European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2018; 22: 5411-5412

Letter to the Editor

Comment on: Correlation between HSD17B4 expression in rat liver cancer tissues and inflammation or proliferation

Dear Editor,

We read with great interest the article of Pan et al[1]. They evaluated the correlations between 17β-estradiol dehydrogenase IV (HSD17B4) and tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and proliferating cell nucleus antigen (PCNA) expression in a rats liver cancer induced. Significantly high phosphorylation level of Akt and ERK, along with the increase of HSD17B3 and PCNA expressions, was found in model group. Serum estradiol (E2) level was statistically decreased, whilst TNF-α and IL-6 were up-regulated. The authors concluded that HSD17B4 was positively correlated with TNF-α, IL-6 and PCNA expressions, suggesting its involvement in inflammation and proliferation of liver cancer cells.

The estrogen-regulated mechanisms of hepatocellular carcinoma (HCC) development and/or progression was also evaluated by Cocciadiferro et al[2] that investigated the expression of Merlin, the product of the neurofibromatosis type 2 (NF2) tumor suppressor gene, in non-tumoral, cirrhotic and malignant liver tissues and cells, in relation to estrogen formation and activity. NF2 expression is elevated in HCC tissues, intermediate in cirrhotic tissues and lower in non-tumoral liver cells.

Impaired sex steroid (both androgen and estrogen) receptors and their variants are one of the key factors of an increased risk for liver cancer. For this reason, the pharmacological modulation of E2 receptors with E2 may be clinically useful in preventing and/or treating HCC, as demonstrated by Jeng et al[3]. Sanaei at al[4] treated HCC HepG2 cells with various concentrations of Genistein (GE) and E2. This experimental work clearly demonstrated that GE and E2 induced apoptosis and inhibited cell growth significantly.

Liver cancer is mainly associated to hepatic fibrosis due to continuous necrosis either in case of inflammations triggered by metabolic and genetic factors or in case of persistent viral replication with immune system escape mechanism[5-7]. Furthermore, overexpression of oncoproteins[8], together with pro-inflammatory factors, play a fundamental role in the process of hepatocarcinogenesis. Pharmacological therapeutics do not guarantee long term survival rate[9,10] and newest therapies could be associated with severe adverse effects too[11]. These are the reasons why research based on molecular markers could be very useful tools for the diagnosis and therapy of HCC, as demonstrated in several studies[12,13].

Abbreviations

17β-estradiol dehydrogenase IV(HSD17B4), Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6), Proliferating Cell Nucleus Antigen (PCNA), Estradiol (E2), Hepatocellular carcinoma (HCC), neurofibromatosis type 2 (NF2), Genistein (GE).

Conflict of interest

The authors declare no conflicts of interest.

Corresponding Author: Stefania Milione MD; e-mail: stefania.milione@gmail.com

References

1) Pan LC, Xiao HY, Yin WJ, Lin Z. Correlation between HSD17B4 expression in rat liver cancer tissues and inflammation or proliferation. Eur Rev Med Pharmacol Sci 2018; 22: 3386-3393.
2) Cocciadiferro L, Miceli V, Granata OM, Carruba G. Merlin, the product of NF2 gene, is associated with aromatase expression and estrogen formation in human liver tissues and liver cancer cells. J Steroid Biochem Mol Biol 2017; 172: 222-223.
3) Jeng LB, Velmurugan BK, Hsu HH, Wen SY, Shen CY, Lin CH, Lin YM, Chen RJ, Kuo WW, Huang CY. Fenofibrate induced PPAR alpha expression was attenuated by oestrogen receptor alpha overexpression in Hep3B cells. Environ Toxicol 2018; 33: 234-247.
4) Sanaei M, Kavoosi F, Pourahmadi M, Moosavi SN. Effect of genistein and 17-β estradiol on the viability and apoptosis of human hepatocellular carcinoma HepG2 cell line. Adv Biomed Res 2017; 6: 163.
5) Rinaldi L, Di Francia R, Coppola N, Guerrera B, Imparato M, Monari C, Nevola R, Rosato V, Fontanella L, Franci G, Porta G, Messina V, Ascione A, Adinolfi LE. Hepatocellular carcinoma in HCV cirrhosis after viral clearance with direct acting antiviral therapy: preliminary evidence and possible meanings. WCRJ 2016; 3: e748.
6) Lonardo A, Nascimbeni F, Maurantonio M, Marrazzo A, Rinaldi L, Adinolfi E. Non-alcoholic fatty liver disease: evolving paradigms. World J Gastroenterol 2017; 23: 6571-6592.
7) Adinolfi LE, Nevola R, Rinaldi L, Romano C, Giordano M. Chronic hepatitis C virus infection and depression. Clin Liv Dis 2017; 21: 517-534.
8) Zhan N, Michael AA, Wu K, Zeng G, Bell A, Tao J, Monga SP. The effect of selective c-MET inhibitor on hepatocellular carcinoma in the MET-Active, β-catenin-mutated mouse model. Gene Expr 2018; 18: 135-147.
9) 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.
10) Berretta M, Rinaldi L, Di Benedetto F, Lleshi A, De Re V, Facchini F, De Paoli P, Di Francia R. Angiogenesis inhibitors for the treatment of hepatocellular carcinoma. Front Pharmacol 2016; 7: 428.
11) Coppola N, De Pascalis S, Messina V, Di Caprio G, Martini S, de Stefano G, Starace M, Stornaiuolo G, Stanzione M, Ascione T, Minichini C, Sangiovanni V, Zampino R, Calò F, Rinaldi L, Persico M, Federico A, Buonomo AR, Borgia G, Gaeta GB, Filippini P, Gentile I. ITPase activity modulates the severity of anaemia in HCV-related cirrhosis treated with ribavirin-containing interferon-free regimens. Antivir Ther 2017; 22: 551-558.
12) 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.
13) Di Benedetto F, Tarantino G, Ercolani G, Baccarani U, Montalti R, De Ruvo N, Berretta M, Adani GL, Zanello M, Tavio M, Cautero N, Tirelli U, Pinna AD, Gerunda GE, Guaraldi G. Multicenter italian experience in liver transplantation for hepatocellular carcinoma in HIV-infected patients. Oncologist 2013; 18: 592-599.

S. Milione[1], E. Allegorico[2], C. Altruda[3]

[1]Department of Medical Surgical, Neurological, Metabolic and Aging Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy
[2]PS/OBI A.O.R.N. Antonio Cardarelli, Naples, Italy
[3]Emergency Medicine, S.M. della Misericordia University, Udine, Italy