DEPDC5 Alteration and Its Role in Hepatocellular Carcinoma

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ABSTRACT: DEPDC5 is a gene part of the DEP domain containing protein 5 and is a part of the GATOR1 protein complex that controls the mTORC1 Pathway. Mutations in the DEPDC5 gene can lead to mTORC1 being overactivated, leading to uncontrolled cell proliferation or growth, which can lead to hepatocellular carcinoma taking place. While there is a clear understanding that there is a connection between DEPDC5 and different types of cancer and diseases, the role of DEPDC5 in hepatocellular carcinoma or liver cancer needs more exploration. The paper attempts to explore and analyze the connection between hepatocellular carcinoma and mutation in the DEPDC5 gene using various resources, including but not limited to the UCSC Genome Browser, NCBI, Human Protein Atlas, CBioPortal, and FireBrowse. When analyzing these various resources related to both hepatocellular carcinoma and DEPDC5, it is shown that mutation and deletion of the DEPDC5 gene are correlated with many patients with hepatocellular carcinoma having a mutated and deleted DEPDC5 gene. It can also be seen that these mutations of the DEPDC5 Gene lead to overactivation of the mTORC1 Pathway, reduced autophagy, and other attributes that progress tumor growth, showing DEPDC5's role as a tumor suppressor gene. In conclusion, DEPDC5 mutations and deletions have a clear connection to hepatocellular carcinoma, as this gene serves as a tumor suppressor in liver tissue. In future practices, DEPDC5 can be a gene that is used as a biomarker when testing for hepatocellular carcinoma.

INTRODUCTION

Hepatocellular Carcinoma is the most common type of primary liver where the disease starts in the liver, making up 75 to 85% of these cases around the world. [7]. Hepatocellular Carcinoma is also the sixth most common cancer diagnosis and the third leading cause of cancer related deaths. Hepatocellular carcinoma grows slowly in early stages making surgery to remove the tumor viable. However, when hepatocellular carcinoma becomes more advanced treatment becomes incredibly hard leading to low survival [1] .It is also hard to detect hepatocellular carcinoma until it is in an advanced stage leading to the large number of deaths.

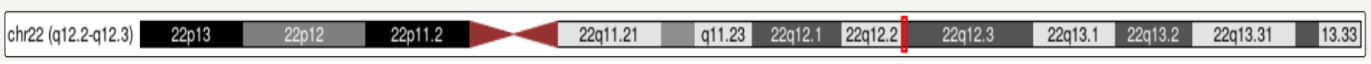
Some of the many symptoms of Hepatocellular Carcinoma include fullness or a knot under your ribs on your right side potentially showing an enlarged liver, fullness under your ribs on your left side potentially showing an enlarged spleen, eyes and skin turning yellow potentially showing jaundice, a swollen stomach with a fluid like feeling, loss of appetite and feeling full after a small meal, unexplained and random weight loss, nausea and vomiting, and itching [2]. Risk factors of hepatocellular carcinoma include infection with Hepatitis B (HBV) or Hepatitis (HCV), Cirrhosis where healthy liver tissue is replaced by scar tissue, consuming a large amount of alcohol and Aflatoxin B1. This also plays a role in why hepatocellular carcinoma has a high death rate [2].

It is important to note when analyzing Hepatocellular Carcinoma that men are more prone than women due to differing sex hormones [3]. Certain ethnic minorities are more affected with higher age specific rates for non-Hispanic, black and hispanic people when compared to non- hispanic whites with Age-adjusted incidence rates are higher for both Hispanics and Blacks (6.3 and 5.0 per 100,000, respectively), compared to Whites (2.4 per 100,000) [4]. Despite the major risk and high death rate of Hepatocellar Carcinoma, early-stage Hepatocellar

Carcinoma which can be defined by when a single tumor nodule is less than 5 cm in diameter or less than 3 nodules that are less than 3 cm in diameter allows for surgery and potential liver transplant as treatment [4]. As Hepatocellular Carcinoma progresses, it is recommended that oral sorafenib which is a medication that targets specific proteins involved in the progression of cancer is used but despite this the survival rate at later stages remains extremely low[5].Some of the therapeutic approaches used throughout these various stages when attempting to fight cancer are liver resection, liver transplantation and local ablative therapy, transarterial therapy, sorafenib and chemotherapy [6] While these developments in medicine exist to treat Hepatocellular carcinoma, it is important that new developments are made [5].

