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Review Article

Gene Expression of Liver Tissue and Primary and Secondary Liver Cancer with a Particular Focus on Hepatocellular Carcinoma: A Mini-review on Basic Biomedical Assessment

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Abstract

Liver cancer is one of the most common malignant solid organ tumors. This cancer is associated with a high death rate. At present, it is possible to investigate a functional dysfunction module of hepatocellular carcinoma (HCC) using the genetic characteristics of liver tissue, revealing its pathogenesis and guiding tailored management and therapy. It not only provides important information for additional diagnostic therapy but also offers new research directions for scientists and medical technologists studying liver cancer.

Introduction

The liver is the body's largest solid organ. It eliminates toxins from the body's blood supply, keeps blood sugar levels stable, regulates blood clotting, and performs hundreds of other essential activities. It is placed in the right upper abdomen, beneath the rib cage. The liver has a variety of enzymatic activities that are required to carry out its particular role in metabolism, and their expression is controlled during the developmental process.[1] The liver-specific phenotype is derived from a developing tissue-specific gene expression set. Several lung-specific structural genes have cis-regulatory regions that influence their transcription. The introduction of chimeric genes into germ lines, the production of transgenic animals, differentiated cultured cells, and a cell-free transcription system have enabled the identification of such cis-regulatory regions capable of regulating hepatocyte-specific gene expression.[1] Specific deoxyribonucleic acid (DNA)-binding nuclear proteins or trans-acting factors that are enriched in hepatocytes and developmentally controlled can identify such cis-components in the DNA.[1] In addition, endoderm-derived cells may differentiate into hepatocytes as a result of the union of known cis-acting elements proximal to liver-specific genes with hepatocyte-specific trans-acting proteins.[1]

In general, liver disease is caused by a complicated interplay between internal and extrinsic variables, such as genetics and exposure to obesogenic environments.[2] These risk factors converge on abnormal gene expression patterns in the liver that are supported by alterations in regulatory networks. Liver regulatory networks are generated in homeostasis and disease states by the coordinated activity of hepatic-enriched transcription factors, which define enhancer landscapes, thus activating large gene programs with spatiotemporal resolution.[1] New developments in DNA sequencing have significantly increased our ability to map active transcripts, enhancers, and TF cistromes as well as to describe the three-dimensional chromatin topology that comprises these components.[2] These new technologies help researchers investigate the biological pathways that control the growth of the liver as well as metabolic balance.[2] Furthermore, genomic studies on patients with liver disease may reveal the gene expression pattern, from which abnormal gene expression patterns may emerge.[2] As a result, this can add an unparalleled amount of knowledge to the study of hepatic cis-regulatory networks, particularly for normal and abnormal conditions.

Gene expression and liver cancer

Liver cancer affects people extremely frequently, and this malignancy can develop anywhere in the liver. On the upper right side of the human stomach, near the ribs, is a large organ called the liver.

Keywords: Gene; Expression; Liver; Tissue; Hepatocellular Carcinoma.

Abbreviations: AEG-1, astrocyte elevated gene-1; complementary DNA, cDNA; DNA, deoxyribonucleic acid; HCC, hepatocellular carcinoma; lncRNA, long noncoding RNA; HCV, hepatitis C virus virus; long noncoding RNA, ; NF-κB, nuclear factor kappa B; RNA, ribonucleic acid; RISC, RNA-induced silencing complex; SND1, staphylococcal nuclease domain containing 1; TGF-1/BMP-7, transforming growth factor-beta 1/bone morphogenetic protein 7.

