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Review Article

Emerging Critical roles of Vitamin in Regulation of Hepatitis C Virus Infection

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Abstract

Hepatitis C Virus (HCV) infection is one of the leading causes of end stage liver disease, such as decompensated cirrhosis and liver cancer. The host immune response during acute infection fails to eradicate HCV in a majority of cases; therefore over 200 million people worldwide are chronically infected. Although recent advances in antiviral drug therapies demonstrate compelling success rates, our history in the fight against human pathogenic viruses implies that antiviral drugs have never contributed to the elimination of pathogens from the world. Thus, a continued effort to better understand HCV virology is desperately required until the establishment of a definitive vaccine. Because virus replication relies on host cell machinery, dietary nutrients that modulate cellular homeostasis are presumed to have great influence on viral replication, pathogenesis, and antiviral therapy response. Vitamins, for example, are organic compounds required for the host homeostasis as vital nutrients. In addition to its classic roles, the non-canonical effects of vitamins have received remarkable attention in the field of immunology, cancer cell biology, and metabolic diseases. Of these compounds, vitamin A, B12, and D have been implicated as a determinant for variety of viral infectious diseases. Thus, this mini-review summarizes our current knowledge on how these critical nutrients modulate the disease course of HCV infection.

ABBREVIATIONS

IFN: Interferon; ADH: Alcohol Dehydrogenase; ALDH: Aldehyde Dehydrogenase; DAAs: Direct Antiviral Agents; IRES: Internal Ribosome Entry Site

INTRODUCTION

Chronic liver disease is the 12th leading cause of death in the United States, of which HCV infection accounts for one-third of those cases [1]. HCV is a blood born pathogen, thus transmitted by exposure **to** infectious blood and body fluids. In the US, the current predominant mode of transmission is through Injection Drug Use (IDU) or in-house tattoo with contaminated needles. In contrast, the incidence of 'blood products' mediated transmission has significantly declined after implementation of screening with nucleic acid detection assay [2]. Currently, over 5 million people (1.5% of population) in the US are chronically infected. Of those, a significant proportion advance to end-stage liver diseases; therefore, a significant threat to public health [3]. The most effective medical intervention to prevent the onset of advanced liver disease is antiviral therapy early in the chronic infection. The antiviral treatment for HCV currently transitions from Pegylated interferon (IFN)+Ribavirin to a regimen containing direct antiviral agents (DAAs). IFN based treatment does not offer satisfactory sustained virological response (SVR) and also associated with sever toxicity [4]. Recent advances in development of DAAs against HCV demonstrate compelling success rates, anticipating that IFN free regimens will become available in the near future. However, it has been shown that IFN free DAA therapy provokes the generation of drug resistant mutations [5]. In contrast, drugs that target host factors necessary for viral replication are much more attractive because such compounds offer high barriers to viral evolution of drug resistance. Therefore DAAs combination with tolerable host factor targeting drugs will be the most promising and intuitive paradigm for viral control. Moreover, lessons from our history of the fight against viral infectious diseases indicate that antiviral drugs have not contributed to the elimination of pathogens from the world. Taken all together, further understanding of HCV virology, host factors exploited for viral replication, and host response to infection is critical for our ultimate goal to establish a global vaccine program.

Host responses, including innate and adaptive immunity, are the major factors in restricting HCV. Moreover, numerous additional factors also have influence over the lifecycle of HCV. Because virus replication completely relies on host cellular machinery, cellular response to nutrients and change in metabolic status are expected to alter viral replication efficiency. Emerging

