

Liver Cancer: Treatment Difficulties and the Application of Experimental Models

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ABSTRACT

Liver cancer is one of the most lethal forms of cancer globally. Liver cancer can be attributed to a number of causes, one of which is the hepatitis B or C virus. Other contributors include: excessive alcohol consumption, obesity, non-alcoholic fatty liver disease, diabetes, smoking, and iron overload. There are different types of liver cancer, and the one most prevalent is hepatocellular carcinoma, which is the only type to be discussed in this paper. The signaling pathways YAP-Hippo, Wnt- β -catenin, and NF- κ B promote liver cancer. This still interests researchers for therapy development. This paper investigates fat metabolizing receptor, PPAR γ , in hepatocellular carcinoma development. Certain liver cancer promoting changes have been documented like histone acetylation, histone methylation, and DNA methylation changes. This paper integrates published work on these topics. The disease has both in vitro and in vivo model systems for studying advanced liver cancer and innovating therapeutics. Each has different strengths and targets different aspects of the disease. The paper ends with a review of the therapeutics that has been approved for treating hepatocellular carcinoma. Pirfenidone is one of these and should be highlighted, given its preclinical data is promising.

Keywords: Hepatocellular cancer, alcohol, liver cirrhosis, and animal models

Introduction

Liver cancer is a big deal, being one of the top four cancer killers worldwide. The WHO predicts liver cancer will cause over one million deaths in the next 6 years (Mathers et al, 2005). Liver cancer is mainly associated with chronic hepatitis B and C infections, heavily drinking alcohol, and the all-too-common non-alcoholic fatty

liver. Of course, the risks only increase with smoking, obesity, diabetes, and excessive iron. In some cases, the body just goes rogue, causing uncontrolled cell proliferation and chronic inflammation and scar tissue (Berasain et al, 2009). Modern pharmacotherapy focuses primarily on aberrant processes. In later stages, patients are given sorafenib which is effective in slowing down cancer growth but only for a short time, as cancer cells quickly adapt and progress (Gauthier et al., 2013). There is a tremendous gap in the market for better, safer, life-prolonging drugs. The study of liver diseases and new pharmacotherapy has benefitted from the use of research lab animals. Currently, all species of lab animals are being used in the study of liver cancer. Each individual lab species has its pros and cons. The choice of species ultimately depends on the goal of the study.

(Oishi et al, 2011) YAP-Hippo, Wnt/ β -catenin, and NF- κ B signaling pathways, among others, have been and are still extensively studied when it comes to the mechanisms involved in liver cancer, as well as the PPAR γ mechanism on lipid metabolism and its regulatory functions on gene expression. histone acetylation and methylation, DNA methylation, and non-coding RNAs (Małodobra et al.,2024). After this, the liver cancer mechanisms will be explained in a more detailed manner. In detail, the main liver cancer drivers are chronic exposure to risk factors in the environment, cleaving the biological triggering pathways. The genes important for the regulation of cell proliferation, malignant transformation, and metastasis are the ones regulated by the YAP-Hippo pathway. (Raj et al.,2019)

The Wnt/AXIN pathway encourages β -catenin to enter the nucleus, where it activates YAP/TAZ and TCF and initiates the expression of myriad fibrosis and proliferation-associated factors, which contributes to the development, spread, and chemotherapy resistance of tumors. The NF- κ B pathway also alters IKK- α and IKK- β controlling the cyto-nuclear shuttling of NF- κ B p50 and p65, which in return promotes proliferation, apoptosis evasion, and malignant transformation, all coupled with acquired drug resistance. PPAR γ , while primarily transcriptionally driving the proliferation, survival, and metastatic diapause of cancer cells, also diminish some of the NF- κ B and β -catenin signaling inhibitory effects. Among the epigenetic cancer drivers, histone modifications, which are the results of the opposing activities of

HATs/HDACs and HMTs/HDMs, and DNA methylation, which is regulated by the DNMT1 enzyme, are the foremost. (Marei, et al, 2025)

