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► **To cite this version:**

Orlando Musso, Naiara Beraza. Hepatocellular carcinomas evolution to sorafenib resistance through hepatic leukaemia factor. *Gut*, 2019, 68 (10), pp.1728-1730. 10.1136/gutjnl-2019-318999. hal-02179669

HAL Id: hal-02179669

<https://univ-rennes.hal.science/hal-02179669>

Submitted on 10 Jul 2020

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Hepatocellular carcinomas: evolution to sorafenib resistance through hepatic leukaemia factor

Orlando Musso,¹ Naiara Beraza²

Hepatocellular carcinoma (HCC) is the second cause of cancer-related death and it represents the leading cause of death in patients with cirrhosis.¹ The vast majority of HCCs develop in a background of severe liver fibrosis, commonly caused by HBV or HCV infection, exposure to aflatoxin B, alcoholic and non-alcoholic

steatohepatitis (NASH), as well as genetic diseases.¹ Despite recent advances in the treatment of viral hepatitis, modelling of the dramatic rise in the incidence of NASH predicts a substantial increase in the global burden of HCC.¹

HCC allocation to treatment options is based on tumour number, size and vascular invasion, as well as on the functional liver reserve. Although HCC aggressiveness can be inferred from these clinical parameters, screening programmes in patients at risk increasingly detect early-stage HCCs that share homogeneous clinical features, but that diverge in terms of biological and molecular features.¹ Therefore, a more

precise prediction of HCC aggressiveness is expected from a better insight on HCC heterogeneity.

Liver transplantation is the most effective curative option for HCC though it suffers from obvious limitations such as donor (organ) shortage. Alternative treatments include hepatic resection and tumour ablation, chemoembolisation and systemic therapy, which is limited to sorafenib and lenvatinib as first-line treatment, and second-line options like regorafenib among others.¹ Sorafenib, a multikinase inhibitor with antiproliferative and antiangiogenic properties, is the gold-standard systemic treatment option improving patient survival.¹ Still, some tumours are resistant to sorafenib, underlining the urge to understand how HCC cells develop treatment resistance.

Cancer progression results from the coevolution of a heterogeneous ecosystem involving genetic diversity, epigenetic reprogramming and remodelling of the tumour microenvironment.² The tumour ecosystem selects quiescent cancer stem

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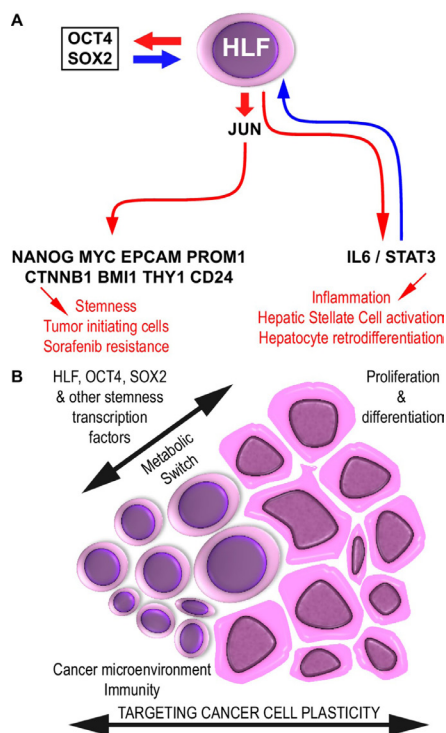


Figure 1 Hepatic leukaemia factor (HLF) as a paradigm for cancer cell plasticity and cancer evolution. (A) *De novo* expression of the oncofetal protein HLF is induced by the pluripotency factors OCT4 and SOX2. HLF, in turn, upregulates OCT4 and SOX2 in a positive feedback loop leading to JUN expression, AP1 signaling and expression of stem cell markers, which concur to induce tumor initiation, progression and sorafenib resistance. HLF also upregulates IL6/STAT3 in a feedforward regulatory circuit. (B) Strategies to tackle tumor evolution to cancer stem cells resistant to therapies may involve combined targeting of the metabolic/detoxification switches in cancer stem cells plus controlling cancer cell proliferation/differentiation and tumor immunity. *Left*, quiescent, metabolically fit cancer stem cells; *right*, proliferating and moderately-to-poorly differentiated cancer cells. Red arrows, HLF-induced effects; blue arrows, feedforward regulatory circuits. HLF, hepatic leukaemia factor.

cells whose particular energy metabolism and detoxifying properties lead to therapeutic resistance.² Cancer progression toward an increasingly aggressive disease correlates with *de novo* expression of oncofetal proteins and with poor prognosis.³ A number of oncofetal proteins have been described, including the pluripotency factors OCT4 and SOX2, as well as AFP, SKA-1, SALL4, IGF2BP, 5T4, ROR1, FOXM1, Nodal and CR1,³ that endow cancer cells with stemness features, such as metabolic switch, drug detoxification,

quiescence, immune escape and cell plasticity (figure 1). Pluripotency confers a high-degree biodiversity to the tumour ecosystem and therefore the ability for selection of the fittest cancer cells in terms of therapeutic resistance.²

