REVIEW ARTICLE

Hepatocyte polarity and plasticity in the wake of HCV Infection

Davies Williams

Williams D. Hepatocyte polarity and plasticity in the wake of HCV Infection. J Genet Disord Genet Med. 2022; 6(3):29-31.

ABSTRACT

Hepatitis C virus (HCV) is an oncogenic virus that enters the hepatocyte and replicates by altering the cell polarity machinery. While these changes are pretty clearly defined, their effects on the disease's progression are rarely established. Since the introduction of direct acting antivirals in 2012, HCV infection has been effectively treated (DAA). Despite this, patients who have been free of HCV infection are nonetheless at significant risk of developing Hepatocellular Carcinoma (HCC). Importantly, despite a Sustained Virologic Response (SVR), some of the deregulations induced by HCV are maintained, including the down-regulation of some hepatocyte functions such as bile acid metabolism, exemplifying cell dedifferentiation, and the up-regulation of the epithelial–mesenchymal transition, Exemplifying Cell Dedifferentiation (EMT) EMT is a process in which epithelial cells lose their differentiation and particular polarity in order to acquire mesenchymal cell characteristics such as motility and extracellular matrix remodelling. It's worth noting that epithelial cell polarity functions as a barrier to EMT. As a result, it's crucial to figure out how HCV affects polarity and promotes EMT, which could play a role in viral-induced hepatic carcinogenesis. In this overview, we describe the fundamental phases involved in epithelial cell polarisation and recall the key cellular players involved. We also discuss the characteristics of hepatocyte polarity, which are responsible for their distinct appearance. The effects of HCV on epithelial cell polarity and the repercussions of hepatocyte transformation in the carcinogenesis process are then discussed

Key Words: *HCV; Hepatocytes; Polarity; EMT; Cell Junctions; Traffic; ECM*

INTRODUCTION

Hepatitis C virus was discovered as a cause of non-A and non-B hepatitis in 1975, and its genome was cloned in 1989. This virus almost exclusively infects and replicates in hepatocytes, and it is a primary cause of numerous liver disorders, including steatosis, fibrosis, cirrhosis, and hepatocellular carcinoma. There is still no HCV vaccination available, and the World Health Organization (WHO) estimates that 58 million individuals are infected with the virus, with 1.5 million new infections occurring each year. Furthermore, the World Health Organization (WHO) anticipated that almost 290,000 individuals died in 2019 from diseases caused by chronic HCV infection, primarily cirrhosis and malignancy. Furthermore, despite the fact that HCV is a hepatotropic virus that primarily affects the liver, multiple studies have connected the virus to a variety of extrahepatic symptoms including the skin, musculoskeletal, renal, cardiovascular, and neurological systems. It has been estimated that up to 74% of chronic HCV patients had at least one extrahepatic symptom . Harvey J. Alter, Michael Houghton, and Charles M. Rice were awarded the Nobel Prize in Medicine in 2020 for their work in identifying the virus and the methods by which it infects

Editorial Office, Journal of Genetic Disorder and Genetic Medicine, London, United Kingdom.

Correspondence: Davies Williams, Editorial Office, Journal of Genetic Disorder and Genetic Medicine, London, United Kingdom.

e-mail:geneticmedres@esciencejournal.org

Received: 2-Mar-2022, Manuscript No. M-4496; Editor assigned: 4-Mar-2022, PreQC No. puljgdgm -4496 (PQ); Reviewed: 18-Mar-2022, QC No. puljgdgm -4496; Revised : 20-Mar-2022 (Q), Manuscript No. puljgdgm -4496(R);Published: 28-Mar-2022, DOI:10.37532/puljgdgm.22.6(3).29-31.

and replicates in hepatocytes. These studies laid the groundwork for the development of Direct-Acting Agents (DAA), the first of which was approved in 2011 and had an efficacy of more than 90% in eliciting a Sustained Virological Response (SVR), compared to about 50% with the prior reference treatment, interferon [1,2]. Beyond the fact that the infection can be cured, new research has shown that the risk of HCC development continues and that some HCV-induced deregulations persist despite the virus's total clearance. In particular,Hamdane et al. Despite the virus's elimination by DAAs, 2193 genes with epigenetic and transcriptional changes were preserved. Furthermore, 1411 of these genes were found to be closely related to the Prognostic Liver Signature (PLS), a well-characterized liver expression signature of 186 genes that has been shown to predict survival and HCC risk in patients with advanced liver disease, regardless of aetiology, including 73 poor prognosis high HCC risk genes and 113 good prognosis low HCC risk genes, according to this study. As a result, it's possible that maintaining some dysregulation in individuals treated with DAA contributes to a deterioration of the HCC clinical picture. EMT remains up-regulated among the processes linked with genes that are still unregulated, whereas hepatocyte-specific functions such as xenobiotic and bile acid metabolism remain down-regulated, indicating hepatocyte dedifferentiation. EMT is a complicated and reversible process in which epithelial cells lose their polarity, epithelial features, and differentiation to become mesenchymal cells with invasive traits that aid in metastasis. Importantly, epithelial cell polarisation acts as a stumbling block to dedifferentiation and EMT. It's crucial to understand the mechanisms of hepatocyte polarisation in order to figure out how HCV disrupts these processes and can lead to cancer even after the virus has been eradicated from the infected liver. Importantly, epigenetic modifications are caused not only by HCV's direct impact on hepatocytes, but also by HCV's indirect action on the environment around the hepatocytes .As a result, it's also crucial to figure out how HCV creates a harmful environment around hepatocytes that encourages their change. In this study, we will outline the key players in epithelial cell polarisation and discuss the peculiarities of hepatocyte polarity that contribute to their distinct shape. The ways by which HCV modifies hepatocyte polarity in order to enter and multiply in the hepatocyte will subsequently be discussed. Finally, we will discuss the effects of these changes on hepatocyte plasticity, which may play a role in liver cancer development.

