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Signatures of resistance associated genes in sorafenib/ regorafenib enriched hepatocellular carcinoma cells

Tsung-Hui Hu[1], Pey-Ru Lin[1], Ming-Hong Tai[2]

1 Division of Hepato-Gastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan

2 Institute of Biological Sciences, National Sun Yat-Sen University, Kaohsiung, Taiwan.

Background

Sorafenib (BAY 43-9006, Nexavar®)

•The first multikinase inhibitor that had demonstrated a survival benefit (2.8-month absolute improvement) over supportive care in advanced HCC in 2006.

Regorafenib (BAY 73-4506, Stivarga®)

•The first small molecule approved by FDA for the treatment of patients with refractory metastatic colorectal cancer after standard therapies.

•The treatment of significantly improved the overall survival of patients with unresectable HCC whose disease has progressed after receiving sorafenib. (randomized/ double blind/ placebo controlled/ multicenter Phase III trial, in 2016)

Resistance to anticancer drugs and tumor relapse are still challenges in clinical cancer management. The resistant cancer cells are enriched after multikinase inhibitors administration and affected the outcomes of disease post-treatment.

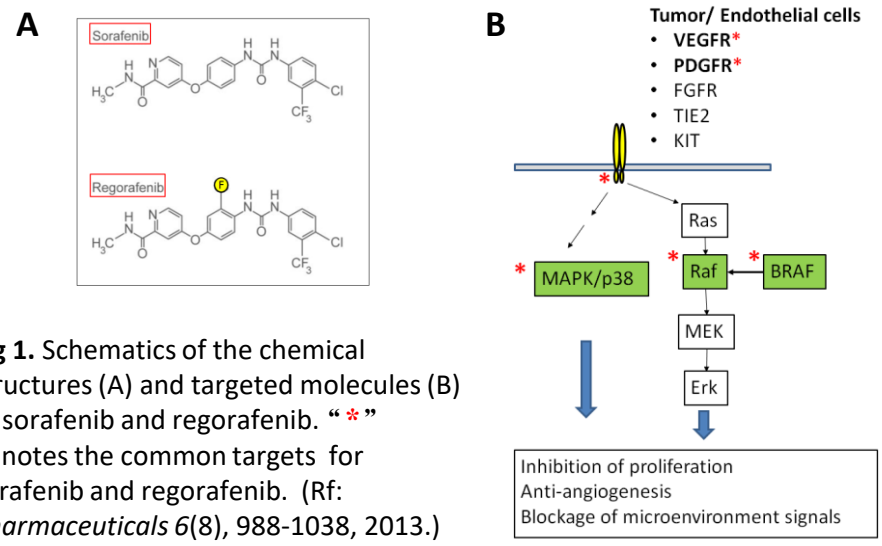

Fig 1. Schematics of the chemical structures (A) and targeted molecules (B) of sorafenib and regorafenib. " * " denotes the common targets for sorafenib and regorafenib. (Rf: *Pharmaceuticals 6*(8), 988-1038, 2013.)

Aims

To explore the drug-resistant associated signatures of HCC cells after long-term sorafenib/ regorafenib exposure through analyzing the microRNA expression profiles and their target gene clusters.

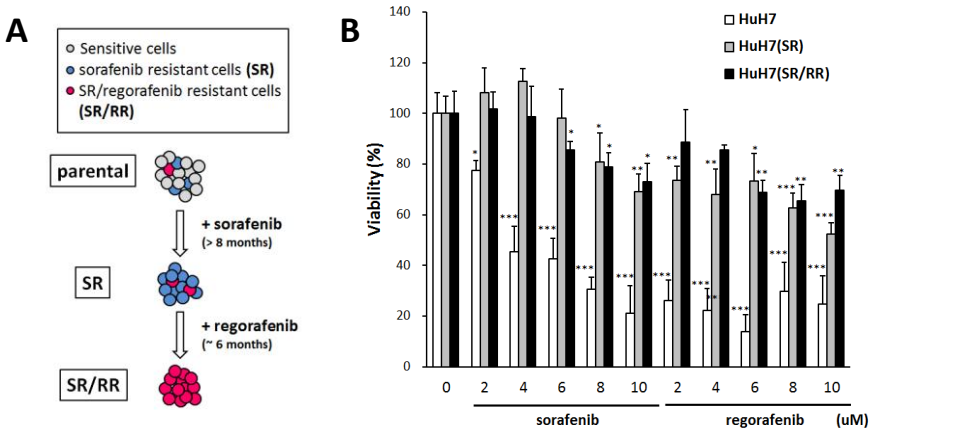

Fig 2. (A) Experimental flow chart of enrichment for sorafenib/ regorafenib resistant HCC cells. (B) The sensitivity of enriched resistant cells and parental HuH7 cells against sorafenib or regorafenib was determined by [3-(4,5-dimethylthiazol-2-yl) -2,5-diphenyltetrazolium bromide] (MTT) assay. Statistic analysis was performed using two-tailed t test (compared to "0" group). *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