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It facilitates digestion and gets rid of toxins. The major site of liver cancer is the liver, although it can also spread to other organs (secondary). Both molecularly and histologically, hepatocellular carcinoma (HCC) is a malignancy that is incredibly varied. Numerous recurring genetic alterations, distinct transcriptome subclasses, and various HCC subtypes delineated by histological traits have all been discovered using high-throughput sequencing and gene expression profiling.[3] Evidence suggests that the HCC phenotype is associated with certain gene alterations, tumor subtypes, and/or carcinogenic pathways.[3]

Because of technological advancements, genetic screens may now be used in HCC model systems to define genes that regulate cancer initiation and growth.[4] Genetic screens provide several advantages over classical methods for diagnostic tumor biology, such as candidate gene approaches or expression analysis: they are unbiased, with no a priori selection; they can directly annotate gene function; and they can identify gene-gene interactions. In HCC, three main types of screening have been undertaken. These three types include (a) knockdown screens utilizing ribonucleic acid interference or the clustered regularly interspaced short palindromic repeats system, (b) transposon-based mutagenesis screens, and (c) overexpression screens using clustered regularly interspaced short palindromic repeats activation or complementary DNA(cDNA)s.[3] These methods can be used in upcoming studies to find novel HCC treatments and to describe the processes causing drug resistance.[3]

Different types of liver cancer and gene expression

The authors here include HCC, cholangiocarcinoma, and hepatoblastoma together among the various forms of liver cancer and gene expression in order to more clearly distinguish between primary liver cancer and metastatic liver cancer.

Primary liver cancer

Primary HCC

HCC is a main cause of mortality worldwide. It is feasible to use cDNA microarrays to characterize gene expression patterns in HCC. The diversity of malignant phenotypes is mirrored in the diversity of gene expression patterns. However, the molecular pathophysiology of HCC is still unknown, and its natural history can vary widely. A systematic investigation of global gene expression patterns in human cancers can provide new insights into pathophysiological pathways and improve clinical prediction. Normal hepatic tissue and liver cancer are both advanced tissues made up of several specialized cells. Each gene expression pattern of HCC appears to present a particular molecular pattern of that malignancy, with several aspects statistically correlated with specific clinical traits of the malignancies. In addition, multiple cancerous samples from the same case usually have recognized and unique gene expression patterns.[4] Those genes whose products are membrane related or secreted are of special focus for their feasibility as treatment targets or serological biomarkers for early detection. Moreover, alpha-fetoprotein has long been utilized as a serum biomarker for HCC diagnosis and monitoring. Nevertheless, it is only detected in 50% of patients with HCC.[5] Multiple pathological nodules from the same case can usually be detected and discriminated from all the others in the huge data set based solely on their gene expression patterns. The differential gene expression patterns are specific to the tumors rather than the patient; for example, the expression programs observed in clonally independent tumor nodules from the same patient were no more comparable than those observed in tumors from different cases.[6] Furthermore, genotypic differences separated clonally have linked tumor masses with diverse expression profiles.[6] Some aspects of the gene expression patterns have been linked to specific phenotypic and genotypic tumor traits, such as growth rate, vascular invasion, and p53 overexpression.[6] Additionally, cyclin-dependent kinase 1 and cyclin B1 were discovered to be involved in substantial protein-protein interaction modules in the cell cycle and p53 signaling pathways.[7] These differentially expressed genes were demonstrated to be more numerous in female malignancies than in male tumors, and they may be used to predict poor prognosis in male patients.[7] Other metabolic pathway genes, such as cytochrome P450 3A4 and serine proteinase inhibitor family, clade A have been revealed to be downregulated in males versus females.[7] These genes have been connected to a reduced rate of survival. Physiological variations between sexes may alter gene expression and/or activity, including gene function linked to oncogenesis and liver cancer outcomes.[7] Other metabolic pathway genes, such as cytochrome P450 3A4 and serine proteinase inhibitor family, clade A, have been revealed to be downregulated in males versus females.[7] These genes were connected to a reduced rate of survival. These results show that sex-specific physiological variations may affect gene expression and/or activity, including genes involved in oncogenesis and HCC outcomes.[7]

