

Letter to the Editor

Comment on: Omega-3 polyunsaturated fatty acid inhibits the malignant progression of hepatocarcinoma by inhibiting the Wnt/ β -catenin pathway

Dear Editor,

We read with great interest the article by Chang et al¹, who aimed to assess the effect of Omega-3 polyunsaturated fatty acid (ω -3 PUFA) either on cell cycle and apoptosis rate, or on invasion and metastasis of hepatocarcinoma (HCC) cells analyzed by trans-well assay. The authors also evaluated the protein levels of key factors in Wnt/ β -catenin pathway by Western blot. The results showed how Omega-3 PUFA regulates the malignant progression of HCC by inhibiting proliferation and promoting apoptosis of HCC cells via the Wnt/ β -catenin signaling pathway. The diet role in the prevention or treatment of hepatocellular diseases is well known^{2,3} as well as its imbalance combined with genetic and metabolic factors. These factors could contribute to chronic hepatitis and related complications, as HCC⁴. Several animal and human studies focused on ω -3 have already been performed. Jump et al⁵ developed a model of non-alcoholic steato-hepatitis (NASH) by using mice with the LDL cholesterol receptor gene ablated fed the Western diet (WD). They induced a NASH phenotype in these mice, including hepatic steatosis, inflammation, oxidative stress, and fibrosis. The authors evaluated the capability of two dietary ω -3 polyunsaturated fatty acids, eicosapentaenoic acid (20:5 ω -3; EPA) and docosahexaenoic acid (22:6 ω -3; DHA) in preventing from WD-induced NASH. The DHA dietary effects were greater than EPA in attenuating WD-induced, the reverse of WD effects on hepatic metabolism, oxidative stress, and fibrosis. The results of these studies suggest that DHA may be useful in preventing NASH and reducing the risk of HCC. In an interesting randomized control trial on NASH patients, Nogueira et al⁶ demonstrated how the supplementation of Omega-3 PUFA from flaxseed and fish oils significantly affected the plasma lipid profile of patients with NASH. Moreover, the plasma increase of PUFAs was associated with better liver histology. The Wnt/ β -catenin signaling pathway is one of the most frequently activated in the pathogenesis of HCC, offering the novel potential treatments targeting⁷, as well as reported by Chang et al¹. In a recent study, Hu et al⁸ evaluated the role of glypican-3 (GPC3)/wnt/ β -catenin signaling pathway and autophagy in the regulation of HCC growth mediated by curcumin in a tumor xenografts mice model. The results showed the activity of curcumin in suppression HCC tumor growth through the down-regulation of the GPC3/wnt/ β -catenin signaling pathway.

We believe Chang's study an interesting experimental study on several factors affecting the development of HCC; however, the focus on the main hepatic fibrosis trigger (viral, molecular and metabolic)⁹⁻¹¹ should remain the pivot role in HCC care.

Abbreviations

Omega-3 polyunsaturated fatty acid (ω -3 PUFA), Hepatocarcinoma (HCC), Non-alcoholic steato hepatitis (NASH), Western diet (WD), Eicosapentaenoic acid (20:5 ω -3; EPA), Docosahexaenoic acid (22:6 ω -3; DHA).

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Conflict of Interest

The Authors declare that they have no conflict of interests.

References

- 1) CHANG FZ, WANG Q, ZHANG Q, CHANG LL, LI W. Omega-3 polyunsaturated fatty acid inhibits the malignant progression of hepatocarcinoma by inhibiting the Wnt/ β -catenin pathway. *Eur Rev Med Pharmacol Sci* 2018; 22: 4500-4508.
- 2) DI MARTINO S, RAINONE A, MAROTTA G, MAZZARELLA M, PUGLIESE S, RINALDI L. Nutraceutical agents with hepatoprotective effects in cancer patients. *WCRJ* 2016; 3: e788.
- 3) DI FRANCA R, RINALDI L, TROISI A, DI BENEDETTO F, BERRETTA M. Effect of anti-oxidant agents in patients with hepatocellular diseases. *Eur Rev Med Pharmacol Sci* 2015; 19: 3993-3995.
- 4) RINALDI L, NASCIMBENI F, GIORDANO M, MASETTI C, GUERRERA B, AMELIA A, FASCIONE MC, BALLESTRI S, ROMAGNOLI D, ZAMPINO R, NEVOLA R, BALDELLI E, IULIANO N, ROSATO V, LONARDO A, ADINOLFI LE. Clinical features and natural history of cryptogenic cirrhosis compared to hepatitis C virus-related cirrhosis. *World J Gastroenterol* 2017; 23: 1458-1468.
- 5) JUMP DB, DEPNER CM, TRIPATHY S, LYTLE KA. Potential for dietary ω -3 fatty acids to prevent non-alcoholic fatty liver disease and reduce the risk of primary liver cancer. *Adv Nutr* 2015; 6: 694-702.
- 6) NOGUEIRA MA, OLIVEIRA CP, FERREIRA ALVES VA, STEFANO JT, RODRIGUES LS, TORRINHAS RS, COGLIATI B, BARBEIRO H, CARRILHO FJ, WAITZBERG DL. Omega-3 polyunsaturated fatty acids in treating non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled trial. *Clin Nutr* 2016; 35: 578-586.
- 7) KHALAF AM, FUENTES D, MORSHID AI, BURKE MR, KASEB AO, HASSAN M, HAZLE JD, ELSAYES KM. Role of Wnt/ β -catenin signaling in hepatocellular carcinoma, pathogenesis, and clinical significance. *J Hepatocell Carcinoma* 2018; 5: 61-73.
- 8) HU P, KE C, GUO X, REN P, TONG Y, LUO S, HE Y, WEI Z, CHENG B, LI R, LUO J, MENG Z. Both glypican-3/Wnt/ β -catenin signaling pathway and autophagy contributed to the inhibitory effect of curcumin on hepatocellular carcinoma. *Dig Liver Dis* 2018; pii: S1590-8658(18)30799-0.
- 9) ADINOLFI LE, NEVOLA R, RINALDI L, ROMANO C, GIORDANO M. Chronic hepatitis C virus infection and depression. *Clin Liv Dis* 2017; 21: 517-534.
- 10) BIONDI A, MALAGUARNERA G, VACANTE M, BERRETTA M, D'AGATA V, MALAGUARNERA M, BASILE F, DRAGO F, BERTINO G. Elevated serum levels of chromogranin A in hepatocellular carcinoma. *BMC Surg* 2012; 12 Suppl 1: S7.
- 11) ADINOLFI LE, NEVOLA R, GUERRERA B, D'ALTERIO G, MARRONE A, GIORDANO M, RINALDI L. HCV clearance by direct-acting antiviral treatments reverses insulin resistance in chronic hepatitis C patients. *J Gastroenterol Hepatol* 2017; 33: 1379-1382.

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