

Pathogenesis of Hepatitis-B Virus-Related Hepatocellular Carcinoma and Human Papillomavirus-Associated Cervical Cancer

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Abstract. Cancer, which can be explained as malignant tumors and neoplasms, is one of the main factors of human mortality and greatly obstructs the extension global human life span. There are various human cancers induced by viruses. Hepatocellular carcinoma (HCC) and cervical cancer (CC) are two common cancers related to viruses. The pathogenesis of these carcinogenic viruses has been studied for a long period of time, and some progress has been made. Hepatitis B virus (HBV) infection functions as a promoter of hepatocellular carcinoma occurrence. The integration of HBV DNA into the host genome is one of the important factors of the development of hepatocellular carcinoma. Besides, miRNA plays an important part in HBV amplification and the progression of HBV-related hepatocellular carcinoma. Another cancer-inducing virus, human papillomavirus (HPV) is highly related to cervical cancer, as the long-term chronic inflammation due to HPV infection can lead to the progression of cervical cancer. Apart from this, APOBECs also give rise to the progression of HPV-induced cervical cancer. This essay will estimate the pathogenesis of HBV-associated hepatocellular carcinoma, such as HBV DNA integration, microRNA. Meanwhile the pathogenesis of HPV-related cervical cancer, such as inflammation, APOBEC3, will also be noted.

Keywords: Hepatocellular carcinoma, hepatitis B virus, cervical cancer, human papillomavirus, miRNA, inflammation, DNA integration, cytosine, APOBEC.

1. Introduction

Cancer, which can be explained as malignant tumours and neoplasms, is one of the main factors of human mortality and greatly obstructs the extension global human life span. Viruses can be seen as a significant factor in human cancers, as approximately 15 percent of cancers are accounting by viruses [1]. In low-income and lower-middle-income nations, cancer-causing infections are responsible for up to 30% of cancer cases. Among cancer-causing viruses, both DNA and RNA viruses are found to be able to lead to human cancer.

As for liver cancer, there are over 90% of liver cancer cases are induced by viruses, and the infection of hepatitis B virus (HBV) accounts for a majority of them. In order to remove HBV, the host immune response induces cytotoxic T-cell responses leading to continuous liver diseases, which contribute to hepatocellular carcinoma (HCC) occurrence. Besides, HBV DNA integrating into the human genome is an essential process of HCC development, as its genomic integration can lead to a series of mutations in HBV gene fractions, imposing a high risk of human genes' wrong expression. Moreover, miRNA function as a regulator of HCC development, since it can promote or suppress tumorigenesis. Some miRNAs mediate a variety of pathways and carcinogenic factors, while others are directly located in fragile regions. Besides, deregulation of cancers is also found to be controlled by miRNAs.

In terms of cervical cancer (CC), a large percentage of the cases are led by the human papillomavirus (HPV) infection. Long-term chronic inflammation caused by continuous HPV infection is one of the most noticeable causes of the progression of CC. Except for inflammation, the collective influence of a series of factors, such as cytokines, chemokines, enzymes, and specific types of miRNAs, also gives rise to the development of HPV-related CC. Furthermore, catalytic polypeptide-like apolipoprotein B mRNA editing enzymes (APOBECs) are also associated with

cervical cancer as their DNA-editing proteins can trigger tumor mutation and its activity is generated from cells infected by virus.

This essay will argue the pathogenesis of HBV-induced HCC, such as HBV DNA integration, and microRNA, as well as the pathogenesis of HPV-related cervical cancer, such as inflammation, APOBEC3.