Additionally, the predictive significance of apoptosis-related genes in primary liver cancer has been suggested.[8] Gene ontology analysis results have demonstrated that many genes are indeed associated with apoptotic function when compared to normal tissues.[8] According to Kyoto Encyclopedia of Genes and Genomes analysis, these genes are associated with mitogen-activated protein kinase, p53, tumor necrosis factor, and phosphoinositide 3-kinase/protein kinase B signaling pathways, and five antibiotic resistance genes (*PPP2R5B*, *TOP2A*, *SQSTM1*, *BMF*, and *LGALS3*) are linked to prognosis, according to Cox regression.[8] Finally, increased Twist gene expression is associated with more aggressive HCC behaviors.[9] Twist is a novel HCC metastasis marker.[9]

A few more oncogenes and their pathways that are connected to HCC should also be addressed, for example, 1) astrocyte elevated gene-1 (AEG-1), which is a major cause of HCC; 2) RNA-induced silencing complex (RISC) assembly and post-transcriptional gene regulation in HCC; 3) a new route involving nuclear factor kappa B (NF-κB) and microRNA (miR)-221 promotes tumor angiogenesis in human HCC; and 4) multifunctional protein staphylococcal nuclease domain containing 1 (SND1), a new oncogene for HCC, is the transcription factor for late SV40 factor. The details of these important oncogenes and pathways are summarized in Table 1.[10–16]

AEG-1, also known as metadherin, 3D3, and LYsine-RIch CEACAM1 co-isolated, has first come to light as a significant oncogene that is overexpressed in all malignancies examined thus far.[10,11] AEG-1 is a very simple protein that is found in the cell membrane, cytoplasm, nucleus, nucleolus, and endoplasmic reticulum.[10] It also has several nuclear localization signals and a transmembrane domain. AEG-1 interacts with particular proteins at each site, influencing a variety of intracellular functions that together lead to its pleiotropic features.[10] AEG-1 functions as a scaffold protein in the pathogenic process of HCC, activating several protumorigenic signal transduction pathways, including mitogen-activated protein kinase/extracellular signal-regulated kinase, phosphoinositide 3-kinase/protein kinase B, NF-κB, and wingless-related integration site/β-catenin while modulating gene expression at the transcriptional, post-transcriptional, and translational stages.[11] Regarding RISC, it is connected to post-transcriptional gene regulation and assembly in HCC. HCC activity is a result of

Table 1. Some HCC-related oncogenes and their pathways

HCC-related oncogenes	Important role	Pathways related to HCC
AEG-1	A key driver of HCC	AEG-1 plays a crucial role in HCC; however, effective AEG-1 targeting as a therapeutic intervention for HCC has not yet been accomplished in the clinic.[10,11] In mouse models of HCC, targeted administration of AEG-1 small interfering RNA has been shown to have the desired therapeutic benefits.[10,11] Recently, peptidomimetic inhibitors based on protein–protein interactions also have been created. It will be possible to design particular AEG-1 inhibitory techniques when new mechanisms in AEG-1's regulation of HCC continue to be uncovered.[10,11]
RISC	Roles in assembly and post-transcriptional gene regulation in HCC	In HCC, post-transcriptional gene regulation and assembly are related to RISC. In regard to its peculiar degenerative pathophysiological mechanism, the imbalance of TGF-1/BMP-7 pathway is a reliable prognostic biomarker, and rectifying the imbalance of this pathway may be a potential therapeutic strategy for HCC.[12]
NF-κB and miR-221	Roles in tumor angiogenesis	NF-κB and miR-221 expression is associated with tumor angiogenesis in HCC.[13] miR-221 also is co-expressed with AEG-1, resulting in phosphatase and tensin homolog/phosphoinositide 3-kinase/protein kinase B upregulation to promote the progression of HCC.[13]
SND1	Role as the transcription factor late SV40 factor	The increase of miR-221 brought on by staphylococcal nuclease domain containing 1-induced NF-κB expression is directly correlated with the upregulation of angiogenic factors.[13]
Cellular inhibitor of apoptosis protein-1	Role as a driver for cell proliferation	In an animal model, Myc, an oncogene that drives proliferation but also promotes apoptosis through both p53-dependent and -independent mechanisms, and cellular inhibitor of apoptosis protein-1 work together to promote HCC.[14]
Hepatitis B virus X protein	Role in activation of other oncogenes	Through the activation of various oncogenes, the hepatitis B virus X protein contributes to the development of HCC.[15,16] By driving the G1/S cycle through arrestin beta 1-mediated autophagy, hepatitis B virus X protein causes hepatocellular carcinogenesis.[15,16]
Yes-associated protein 1	Role as a driver for cell proliferation	It is intriguing because cellular inhibitor of apoptosis protein is coamplified with yes-associated protein 1 during tumor growth in humans and occupies a nearby chromosomal position.[14]