HCV PROTEINS

HCV is a Flaviviridae virus with a positive strand RNA oncogenic gene. With seven genotypes and 67 subgroups discovered, this virus has a lot of genomic diversity. HCV primarily infects the liver and crosses the plasma membrane of hepatocytes to release its genomic RNA using specialised attachment and entry factors. The viral and host translation machinery use the RNA as a template for replication and translation in the rough Endoplasmic Reticulum (ER). The 9.6-kilobase genome codes for a massive polyprotein that is broken down into three structural proteins, the core capsid protein and the envelope proteins E1 and E2, as well as at least seven non-structural proteins (NS proteins), NS1 (also known as p7), NS2, NS3, NS4A, NS4B, NS5A, NS5B. The nucleocapsid is made up of a 191 amino acid protein at its core. It has been demonstrated that it binds Lipid Droplets (LD), which are fatty acid storage organelles, and that this association is needed for viral replication. Core protein also affects a variety of cellular functions, including transcription, lipid metabolism, and apoptosis. The E1 and E2 proteins are crucial in the virus's entrance into hepatocytes and create the envelope. For virus propagation, non-structural proteins are necessary. NS5A expression, for example, causes the production of Double Membrane Vesicles (DMV). In conjunction with LD, DMV is thought to be the organelle where HCV replication occurs. Although NS5A expression alone can cause the production of these DMV, expressing the entire HCV genome considerably enhances the number of DMV generated.Furthermore, NS5A controls interferon response, imparting resistance to this chemical. Until the discovery of DAA, which targets the virus's nonstructural proteins, this was thought to be the gold standard treatment [3].

HCV proteins interact together to create a harmful environment for hepatocytes, which can lead to the development of hepatocellular carcinoma over a long period of time, anywhere from 20 to 40 years (HCC). HCV infection affects gene expression, metabolism, signalling pathways, hepatocyte polarity, and the extracellular milieu surrounding these cells, among other things.

Hepatocyte Polarity

The liver is made up of five different cell types. Endothelial cells that line blood vessels, Kupffer cells, resident macrophages of the liver, stellate cells that regulate extracellular matrix, and two types of epithelial cells: cholangiocytes that line bile ducts and hepatocytes. Hepatocytes are polarised epithelial cells that make up almost 70% of the total number of liver cells and make up the liver parenchyma. These cells have a role in the majority of the liver's metabolic and biosynthetic tasks, as well as transporting a variety of endogenous and foreign substances from the bloodstream to the bile canaliculi. The formation of hepatocyte polarity, like that of all epithelial cells, is critical for their final differentiation and ability to fulfil numerous tasks. The apical domain faces the tube lumen, while the basolateral membranes bind to neighbouring cells and the Extracellular Matrix (ECM).Epithelial cells have an apico-basal polarity, with an apical domain facing the tube lumen and a basolateral membrane that binds to neighbouring cells and the ECM [4-6]. Cascades of signalling pathways from cell–cell and cell–ECM junctions start the process of establishing apicobasal polarity. Changes in the intracellular cytoskeleton, which organises the cell cortex, result in polarised endosomal trafficking, which leads to the creation of the apico-basal axis and lumen. The polarity complexes are a type of polarity complex that is composed of two Crumbs (composed of three proteins: Crumbs/proteins associated with Lin seven (PALS)/tight junction associate protein (PATJ)), Par (partition-defective 3 partition-defective 3 Atypical protein kinase C (aPKC)), and Scribble (Scribble/Discs large homolog (Dlg1)/lethal giant larvae (Lgl)) are all involved in cytoskeleton, For epithelial cell polarisation, cell trafficking and cell–cell junctions are necessary. Phosphoinositides and enzymes involved in their metabolism, such as Phosphatase and TENsin homolog (PTEN), Phosphoinositide 3-kinase (PI3K), and SH2 domain containing inositol 5-phosphatase 2 (SHIP2), are also required for polarisation, particularly for establishing apical and basolateral membrane identities [7,8].

