal metaplasia; DYS: dysplasia; GC: gastric cancer.
immunoreactivity was located mainly in the cytoplasm and cell membrane (Figure 1A-E).

The positive immunostaining rate for ODC was very low in CSG and CAG (without IM), and slightly increased in CAG (with IM) and DYS, and significantly increased in GC. ODC protein accumulation was higher in the GC than in CSG and CAG (without IM). In the cases of CAG (with IM) and DYS, it was also higher than in CSG and CAG (without IM). But it did not show significant difference among the groups with CAG (with IM), DYS and GC (Table 1). ODC positive immunostaining rate in the well-differentiated GC was lower than that in poorly-differentiated GC (Table 2).

**DISCUSSION**

Gastric cancer has a high incidence in China and around the world. Gastric carcinogenesis is considered as a multistage, progressive process. It is of great importance to understand the biological processes of cancer initiation for early cancer detection. An early indicator for a patient predisposed to GC is abnormal hyperproliferation of gastric epithelial cells, such as in CAG, DYS and IM, which have all been considered as precancerous lesions for GC[22,23]. However, information about the mechanism of gastric carcinogenesis is very limited. Studies of ODC protein expression levels at different stages of gastric carcinogenesis may help answer why different stages of cancerous development occur.

Polyamines, such as putrescine, spermidine and spermine, play important roles in cell proliferation and differentiation. ODC is a rate-limiting enzyme in the biosynthesis of polyamines, and the ODC gene is considered as an immediate early gene as well as an oncogene[22,23,24]. The expression rate of ODC is invariably associated with a cell's proliferate activity. ODC protein is 50 kDa monomer and about 100 kDa as the active

![Figure 1](image_url) Immunoreactivity of ODC protein in gastric precancerous and cancerous lesions. A: Immunostaining of ODC in CSG, SP × 200; B: Immunostaining of ODC in CAG (Without IM). SP × 200; C: Immunostaining of ODC in CAG (with IM) SP × 200; D: Immunostaining of ODC in DYS, SP × 200; E: Immunostaining of ODC in GC, SP × 200. CSG: chronic superficial gastritis; CAG: chronic atrophic gastritis; IM: intestinal metaplasia; DYS: dysplasia; GC: gastric cancer.
homodimer is formed. It has a rapid turnover rate with a half-life at 15 min[28]. While ODC activity may be correlated with the oncogenesis and progression of gastric cancer, the expression pattern of ODC in precancerous gastric lesions have not yet been elucidated.

In the present study, we conducted a detailed IHC comparison between precancerous and cancerous gastric lesions. The expression of ODC is positively correlated with the degree of malignity of gastric mucosa and the development of gastric lesions. With the likelihood of malignant lesions progressed from normal to CSG < CAG < DYS < GC, the positive immunostaining rates for ODC similarly increased, showing a good linear correlation between ODC expression and lesion progression. We found that the positive immunostaining rate of ODC is abnormally high in CAG (with IM), DYS and GC, indicative of abnormally high cell proliferation activity. This indicates that ODC expression may be related to the proliferative status of gastric mucosa epithelial cells. These data are consistent with the views of Patchett and others who have suggested that the presence of atrophy and intestinal metaplasia are strongly associated with increased levels of ODC activity[29]. The present results indicate that increased expression of ODC may be an important molecular event, involved in the early stages of gastric carcinogenesis. The high coincidental expression of ODC protein accumulation may be an important event to enhance GC and a useful biomarker to assess risk for the development of GC[27]. This conclusion differs from Patchett’s, which suggested that measurement of mucosal ODC activity may not be a valuable clinical marker of increased cancer risk[28]. We believe that variations in technique, materials and methods may partly explain these distinctions.

Another interesting observation is that the expression of ODC directly correlates with the differentiable condition of GC. The ODC positive immunostaining rate in well-differentiated GC was lower than in both the poorly-differentiated and moderately-differentiated GC. This result is consistent with findings in human colon carcinomas[29]. The present results indicate that increased expression of ODC may reflect the differentiated condition of stomach mucosa.