2. HBV-induced Hepatocellular Carcinoma Pathogenesis

2.1. Role for HBV in the pathogenesis of Hepatocellular carcinoma

Among all the cancer cases, lung cancer is responsible for most cancer mortality, followed by liver cancer, which increases with a climbing death rate. Hepatocellular carcinoma (HCC) is the most common liver cancer. It is counted that over 90 percent of liver cancer cases have a viral etiology, and chronic HBV infection is the main factor of them [2]. Hepatitis B virus (HBV) is a noted hepatocarcinogen. Its genome gets into the nucleus and presumes a configuration with high stability, called covalently closed circular DNA, after attachment to the hepatocyte. HBV RNA is transcript according to the covalently closed circular DNA and following that this RNA is translated into HBV proteins. The HBV polymerase, which is responsible for reverse transcription and replication of HBV DNA, tends to cause mutations due to the deficiency of proofreading ability.

However, the exact process of the way that HBV leads to HCC is unidentified. Therefore, the proper plan to prevent and cure HCC induced by HBV is still not founded. To maximize the methods of inhibiting hepatocarcinogenesis, it is important to figure out the relevant molecular processes. The development of HBV-related HCC can be promoted by various factors, such as HBV genomic integration, inflammatory response, miRNA-induced HBV replication, and dysregulation of miRNAs.

HBV infection results in continuous liver diseases, which progress from the initial state to eventually HCC [3]. In order to eliminate HBV, the host immune response induces cytotoxic T-cell responses, which cause hepatic damage. HBV genomic integration into the genome of human liver cells also plays a significant part in hepatocarcinogenesis, as it induces apoptosis, regeneration, early senescence, and genomic instability.

2.1.1. Hepatitis B virus DNA integration in Chronic B Infections.

HBV can give rise to an acute infection or a chronic infection. Acute B infection happens, once an individual is exposed to HBV for the first time. The majority of infected people can remove HBV without showing any symptoms. However, chronic infection is diagnosed when individuals fail to remove such a virus after half of a year. The possibility of progressing chronic B infection from acute B infection is found to be highly associated with the age of the individual infected with HBV for the first time. Such probability has a negative relationship to the age of a person.

Chronic HBV infection highly increases the patients' possibility of getting the liver disease, such as HCC. HBV DNA integrating into the human genome exists in about 85-90 percent of HCC patients' tumor cells. There are also a series of finding indicating that HBV DNA integration is a critical factor in HCC development.

HBV infection is the main cause of the majority of immune-mediated continuous necroinflammation that injures the liver. Since HBV DNA integration tends to occur in the early stage of infection, its integration is closely related to the continual inflammatory response regulated by the immune system. This results in the oxidative damage of liver cells' DNA, which is characterized by the break of double-stranded DNA (dsDNA). This means that the degree to that dsDNA breaks into single strands is positively associated with how many HBV genomic integration activities occur in the affected liver. Therefore, this relationship is used to identify whether an individual is infected by HBV or not. Moreover, as HBV-infected liver cells are killed by cytotoxic T lymphocytes, liver cells need to regenerate. As a result of the persistent immune killing, HBV integration through clonal hepatocyte expansion is put at advantage. The reason for this is that HBV-specific cytotoxic T

lymphocytes tend to remove HBV-replicating cells, while the clonal proliferation of cells with HBV DNA has a higher possibility to be free from the immune killing [4].

2.1.2. Hepatitis B virus Integration in Acute B Infections.

Different from chronic B infections, researches in terms of HBV integration in acute B infections are scanty, because of the ethical issues about acquiring affected liver samples from individuals suffering from such disease. HBV integration is observed in individuals with fulminant hepatitis. Fulminant hepatitis is a disease that features abrupt and substantial damage to liver cells. This can result in multiorgan failure in people who do not have previous liver disease.

Even with only a small number of samples, it is found that patients with fulminant hepatitis displayed the existence of HBV genomic integrating with the human genome, showing that HBV DNA integrating might happen in the initial stage of infection and have no relationship with the duration of infection. Moreover, the serum, HBV DNA of fulminant hepatitis patients keeping HBV genomic integrating with the hepatocyte genome is negative, and HBV-replicating mediators are absent in the liver. This illustrates that cells with integrated viral sequences might avoid being destroyed by the acute immune response that targets the cells with HBV. Furthermore, in acute hepatitis, various events which prefer the clonal expansion of hepatocytes with HBV integration, happen during the short endurance of viral replication [4].