HCV Infection and EMT

Changes in essential actors involved in the establishment and maintenance of apico-basal polarisation caused by HCV will

contribute to the progressive transformation of the hepatocyte, primarily by EMT, which could accompany the progression of the disease from chronic HCV infection, steatosis, fibrosis, and HCC. Tumor suppressors are junctions and polarity complexes. These actors, in particular, serve as gatekeepers for EMT. Snai1, a transcription factor that inhibits the production of E-cadherin, claudin, and cytokeratin 8, is a powerful inducer of EMT. Snai1 protein breakdown is promoted by aPKC-mediated Snai1 phosphorylation in polarised cells (and only in polarised cells), which prevents EMT. Infected hepatocytes are more prone to EMT as a result of HCV-induced changes in cell junction and polarity complexes, which may have consequences in hepatic carcinogenesis. HCV core protein-induced scribble delocalization from the plasma membrane to the cytoplasm promotes liver tumour development and tumour cell invasiveness. Scribble localisation was disturbed in HCC, with the protein migrating from the membrane to the cytoplasm. Furthermore, c-MYC-induced tumour formation in the mouse liver was aided by the production of a scribble mutant with a preferred cytoplasmic location. Hepatic steatosis, a condition characterised by a buildup of LD in the hepatocytes, is caused by HCV infection. Steatosis is 2.5 times more common in HCV-infected patients than in non-infected people. Furthermore, hepatic steatosis affects more than half of all chronic hepatitis C patients. HCV genotype has an effect on the development of steatosis, which is interesting. Genotype 3 in particular causes more steatosis than the others. Furthermore, Huh7.5 cells transfected with genotype 3a sequences have more neutral lipids in lipid droplets and larger lipid droplets than Huh7.5 cells transfected with genotype 1b sequences, implying that HCV core protein–lipid droplet interaction may play a role in virus-induced steatosis. Importantly, no genetic or functional differences between genotype 3a core proteins from patients with and without HCV-induced steatosis were discovered, implying that other viral proteins and/or host factors are involved in the development of hepatic steatosis in HCV genotype 3a patients. Many aggressive tumours include an overabundance of LD. It was recently shown that the accumulation of LD in tumour cells in response to acidosis played a key role in initiating the EMT process. Notably, the scientists demonstrated that inhibiting LD formation by pharmacological inhibition of Diacylglycerol O-Acyltransferase 1 (DGAT1) resulted in a significant reduction in cancer cell invasion capacity, showing that LD is necessary in the EMT process involved in cancer tumor cells invasion [9,10].

CONCLUSION

The intimate relationships between HCV and the cell polarisation machinery have been discussed in depth in this article. HCV enters the cell and replicates by hijacking important aspects of the polarisation processes, such as molecules from cell–cell junctions and intracellular trafficking. HCV also modifies the ECM and the cellular response to TGF, contributing to hepatocyte transformation and cancer progression. Importantly, some of these HCV-induced changes persist even after the virus has been eradicated. As a result, more research is needed to identify the mechanisms that contribute to the maintenance of these deregulations, so that treatments may be proposed to reduce the risk of HCC development in both cured and non-cured HCV patients.

REFERENCES

1. Feinstone SM, Kapikian AZ, Purcell RH, et al. Transfusion-Associated Hepatitis Not Due to Viral Hepatitis Type A or B. N Engl J Med. 1975;292(15):767-770.
2. Choo Q L Kuo, G Weiner AJ.et al.Isolation of a cDNA cLone Derived from a BloodBorne Non-A, Non-B Viral Hepatitis Genome. Science 1989;244(4902):359-362.
3. Clouston AD Powell, E Walsh J Richardson, MM Demetris, et al. Fibrosis correlates with a ductular reaction in hepatitis C: Roles of impaired replication, progenitor cells and steatosis. Hepatology 2005;41(4):809-818.
4. Colombo M Choo, Q Del Ninno, E Dioguardi N, et al. Prevalence of Antibodies to Hepatitis C Virus in Italian Patients with Hepatocellular Carcinoma. Lancet 1989;334(8670):1006-1008.
5. Kew M Houghton, M Choo, Q Kuo. Hepatitis C virus antibodies in southern African blacks with hepatocellular carcinoma. Lancet 1990;335(8694):873-874.
6. Lonardo A Adinolfi, LE Loria, P Carulli, et al. Steatosis and hepatitis C virus: Mechanisms and significance for hepatic and extrahepatic disease. Gastroenterology 2004;126(2):586-597.
7. Polo ML, Laufer N. Extrahepatic manifestations of HCV: The role of direct acting antivirals. Expert Rev Anti-Infect Ther. 2017;15(8):737-746.
8. Cacoub P, Poynard T, Ghillani P, et al. Extrahepatic manifestations of chronic hepatitis C. Arthr Rheum. Off J Am Coll Rheumatol. 1999;42(10):2204-2212.
9. Carrat F, Fontaine H, Dorival C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: A prospective cohort study. Lancet 2019;393(10179):1453-1464.
10. Hamdane N, Jühling F, Crouchet E, et al. HCV-Induced Epigenetic Changes Associated with Liver Cancer Risk Persist after Sustained Virologic Response. Gastroenterology. 2019;156(8):2313-2329.