DEPDC5 is one of the many genes involved in potentially causing hepatocellular carcinoma. DEPDC5 is the gene which is a part of the DEP domain-containing protein 5 and is the gene of focus in this study. The alternative names of aliases of the DEPDC5 Gene are DEP.5, FFEVF, FPEVF, DEE111 and FFEVF1. DEPDC5 is located at Chromosome 22p12.29 and is widely known as a protein coding gene with up to 64 different unique transcript variants. DEPDC5 is an extremely interesting gene with various vital functions and proteins being encoded that are required for optimal function for a human. DEPDC5 contains 43 exons and 40 introns with 42 of the exons being coding exons. DEPDC5 plays a role in GTPase activator activity, macromolecular complex binding, regulation of autophagy or a cell degrading and recycling its own components, negative regulation of TOR Signaling, cellular response to amino acid starvation, intracellular signal transduction, positive regulation of GTPase activity and negative regulation of TORC1 Signaling. This paper will aim to understand how mutation and alteration of the DEPDC5 gene causes hepatocellular carcinoma.

Figure 1: Location of Chromosome: DEPDC5's location of a Chromosome derived from University of California Santa Cruz Genome Browser (UCSC Genome Browser) showing



MATERIALS AND METHODS

Various databases were used for the acquisition of information relating to both hepatocellular carcinoma and DEPDC5. The National Center of Biotechnology Information (NCBI) was used to retrieve information on the gene and protein. The search engine with the Databases of Gene, Protein, Nucleotide and GEO Profiles were used to learn more about the gene and the clear connection to hepatocellular carcinoma. 2 GEO Profiles were used Biological Processes are other functions that were also analyzed from here. The PubMed link on the site also provided access to various research articles related to DEPDC5 providing important information about DEPDC5

helping determination of the function causing Hepatocellular Carcinoma.The University of California Santa Cruz Genome Browser (UCSC Genome Browser) was utilized to understand the location of the gene along with other important data including RNA-Seq Expression Data from GTEx for 53 tissues. Alphafold was used to understand and analyze the structure of the protein to understand the factors of the protein connecting to hepatocellular carcinoma. The Human Protein Atlas was also used to find data relating to both RNA and Protein Expression along with Kaplan Meier Cancer survival data.

RESULTS

Based on analysis of Data a clear connection, there is a clear connection between DEPDC5 and mutations or other alteration of DEPDC5 causing hepatocellular carcinoma. DEPDC5, a gene part of the DEP domain containing protein 5, is expressed at a significantly lower rate towards and is downregulated in the presence of hepatocellular carcinoma. The biological processes described show a clear connection to those causing cancer when these functions are down regulated. It is also visible that there is high expression of the gene in tissues related to Hepatocellular carcinoma in the spleen, ovary and liver along with a strong interior protein structure showing the importance of DEPDC5 function and how mutation is likely to cause drastic change along with the higher rate of survival with expression in comparison to without expression all support the clear connection between DEPDC5 and mutations or other forms of alteration of the DEPDC5 gene causing hepatocellular carcinoma.

Figure 2: Biological Process controlled by DEPDC5: Table extracted from National Center of Biomedical Information (NCBI) displaying the Biological Processes that the DEPDC5 Gene controls. Displays Name, GO ID and Evidence Code display further information about each e related role.

Biological process

Name	GO ID	Evidence Code	Qualifier
TORC1 signaling	GO:0038202	IDA	acts_upstream_of_or_within
cellular response to amino acid starvation	GO:0034198	IBA	involved_in
cellular response to amino acid starvation	GO:0034198	IDA	involved_in
cellular response to amino acid starvation	GO:0034198	IMP	involved_in
cellular response to nutrient levels	GO:0031669	IDA	acts_upstream_of_or_within
cytoplasmic translation	GO:0002181	IDA	acts_upstream_of_or_within
intracellular signal transduction	GO:0035556	IEA	involved_in
negative regulation of TORC1 signaling	GO:1904262	IBA	involved_in
negative regulation of TORC1 signaling	GO:1904262	IDA	involved_in
negative regulation of TORC1 signaling	GO:1904262	IMP	involved_in
negative regulation of TORC1 signaling	GO:1904262	NAS	involved_in
negative regulation of translational initiation	GO:0045947	IDA	acts_upstream_of_or_within
positive regulation of TORC1 signaling	GO:1904263	IDA	acts_upstream_of_or_within
positive regulation of autophagy	GO:0010508	IBA	involved_in
positive regulation of translational initiation	GO:0045948	IDA	acts_upstream_of_or_within
protein localization to lysosome	GO:0061462	IDA	acts_upstream_of_or_within

