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Review

Hepatocellular carcinoma: Where there is unmet need

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ABSTRACT

Hepatocellular carcinoma (HCC) is a complex and heterogeneous tumor most commonly associated with underlying chronic liver disease, especially hepatitis. It is a growing problem in the United States and worldwide. There are two potential ways to prevent HCC. Primary prevention which is based on vaccination or secondary prevention involving agents that slow down carcinogenesis. Several pathways have been thought to play a role in the development of HCC; specifically, those involving vascular endothelial growth factor (VEGF)-mediated angiogenesis, WNT, phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), and c-MET. Currently, there are only a limited number of drugs which have been proven as effective treatment options for HCC and several clinical trials are testing drugs which target aberrations in the pathways mentioned above. In this review, we discuss currently approved therapies, monotherapies and combination therapy for the treatment of HCC.
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1. Introduction

Hepatocellular carcinoma (HCC) is a complex and heterogeneous tumor most commonly associated with underlying chronic liver disease, especially hepatitis. It is a growing problem in the United States and worldwide. Globally, HCC is the third leading cause of cancer death and it is the most common cause of death among patients with cirrhosis in western countries (Villanueva et al., 2008; Goyal et al., 2013). The prevalence of HCC is increasing by 1.75% in the US per year (Buitrago-Molina and Vogel, 2012), and advanced HCC has a poor prognosis, with a 5-year overall survival rate of less than 10% (Goyal et al., 2013). Typically, hepatitis B and C infections, exposure to alphatoxins, and alcoholic and non-alcoholic steatohepatitis (NASH) are risk factors for HCC (Buitrago-Molina and Vogel, 2012). It is estimated that about 20–30% of patients diagnosed with HCC are eligible for curative treatments such as resection, ablation, or liver transplantation (Llovet and Bruix, 2008). The prognosis for patients with advanced disease is rather bleak (Buitrago-Molina and Vogel, 2012). No standard systemic therapy was available for patients with advanced disease until 2007, when the molecular therapy sorafenib was approved for unresectable HCC (Llovet and Bruix, 2008).

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There are two potential ways to prevent HCC. Primary prevention is based on vaccination, for example, the hepatitis B vaccine (Buitrago-Molina and Vogel, 2012). Secondary prevention involves the use of agents that slow down carcinogenesis in patients with potential cancer precursors (Buitrago-Molina and Vogel, 2012). For both prevention and treatment, in recent years, the practice of oncology has undergone a paradigm shift from broader disease-based treatments to therapies that target specific aberrant cellular pathways and subcellular structures. In keeping with this shift, an explosive number of "targeted agents" have been developed to address a broad range of tumor types. In this article, we describe the molecular pathways that have been identified in HCC and efforts to target them, both established and investigational.

2. Molecular pathways in HCC

Several molecular alterations have been observed in HCC (Figure 1). Accumulation of these genetic alterations and aberrant activation of several signaling pathways have been thought to play a role in the development of HCC (Llovet and Bruix, 2008); specifically, those involving vascular endothelial growth factor (VEGF)-mediated angiogenesis, WNT, phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), and c-MET.

2.1. *VEGF-mediated angiogenesis pathway*

Genetically unstable cancer cells and mutations that have accumulated within these cells are therapeutic targets of most novel agents. However, anti-angiogenic therapy targets endothelial cells because they do not have any genetic mutations. The genetic stability of endothelial cells may render them less susceptible to acquired drug resistance. Thus, angiogenesis inhibitors are emerging as single agent therapies as well as in novel combinations.

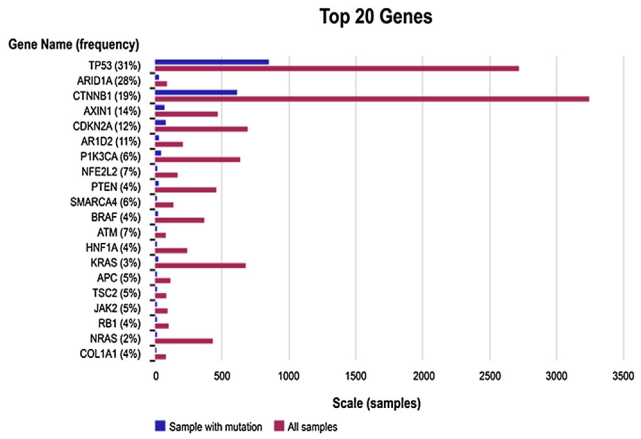

Figure 1 – Key molecular alterations in HCC as documented in the Catalogue of Somatic Mutations in Cancer (COSMIC) database. This is a diagram illustrating the top 20 genes with highest prevalence of molecular alterations in patients with HCC. The most common among them are mutations in the *TP53*, *ARID1A*, *CTNNB1*, *CDKN2A* and *ARID2* gene (http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/) at the time of this manuscript (March 24, 2014).

Angiogenesis role in the initial progression from premalignant tumor to cancer prompted investigators to study the role of VEGF in the natural history of HCC (Hanahan and Folkman, 1996). In 1999, a group of researchers suggested that the degree of tissue VEGF expression increased in accord with the stepwise development of HCC (Park et al., 2000). In addition, studies showed that VEGF was frequently expressed in HCC. A quantitative study reported VEGF tissue expression in 89% (32/36) of HCCs (Huang et al., 2005). Notably, studies have suggested a correlation between the degree of tissue VEGF expression and the intensity of both the magnetic resonance signal and the computed tomographic enhancement of the hepatic artery, which represent radiological vascular signals (Kanematsu et al., 2004, 2005; Wang et al., 2005). Hence, the hypervascular nature of HCC has led to increasing interest in exploring the potential of anti-angiogenic therapy in this disease.

In HCC, hypoxia is believed to increase the expression of VEGF through the expression of hypoxia inducible factor-1α (Torimura et al., 2004). VEGF is also known as the vascular permeability factor and stimulates proliferation of endothelial cells specifically through tyrosine kinase receptors (Ferrara and Davis-Smyth, 1997). Angiopoietin 1 and 2 are ligands for the tyrosine kinase receptor Tie2. VEGF and angiopoietin-2 (Ang-2) are expressed on cancer cells, whereas angiopoietin-1 (Ang-1) is predominantly in supportive cells of large blood cells, stromal cells, endothelial cells, and tumor cells. Ang-2 is a partial agonist and antagonist of Ang-1 and is expressed for vascular remodeling preventing vascular stability thus allowing VEGF to stimulate endothelial cells (Moon et al., 2003).

2.2. *WNT pathway*

The WNT pathway has a crucial role in the regulation of diverse disease processes, which include cell proliferation, survival, migration, and cell fate. This pathway is involved in multiple normal physiological processes and embryonic development. In this pathway, when normally active, WNT ligand binds to a receptor leading to cytosolic accumulation of β-catenin; thereafter, β-catenin can translocate to the nucleus to initiate transcription (Klaus and Birchmeier, 2008). WNT can be activated if there is a mutation in the β-catenin gene (*CTNNB1*), which is the third most frequent mutation seen in HCC after *p53* mutation (Boyault et al., 2007).

2.3. *PI3K/AKT/mTOR pathway*

The PI3K/AKT/mTOR pathway plays an important role in cell regulation. This pathway is involved in many cellular processes, such as cell division, cell growth, and programmed cell death (Yothaisong et al., 2013), and can be activated by many different stimuli, such as activated tyrosine kinase growth factor receptors, G-protein-coupled receptors, and oncogenes such as *RAS* (Hassan et al., 2013). Furthermore, the mTOR complex is an important therapeutic target, as it is a key intracellular node for a number of cellular signaling

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