Background

Sorafenib is a multi-kinase inhibitor and one of the few systemic treatment options for patients with advanced hepatocellular carcinomas (HCCs). Resistance to sorafenib develops frequently and could be mediated by the NAD dependent deacetylase sirtuin (SIRT) 1, a master regulator of cellular energy metabolism and stress responses. We aimed to find out if sorafenib effects depend on changes in cellular NAD levels as well as activity of SIRT1 and the cellular energy sensor adenosine monophosphate kinase (AMPK).

Results

Sorafenib decreases phosphorylation of ERK and induces apoptosis in hepatocellular cell lines

Sorafenib decreases NAD levels in HUH7 cells which is not mediated by NAMPT or SIRT1.

Sorafenib incubation induces mitochondrial dysfunction

Conclusion

Sorafenib targets multiple cellular pathways including the SIRT1/AMPK axis and that overexpression of SIRT1 could be an underlying mechanism of resistance to sorafenib treatment in HCC.