Figure 2 lists out the important biological processes controlled by DEPDC5 showing how important its roles are and also illustrating how function stopping can lead to cell proliferation. Understanding this figure is vital in knowing what will happen without the optimal and required function of the DEPDC5 gene and specifically with the

TORC1 Pathway being overexpressed, lack of autophagy.

Figure 3: RNA Expression among different Tissues: This Graph shows the RNA Expression among 50 different Tissues all over the body. This graph displays nTPM showing the expression levels of these various tissues. This graph was found on the Human Protein Atlas Database.

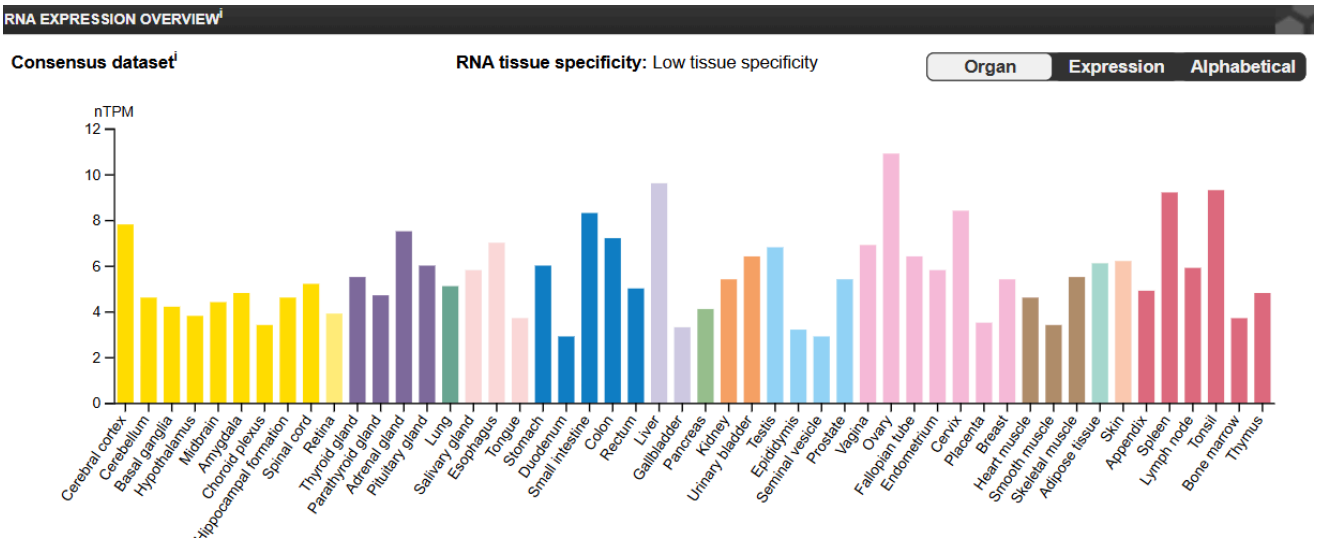
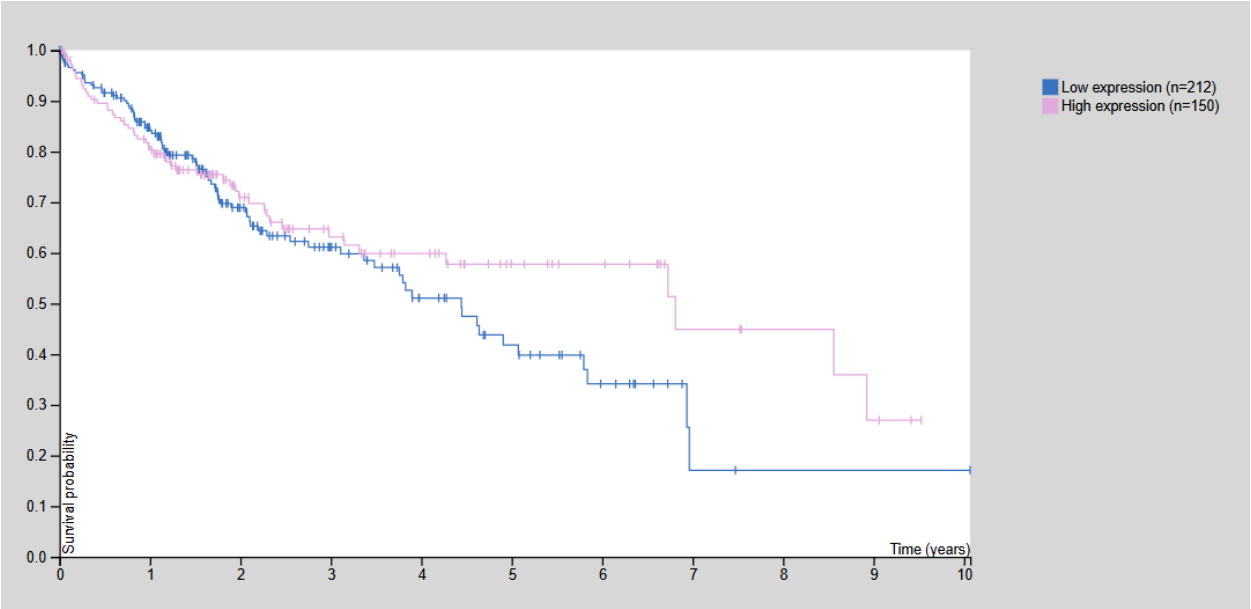