The regulation of ODC expression can occur at multiple levels including transcription, translation and protein degradation[30-32]. The ODC antizyme is a major factor in the regulation of ODC[33,34]. ODC antizyme binds to monomeric ODC, stimulating the degradation of ODC, and therefore, decreasing the exogenous level of ODC protein[33]. We presume that gastric mucosa epithelial cells may have different intrinsic ODC antizyme levels. ODC antizyme levels may decrease significantly while the degree of malignity of the gastric mucosa increases. This hypothesis requires careful investigation in follow-up studies.

In conclusion, the expression of ODC is positively correlated with the degree of malignity of gastric mucosa and development of gastric lesions. This finding indicates that ODC may be used as a good biomarker in the screening and diagnosis of precancerous lesions.

ACKNOWLEDGMENTS

The authors wish to thank Professor Ouyang Q of Huaxi Hospital of Sichuan University and Professor Zhen Tan of the Department of Pathology, the Affiliated Hospital of Hainan Medical College for revisions of this manuscript.

COMMENTS

Background
Ornithine decarboxylase (ODC) catalyzes the first step in the polyamine biosynthetic pathway forming putrescine, which is then converted into the polyamines spermidine and spermine. Polyamine content plays an important role in both normal and neoplastic growth and alterations of polyamine synthesis via changes in ODC content occur in response to tumor promoters and carcinogens. The amount of ODC is altered in response to many growth factors, oncogenes, and tumor promoters and to changes in polyamine levels. ODC is overexpressed in a variety of cancers. Gastric cancer has a high incidence in China and around the world. Gastric carcinogenesis is considered as a multistage, progressive process. It is of great importance to understand the biological processes of cancer initiation for early cancer detection. An early indicator for a patient predisposed to GC is abnormal hyperproliferation of gastric epithelial cells, such as in CAG, DYS and IM, which have all been considered as precancerous lesions for G. Studies of ODC protein expression levels at different stages of gastric carcinogenesis may help answer why different stages of cancerous development occur.

Research frontiers
It can be seen in the following four aspects: (1) expression of ODC in cancers; (2) regulation of ornithine decarboxylase; (3) inhibitor of ODC-antizyme; and (4) role of ODC and antizyme in carcinogenesis.

Innovations and breakthroughs
Although several studies have evaluated ODC expression in gastric cancer, to date, no one has investigated its associations with precancerous gastric lesions, namely, in chronic atrophic gastritis (CAG), intestinal metaplasia (IM) and gastric dysplasia (DYS). The authors found the expression of ODC is positively correlated with the degree of malignity of gastric mucosa and the development of gastric lesions. The positive immunostaining rates for ODC similarly increased, showing a good linear correlation between ODC expression and lesion progression. This finding indicates that ODC may be used as a good biomarker in the screening and diagnosis of precancerous lesions.

Applications
The authors found the expression of ODC is positively correlated with the degree of malignity of gastric mucosa and the development of gastric lesions. With the likelihood of malignant lesions progressed from normal to CSG < CAG < DYS < GC, the positive immunostaining rates for ODC similarly increased, showing a good linear correlation between ODC expression and lesion progression. Therefore, ODC may be used as a future biomarker in an early indicator for a patient predisposed to GC.

Terminology
ODC: ornithine decarboxylase; CAG: chronic atrophic gastritis; IM: intestinal metaplasia; DYS: gastric dysplasia; GC: gastric cancer.

Peer review
This paper investigates the expression and diagnostic value of ODC, a key rate-limiting enzyme in polyamine biosynthesis, in gastric precursor and cancer. The expression of ODC is positively correlated with the degree of malignity of gastric mucosa, in the order of chronic superficial gastritis, chronic atrophic gastritis (without intestinal metaplasia), chronic atrophic gastritis (with intestinal metaplasia), gastric dysplasia and gastric cancer. They concluded that ODC can be a good indicator in the screening and diagnosis of gastric precursor and cancerous lesions.