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CONTACT INFORMATION

Tsung-Hui Hu, MD, PhD

E-mail: dr.hu@msa.hinet.net

TEL: +886-7-731-7123 ext.8301

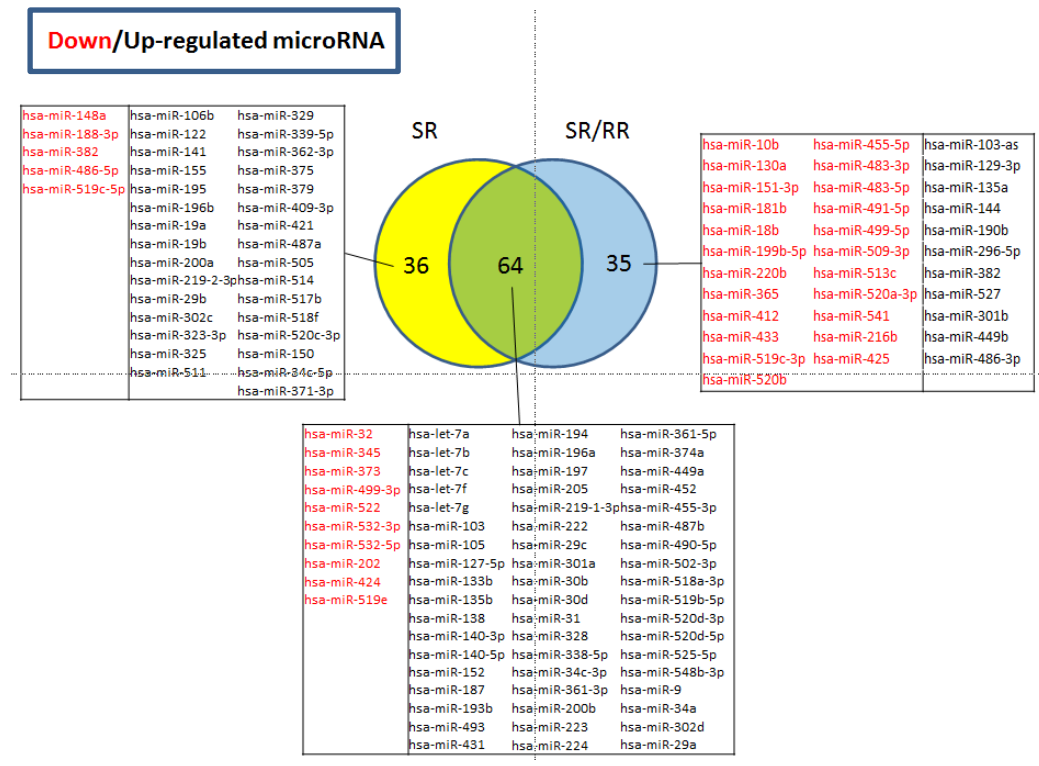
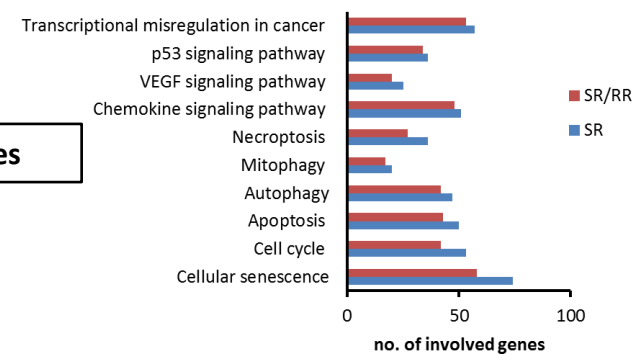


Fig 3. Venn diagram showing the deregulated microRNA in enriched resistant cells screened using real-time PCR based microarray (QuantiMir™ kit). The number of deregulated miRNAs was indicated in the diagram and colored (black: up-regulated; red: down-regulated). The relative level of miRNAs was determined by comparing to those in HuH7 cells.

Survival-related genes



Stemness-related genes

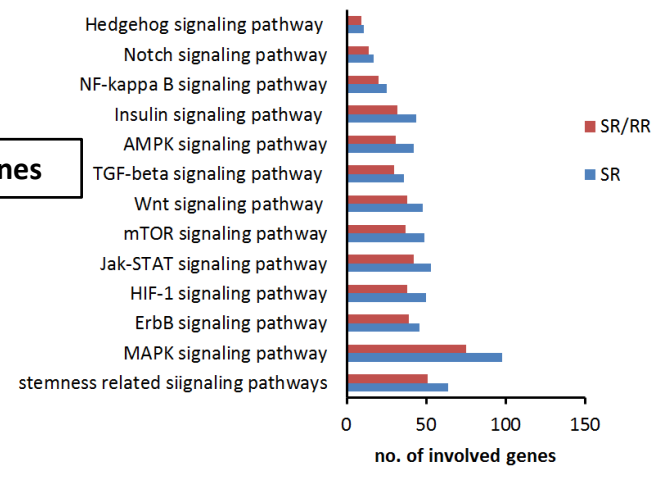


Fig 4. Classification of functional annotations of genes regulated by mRNAs based on the KEGG pathway database. Micro RNAs-targeted mRNAs were browed by functional miRNA-target interactions (MTIs) in miRTarBase 7.0 database (**at http://miRTarBase.mbc.nctu.edu.tw/).**

Conclusions

- Apparent dysregulation of cellular miRNAs profiles was found in resistant cells, which affects the expression of drug-resistant gene clusters , including survival- and stemness-related genes.
- The miRNA-mRNA interaction network needs further validation in the future.