In *Gut*, Xiang and colleagues identified hepatic leukaemia factor (HLF) as a novel oncofetal protein driving HCC progression and resistance to sorafenib.⁴ HLF is a member of the proline and acidic amino acid-rich basic leucine zipper family of transcription factors.⁵ It was first identified as part of the t(17:19)(E2A-HLF) translocation, in a rare subtype of child acute lymphoblastic leukaemia.⁶ HLF is essential for haematopoietic stem cell development and xenobiotic detoxification,⁵ and maintains quiescence of haematopoietic stem cells, protecting them from radiation or drug-induced injury and increasing drug resistance in acute lymphoblastic leukaemia.⁶

In fibrotic livers, HLF is expressed by hepatic stellate cells, which leads to a positive feedback loop further promoting HLF expression via activation of the proinflammatory IL6/STAT3 pathway.⁷ Interleukin 6 signalling plays a major role in hepatocyte retrodifferentiation and in the proinflammatory and preneoplastic microenvironment that contributes to the emergence of HCCs in severely fibrotic livers.^{1,8} Therefore, it may be hypothesised that HLF fosters the emergence of quiescent cancer stem cell populations from the onset of liver carcinogenesis. This assumption may be substantiated by evidence provided by Xiang *et al* in this issue of *Gut*,⁴ whereby the pluripotency factors SOX2 and OCT4 synergistically upregulate HLF expression and, conversely, HLF upregulates expression of the pluripotency factors SOX2 and OCT4 in a positive feedback loop. As well, HLF may upregulate stemness through NANOG, MYC and CTNNB1 (figure 1), as shown by the authors in this issue of *Gut*.⁴

The study by Xiang and colleagues also demonstrates that the induction of HLF expression in healthy adult hepatocytes leads to the expression of tumour-initiating cell (TIC)-associated markers and that the depletion of HLF protects the liver from HCC development in mice. Further mechanistic evidence established HLF as an upstream regulator of the transcription of *JUN*, a well-known oncogene⁹ that mediates the promotion of HLF-dependent TIC-like properties and tumour progression. Importantly, the authors show that the activation of the HLF/c-Jun axis confers tumour cell resistance to sorafenib, supporting

previous work showing that *JUN* expression associates with sorafenib resistance *in vitro* and in patients with HCC¹⁰ and establishing HLF as an upstream regulator of sorafenib resistance induced by c-Jun.⁴

Overall, these results support the value of HLF expression as a prognosis marker of survival of patients with HCC by predicting resistance to sorafenib, providing a key tool for patient stratification. Still, establishing HLF as a cancer marker has obvious limitations. These include the fact that the detection of HLF must be done in tissue and that biopsies are rarely taken for diagnosis or surveillance, which is commonly carried out combining imaging with analysis of serum markers.¹

Xiang *et al*⁴ propose HLF as a therapeutic target for HCC. Based on stemness and multipotency, oncofetal proteins are attractive therapeutic targets for pharmacological approaches to treat HCC. Yet, we are still far from the ‘magic bullet’ to treat HCC: a complex multifactorial disease, involving stemness, proliferation, angiogenesis, immune exhaustion and profound metabolic changes in the tumour and its microenvironment.

From the perspective of Darwinian evolution, tumour progression results from the competition of diverse cancer cell clones for the cancer cell niche. Aggressive anticancer therapies sweep away proliferating cells, thereby releasing the competitive pressure from quiescent cancer stem cells endowed with detoxification, survival and metabolic fitness.¹¹ The work by Xiang *et al* suggests that anticancer therapy should combine conventional antiproliferative and tumour mass-reducing approaches (including biotherapy and immunotherapy), with strategies to prevent the development of cancer stem cell contingents by attacking their specific attributes, such as metabolic reprogramming⁸ or the development of pluripotency features (figure 1B).² Therefore, future cancer treatments may consider a wider range of cancer cell diversity to prevent the emergence of fitter cancer cell populations.

Funding This work was supported by the Institut National de la Santé et de la Recherche Médicale; the University of Rennes 1; the Ligue contre le cancer, Comités d’Ille-et-Vilaine et Vendée and the Institut National du Cancer, Grant number: 12688 (to OM); Biotechnology and Biological Sciences Research Council (BBSRC); this research was funded by the BBSRC Institute Strategic Programme Gut Microbes and Health BB/R012490/1 and its constituent project BBS/E/F/000PR10355 (to NB).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.



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To cite Musso O, Beraza N. *Gut* 2019;**68**:1728–1730.

Received 10 June 2019

Accepted 12 June 2019

Published Online First 3 July 2019



► <http://dx.doi.org/10.1136/gutjnl-2018-317440>

Gut 2019;**68**:1728–1730.

doi:10.1136/gutjnl-2019-318999

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