An Introduction to Liver Cancers

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The liver is the largest and most functionally diverse organ in the human body, and is known to be a critical hub for multiple physiological processes. It is highly vascularized in its nature, making it the most common site for cancer development, especially metastatic cancers.

liver cancer metabolism immuno-oncology

1. The Liver, a Multifunctional Organ

Being the largest and most functionally diverse organ in the human body, the liver is a heterogeneous organ composed of several cell types, including hepatocytes (primary epithelial cell population), cholangiocytes (also known as biliary epithelial cells), stellate cells, Kupffer cells and liver sinusoidal endothelial cells. Considering their unique functions, these cell types work together to regulate the normal liver function at different levels. Thus, the liver is known to be a critical hub for multiple physiological processes, which include the metabolism of nutrients (glucose, lipids and amino acids), the regulation of blood volume, lipid and cholesterol homeostasis, the support of the immune system and the metabolism of xenobiotic drugs. The energy provided by the processing and metabolism of nutrients is the driving fuel for all of these processes. The liver is a highly adaptive organ which has the capacity to store glucose in the form of glycogen under feeding conditions and can breakdown glycogen via glycogenolysis or assemble glucose through gluconeogenesis under fasting conditions. It can also oxidize lipids for energy when the glycogen reservoir is depleted, while it regulates the storage of excess lipids in adipose tissues. Moreover, it is the main site for protein and amino acid metabolism where it can process the latter for energy production, produce the majority of proteins secreted in the blood and can eliminate nitrogenous wastes resulting from protein degradation via urea metabolism [1][2].

The liver is highly vascularized in its nature, making it the most common site for cancer development, especially metastatic cancers. According to the GLOBOCAN 2020 estimates of cancer incidence and mortality, liver cancer ranks the sixth among the most commonly diagnosed cancers and the third leading cause of cancer-related deaths worldwide. Every year more than 900,000 new cases of liver cancers are diagnosed and 830,000 deaths are recorded. Notably, the incidence and mortality rates are 2 to 3 times higher in males than in females [3].

2. Adult Liver Cancer: Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma (HCC) is the most common form of adult primary liver cancer, accounting for ~90% of all cases [4]. It is associated with poor prognosis and an overall survival rate of 3–5% [5]. It is of no surprise that the

incidence rate of HCC is increasing worldwide as it is accompanied by many different risk factors, including chronic hepatitis B and C viral (HBV/HCV) infection, alcohol abuse, exposure to aflatoxin B1 and all cirrhosis-causing conditions, such as non-alcoholic fatty liver diseases (NAFLD) [6]. For instance, non-alcoholic steatohepatitis (NASH) (a form of NAFLD) associated with metabolic syndrome or diabetes mellitus is considered the second most common etiology of HCC [7]. Nonetheless, the etiology of HCC can also arise from alterations in oncogenes and tumor-suppressor genes (e.g., p53), genes leading to aberrant signaling pathways (e.g., Wnt-β-catenin pathway), the overexpression of epidermal growth factor (ErbB) receptors and telomerase activation (*TERT* mutations), as well as chromosomal instabilities [6][8].

The management of HCC not only includes its early diagnosis but also the staging of the disease and the suitable treatments of patients and those who are at risk of developing the disease, which is why the surveillance of HCC is very important, where subjects at risk are periodically diagnosed for HCC development. Cancer surveillance allows the early detection of tumors in patients at high risk, thus increasing the opportunity for curative treatments and improving survival by decreasing the disease-related mortality. The American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) guidelines suggest surveillance programs of high-risk patients, including all cirrhotic patients (HBV/HCV infection, AFLD, NAFLD/NASH), HBV carriers from regions of high HBV incidence, such as Asia and Africa, as well as HCV patients for whom infection is not associated with cirrhosis [8][9]. The diagnosis of HCC can be carried out using the following: serologic testing (α-fetoprotein (AFP), glypican 3 (GPC3)), diagnostic imaging (multidetector computed tomography (MDCT) or magnetic resonance imaging (MRI)) and histology [9][10][11][12].