evidences indicate that an ordinary nutrient such as vitamins, have significant influence on HCV lifecycle [6]. Vitamins are organic compounds that exhibit critical biological activity and are thus required for host cellular homeostasis. With the exception of Vitamin D, the host is incapable to synthesize vitamins, therefore exclusively relying on dietary sources. The classic role of vitamins has been known as the following: Vitamin A for vision, B for energy production, C for wound healing, D for bone maintenance, E for its role as an antioxidant, and K for coagulation. In addition to these "historical/classic" properties, numerous non-canonical bioactivities of vitamins have received tremendous attention in recent years. This includes, but not limited to, the "anti-infective" properties of Vitamin A [7]. Similarly, the protective effect of Vitamin D (cod liver oil) has been believed to have part in regulation of Mycobacterium Tuberculosis [8]. Thereafter, a number of epidemiological studies were conducted and provided evidences of the anti-infection effect of vitamin A in a broad spectrum of infectious diseases [9,10]. A mechanistic explanation for the antimicrobial effect of these vitamins has emerged in recent 10 years. For example, Retinoic Acid (active metabolite of Vitamin A) plays a role in differentiation/maturation of a broad spectrum of immune cells [11]. With regards to Vitamin D, recent studies have shown its critical roles in antigen presenting cells (APC), such as dendritic cells and macrophages. Of great interest, these innate immune cells induce the expression of Cytochrome P450 (CYP) 27B1 in response to IFN-γ. It has been known that CYP27B1 are highly expressed in renal tubular cells, wherein 25D receives additional hydroxylation to become an active metabolite. The IFN-γ mediated production of the active form of Vitamin D in DC and macrophage appeared to be critical for antigen presentation and T cell maturation. These immune-modulatory functions of vitamins can be involved in regulation of a variety of pathogens including HCV.

With regards to vitamin B12, non-immune-modulatory effects have been implicated in HCV regulation. In general, vitamin B12 is a critical co-factor for the energy production pathway, such as protein and fatty acid metabolism. Thus, its deficiency or impairment of associated metabolic pathway is expected to cause cellular dysfunction in a variety of cells and organs. Indeed, the importance of vitamin B12 has been well recognized in non-alcoholic fatty liver disease (NAFLD) [12-15]. In addition to its roles in hepatic steatosis, the antiviral effect of Vitamin B12 has been reported in molecular virological and clinical studies.

This review article discusses the critical roles of vitamin in regulation of HCV through the introduction of both emerging mechanistic studies and clinical observations.

DISCUSSION AND CONCLUSION

Vitamin A

Vitamin A is essential in a broad range of physiological functions such as vision, growth, reproduction, hematopoietic cell differentiation, and immunity [16]. Since 1928, vitamin A has been recognized as an antiviral compound [7]. Accordingly, the protective effect of vitamin A has been shown in various human pathogenic viral infectious diseases. To date, many studies have demonstrated that vitamin A supplementation reduces severe morbidity and mortality of multiple viral infectious diseases including measles, herpes simplex virus, influenza A virus, HIV, respiratory syncytial virus, and HPV [10,17-25]. A few mechanistic studies indicate that vitamin A enhances both innate and adaptive immunity, with its important role in immunoglobulin production, T cell differentiation/maturation, and cellular sensitivity to IFN [26,27]. These observations suggest that vitamin A regulates viral infectious diseases through its immune-modulating function. Of particular note, the patient population suffering from chronic liver diseases, such as HCV infection, also suffer from symptoms of vitamin A deficiency [28,29]. This is likely a consequence of HCV-mediated chronic inflammation that promotes trans-differentiation of hepatic stellate cells (HSCs) to myofibroblast. In healthy conditions, HSCs store up to 80% of total body vitamin A as a retinol and retinyl ester [30,31]. The trans-differentiation of HSC to myofibroblast like cells is associated with loss of vitamin A storage, resulting in lowering the degree of vitamin A contribution to antiviral immunity [32]. This could be an explanation for the poor success rate of IFN based antiviral therapy among cirrhotic patients, because therapeutic IFN exhibits an antiviral effect though its immune boosting property [28]. The immune-modulatory effect of vitamin A is believed to be mediated by its active metabolite, Retinoic Acid (RA) [18,26]. RA has been shown to govern more than 500 genes [33,34], of which include a number of immunity related genes [35]. In fact, a clinical observation demonstrated that RA potently suppressed serum HCV titer as well as the enhancement of IFN efficacy [36,37]. Because IFN exhibits its antiviral effect through the induction of interferon stimulated genes (ISGs), the aforementioned observations indicate the potential contribution of RA in the induction of ISGs. Lastly, it is important to recognize that RA production in the hepatocytes, where HCV replicates, utilize the ADH-ALDH pathway for the conversion of retinol to RA [38]. Because the ADH-ALDH pathway in hepatocytes is a major pathway for the alcohol metabolism, it is possible to speculate that vitamin A and EtOH metabolic competition can be an explanation for enhanced HCV pathogenesis among drinkers [39,40]. In summary, these lines of evidences imply the particular importance of vitamin A homeostasis in HCV regulation (Figure 1).