AEG-1, astrocyte elevated gene-1; HCC, hepatocellular carcinoma; miR, microRNA; NF-κB, nuclear factor kappa B; RISC, RNA-induced silencing complex; SND1, staphylococcal nuclease domain containing 1.

elevated RISC. The imbalance of the transforming growth factor-beta 1/bone morphogenetic protein 7 (TGF-1/BMP-7) pathways, in relation to its distinct degenerative pathophysiological manner, is a viable predictive biomarker, and reversing the imbalance of TGF-1/BMP-7 pathways may be a potential therapeutic approach for HCC.[12]

Similarly, SND1 activates NF-κB and miR-221.[13] Through a new expression route involving NF-κB and miR-221 in human HCC, SND1 enhances tumor angiogenesis.[13] The increase of miR-221/222 suggests that stellate cells are becoming more active and that liver fibrosis is progressing. which can ultimately lead to liver cancer.[17] In addition, hepatitis C virus (HCV) infection causes the overexpression of miR-221 in a situational manner that is NF-κB dependent.[18] HCV infection specifically activates NF-κB, a key pathobiological step in the development of liver cancer, and the overexpression of miR-221 by HCV infection can be completely stopped by an NF-κB inhibitor.[18]

The final point is that SND1 is a multifunctional protein that is overexpressed in several cancers, including HCC. There is a direct correlation between the upregulation of angiogenic factors and the upregulation of miR-221 caused by SND1-induced NF-κB.[13] Angiogenin and C-X-C motif chemokine ligand 16 are believed to be the main pathogenic pathways for this oncogene.[13] The significant decrease in SND1-induced angiogenesis that occurred when one of these components was suppressed served to emphasize the importance of this metabolic cascade in regulating SND1 function.[13] Since NF-κB and miR-221 are two essential elements directing the aggressive phenotype of HCC, SND1 regulation may be an effective strategy to treat this terrible illness.[13] The carcinogenic crosstalk between various genes can be proven using the information provided for these sets of gene expression profiles (Fig. 1).

Cholangiocarcinoma

A specific type of cancer known as cholangiocarcinoma develops in the thin tubes (bile ducts) that transport the digestive fluid bile. There are two main kinds of cholangiocarcinoma: intrahepatic and extrahepatic types. The extrahepatic type is a deadly tumor and can result in severe jaundice. According to reports, this type of cancer is also linked to liver fluke. In some tropical regions, liver fluke-associated cholangiocarcinoma is very common. However, as this type of malignant tumor is extrahepatic biliary duct cancer and not liver cancer, it is not expressly included in the present minireview on liver cancer. Since there is a different origin between two types of cholangiocarcinoma, there is a difference in the gene expression profiles.[19] Brief details on the difference between gene expression profiles in intrahepatic and extrahepatic cholangiocarcinoma are summarized in Table 2.[17,19,20]

The authors will go into more detail and have a discussion on the second type of cholangiocarcinoma, intrahepatic cholangiocarcinoma, which is also a primary liver cancer.