Once diagnosed, patients will be stratified according to the Barcelona Clinic Liver Cancer (BCLC) staging system which relies on the number and size of the tumors as well as the liver function and health status of the patient (Eastern Cooperative Oncology Group [ECOG] Performance Status [PS]) [4][8]. So far, BCLC is the best staging system proposed, as it is the most commonly used system for HCC. The algorithm used by this system links the tumor stages (BCLC 0, A, B, C and D) to their corresponding treatments [13]. Treatments are the fundamental therapies that aim to either cure HCC using radical therapies or find palliative options that help to improve overall survival. Radical therapies include ablation, resection and transplantation, whilst palliative therapies involve chemoembolization and systemic therapies such as: multikinase inhibitors (sorafenib), immune-checkpoint inhibitors (atezolizumab: anti-programmed cell death ligand 1 (PDL1) antibody) alone or in combination with bevacizumab (anti-vascular endothelial growth factor (VEGF) antibody) which was recently approved by the Food and Drug Administration (FDA) on May 2020 [4][13][14].

3. The Pediatric Liver Cancer: Hepatoblastoma (HB)

Hepatoblastoma (HB) is a rare malignant embryonic tumor accounting for only 1% of all pediatric neoplasms, yet it is the most common primary hepatic tumor in babies [15]. Approximately one in million children are affected by HB, which usually develops between six months and three years after birth in around 95% of cases, with a median age of 18 months [16]. The remaining 5% are diagnosed in children over 4 years old and exceptionally in some adult cases [16][17]. The etiology of HB is still not fully understood; however, tumorigenesis is believed to arise from

immature hepatocytes that differentiate into other cell types, such as hepatocytes, epithelial, biliary and mesenchymal cells. This explains the heterogeneity observed at the cellular and histological levels among patients —56% epithelial or 44% mixed forms (epithelial and mesenchymal), with the former being associated with poor prognosis [15].

Most HB tumors develop sporadically; however, one-third of the cases could be associated with inherited syndromes, such as familial adenomatous polyposis (FAP) and Beckwith–Wiedemann syndrome (BWS), and gestational factors, such as pre-mature birth and very low birth weight, as well as some environmental factors, such as maternal exposure to alcohol and smoking [18]. The most common genetic mutation detected in HB involves the Wnt signaling pathway (β-catenin (*CTNNB1*), adenomatous polyposis coli (*APC*) and axis inhibition protein 1 (*AXIN1*)), reflecting its importance in the tumorigenesis of HB [19][20][21][22]. The overall survival rate of HB recorded so far is around 80% [23], thanks to the modern imaging techniques used to detect it [24] as well as the adapted chemotherapeutic regimes being used [25].

The diagnosis of HB is carried out in a similar manner to that of HCC using imaging modalities, serologic testing or histology. This disease is characterized by elevated levels of AFP, which is not only helpful for diagnosis but also in assessing the efficacy of a given treatment [26]. Regarding which, treatments include surgical resection, if possible, chemotherapy (Cisplatin) or liver transplantation. Thanks to the combined efforts of four international groups, a standardization of risk criteria and patient stratification has been put in place to help treat HB patients [27].

Despite all the advances made in stratifying HB patients (and even HCC patients) before choosing the suitable treatment options and hence improving their lifestyle, it is hard to neglect the fact that some patients do not respond to such treatments, with some developing resistance to chemotherapy or even relapsing in a short period of time. Because of this, it is more urgent than ever to find alternative therapeutic approaches that are less toxic and more efficient by conducting in-depth research on the molecular biology of HB and HCC. Recently, two emerging hallmarks of cancer, i.e., energetic metabolism reprogramming and the escaping of immune destruction, have been the focus by many researchers who aim to understand the possible connections between both, thus attaining new therapeutic strategies.

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