Sorafenib downregulates nuclear factor E2-related factor 2 (Nrf2)-regulated thioredoxin 1 (Trx1) expression in liver cancer cells

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Hepatocellular carcinoma (HCC) represents 80% of the primary hepatic neoplasms. It is the sixth most frequent neoplasm, the fourth cause of cancer-related death, and 7% of registered malignancies. Although immunotherapy and antiangiogenic combined treatment is emerging as first line therapy, Sorafenib is a useful treatment in the actual pipeline for patients in advanced stage of HCC. The administration of Sorafenib, and other tyrosine kinase inhibitors, is widely associated with mitochondrial dysfunction and the generation of reactive oxygen (ROS) and nitrogen (RNS) species. However, Sorafenib exerts a role as a free radical scavenger assessed by electron paramagnetic resonance, EPR. We also observed that Sorafenib downregulates nuclear factor E2-related factor 2 (Nrf2)-regulated thioredoxin 1 (Trx1) expression in liver cancer cells. In order to elucidate the function of Trx1 in our system, siRNA strategies and/or its overexpression showed that Trx1 induced activation of nitric oxide synthase (NOS) type 3 (NOS3) and S-nitrosation (SNO) of CD95 receptor leading to an increase of caspase-8 activity and cell proliferation, as well as reduction of caspase-3 activity in liver cancer cells. Sorafenib also transiently increased mRNA expression and activity of S-nitrosoglutathione reductase (GSNOR) in HepG2 cells. Different experimental models of hepatocarcinogenesis based on the subcutaneous implantation of HepG2 cells in nude mice, as well as the induction of HCC by diethylnitrosamine (DEN) confirmed the relevance of Trx1 downregulation during the proapoptotic and antiproliferative properties induced by Sorafenib. In conclusion, the induction of apoptosis and antiproliferative properties by Sorafenib were related to Trx1 downregulation that appeared to play a relevant role on SNO of NOS3 and CD95 in HepG2 cells. The transient increase of GSNOR might also participate in the deactivation of CD95-dependent proliferative signaling in liver cancer cells.

Jordi Muntané is Associate Professor in the Department of Medical Physiology and Biophysics, School of Medicine, University of Seville (Spain). The group is deciphering the molecular mechanism related to the antitumoral properties of tyrosine kinase inhibitors (TKIs) in liver cancer cells. In particular, the impact in mitochondrial dysfunction, oxidative and nitrosative stress and cell metabolism, endoplasmic reticulum stress, autophagy and apoptosis in the effectiveness of TKIs in liver cancer cells. The translational impact of the research involves the identification of circulating tumor cells (CTCs), extracellular vesicles (EVs) and miRNA and lncRNA signatures in blood from patients used as prognostic value of the disease and treatment response in patients with advanced HCC. In particular for the participation of our group in BenBedPhar network we will be focus on: 1) Molecular mechanism of Nrf2 regulation by TKIs. 2) Impact of NRf2-regulated genes in the antitumoral properties of TKIs and 3) Impact of drugs regulating Nrf2 in liver cancer cells.