The majority of risk factors, regardless of cause, culminate in persistent inflammation or cholestasis. Chronic inflammation ex-

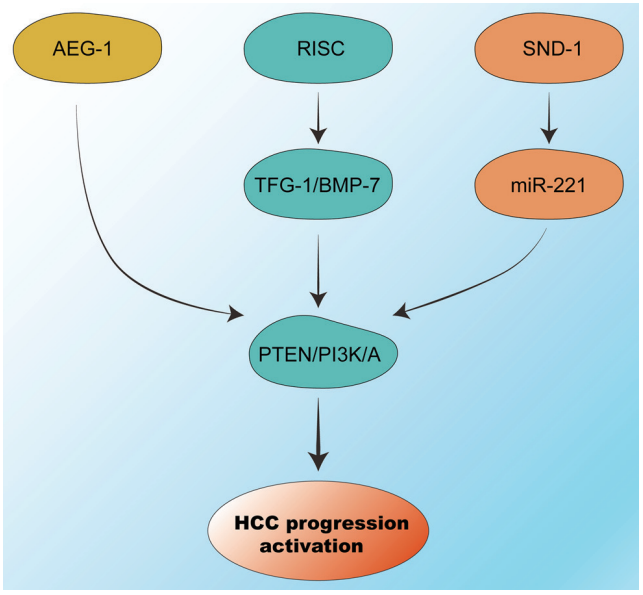

Fig. 1. The carcinogenic crosstalk between various genes related to the carcinogenesis of HCC. AEG-1, astrocyte elevated gene-1; BMP-7, bone morphogenetic protein 7; HCC, hepatocellular carcinoma; miR, microribonucleic acid; PTEN/PI3K/A, phosphatase and tensin homolog/phosphoinositide 3-kinase/protein kinase B; RISC, ribonucleic acid-induced silencing complex; SND-1, staphylococcal nuclease domain containing 1; TGF-1/BMP-7, the transforming growth factor-beta 1/bone morphogenetic protein 7.

poses cholangiocytes to inflammatory mediators like interleukin-6, tumor necrosis factor, cyclooxygenase-2, and wingless-related integration site, causing progressive changes in DNA mismatch repair, tumor suppressor, and proto-oncogene genes.[20] Furthermore, cholangiocarcinoma has elevated levels of transforming growth factor, hepatocyte growth factor, vascular endothelial growth factor, and several microRNAs.[20] Increased levels of the glucose transporter glucose transporter 1, the sodium iodide symporter, and the cell surface receptor c-Met all promote tumor development, angiogenesis, and cell migration.[20] Compared to noncancerous tissues, long noncoding RNA (lncRNA) expression profiling in cholangiocarcinoma tissues is significantly different.[21] As a result, lncRNAs may be promising biomarkers for both the diagnosis and prognostic prediction of cholangiocarcinoma.[21] Additionally, the survival of patients with cholangiocarcinoma may be predicted by combining the analysis of lncRNA and mRNA expression.[21] Similar to HCC, cholangiocarcinoma pathobiology can be better understood by using gene expression analyses. According to a recent protein-protein interaction network analysis, histone deacetylase 1, cullin-related neural precursor cell expressed, developmentally downregulated 8 dissociated protein 1, early growth response protein 1, ubiquitin D, and glycogen synthase kinase 3 were the major hub proteins.[22]

Hepatoblastoma

Hepatoblastoma is a rare type of liver cancer. Long-term overexpression of Achaete-Scute family BHLH transcription factor 2 and fetal liver-like methylation patterns of insulin-like growth factor 2 promoters point to cells with origins in premature hepatoblasts, which are highly proliferative and resemble intestinal epithelial cells. A promising strategy for figuring out the epigenetic factors that influence hepatoblast carcinogenesis and obtaining information for risk assessment is systematic molecular profiling of hepatoblastoma.[23] A circular RNA microarray was used to determine circular RNAs associated with hepatoblastoma, according to a recent study by Liu *et al*.[23] According to Liu *et al*'s findings, Circ 0015756 is a promising target for the prognostic prediction, diagnosis, and therapy of hepatoblastoma.[24] Circular RNAs are involved in the pathogenesis of hepatoblastoma. Last but not least, there is enhanced catenin protein translocation from the cell surface to the cytoplasm and nucleus, and intracellular accumulation is directly associated with the severity of the malignancy.[25] Yes-associated protein 1, solute carrier family 38 member 1, glypican 3, mammalian target of rapamycin 1, NF κB-light-chain-enhancer of activated B cells, regenerating islet-derived protein 1A and 3A, epidermal growth factor receptor, extracellular signal-regulated kinase 1/2, and tumor necrosis factor-alpha are all implicated in hepatoblastoma.[25]