Hippo's Yes-Associated Protein (YAP-)

YAP1 carries significant influence over cell survival and cell growth transcriptional regulatory genes. By definition as well, YAP1 is classified as an oncogene. (Weber et al, 1987). YAP1 and its paralog TAZ, along with other proteins, post-translationally modify and thus, TAZ and YAP1 negatively regulate and retain the protein in the cytoplasm. The cytoplasmic retention of YAP1 is critical for cellular health and homeostasis. Aberrant activation of the Hippo pathway results in dephosphorylation of TAZ and YAP1, causing them to gain access the nucleus, leading to an alteration of transcriptional programs. The Hippo-YAP pathway is a key in regulating organ size as well as controlling cellular growth and death, movement and metastasis of tumors (especially the liver). (Nishina et al, 2022). YAP1 over expression in mice models observed post-natal week one to have hepatocyte hyperplasia and to have an enlarged liver.

Conversely, when YAP1 levels were normalized, there was reduction in tumors and improvement in previously injured liver tissue. Varelas et al. showed how Hippo-YAP modules are capable of inhibiting Wnt/ β -catenin signaling. In the absence of TAZ, the DVL2 protein was unleashed and hence Wnt/ β -catenin signaling was activated, seen in culture and also kidneys of TAZ deficient mice. This showed how different YAP and TAZ family members can act as oncogenes or tumor suppressers, depending on the cell surrounding environment. In addition, liver tumorigenesis depends on the YAP-Hippo signaling axis, suggesting it can provide the basis for new targeted approaches in liver cancer.

(Piccolo et al, 2014)

Models of Experiments for HCC Studies

Animal models are used to analyze different phases of liver carcinogenesis. Different models develop tumors and advance to metastasis at different speeds and at different stages of human development, particularly the first developmental stages (Farber et al. 1984). These differences highlight the varying usefulness of specific models. Take the modified resistant hepatocyte model (MRHM), for instance; over the course of

several liver cancer development stages, this model incorporates the most time. Initially, the animals are treated with the chemical, diethylnitrosamine (DEN), which is a DNA damaging agent and acts on the DNA organizational structure (Mansour et al. 2019). Seven days later, an orally administered chemical, 7-acetylaminofluorene, is given which suppresses the normal growth of liver cells. On the tenth day, about 75% of the liver is excised which is after the DEN treatment; this greatly stimulates liver cell growth after experiencing DNA damage. This is the only technique where 30 days post treatment, pre-cancerous nodules form and by 12 months, visible solid tumors are present and the cancer is metastatic.

With this model, researchers can study the full progression of cancer, including HCC's early development, advanced stages, and all the intermediary phases. (Zender et al .2010). It also produces more dependable results and a higher rate of tumor development in the test animals. On the other hand, fewer models ignore the influence of toxic chemicals on the organism and often do not foresee tumor development at all. The DEN model, which produces tumors in all animals, is used the most. It induces liver scarring, inflammation, and weight loss, all of which complicate the toxic uterine environment. However, starting at 5 weeks of age, the production is continuous and weekly for 15 weeks. It is very difficult to appreciate when the abusive exposure really begins, which greatly hinders the study of the disease's early stage. (Meneghini et al .2013).

Use in Potentially Innovative Therapeutic Targets for Liver Cancer

It is critical to conduct further studies to formulate better therapies for liver cancer. One useful research approach is the Patient-Derived Xenograft or PDX model, which helps investigate an oncogenic tumor. There was tumor regression when researchers used a virus to silence LINC01132 in the liver cancer PDX model. The outcome was further improved with the addition of a therapeutic agent directed against the protein called programmed death ligand-1 (PD-L1). Thus, LINC01132 is likely a potential therapeutic target for liver cancer. Another long oncogenic RNA, DANCR, is over expressed in liver cancer and contributes to its aggressiveness (Ghafouri et al., 2022). Through viral targeting of DANCR in the PDX model, tumor lysis was possible. The absence of DANCR significantly reduced the tumor proliferation rate, thereby presenting DANCR as a valuable therapeutic target (Yan

