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Relationship between cellular senescence and sorafenib efficacy in hepatocellular carcinoma

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Statement of the Problem: Sorafenib is the only approved drug for the treatment of advanced hepatocellular carcinoma (HCC). However, its efficacy is largely limited by the emergence of primary and/or acquired resistance. Senescence-associated secretory phenotype (SASP) is now recognized as one of the darkest sides of senescence response because many factors that can promote tumor development are major components of SASP, such as IL6. SASP-mediated chemo-resistance has attracted increasing attention but never revealed in HCC. The purpose of this study is to investigate the effect of SASP on sorafenib resistance in HCC.

Methods: The cytotoxicity of sorafenib in different HCC cell lines was determined by MTT assay. Cells were stained with senescence-associated β-galactosidase, which is a typical biomarker of cellular senescence. Secreted IL6 proteins were measured using ELISA. Acquired sorafenib-resistant cells were constructed based on sensitive cells that treated were with increased concentrations of sorafenib.

Findings: HCC cell lines exhibited different sensitivities to sorafenib. The cells with a strong SASP exhibited a low sensitivity to sorafenib. IL6 blocking in sorafenib-resistant HCC cells could significantly increase the cytotoxicity of sorafenib. A reduced cytotoxicity of sorafenib was detected when sorafenib-sensitive cells incubated with conditioned media from the acquired-resistant cells, in which IL6 level is higher than parent sensitive cells, accompanied by the stimulation of AKT phosphorylation. The reversal of sorafenib resistance in acquired-resistant cells could be achieved through IL6 blocking and AKT pathway inhibition.

Conclusion: SASP can be used to account for sorafenib resistance. Combination therapy of sorafenib with IL6 blocking or AKT pathway inhibition can be considered as an effective strategy for HCC patient who is resistant to sorafenib.

Biography

Leilei Niu earned her MS from Shandong University in 2014, and now pursuits PhD at The Chinese University of Hong Kong. Her previous study focused on the contribution of inflammation to docetaxel resistance in prostate cancer. She successfully identified Marchantin M, which is a naturally occurring compound; can be used to overcome docetaxel resistance through exerting its anti-inflammatory activity (Leilei Niu. Cancer lett, 2014). Her PhD study mainly focuses on the effect of cellular senescence on sorafenib efficacy in hepatocellular carcinoma, and now some novel findings have been obtained. During the period between Dec 01, 2016 and Feb 15, 2017, she was invited to work as a Post-graduate fellow in Sidi Chen lab (http://medicine.yale.edu/lab/sidichen/people/sidi_chen.profile), Yale University School of Medicine.

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