Metastatic (secondary) liver cancer

Based on changes in global gene expression patterns, primary HCC can be easily distinguished from cancers metastatic to the liver (Table 3).[6] Metastatic tumors from the same primary site show distinct gene expression patterns that appear to be linked to their cellular progenitor. Metastatic malignancies with an unknown initial cause are prevalent. The classification of these cancers depending on the primary tumor of origin has significant therapeutic implications.[6]

The expression levels of various proteins, along with their interactions and the various tissue microenvironments, imply that primary liver tumors have impaired autophagy flux, which is essential for promoting tumorigenesis, and secondary liver tumors

Table 2. Difference of gene expression profiles in intrahepatic and extrahepatic cholangiocarcinoma

Intrahepatic cholangiocarcinoma	Extrahepatic cholangiocarcinoma
Interleukin-6, tumor necrosis factor, cyclo-oxygenase-2, and wingless-related integration site are some of the inflammatory mediators that are exposed to cholangiocytes during chronic inflammation, and these mediators gradually alter DNA mismatch repair, tumor suppressor, and proto-oncogene genes.[20] Additionally, cholangiocarcinoma has increased the levels of transforming growth factor, hepatocyte growth factor, vascular endothelial growth factor, and many microRNAs.[20] Tumor growth, angiogenesis, and cell migration are all facilitated by elevated levels of glucose transporter 1, the sodium iodide symporter, and the cell surface receptor c-Met.[17]	There is a lack of liver-specific gene expression in this kind of cholangiocarcinoma, but there is biliary tract-specific gene expression. Kirsten rat sarcoma viral oncogene homolog, tumor protein p53, AT-rich interactive domain-containing protein 1A, and mothers against decapentaplegic homolog 4 are the most prevalent mutations, with a quarter of tumors having a putatively actionable genomic alteration.[19] The MYC proto-oncogene target enrichment, v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 mutations/amplifications, and activation of mammalian target of rapamycin signaling are characteristics of the proliferation class, which is more prevalent in patients with distant tumors.[19]

DNA, deoxyriboNucleic acid; RNA, ribonucleic acid.

Table 3. Differences in the gene expression profiles between primary and secondary liver cancers

Primary liver cancer	Secondary liver cancer
Pathological gene expression can be detected. The identified gene expression profile can provide information about the liver cell's origin. Examples are expression of AEG-1, RISC, SND1 and nuclear factor b and miRNA-221 expressions.	Pathological gene expression can be detected. The identified gene expression profile can provide information about the origin of nonliver cell. Examples are liver kinase B1, v-raf murine sarcoma viral oncogene homolog B1, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, anaplastic lymphoma kinase, rearranged during transfection, breast cancer 1, and breast cancer 2 expression.

AEG-1, astrocyte elevated gene-1; RNA, ribonucleic acid; RISC, RNA-induced silencing complex; SND1, staphylococcal nuclease domain containing 1.

have both autophagy inhibition and activation mechanisms present.[26] Differences in mammalian target of rapamycin and light chain 3 transcripts have been found in pathological-free tissue.[10] HCC must be distinguished from liver metastatic tumors, since doing so has important therapeutic and prognostic ramifications.[27] Because metastatic liver tumors, particularly adenocarcinomas, may mirror the shape and immunoexpression of HCC, this differential diagnosis can be challenging.[27] Additionally, hsa-miR-141 and hsa-miR-200c, two microRNAs that support epithelial features, have been found in substantially higher concentrations in nonhepatic epithelial malignancies.[6] Moreover, the expression levels of claudin-1, -2, -3, -4, and -7 are also different between primary cancer and metastasized cancer.[7] A total of ten important genes for HCC, including those for cell division cycle 20, cyclin B1, eukaryotic translation initiation factor 4A3, aurora kinase A, H2A histone family member X, nucleolar protein 56, replication factor C subunit 4, nucleolar protein 58, proliferating cell nuclear antigen, and flap structure-specific endonuclease 1, were identified by a recent study employing the Germ Cell Nuclear Acidic Peptidase–Kernel Principal Component Analysis algorithm.[8] These data might be helpful in differential diagnosis between primary HCC and metastatic liver cancer. So, it may be beneficial to use diagnostic methods that are specifically expressed in primary HCC or metastatic adenocarcinoma.[27]