Vitamin B12

Vitamin B12 is stored in high concentrations in the human liver and governs DNA synthesis and energy production through fatty acid metabolism, thus playing a critical role in the maintenance of cellular homeostasis [41]. Biochemically, vitamin B12 is a cofactor for methylmalonyl coenzyme A Mutase (MUT) and 5-Methyltetrahydrofolate-homocysteine Methyltransferase (MTR), playing a critical role in the production of succinyl-CoA and methionine respectively [41]. As a positive feedback, vitamin B12 increases the expression of MTR by enhancing Internal Ribosome Entry Site (IRES) dependent translation [42]. This mechanism is explained by vitamin B12 binding to IRES Trans-Activating Factors (ITAFs) such as hnRNP I/polypyrimidine tract-binding protein and La autoantigen [42]. However, vitamin B12 has a negative effect on IRES-dependent translation of HCV protein in a concentration dependent manner [43,44]. Because HCV genome lacks 5´ terminal m^7G (CAP), HCV viral protein translation is solely IRES dependent. Although, the exact molecular mechanism on why vitamin B12 exhibits opposite IRES-regulation between HCV and MTR remains elusive, these observations suggest vitamin B12 has specificity to the structure

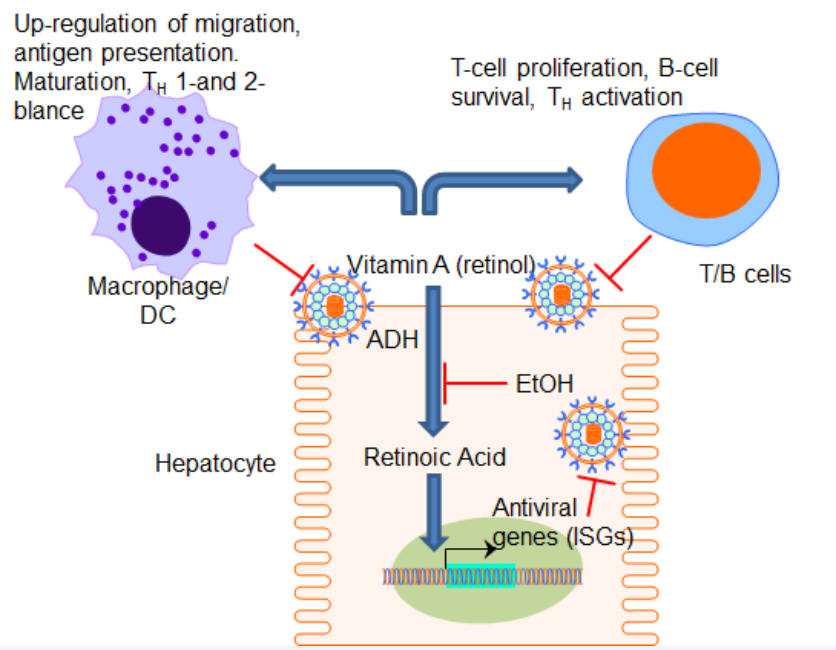

Figure 1 Vitamin A regulation of HCV. Vitamin A enhances maturation and function of professional innate immune cells (Macrophage/DCs) such as migration and antigen presentation. Vitamin A also support T/B cell. In hepatocytes, ADH-ALDH pathway facilitates conversion of retinol to its active metabolite, retinoic acid (RA). RA governs ~500 gene expression, which contains numerous antiviral genes, namely interferon stimulated genes.

of IRES. Indeed, vitamin B12 does not suppress other IRES-dependent viruses such as Encephalomyocarditis Virus (EMCV) or Classical Swine Fever Virus (CSFV) [43-45]. More importantly, these in vitro based observations have been recently confirmed by several clinical observations, demonstrating that serum vitamin B12 concentration is correlated to HCV RNA titer and success rate of IFN based antiviral treatment [46]. In addition to its direct antiviral effect, it has been proposed that vitamin B12 indirectly influences HCV pathogenesis through deregulation of lipid metabolism. Insufficient vitamin B12 leads to the impaired production of succinyl-CoA and methionine, resulting in the increased risk of hepatic steatosis. The formation of lipid droplets in hepatocytes offers a foundation for the HCV replication complex [47,48], thereby insufficient vitamin B12 status presumably enhances the HCV lifecycle through the formation of lipid droplets where the HCV replication complex is formed [49] (Figure 2).