Figure 3 was to see the tissues with the highest expression levels with the inclusion of various tissues all over the body. It was found through searching the DEPDC5 gene on the Human Protein Atlas Database and then going to the tissue tab. I attempted to connect the tissues with highest expression levels to the specific tissues in the body related to hepatocellular carcinoma. There was an emphasis put on the Spleen and Liver as both these are involved in Hepatocellular Carcinoma.

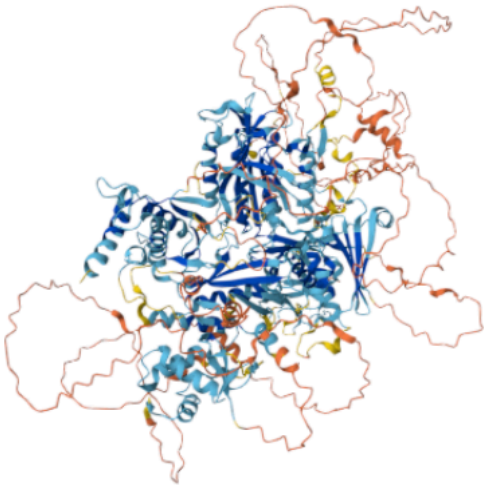
Figure 4: Kaplan Meier Graph: This graph below is a Kaplan Meier graph comparing survival rate with high expression of DEPDC5 and low expression of DEPDC5 relative to Hepatocellular Carcinoma. This graph was found through research on the Human Protein Atlas Database.



This Kaplan Meier Graph on Figure 4 aims to compare survival probability with low expression of DEPDC5 and high high expression of DEPDC5 in the the context of Hepatocellular Carcinoma. A time span of 10 years is implemented and the chance of survival is indicated over these 10 years in both High Expression and Low Expression. To access this graph I went to the Human Protein Atlas website then navigated to the cancer tab selecting liver cancer. Based on the results of this graph, it can be concluded that low expression of DEPDC5 leads to more death from hepatocellular carcinoma showing the importance in function of the DEPDC5 Gene and why mutation can lead to hepatocellular carcinoma.