The gene expression profile analysis becomes an advanced investigation when the gene expression profiles of primary liver cancer and metastatic cancer are compared. Genes that are involved in the production and maintenance of HCC might be identified. Nonliver-specific but organ-specific gene expression may provide a clue for the diagnosis of metastatic cancer. The previous reports on gene expression profile analysis of liver metastasis from colon cancer are good examples of the possible application of the new gene expression profile approach for differential diagnosis between primary and secondary liver cancers.[28] In fact, a recent report shows that the overall accuracy of more than 90% demonstrates the encouraging performance of the gene expression assay in identifying the primary sites of liver tumors.[29] Future incorporation of the gene expression assay in clinical diagnosis will aid oncologists in applying precise treatments, leading to improved care and outcomes for secondary liver cancer patients.[29] The gene expression assay exhibits encouraging performance in detecting the primary areas of liver cancers.[29] The future integration of this assay for clinical diagnosis will help oncologists administer accurate treatments, thus improving care and outcomes for patients with secondary liver cancer.[29]

Clinical application of gene expression profiles in clinical oncology for liver cancer management

The importance of gene expression profile analysis in the early detection and management of liver cancer has already been mentioned. In essence, any tissue, even liver tissue, has genes that are expressed at a healthy, normal stage. In healthy individuals, a typical expression profile is observed. However, a new set of expression profiles produced by the oncogene can be seen when there is a malignant alteration. The foundation for using gene expression profile analysis in diagnostic oncology is presented here.

Additionally, a cancer's aberrant profile has a distinct pattern. In laboratory medicine, a key pathognomonic marker is the organ-specific pattern of abnormal expression. According to an analysis of HCC gene expression profiles from The Cancer Genome Atlas, most hepatoma tissues reveal gene expression patterns that are comparable to those in the hepatocyte-like cluster.[30] This aids in the differential diagnosis of cases with a challenging histology.

The basic information on the precise cause of the cancer is conceptually provided by the gene expression profile analysis. This leads to the primary clinical application, which is cancer origin diagnosis. Determination of the cancer origin can help to ascertain the precise type of liver cancer. A malignancy with a gene expression profile indicative of a nonspecific liver origin is most likely not a primary liver cancer. For instance, liver metastases resulting from lung or colon malignancies typically do not display any liver-specific gene expression profiles.[28,29] The case of cholangiorcarcinoma is yet another excellent illustration of the use of differential diagnosis. When a tumor develops in a junctional area, it might be challenging to determine whether it originated in the liver or in the extrahepatic biliary system.[21] At this step, the use of gene expression profiles is important.[21]

The expression level, which is frequently correlated with the disease severity and progression, can be provided via a gene expression profile in terms of therapy. Consequently, the gene expression level in a liver cancer case is a helpful biomarker for assessing the efficacy of cancer therapy. There is no denying that gene expression profile analysis has a number of benefits. The test is only occasionally offered, though, and is typically utilized for research. The expense of the analysis is likewise high. The direction that research in this area may go in the future may serve to provide important information for the creation of new diagnostic tests. The gene expression profile assay will be more widely available and more affordable for clinical use once the technology is complete and economies of scale in production are attained.

