Tumori, 96: 90-96, 2010

Relevance of two genes in the multidrug resistance of hepatocellular carcinoma: *in vivo* and clinical studies

Zhengang Sun[1*], Zizhuo Zhao[2*], Gaopeng Li[2,3*], Shengli Dong[4], Zhiyong Huang[3], Lu Ye[5], Huifang Liang[3], Junyuan Qu[6], Xi Ai[3], Wanguang Zhang[3], and Xiaoping Chen[3]

[1]Department of Hepatobiliary Surgery, Jingzhou Central Hospital, JingZhou, Hubei Province; [2]Department of Ultrasound, the second affiliated hospital, Sun Yat-sen University, Guangzhou, Guangdong Province; [3]Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province; [4]Department of General Surgery, the second affiliated hospital, Shanxi Medical University, Taiyuan, Shanxi Province; [5]Infection Department, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province; [6]Department of Galactophore Surgery, Shanxi Tumour Hospital, Taiyuan, Shanxi Province, China

*These authors contributed equally to this work and should be considered co-first authors.

ABSTRACT

Aims and background. A former study evaluated the roles of four multidrug resistance-related proteins, namely multidrug resistance protein 1 (MDR1), breast cancer resistance protein (BCRP), multidrug resistance-related protein (MRP1), and lung resistance-related protein (LRP), in the MDR mechanism of the multidrug resistant hepatoma HepG2/ADM cell line and proposed that up-regulated MDR1 and BCRP are responsible for the MDR of hepatocellular carcinoma. This work aims to confirm that assumption *in vivo* and in clinical specimens.

Methods. First, the chemotherapeutic resistance of subcutaneous HepG2/ADM tumor and hepatocellular carcinoma samples post-transarterial chemoembolization (TACE) was determined by MTT, contrary to subcutaneous HepG2 tumor and hepatocellular carcinoma samples without TACE, respectively. Then, the mRNA and protein differential expression of the four genes between the MDR tissues and drug-sensitive tissues were quantitatively investigated by real-time RT-PCR and enhanced chemiluminescence western blot analysis, respectively.

Results. 1) mRNA expression of BCRP and MDR1 was respectively amplified 38.3 and 20.1 fold in tumors of HepG2/ADM mice compared to those of HepG2 mice, whereas they were respectively augmented for 14.6 and 9.3 times in TACE samples, contrary to the tumor tissues without TACE. 2) The protein presence of MDR1 and BCRP in MDR tumors was also significantly higher than those in the control group *in vivo* and in clinical specimens. 3) The mRNA expressions of MDR1 and BCRP were correlated to their protein levels.

Conclusions. The study showed that MDR1 and BCRP may be the most important factors for drug resistance in hepatocellular carcinoma. Moreover, the positive correlation between their mRNA and protein expression indicates the easy prediction of HCC MDR and possible inhibitive target of drug resistance at multi-levels. **Free full text available at www.tumorionline.it**

Key words: athymic mice, hepatocellular carcinoma, multi-drug resistance protein, multi-drug resistance.

Acknowledgements: This work was supported by grants from the general Program of National Natural Science Foundation of China (Grant No. 30872996), the National Key Technologies R & D Program of China during the 10th Five-Year Plan Period (2004BA714B08) and the Key Project of the National Natural Science Foundation of China (Grant No. 30430670), the Chinese Ministry of Public Health for Key Clinical Projects (Grant No. 353 [2007]) and Hepatic Surgery Medical Clinical Research Centre of Hubei, China (2007).

Correspondence to: XiaoPing Chen, MD, PhD, FACS, Professor & Chairman, Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China.
Tel +86-27-83662599;
fax +86-27-83662851;
e-mail ligaopeng@medmail.com.cn

Received January 21, 2009;
accepted July 30, 2009.