Figure 5: Structure of the DEPDC5 A) This is the structure of the DEPDC5 Protein with Dark Blue parts being Very High Confidence of Over 90%, Light Blue being confident from 70% to 90%, Yellow being low between 50% and 70% and Orange being very low confidence being under 50%. This graph was taken from the AlphaFold Database. B) This is a graph displaying the TED Domains and Predicted Aligned Error with a Heat Map comparing aligned residue with scored residue showing Expected Position error. This graph is also from the alphafold database.

A.



B.

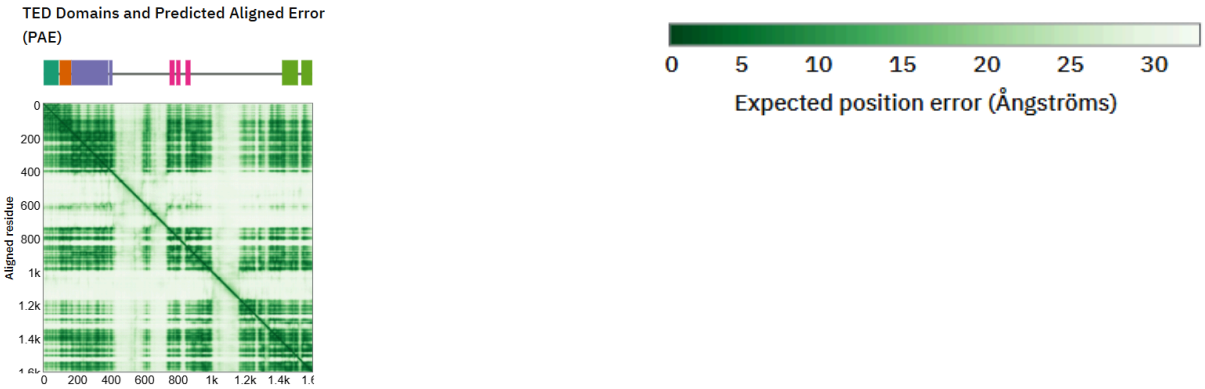
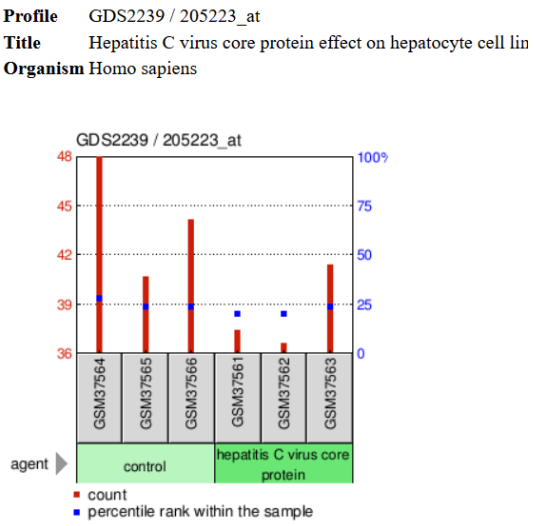


Figure 5A was utilized to analyze the structure of the DEPDC5 protein and if any insights could be derived that would provide information of the role of DEPDC5 and how when mutated it can cause Hepatocellular Carcinoma. This image of the protein was accessed through visiting the Alpha Fold Database and using the search engine for DEPDC5. Alpha Fold developed a prediction of the protein through the use of Artificial Intelligence. This protein mainly is made up of areas with high confidence in prediction especially towards the interior, but the outside is significantly less confident. The interior of the protein is highly ordered with the present of both alpha helices and beta sheets showing strong interior structure. Figure 5B is a TED Domains and Predicted Aligned Error with a heatmap used to show expected position error along with the Domains and their location listed at the top. This was also accessed through visiting the Alpha Fold Database and using the search engine for DEPDC5.

Figure 6 Hepatitis C virus core protein effect on hepatocyte cell line: A) Graph showing the affection of the implementing hepatitis C Virus core protein on the hepatocyte cell line. Accessed from the National Center of Biological Information (NCBI). B) Table showing alternative view of Same data.

A.



B.

