Molecular mechanism of HCC progression and strategy to management

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Hepatocellular carcinoma (HCC) ranks the second cancer mortality in Taiwan and the fifth in the world. Early detection and curative treatment provide a better chance for long-term outcome. However, cumulated 5 year post-operative recurrence may be up to 70% and is the most important cause influencing survival. Early post-operative HCC recurrence (within 2 years after surgical resection) is closely related to metastasis from the original tumor. Large tumor size, multi-nodularity, venous invasion, etc. are factors associated with recurrence. Underlying tumor behavior may play the most critical role for metastasis. Epithelial-mesenchymal transition (EMT) is an important mechanism of metastasis of many cancers including HCC. Downregulation of E-cadherin and membranous β-catenin and upregulation of mesenchymal genes, such as vimentin and N-cadherin, are the key features of EMT. EMT and the subsequent activation of downstream genes contribute to invasiveness. The expression of EMT regulators, such as Twist and Snail, down-regulates E-cadherin and membranous β-catenin and is closely associated with recurrence and shorter survival. Lymphoid enhancing factor (LEF) 1 is important in the progress of several types of cancers. Microarray analysis showed that LEF 1 was associated with postoperative recurrence ($p<0.0001$). Over-expression of LEF1 was associated with Twist over-expression ($p=0.018$), a trend of Snail over-expression ($p=0.064$), multi-nodular tumors ($p=0.025$). Downregulation of LEF1 by shRNA decreased tumor sphere, soft agar colony formation, and trans-well invasion of Mahlavu cells. Xenotransplant and tail vein injection revealed disruption of LEF1 expression significantly reduced the tumor size and the invasiveness of Mahlavu cells, respectively. CHIP and reporter assays revealed that LEF1 can physically interact with and transcriptionally activate the promoter regions of Oct4, Snail, Slug and Twist. Therefore, LEF1 is pivotal in the progression of HCC through the transcriptional regulation of Oct4 and EMT regulators. Currently, the only approved target therapy, Sorafenib, can only prolong survival for about 3 months. Our preliminary data showed a promising lead compound with broad activity against invasion by inhibiting Twist, proliferation and angiogenesis, SOX2, anti-apoptosis and drug resistance. In addition, it promotes apoptosis and has a synergistic effect with Sorafenib and Doxorubicin. Further studies are needed.

Late recurrence that occurs 2 years after surgical resection mostly results from secondary primary HCCs that have different clonality from the original one. High viral load and hepatic inflammation are significant factors associated with late recurrence. Pre-S deletion HBV mutant is associated with recurrence only in the presence of high viral load. In multivariate analysis, antiviral

therapy can counteract the effects of high viral load and hepatic inflammation and is an independent factor associated with reduced recurrence.

In summary, early HCC recurrence is closely related to metastasis induced by EMT and late recurrence is de novo second primary HCC induced by high viral load and hepatic inflammation. The development of an effective novel target therapy against mechanisms of EMT, self-renewal, angiogenesis, anti-apoptosis and drug resistance may contribute to reduce early recurrence. Long-term and sustained antiviral therapy is needed to reduce viral load and hepatic inflammation and is critical to reduce late recurrence.