Laboratory concern in gene expression analysis for liver tissue and cancer

As mentioned above, the analysis of gene expression in normal liver tissue and cancer is useful for both diagnostic and therapeutic purposes. Based on the laboratory medicine concept, the basic principles of quality control and standardization must be followed for the whole process of analysis, ranging from the pre-analytical to post-analytical phases. A recent study found that the gene expression assay does not always successfully pinpoint the main lo-

cations of liver cancers.[29] The overall accuracy of 93.8 % suggests that an erroneous diagnosis is possible.[29]

To perform a laboratory test for gene expression analysis, a standard molecular laboratory is required. The prospect of using gene expression profile data to derive biomarkers of disease or toxicity, predict prognosis, or select treatments raises the validity and reliability bar substantially.[31] The potential future payoffs are huge in terms of faster approval of more efficacious and safer medical interventions as well as a more personalized implementation of them.[31] It can show that external technical standards evaluation in gene expression profile analysis laboratories is both necessary and desirable.[32] A benchmark for defining acceptable working standards in this developing technology will be provided by the reagent design and the statistical tools created within this international quality assurance initiative.[32]

Innovations in gene expression analysis for clinical oncology applications

The current status of gene expression profile analysis in clinical oncology is still in its early phases. It is still not routinely available. However, there are many new innovations in this specific field. Based on genetic changes and transcriptome dysregulation that are strongly associated to risk factors, clinical characteristics, and prognosis, several subclasses of HCC have been established.[33] Unquestionably, the identification of reliable predictive biomarkers of response to targeted biotherapy and immunotherapy can be sped up with the integration of data gathered from both preclinical models and human investigations.[33]

Regarding innovative diagnostics, the use of biosensors in clinical cancer testing has a number of potential benefits over other clinical analytical techniques, including the ability to perform multitarget analyses, automation, lower diagnostic testing costs, and the potential to make molecular diagnostic assays available to underserved populations and community health care systems.[34] They may help with point-of-care testing, which allows cutting-edge molecular analysis to be done without the need for a cutting-edge laboratory. However, few biosensors for cancer testing have been developed.[34] Nanotechnology has become an important technology to support the new development of biosensors for gene expression profile analysis for cancer. This area is the subject of current research. A noteworthy example is the use of organic quantum scale semiconductors for surface-enhanced Raman scattering detection of DNA methylation and gene expression.[35] With a single test, this type of sensor can identify structural, molecular, and gene expression abnormalities at femtomolar concentrations of genomic DNA. Additionally, it can highlight the differences between the genomic DNA of cancerous and noncancerous cells, which is another important objective of clinical oncology medical diagnosis.[35] Rapid and multiplex microRNA detection on visually encoded silica suspension arrays is another excellent example of how nanotechnology is being applied to the development of novel biosensors for gene expression profile analysis in clinical oncology.[36]

Conclusion

Liver cancer is one of the most common malignant tumors in the world, but it also has a high mortality rate. Using the genetic characteristics of the liver tissue, the pathophysiology of HCC can be determined, thus providing individualized care and treatment. It not only opens fresh research directions for biologists and medical specialists in the field of HCC, but it also serves as a vital resource for upcoming diagnostic procedures. Understanding carcinogenesis requires an in-depth examination of the genes that are differentially expressed in malignant and healthy tissues. Global gene expression profiling with microarrays is currently a powerful method for analyzing the changes of thousands of genes in any cancer tissue to find these essential disease-related genes. As a concise review of the research state in this area, the authors can also offer a fresh and distinctive academic viewpoint and assessment of potential future trends. There are numerous gene expression profiles that could serve as biomarkers for diagnostic purposes, such as differential diagnosis and precise confirmation of the type of liver cancer, according to the current paradigm. Additionally, prognosis prediction can benefit from a profile. The ongoing study in this field can contribute to the production of fresh information to support the clinical use of gene expression profiling. In the future, there will be a greater variety of applied gene expression profiling research that can be used to treat liver cancer clinically. The most recent testing will support liver cancer treatment and diagnosis. In parallel, it will become crucial to pay attention to how well the newly developed gene expression profiles are managed.

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Conflict of interest

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Author contributions

JB and WV gave ideas, analyzed the data, and wrote the manuscript; all authors read and approved the final manuscript.

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