J Cachexia Sarcopenia Muscle (2012) 3:277–278
DOI 10.1007/s13539-012-0091-5

LETTER TO THE EDITOR

Ursodeoxycholic acid and its emerging role in attenuation of tumor growth in gastrointestinal malignancies

Shailendra Kapoor

Received: 17 October 2012 / Accepted: 25 October 2012 / Published online: 13 November 2012

Dear Editor,

I read with great interest the recent article by Tschirner et al. [1]. Interestingly, recent data suggest that ursodeoxycholic acid (UDCA) may attenuate tumor growth in a number of gastrointestinal malignancies.

For instance, tauro-ursodeoxycholic acid when administered along with celecoxib attenuates proliferation and tumor growth in colonic adenomas [2]. Interestingly, UDCA decreases the odds of advanced lesions in males only [3]. Similarly, UDCA downregulates c-Myc expression [4]. As a result, it attenuates tumor growth in colon carcinomas. CDK6 expression is also decreased secondary to UDCA administration. UDCA downregulates Cox-2 also, thus further inhibiting tumor growth. It also attenuates CCAAT/enhancer binding protein beta (C/EBPbeta) at the same time [5]. It also effects p38 and Ras expression and thereby further modulates Cox-2 function. Recently, UDCA conjugates with glutamic acid have been developed that result in enhanced intraluminal delivery of UDCA inside the colon [6].

Similarly, UDCA inhibits gastric carcinogenesis. It does this by modulating the MEK/ERK pathway. It accentuates MEK1/2 phosphorylation as well as ERK1/2 phosphorylation [7]. DR 5 receptors are necessary for UDCA-mediated apoptosis. Modulation of the raft formation/ROS production/PKCδ activation pathway can effect UDCA-mediated apoptosis as it in turn effects and controls DR5 expression [8]. Apoptosis secondary to UDCA is attenuated by U0126 as well as by PD98059.

Similarly, DLC1 degradation by proteosomes is attenuated by UDCA [9]. Subsequently, there is decreased proliferation and growth in hepatocellular carcinomas. UDCA administration is simultaneously accompanied by a decrease in RhoA activity. Similarly, UDCA upregulates Bax expression and downregulates Bcl-2 expression. Interestingly, the p53-caspase 8 pathway is activated by UDCA which mediates the conversion from oxaliplatin-induced necrosis to apoptosis in hepatocellular carcinomas [10]. At the same time, UDCA inhibits ROS production. Hence, combination therapy in hepatocellular carcinomas may benefit from the addition of UDCA. Similarly, UDCA has a negative impact on the incidence rate of cholangiocarcinomas in patients with primary sclerosing cholangitis [11].

It is clearly evident from the above examples that UDCA can play a major role in attenuating carcinogenesis in the gastrointestinal tract. There is a clear and urgent need for further studies in this regard.

Acknowledgment The author of this manuscript certifies that he complies with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle* (von Haehling S, Morley JE, Coats AJ, Anker SD. Ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*. J Cachexia Sarcopenia Muscle. 2010;1:7–8.)

Conflict of interest The author has no conflicts of interest.

References

1. Tschirner A, von Haehling S, Palus S, Doehner W, Anker SD, Springer J. Ursodeoxycholic acid treatment in a rat model of cancer cachexia. J Cachexia Sarcopenia Muscle. 2012;3:31–6. doi:10.1007/s13539-011-0044-4.
2. van Heumen BW, Roelofs HM, Te Morsche RH, Marian B, Nagengast FM, Peters WH. Celecoxib and tauro-ursodeoxycholic acid co-treatment inhibits cell growth in familial adenomatous

A reply to this comment can be found at doi 10.1007/s13539-012-0092-4.

S. Kapoor (✉)
University of Illinois at Chicago,
Chicago, IL, USA
e-mail: shailendrakapoor@yahoo.com

polyposis derived LT97 colon adenoma cells. Exp Cell Res. 2012;318:819–27.
3. Thompson PA, Wertheim BC, Roe DJ, et al. Gender modifies the effect of ursodeoxycholic acid in a randomized controlled trial in colorectal adenoma patients. Cancer Prev Res (Phila). 2009;2: 1023–30.
4. Peiro-Jordan R, Krishna-Subramanian S, Hanski ML, Luscher-Firzlaff J, Zeitz M, Hanski C. The chemopreventive agent ursodeoxycholic acid inhibits proliferation of colon carcinoma cells by suppressing c-Myc expression. Eur J Cancer Prev. 2012;21:413–22.
5. Khare S, Mustafi R, Cerda S, et al. Ursodeoxycholic acid suppresses Cox-2 expression in colon cancer: roles of Ras, p38, and CCAAT/enhancer-binding protein. Nutr Cancer. 2008;60:389–400.
6. Asciutti S, Castellani D, Nardi E, et al. A new amino acid derivative of ursodeoxycholate, (N-L-glutamyl)-UDCA (UDCA-Glu), to selectively release UDCA in the colon. Anticancer Res. 2009;29:4971–9.
7. Lim SC, Duong HQ, Parajuli KR, Han SI. Pro-apoptotic role of the MEK/ERK pathway in ursodeoxycholic acid-induced apoptosis in SNU601 gastric cancer cells. Oncol Rep. 2012;28:1429–34.
8. Lim SC, Duong HQ, Choi JE, et al. Lipid raft-dependent death receptor 5 (DR5) expression and activation are critical for ursodeoxycholic acid-induced apoptosis in gastric cancer cells. Carcinogenesis. 2011;32:723–31.
9. Chung GE, Yoon JH, Lee JH, et al. Ursodeoxycholic acid-induced inhibition of DLC1 protein degradation leads to suppression of hepatocellular carcinoma cell growth. Oncol Rep. 2011;25:1739–46.
10. Lim SC, Choi JE, Kang HS, Han SI. Ursodeoxycholic acid switches oxaliplatin-induced necrosis to apoptosis by inhibiting reactive oxygen species production and activating p53-caspase 8 pathway in HepG2 hepatocellular carcinoma. Int J Cancer. 2010;126:1582–95.
11. Rudolph G, Kloeters-Plachky P, Rost D, Stiehl A. The incidence of cholangiocarcinoma in primary sclerosing cholangitis after long-time treatment with ursodeoxycholic acid. Eur J Gastroenterol Hepatol. 2007;19:487–91.