Sample	Title	Value	Rank
GSM37564	HCV_Control_1	47.9932	28
GSM37565	HCV_Control_2	40.7285	24
GSM37566	HCV_Control_3	44.1863	24
GSM37561	HCV_Core_1	37.4517	20
GSM37562	HCV_Core_2	36.6999	20
GSM37563	HCV_Core_3	41.4207	24

Figure 6A is a graph showing the HCV core proteins' effect on the production of hepatocyte cell lines. Hepatitis C Virus or HCV is one of the main causes of hepatocellular carcinoma with those affected being more likely to be diagnosed with hepatocellular carcinoma. This shows the presence of HCV core proteins inhibits production of hepatocyte cell lines therefore leading to more hepatocellular carcinoma. HCV proteins play a major role in hepatocellular cancer and mutations of the DEPDC5 gene or presence of the HCV proteins causing mutation of the DEPDC5 or altering its function leads to hepatocellular carcinoma. It is also important to note that Figure 6B is just a table providing a more specific view with all of the information displayed in the graph.

DISCUSSION

Throughout this paper there is a clear connection between mutation and deletion of DEPDC5 and hepatocellular carcinoma. DEPDC5 plays an important role in many important biological processes like regulation of TORC1 Signaling, regulation of

autophagy, cytoplasmic translation, and many more, as listed in Figure 2. With mutation or deletion of DEPDC5, these key biological processes are blocked, leading to vital functions for optimal body performance being neglected. For example, the lack of presence of the DEPDC5 gene leads to the mTORC1 pathway being overactivated leading to cell proliferation. When considering what happens without DEPDC5, tissues and areas most affected and related to DEPDC5 must be examined. This can be seen on Figure 3, where tissues with high expression of DEPDC5 with the Liver, Ovary, and Spleen being the 3 highest tissues. Both the spleen and liver have a connection to hepatocellular carcinoma showing a clear connection to hepatocellular carcinoma. After examining the clear connection with where the gene is affecting in terms of tissue, another helpful resource would be comparing survival rate with high expression and low expression of the gene in the context of hepatocellular carcinoma. The Kaplan Meier Graph on Figure 4 displays information comparing survival rates and it can be concluded that low expression of Gene leads to lower survival rates. This provides support to the idea that DEPDC5 is important for optimal function of the body and that without DEPDC5's function, Hepatocellular Carcinoma is higher leading to more deaths and lower survival rate as displayed on the Figure 4 Graph. The protein structure would also provide valuable insight on the function of the DEPDC5 gene which can be connected to hepatocellular carcinoma. The protein structure displays a strong interior structure with the presence of alpha helices and beta sheets. The highly structured interior is vital for structure and mutation can see major change to the important functions related to the high rate of hepatocellular carcinoma with mutation. Understanding hepatocellular carcinoma and major causes in relation to DEPDC5 help provide important context and support.Figure 6 shows a Graph about Hepatitis C Virus core proteins and their effect on hepatocyte cell line production. This shows that the presence of the HCV proteins causes more cancer relating to the idea that people with Hepatitis C are more likely to be diagnosed with Hepatocellular carcinoma. This shows the role of HCV genes and connections with how HCV genes can alter genes like and including DEPDC5 which leads to higher rates of Hepatocellular Carcinoma. Overall, after viewing all the figures and evidence, they all are able to work together and target the idea that hepatocellular carcinoma is caused by the mutation, deletion or any other form of alteration of the DEPDC5 gene. The importance in the function of the Gene is highlighted throughout along with the potential effects of what occurs when these mutations or other alterations occur in the high expression of hepatocellular carcinoma.

However limitations exist when attempting to analyze the connection with DEPDC5 and the connection to Hepatocellular Carcinoma. Most resources and databases are taken and analyzed from public resources which lowers the specificity and consistency when comparing results, data etc with low personal control in experiment. Specifically, parts of the evidence and support were predicted with specifically the AlphaFold Predicted Structure being not 100% guaranteed but rather an AI prediction with different levels of confidence. There is also no real consideration for other ethnic and other similar factors when analyzing DEPDC5 alteration's effect on Hepatocellular carcinoma.

Future research in this field must continue to dive into and support the statement that alteration of the DEPDC5 gene causes

hepatocellular with innovative and progressive methods of research. For example, testing and trials can be done with the use of the CRISPR gene to take out the DEPDC5 gene and understand the effect on liver cancer by viewing the mTORC1 signaling pathway and how it responds. It is also possible to implement DEPDC5 as a biomarker for studies related to Liver Cancer.

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