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Effects of small molecule inhibitors on liver cancer stem cells in comparison with Sorafenib

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Hepatocellular carcinoma (HCC) is resistant to both conventional and targeted chemotherapy due to its highly heterogenous nature. Activation of RTK pathways is an important signaling mechanism involved in the development and the progression of liver cancer stem cell (LCSC) population in response to the drug resistance. Therefore, it is crucial to identify novel targets and therapeutic molecules against HCC. This study focuses on the effects of two groups of small molecule inhibitors on liver cancer stem cells.

First group of molecules involve a series of novel NSAID triazolothiadiazine derivatives. Following the bioactivity screening of 32 triazolothiadiazine derivatives on 9 different HCC cell lines, the most potent compound, 7b (IC50 = 0.2-1.0 μM) was identified to cause G2/M phase cell cycle arrest and apoptosis in Huh7, HepG2, Mahlavu, FOCUS, SNU475 and SNU387 cells. This was due to the reactive oxygen species (ROS) accumulation involving JNK protein activation. The upstream ASK1 and MKK7 and downstream c-Jun proteins were also involved in the actions of 7b. Furthermore, 7b treatment reduced the tumor size and prolonged the disease-free survival of nude mice significantly. Additionally, compound 7b inhibited liver cancer stem cell enrichment and sphere formation capacity of HCC cells compared to Sorafenib. The anti-tumor effects of compound 7b approves that this small molecule can be considered as an anti-cancer agent for liver cancer therapeutics.

The second group of molecules involve 10 different PI3K/Akt/mTOR pathway inhibitors which were exploited as an alternative to clinically approved drugs Sorafenib and Regorafenib. We compared the bioactivities of small molecule PI3K/Akt/mTOR pathway inhibitors with Sorafenib, DNA intercalators and DAPT (CSC inhibitor) on CD133/EpCAM positive LCSCs. LCSCs were enriched upon treatment with Sorafenib, and DNA intercalators, but not with Rapamycin and DAPT. Differential expression analysis of 770 cancer pathway genes using network-based systems biology methods allowed us to associate IL-8 with LCSC enrichment. Upon IL-8 signaling inhibition with IL-8R inhibitor Reparixin, LCSC-sphere formation capacity and stemness-related protein levels in liver cancer cells were significantly reduced. This study indicates the involvement of autocrine inflammatory cytokines in hepatic CSC population survival under chemotherapeutic stress.

Keywords: Hepatocellular carcinoma,Small molecule, Liver cancer