REFERENCES

1. Thomas T, Thomas Tj. Polyamine metabolism and cancer. I. Cell Mol Med 2003; 7: 113-126
Ornithine decarboxylase in precancerous and cancerous gastric lesions

Miao XP et al.

2 Auvinen M, Paasinen A, Andersson LC, Holttia E. Ornithine decarboxylase activity is critical for cell transformation. Nature 1992; 360: 355-358

3 Pegg AE. Polyamine metabolism and its importance in neoplastic growth and a target for chemotherapy. Cancer Res 1988; 48: 759-774

4 Tabib A, Bachrach U. Role of polyamines in mediating malignant transformation and oncogene expression. Int J Biochem Cell Biol 1999; 31: 1289-1295

5 O’Brien TG, Megosh LC, Gilliard G, Soler AP. Ornithine decarboxylase overexpression is a sufficient condition for tumor promotion in mouse skin. Cancer Res 1997; 57: 2630-2637

6 Soler PA, Gilliard G, Megosh L, George K, O’Brien TG. Polyamine regulates expression of the neoplastic phenotype in mouse skin. Cancer Res 1988; 58:1654-1659

7 Megosh LC, Hu J, George K, O’Brien TG. Genetic control of polyamine-dependent susceptibility to skin tumorigenesis. Genomics 2002; 79: 505-512

8 Mori M, Honda M, Shibuta K, Baba K, Nakashima H, Haraguchi M, Koba F, Ueo H, Sugimachi K, Akiyoshi T. Expression of ornithine decarboxylase mRNA in gastric carcinoma. Cancer 1996; 77: 1634-1638

9 Ernestus RI, Roher G, Schröder R, Els T, Klekner A W, Klug N. Polyamine metabolism in brain tumours: diagnostic relevance of quantitative biochemistry. J Neurol Neurosurg Psychiatry 2001; 71: 88-92

10 Mimori K, Mori M, Shiraishi T, Tanaka S, Haraguchi M, Ueo H, Shiraaka C, Akiyoshi T. Expression of ornithine decarboxylase mRNA and c-myc mRNA in breast tumours. Int J Oncol 1998; 12: 597-601

11 Canizares F, Salinas J, de las Heras M, Diaz J, Tovar I, Martinez P, Peñañiel R. Prognostic value of ornithine decarboxylase and polyamines in human breast cancer: correlation with clinicopathologic parameters. Clin Cancer Res 1999; 5: 2033-2041

12 Berdinskikh NK, Ignatenko NA, Zaletok SP, Ganina KP, Chorniy VA. Ornithine decarboxylase activity and polyamine content in adenocarcinomas of human stomach and large intestine. Int J Cancer 1991; 47: 496-498

13 Subhi AL, Tang B, Balsara BR, Altomare DA, Testa JR, Cooper HS, Hoffman JP, Meropol NJ, Kruger WD. Loss of methylthioadenosine phosphorylase and elevated ornithine decarboxylase is common in pancreatic cancer. Biochem Cell Biol 1996; 74: 933-940

14 Young L, Salomon R, Au W, Allan C, Russell P, Dong Q. Ornithine decarboxylase (ODC) expression pattern in human prostate tissues and ODC transgenic mice. J Histocomp Cytochem 2006; 54: 223-229

15 Konturek PC, Rembiasz K, Konturek SJ, Stachura J, Bielanski W, Galuschka K, Karcz D, Hahn EG. Gene expression of ornithine decarboxylase, cyclooxygenase-2, and gastrin in atrophic gastric mucosa infected with Helicobacter pylori before and after eradication therapy. Dig Dis Sci 2003; 48: 36-46

16 Mosher JA, Doeschu J, Skuna M, Luk GD. Transformation of NIH/3T3 cells by ornithine decarboxylase overexpression. Cancer Res 1993; 53: 2618-2622

17 Wang LD, Shi ST, Zhou Q, Goldstein S, Hong JY, Shao P, Qiu SL, Yang CS. Changes in p53 and cyclin D1 protein levels and cell proliferation in different stages of human esophageal and gastric-cardia carcinogenesis. Int J Cancer 1994; 59: 514-519