2.1.3. HBV Integration and Hepatocellular Carcinoma.

HBV DNA integrating into the human genome is highly related to HCC occurrence since it is found in a majority of HBV-induced HCC and often prior to the HCC occurrence.

However, the driving processes of HBV-induced HCC are unclear. HBV genomic integration can lead to mutations in HBV sequences since it is often incomplete. As a result, oncogenes and tumor suppressor genes express in an irregular way, which can result in the occurrence of HCC. Furthermore, in the fragile sites or other segments relevant to cancer in the human genome, a large number of integrated events are found. These events can lead to high genetic instability, leading to the alteration of the expression of oncogenes, tumor suppressor genes, and microRNAs, contributing to hepatocarcinogenesis [5]. Compared to non-tumor tissue, in HCC, the numbers of integration activities are greater and integration happens more frequently in coding sequences. Despite this finding, it is still unclear whether HBV integration into these genomic areas inducing HCC or tumor-derived cells having a greater possibility of integration is the exact mechanism of hepatocarcinogenesis.

2.2. Impact of microRNA on the expression of the host/HBV genome

2.2.1. microRNA: a regulator of gene expression.

There is only a small percentage of the human genome that are transcribed into mRNAs, while most of the genome is transcribed into non-coding RNAs. A large proportion of such RNAs are regulated in human diseases, such as cancer. Non-coding RNAs are composed of small non-coding RNAs and long non-coding RNAs. Small non-coding RNAs refer to the RNAs that have less than 200 nucleotides in length, and microRNA (miRNA) is one of them.

microRNAs function as regulators of gene expression, by influencing the stability of messenger RNAs (mRNAs), which means that miRNAs can adjust the mRNA expression level. Apart from this, by bounding with the untranslated region of particular mRNAs, miRNAs can suppress the translation. Moreover, in human tissues and body fluids, a large number of miRNAs exist. Therefore, miRNAs are commonly used as makers of human cancer and are the most well-studied small non-coding RNAs. Apart from the regulation of transcription, miRNA can also influence the production of itself. By connecting with long non-coding RNAs, miRNAs can promote inhibition of miRNA or the function of other factors competing with miRNA. Such interaction between miRNA is found to be related to the progression of cancer. For instance, miR-484 and miR503 can downregulate the expression of pri-miR-9. Once the regulation is interfered, the miR-9 expression will increase. As a result, the cell will present in an undifferentiated state, which is a characteristic of cancer cells.

2.2.2. Liver regeneration and MicroRNAs.

The liver has a particularly high regeneration ability. Liver cells in the rest of the liver amplify to recover the volume and activities of the liver, in cases of liver injury that might be caused by HBV infection. Liver regeneration is accurately regulated by a series of molecular mechanisms, among which miRNAs is important in the processes of cell proliferation. During liver regeneration, hepatocytes experience three stages: initiation, growth, and termination. In the initiation stage, miRNAs increase temporarily to stimulate cell proliferation, which offers negative feedback leading to the change of miRNA and promotion of cell proliferation [3]. In the growth stage, the quantity of several miRNAs also drops and gene expression in terms of cell cycle and proliferation were accordingly increased. These are corresponding to what Sartorius has stated that the number of miRNAs becomes transiently dysregulated when environmental conditions change temporarily [6]. It returns to order when homeostasis is restored.

