Editorial

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Why Liver Cancer is so Highly Refractory to Chemotherapy?

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Abstract

In contrast to important advances in early diagnosis of primary liver cancer, both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), and the curative alternatives available to treat these patients, the pharmacological strategies used in adjuvant chemotherapy and in advanced tumors are poorly effective, whereas similar regimes result in much better outcome in other types of cancer. The reason for the marked refractoriness of liver cancer to antitumor drugs, even the newest inhibitors of receptors with tyrosine kinase activity (TKI), is the participation in the overall multidrug resistance (MDR) phenotype of very different mechanisms that are yet poorly understood. This justifies the effort that is being carried out to obtain a complete picture of the question, which will allow us to identify the precise genetic fingerprint accounting for the MDR phenotype present in each tumor at each moment, from diagnosis to the end of treatment. This information shall be valuable to prevent unnecessary use of pharmacological regimes without expected beneficial effect but with potential noxious consequences. Finally, a better understanding of the molecular bases of the problem is also required to develop novel strategies aimed to fight HCC and CCA chemoresistance.

Keywords: Cancer; Chemotherapy; Chemoresistance; Cholangiocarcinoma; Hepatocellular carcinoma;Introduction

Why liver cancer is so highly refractory to chemotherapy? The response to this question is complex. In the first place it should be considered that liver cancer is diverse in origin as well as in biological and clinical characteristics. The most frequent type of primary liver cancer is hepatocellular carcinoma (HCC) - derived from hepatocytes - followed at a considerable distance by cholangiocarcinoma (CCA) - derived from epithelial cells of the biliary tree (cholangiocytes) -. Both tumors share a frequent fatal prognosis together with a very poor response to treatment with chemotherapeutic regimes incorporating sorafenib is effective in the treatment of several types of tumors, but scarcely in the majority of patients. High expression of pumps belonging to the ATP-binding cassette (ABC) superfamily of proteins, such as P-glycoprotein or MRP family, are able to actively export a large variety of drugs, such as doxorubicin, etoposide, paclitaxel and vinblastine [12, 13], and hence play an important role in decreasing their intracellular levels. Since not only drug concentrations are important, but also the proportion of active molecules reaching tumor cells, mechanisms of chemoresistance found in HCC and CCA include the decreased activation of prodrugs. For instance, impaired activity and/or expression of enzymes involved in the activation of 5'-fluorouracil (5'-FU) and gemcitabine may be involved in the poor response of advanced CCA to the treatment with these drugs [14, 15]. In the opposite direction, up-regulation of enzymes accounting for drug inactivation, such as several isozymes of glutathione-S-transferase (e.g., GSTP1) [16, 17], whose expression may be stimulated by the pharmacological treatment, also results in reduced response to chemotherapy. An important characteristic that may
determine the efficacy of chemotherapy is the presence in HCC and CCA cells of changes in the molecular targets for antitumor drugs. This is particularly relevant in the case of TKIs, the appearance of mutations that either induce constitutive activation of the receptors or hinder the potential interaction of these proteins with TKIs, results in the lose of activity of these drugs [6, 9]. Enhanced ability of tumor cells to repair damaged macromolecules also results in chemoresistance. For example, the major route to repair 5'-FU-induced misincorporation of fluoronucleotides, i.e., base-excision repair system, is activated in 5'-FU-resistant CCA cells [18]. In the case of agents, such as cisplatin, whose mechanism of action is based on the inactivation of tumor cell machinery for genome replication by the formation of DNA adducts, the enhanced ability of these cells to repair DNA damage permits them to overcome the pharmacological challenge and hence escape apoptosis [19]. In fact, the goal of most antitumor drugs is to stimulate cell death. Accordingly, enhanced expression/function of pro-survival proteins, such as BIRC5, or decreased activity of pro-apoptotic proteins, such as p53, may lead to changes in the balance that determines the escaping of tumor cells from drug-induced apoptosis. In sum, at present, there is a considerable interest in elucidating all mechanisms accounting for HCC and CCA chemoresistance. To obtain a complete picture of the question will allow us to identify the precise genetic fingerprint present in each tumor at each moment from diagnosis to the end of treatment. This information shall be valuable to prevent unnecessary use of regimes without expected beneficial effect but with potential noxious consequences. Finally, a better understanding of the molecular bases of the problem is also required to develop novel strategies aimed to fight HCC and CCA chemoresistance [20].

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