et al., 2020). SLC12A5 is over expressed in several other malignancies as well. Researchers investigated the effects of targeting SLC12A5 in PDX models. Tumors grew because SLC12A5 was expressing the oncogene and inhibiting a type of regulated cell death called ferroptosis, which also fueled tumor growth. According to Teng et al. (2016), liver cancer treatment can be improved by focusing on SLC12A5. YTHDF1 expression increased in liver cancer specimens during the study and was shown to correlate with poorer outcomes. This was also seen in PDX models, wherein decreased YTHDF1 expression was associated with the tumor growing at a slower rate, and increased YTHDF1 levels fueling faster tumor growth. Evaluating the levels of YTHDF1 can aid in determining possible treatment response and in prognostic assessment, thus, more studies are needed. In liver cancer, poorly performed radiofrequency ablation (RFA) may result in recurrence. One PDX model studied the post-ablation behavior of the VEGF axis. Following incomplete ablation, there was an increase in VEGFR1 and a decrease in VEGFR2, which shifted the balance in favor of the cancer cells to metastasize. After incomplete RFA, the recurrence of cancer appears to be driven in part by VEGFR1, which may be a viable target (Ribatti et al., 2021).

Drug Resistance Targets for Use in Liver Cancer

The first two lines of treatment for liver cancer demonstrate targeted therapy with Sorafenib, Lenvatinib, and Regorafenib. According to VSogel et al., (2007), Lenvatinib treated patients' survival increased to 13.6 months. These advances are not tremendous improvements since most patients treated still live for less than 2 years. Hence, evidence-based understandings of the drugs mechanism of action, targeting identification and treatment plans are crucial for clinician longevity (Ganz et al, 2008). Certain PDX models, particularly ones made with human tumors and maintained in mice, are able to respond to treatment just like human patients do. Such close relation makes it possible to develop new targeted therapy. Certain RAS/RAF/ERI signaling pathways show persistent ERK (p-ERK) as a marker sorafenib responds to PDX tumors. Murphy et al 2006, define evidence to conclude persistence of ERK (p-ERK) may redefine a potential biomarker for sorafenib responses in patients. KPNA3 over expression with sorafenib resistant tumors is a significant finding. KPNA3 has the capability to indicate the patient's outcome

regarding sorafenib therapy. KPNA3 may be a new target to circumvent sorafenib resistance. (Hu et al., 2019) Higher levels of Cripto-1 were reported in tumors that were resistant to sorafenib. Cripto-1 levels were decreased and tumor growth was arrested. Cripto-1 is part of the Wnt signaling pathway, thus, it is possible that Cripto-1 can mediate Wnt signaling and sorafenib resistance. HNF3 β is a regulatory protein of liver development and function. In clinical studies, low HNF3 β was reported as an aggressive liver cancer poor prognostic indicator and shorter survival (Méndez et al., 2019). In PDX models, however, HNF3 β was hypothesized to be an HNF3 β response enhancer for sorafenib as higher levels were correlated with poor sorafenib response. Resistant PDX models subjected to RNA sequencing demonstrated increased activity of the kinase EPHB2 in resistant tumors. EPHB2 activity was decreased along with sorafenib and a virus to reduce EPHB2 was used to arrested tumor growth.

This indicates that EPHB2 is a target that can be used with sorafenib and is a possible treatment alternative. VRK2 is a protein that counteracts the effects of sorafenib by shifting the equilibrium between the processes of cell death and self-eating. Unfortunately, many patients do not even live for two years, which highlights the need for research to focus on better treatments that prolong survival. To better the survival rates of patients, the pharmacological mechanisms of action must be prioritized, as well as exploring new pathways to counteract resistance to existing drugs. This opens up the potential for new therapies to be created that would prolong patients' lives (Ganz et al, 2008). Compared to other animal models, the PDX (patient-derived xenograft) model which grows human tumor tissue in mice, is one of the most effective. This is because these mice not only respond to treatment, but the results of treatment are comparable to that of human cancer patients. As a result, it is possible to find new research pathways and maximize treatment results. Of all the raf/MEK/ERK signaling pathways, p-ERK completes the most critical functions. In the PDX model, p-ERK positive tumors were noted to respond better to treatment of sorafenib, thus suggesting p-ERK may be a positive predictive biomarker for the efficacy of sorafenib (Murphy et al, 2006). More negative sorafenib tumors were noted to contain the protein KPNA3, thus