18 Rugger M, Corpea P, Dixon MF, Hattori T, Leandro G, Lewin K, Riddell RH, Sipponen P, Watanabe H. Gastric dysplasia: the Padova international classification. Am J Surg Pathol 2000; 24: 167-176

19 Fengglo-Priester C, Muñoz N, Carneiro F. Tumors of the stomach. In: Hamilton SR, Aaltonen LA. World Health Organization classification of tumours. Pathology and genetics of tumours of the digestive system. 1st ed. Lyon: International Agency for Research on Cancer, 2000: 37-38

20 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma, 2nd ed, Tokyo: Kanehara & Co. Ltd Pub, 1998; 10-24

21 You WC, Blot WJ, Li JY, Chang YS, Jin ML, Kneller R, Zhang L, Han ZX, Zeng XR, Liu WD. Precancerous gastric lesions in a population at high risk of stomach cancer. Cancer Res 1993; 53: 1317-1321

22 Correa P. Human gastric carcinogenesis: a multistep and multifactorial process—First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res 1992; 52: 6735-6740

23 Rousseau D, Kaspar R, Rosenwald I, Gehrke L, Sonenberg N. Translation initiation of ornithine decarboxylase and nucleocytoplasmic transport of cyclin D1 mRNA are increased in cells overexpressing eukaryotic initiation factor 4E. Proc Natl Acad Sci USA 1996; 93: 1065-1070

24 Pendeville H, Carpio N, Marine JC, Takahashi Y, Muller M, Martial JA, Cleveland JL. The ornithine decarboxylase gene is essential for cell survival during early murine development. Mol Cell Biol 2001; 21: 6549-6558

25 Patchett SE, Katelaris PH, Zhang ZW, Alstead EM, Domizio P, Farthing MJ. Ornithine decarboxylase activity is a marker of premalignancy in longstanding Helicobacter pylori infection. Gut 1996; 39: 807-810

26 Okuzumi J, Yamane T, Kitao Y, Tokiwa K, Yamaguchi T, Fujita Y, Nishino H, Ishiwashita A, Takahashi T. Increased mucosal ornithine decarboxylase activity in human gastric cancer. Cancer Res 1991; 51: 1448-1451

27 Patchett SE, Alstead EM, Butruk L, Przytulski K, Farthing MJ. Ornithine decarboxylase as a marker for premalignancy in the stomach. Gut 1995; 37: 13-16

28 Pegg AE. Recent advances in the biochemistry of polyamines in eukaryotes. Biochem J 1986; 234: 249-262

29 Hu HY, Liu XX, Jiang CY, Zhang Y, Bian JF, Lu Y, Geng Z, Liu SL, Liu CH, Wang XM, Wang W. Cloning and expression of ornithine decarboxylase gene from human colorectal carcinoma. World J Gastroenterol 2003; 9: 714-716

30 Pegg AE, Shantz LM, Coleman CS. Ornithine decarboxylase: structure, function and translational regulation. Biochem Soc Trans 1994; 22: 846-852

31 Shantz LM, Pegg AE. Translational regulation of ornithine decarboxylase and other enzymes of the polyamine pathway. Int J Biochem Cell Biol 1999; 31: 107-122

32 Ivanov IP, Matsufuji S, Murakami Y, Gesteland RF, Atkins JF. Conservation of polyamine regulation by translational frameshifting from yeast to mammals. EMBO J 2000; 19: 1907-1917

33 Coffino P. Regulation of cellular polyamines by antizyme. Nat Rev Mol Cell Biol 2001; 2: 188-194

34 Ivanov IP, Rohrwater A, Terrerros DA, Gesteland RF, Atkins JF. Discovery of a spermatogenesis stage-specific ornithine decarboxylase antizyme: antizyme 3. Proc Natl Acad Sci USA 2000; 97: 4808-4813

S-Editor Zhu LH  L-Editor Ma JY  E-Editor Ma WH

www.wignet.com