Vitamin D

The liver plays a critical role in conversion of vitamin D2 and 3 to 25(OH)D2 and 3 by utilizing 25-hydroxylase (CYP27A1) [50]. 25(OH)D receives additional modification in renal tubular cells, wherein 1α-hydroxylase (CYP27B1) mediates the production of 1,25(OH)D. 1,25(OH)D is the active form of vitamin D, which is expected to regulate up to 2800 genes through the activation of its nuclear receptor (VDR) [50,51]. In recent years, the non-canonical role of vitamin D has been rapidly emerged in addition to its classic roles in bone/calcium homeostasis. This includes, but not limited to, the vitamin D regulation of innate and adaptive immunity in response to a variety of infectious diseases [9,52]. One example of this is in cod liver oil, which contains high quantities of Vitamin D, and has been historically used to restrict Tuberculosis (TB) [8]. Follow-up molecular studies revealed that professional innate immune cells such as Dendritic Cells (DCs) and macrophages are equipped with CYP27B1, allowing these cell types to metabolize 25(OH)D to 1,25(OH)D [52]. The production of active ligand in innate immune cells plays critical roles for its activation as well as mounting of T and B cell maturation, a likely explanation for the anti-TB effect of Vitamin D [26,52]. With regards to its role in HCV regulation, a screening for the identification of dietary nutrition that regulate HCV lifecycle discovered that Vitamin D2 is one potent hit that suppressed HCV replication [6]. Following this observation, numbers of studies have provided clinical evidences that Vitamin D indeed plays a role in HCV disease outcomes. For example, genetic variants or polymorphisms of Vitamin D related molecules such as Vitamin D receptor, Vitamin D binding protein, and CYP27B appeared to be associated with HCV pathogenesis, replication, and therapeutic responses [53-56]. Moreover, the serum Vitamin D level or supplementation significantly influenced HCV replication and IFN+RBV response in a pan-genotypic manner, although there was some controversy [57-60]. The exact molecular mechanisms of how Vitamin D regulates HCV infection have not been fully understood. One interesting observation demonstrated the specific anti-HCV effect of 25(OH)D3, but not other forms of vitamin D metabolites [61]. Because 25(OH)D3 is not a transcription active form of Vitamin D, this observation suggests an alternative anti-HCV mechanism independent of VDR mediated immune gene regulation. Indeed, the study demonstrated that the antiviral effect of 25(OH)D3 is due to the inhibition of virion assembly, however the mechanism of this phenomenon remains elusive [61]. Lastly, one study also showed modest up-regulation of ISGs in hepatoma cell lines