reinforcing the idea that this protein should be the focus of the resistance mechanism research. Therefore, KPNA3 should be the target in the development of new resistance overcoming therapies (Hu et al, 2019). Regulation of liver and liver cells growth and functioning is controlled by HNF3 β . Cancers that are more aggressive and have shorter life expectancies are associated with lower levels of HNF3 β (Méndez et al, 2019). However, in PDX models, higher levels of HNF3 β were predictive of greater efficacy towards sorafenib, therefore suggesting HNF3 β could help achieve maximal therapeutic efficacy. Resistant PDX models RNA sequencing determined that the kinase EPHB2 was more active in the resistant tumors. EPHB2 was silenced via a virus and EPHB2 and sorafenib combined therapy was then used and resulted in arrested tumor growth. This demonstrates a strong novel therapeutic combination of EPHB2 and sorafenib. In sorafenib resistant PDX models and PDX models, the protein VRK2 is highly expressed, therefore decreasing the efficacy of sorafenib by disrupting the balance of apoptosis and autophagy. This suggests that escaping autophagy by targeting VRK2 might alleviate sorafenib resistance (Jiang et al, 2023). Here are first-line therapy choices: sorafenib, lenvatinib, and regorafenib for liver cancer. While patients on sorafenib live for a median overall survival of 12.3 months, those taking lenvatinib live for 13.6 months on average (Vogel et al. 2007). Still, many patients do survive 2 years. There is a need for expanding the treatment arsenal. For that, the mechanisms of these drugs need to be better understood and novel mechanisms have to be developed for when the drugs become ineffective. This can lead to the clinically relevant improvement of patients' lives (Ganz et al. 2008).

The patient-derived xenograft (PDX) model, which consists of transplanting drug-sensitive patient tumor bits into mice, serves as a good target discovery preclinical model for the treatment improvement because it customizes the patient response to treatment. Regarding PDX model studies, sorafenib tends to do well when treating p-ERK-rich tumors, and performs poorly with p-ERK-poor tumors. p-ERK is a terminal component of the RAF/MEK/ERK signaling pathway. This means that the level of p-ERK in a patient might help predict the outcome of the treatment with sorafenib (Murphy et al. 2006). Examining sorafenib-resistant tumors revealed increased expression of the KPNA3 protein. This could mean that KPNA3

will show us the responsiveness of an individual to sorafenib. Targeting KPNA3 could be a solution to sorafenib resistance (Hu et al. 2019). Resistant tumors also had increased expression of the Cripto-1 protein. Cripto-1 protein reduction led to slowed tumor growth, and since it is a component of the Wnt pathway, it could be a potential target to combat sorafenib resistance. HNF3 β is part of the regulation of intra-hepatic development and function. Correlation exists between HNF3 β and advanced cancer, the less HNF3 β , the more poorly differentiated the liver tumor, the more aggressive the cancer, and the lesser the overall survival (Mendez et al. 2019). This is paradoxical because the PDX models indicated that greater HNF3 β expression equated to greater sorafenib efficacy. This correlates with the notion that HNF3 β is a likely target to enhance overall efficacy. Resistant PDX models showed RNA sequencing, and the PDX models showed that the resistant tumors had gained prominence of the kinase, EPHB2. The use of EPHB2 down regulation alongside sorafenib completely stopped tumor growth. This synergy highlights the potential of integrating EPHB2 suppression into sorafenib treatment as a novel approach.

