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Review

Hepatocellular carcinoma: Exploring the impact of ethnicity on molecular biology

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ABSTRACT

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and the third leading cause of cancer-related death. The high rate of diagnosis in non-curable stages and the lack of novel active treatments make it necessary to review all the possible sources of misleading results in this scenario. The incidence of HCC shows clear geographical variation with higher annual incidence in Asia and Africa than in Western countries; we aimed to review the literature to find if there are different trends in the main activated molecular pathways. Hyperactivation of RAS/RAF/MEK/ERK and PI3K/AKT/mTOR signalling and epithelial to mesenchymal transition (EMT) process are more prevalent in the Western population; however, fibroblast growth factor (FGF), transforming growth factor β (TGFβ) and Notch pathways seems to be more relevant in Asian population. Whether these

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variations just reflect the distinct distribution of known causes of HCC or proper ethnical differences remain to be elucidated. Nevertheless, these clearly different patterns are relevant to regional or worldwide clinical trial design. If this information is neglected by sponsors and researchers the rate of failure in HCC trials will not improve.

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and the third leading cause of cancer-related death (Siegel et al., 2013). Its poor prognosis is mainly related to high rate of diagnosis in non-curable stages, in which patients are suitable for palliative treatment. Sorafenib is the only treatment option available that has shown to improve overall survival in patients with advanced HCC (Llovet et al., 2008a). A better understanding of the biochemical pathways involved in HCC, clarifying the mechanisms by which the tumour evades treatment, seems to be the main way forward to improve clinical outcomes (Llovet et al., 2015). Hepatocarcinogenesis is a complex multistep process, known to be mainly driven by chronic hepatitis which creates a protumourigenic hepatic environment and leads to pro-oncogenic, epigenetic and genetic changes (Szabo and Lippai, 2012). The molecular biology of carcinogenesis and tumour progression of HCC has been increasingly understood during the last decades. Several important intracellular pathways, such as the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathways; growth factors such as fibroblast growth factor (FGF); and critical processes such as epithelial to mesenchymal transition (EMT) and angiogenesis seem to be involved in the development of HCC (Pang and Poon, 2007; Marquardt and Thorgeirsson, 2014). In contrast, an important hallmark of HCC is the absence of a clearly identified addiction to an oncogene or pathway.

The Inhibition of some of these pro-oncogenic pathways has led to targeted therapy options, such as sorafenib (Llovet et al., 2008b; Cheng et al., 2009). However, the clinical benefit to systemic treatment in HCC seems to differ between countries (Cheng et al., 2009). In addition, the incidence of HCC shows clear geographical variation with higher annual incidence in Asia and Africa than in Western countries (Parkin et al., 2005). When analysing the different next generation sequencing projects, it is noticeable that there are at least different patterns of gene-alterations depending on the different areas of the world (Guichard et al., 2012; Roberts and Wheller, 2015; Totoki et al., 2011; Nakagawa and Shibata, 2013). As an example, we plot the percentage of mutations per sample for the 100 most altered genes extracted from the International Cancer Genome Consortium (ICGC) data portal (ICGC, 2015), see Fig. 1 and Supplementary Material 1. One of the postulated explanations for these facts could be pre-existing molecular discrepancies throughout different ethnicities.

The aim of this review is to explore the evidence supporting the potential biological differences across the world. Do they really exist? If they do, how relevant are they and how much evidence do we have? What are the implications for trial design?

2. Molecular pathways

2.1. RAS/RAF/MEK/ERK pathway

This pathway is one of the key signalling cascades involved in the development of multiple cancers, resulting in cell cycle progression, apoptosis resistance, extracellular matrix remodelling, cellular migration and angiogenesis. As previously described

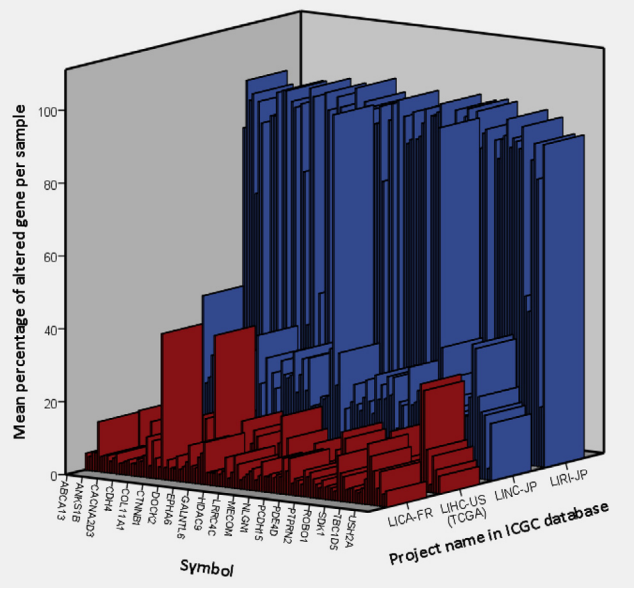

Fig. 1. Differential analysis of mean percentage of mutated gene per sample (100 genes with the highest rate of mutation have been selected for this graphical representation; symbol X axis lists contents name of only 20 genes for visualisation purposes; please refer to Supplementary Material 1 for full list of genes and percentage of altered genes represented in this graphic). Fig. 1 shows differences between Asian (blue) and Western (red) data. Data from International Cancer Genome Consortium were employed in this graphic; specifically, data from LICA-FR (10), LIHC-US (11), LINC-JP (12) and LIRI-JP (13) studies are shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in other malignancies, *EGFR* (epidermal growth factor receptor), *K-RAS* (Kirsten rats sarcoma) and *B-RAF* (rapidly accelerated fibrosarcoma homolog B) mutations are the main mechanisms for the activation of this pathway.

Analysis of *RAS* (rats sarcoma) gene mutation has been widely explored in multiple ethnicities in HCC. *RAS* mutations did not seem to play an important role in HCC carcinogenesis in Black Africans (Leon and Kew, 1995). Even though the mutations of *RAS* family genes are infrequent in Asian population (1.7–5.6% *K-RAS*, 0% *B-RAF*, 0–71% *H-RAS* (Harvey rats sarcoma), 0% *N-RAS* (rats sarcoma neuroblastoma homolog)) (Hou et al., 2014; Taketomi et al., 2013; Zuo et al., 2012; Sui et al., 2012), mutation rate seems to be higher in Western population (2–16% *K-RAS*, 0–23% *B-RAF*, 14% *N-RAS*) (Janku et al., 2014; Stork et al., 1991; Colombino et al., 2012; Tannapfel et al., 2003). One of the highest rate of *K-RAS* mutation (42%) has been described in Western workers exposed to vinyl chloride, which seems to have a direct toxic effect in the hepatocytes (Weihrauch et al., 2001). It is worth mentioning that there seems to be a significant variation in the mutation rate not only between ethnicities, but also between studies within the same population group (i.e. range for *H-RAS* mutation varies from 0 to 71% in Asian population (Janku et al., 2014; Stork et al., 1991; Colombino et al., 2012; Tannapfel et al., 2003)), which is probably related to studying sample size and sequencing technique employed. Finally, and based on the higher rate of *EGFR* mutation rate found in non-small