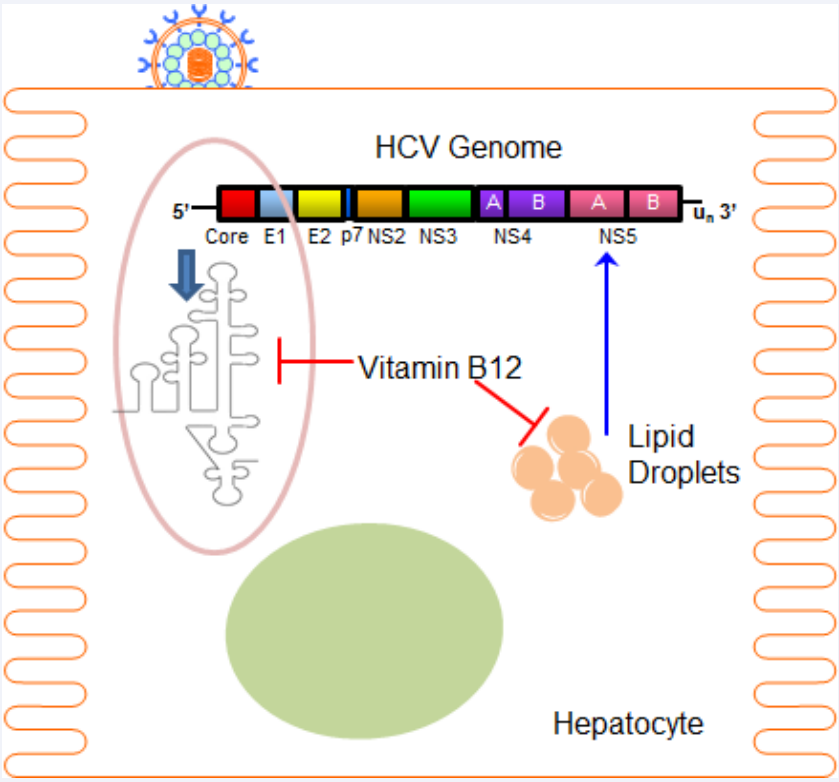

Figure 2 Vitamin B12 regulation of HCV. Significant amounts of Vitamin B12 are stored in hepatocytes. Vitamin B12 prevents steatosis (lipid accumulation) of the hepatocytes and also inhibits HCV polyprotein translation through inhibition of IRES.

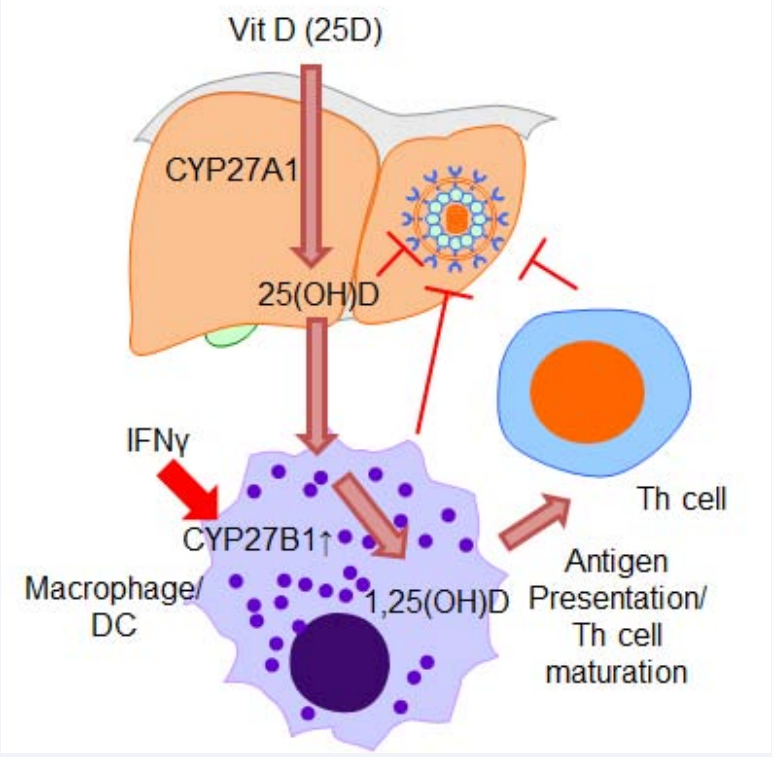

Figure 3 Vitamin D regulation of HCV. Hepatocytes metabolize vitamin D: 25D with CYP27A1 for the generation of 25(OH)D. In professional innate immune cells, CYP27B1 converts 25(OH)D into an active metabolite, 1, 25(OH)D. The active metabolite of vitamin D enhances both innate and adaptive immune cells.

treated with Vitamin D [62]. Thus, despite the lack of in depth explanation of the antiviral effect of Vitamin D, numerous evidences collectively promise the importance of Vitamin D in HCV regulation (Figure 3).

CONCLUDING REMARKS

The cumulative understanding of non-canonical role of vitamins clearly illustrates how these critical nutrients modulate the outcome of HCV related liver diseases. Due to the maturation of antiviral drug development against HCV in recent years, it is expected that patients will receive highly tolerable but promising combinations of Direct Antiviral Agents (DAAs). However, our history of the fight against viral pathogens clearly indicates that there is no single disease eliminated by antimicrobial agents. Thus, continued research focus to understand comprehensive HCV virology and host regulation of pathogen is desperately required until the establishment of a highly effective global vaccination strategy.

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