Drug Evaluations or Clinical Trials for Liver Cancer

Not all newly developed cancer therapies achieve all the hoped-for results. One reason could be the difference in understanding how various tumors can be, even in the same individual. While cell lines have contributed to cancer research, they do not always predict the effectiveness of the treatment in a patient. The PDX model improves this defect by using human tumor tissue specimen, which greatly improves the approximation of the morphology and genetic makeup of the tumor (Liu et al., 2023). This model improves evaluation of potential therapies. Prognosis is particularly poor in individuals with elevated CDK1 levels. In the PDX model, they were administered the CDK1 inhibitor, sorafenib, or the combination of both. The combination substantially reduced tumor growth and resistance to sorafenib (Niu et al., 2017). The combination of CDK1 inhibitors with sorafenib will be of tremendous benefit to CDK1 over expressing patients with HCC. Tumors escape and enhance their growth with the help of the tryptophan derivative kynurenine. In contrast, the kynurenine analog, 3-HAA, can induce death of tumor cells by raising some enzymes which in turn lead to heightened sensitivity to sorafenib. Tumor growth was halted

with the combination of sorafenib with 3-HAA in a model that exhibited resistance to sorafenib.

SCD1 blockage causes cancer to become re-sensitized to sorafenib because alterations to liver stem cells due to SCD1 blockage cause cancer cells to dehinhibit. An SCD1 blocker in combination with sorafenib was documented to temporize the progression of tumors, which seems to be a feasible approach for SCD1 positive HCC. BCL-xl protein blockers induce apoptosis (Matsunaga et al., 2015). In a PDX model, the BCL-xl blocker A-1331852 potentiated the action of regorafenib and led to tumor shrinkage. So, this combination is advantageous for HCC patients who have excess BCL-xl. AST-3424 is a targeted cancer therapeutic which causes cell death by releasing a DNA binder. It is PDX model-validated in combination with oxaliplatin, apatinib, sorafenib, and elemene. Compared to the absence of AST-3424, AST-3424 resulted in improved outcomes with those drugs (Meng et al., 2021). Sulfarotene, a retinoid, was identified by Qi et al. to be a downstream potent inhibitor of cancer stem cells and noted to have a positive side effect profile. It causes HCC cell death by decreasing SOS2. In an HI SOS2 PDX model of HCC cells with sulfarotene, notable improvement was seen.

Tumor growth stopped in PDX models when PDX models had MDM2 high negative P53 HCC cells, and SP141, an MDM2 blocker, was administered. Gefitinib is a pill that blocks the EGFR protein which promotes the growth of some cancer cells. It was the first of its kind to be developed for non-small cell lung cancer. It was demonstrated by the PDX model that using Gefitinib together with lenvatinib, helped the growth of liver tumors in very sick patients, when lenvatinib alone was ineffective. Infigratinib inhibits the activity of FGFR proteins which are implicated in some cancers, including cholangiocarcinoma (Goyal et al., 2021). It is useful for liver cancer that is dependent on FGFR, however, prolonged treatment is associated with the development of drug resistance. In an attempt to understand the reasons, one set of researchers investigated infigratinib in combination with ribociclib. Using model PDX, Just infigratinib was sufficient to cause resistance in the FGFR1-3-dependent PDX model. In contrast, ribociclib when combined, blocked tumor growth and resistance was not developed. One researcher investigated the combination of infigratinib with varlitinib, which targets and inhibits resistant

cancer proteins, and there was a successful outcome (Javle et al., 2021).

Conclusion

Hepatocellular carcinoma, or HCC, is the most common form of liver cancer. It occurs when the sophisticated systems that manage the processes of cell growth, death, and the intricate interplay of chronic inflammation and fibrosis become unbalanced. HCC patients have a variety of options which can help maintain liver function, manage symptoms, and extend survival. However, only a limited number of options are actually beneficial, and the risk of serious adverse effects is low. Hence, most new preclinical therapy research is using custom models of the disease. The target is to design monotherapy or polytherapy approaches using drugs with specific mechanisms of action aimed at the various HCC driving factors.

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