2.2.3. Hepatitis B virus and MicroRNA.

miRNAs can inhibit or enhance HBV replication by regulating host gene expression. Therefore, miRNA is not only important for HBV replication but also influences the HCC progression [3]. miRNAs mediate HBV replication by directly targeting HBV transcripts. For instance, miR-199-3p attaches to the coding region of S protein, while miR-201 attaches to the pre-S region. And the two kinds of miRNAs are found to play a suppressive effect on HBV replication [7].

miR-122 down-regulation that is activated by HBV influences HBV amplification and might enhance HBV persistence and hepatocarcinogenesis. Compared with healthy liver cells, noticeable downregulation of miR-122 is found in HBV-infected liver cells. As an anti-sense inhibitor of miR-122 depletes miR-122, HBV replication is promoted. The reduced miR-122 expression level in HBV also results in the increase of HBV replication by upregulating cyclin G1 [8]. The miR-99 family also functions as an activator of HBV multiplication. Compared with the initial liver cells, miR-99 family expression is decreased in hepatoma cells. HBV replication is promoted via the transfection of the miR-99 family. However, miR-99family makes no difference in HBV transcription. This means that these miRNA impact HBV amplification after transcription. Besides, IGF-1R/Akt/mTOR pathway signaling is diminished in HCC cells through ectopic expression of the miR-99 family [9].

Table 1. MicroRNA Regulating HBV Replication

MicroRNA	Targets	Function	Reference
miR-199a-3p	VEGFA, VEGFR1-2, Matrix metalloproteinase 2 (MMP2), Hepatocyte growth factor (HGF), Yes 1 associated transcriptional regulator 1 (YAP1)	Suppress HBV replication	[7]
miR-201	pre-S region	suppression of HBV replication	[7]
miR-122	Cyclin G1	Promote HBV replication	[8]
miR-99 family (miR-99a, miR-99b, and miR-100)	attenuated IGF-1R/Akt/mTOR signaling pathway	Promote HBV DNA replication Promote HBV protein production	[9]

2.2.4. Dysregulation of miRNAs in HCC.

Genetic variation occurs in the regions encoding miRNAs that are related to dysfunction. Carcinogenesis transcription factors can inhibit the transcription of some miRNA, whereas other miRNAs are mediated by DNA methylation and histone modifications. Moreover, miRNA machining

genes are inhibited, which results in the decrease of mature miRNA synthesis, eventually inducing hepatocarcinogenesis and HCC development [3].

Moreover, many miRNAs are upregulated in HCC, functioning as a promoter of HCC progression. For example, compared with normal tissues, miR-10b expressed in HCC tissues is significantly enhanced. In vitro, Hepatoma cell viability, transference, and intrusion are promoted via miR-10b overexpression. In contrast, these properties are inhibited by the reducing miR-10b expression in HCC cells. Likewise, the growth of miR-92a expression occurs in liver cancer tissues, in contrast to matched tumor-contiguous tissues. By inducing amplification and cell cycle transformation, and inhibiting programmed cell death of hepatoma cells, upregulation of miR-92a contributes to the tumor growth. However, there are some miRNAs that serve as tumor suppressors in HCC via downregulation. For instance, miR-26a and miR-26b expression levels decreased in hepatoma cells, whereas in normal tissues, they are higher. By targeting ULK1, miR-26a/b suppresses autophagic flux at the beginning. This means that miR-26a/b induces apoptotic progression by suppressing autophagy [10].

3. Human Papillomavirus-associated Cervical Cancer Pathogenesis

3.1. Cervical cancer and HPV

The cervix is a tissue linking the vagina and uterus. It is lined by squamous epithelium that covers the ectocervix and mucus-secreting columnar epithelium. Squamocolumnar junction is the transition between the two groups of cells. The viral neoplastic transformation has the greatest risk to happen in this area. The majority of tumors that appear in the ectocervix are usually squamous cell carcinomas. This kind of cancer occupies nearly 75% of invasive cervical carcinoma cases. On the contrary, tumors occurring in the endocervix have a large possibility to be adenocarcinomas.

Cervical cancer is a commonly arising malignant tumor in female, and in low-income and lower-middle-income countries (LMICs), it is the second most common cancer among women. Many cervical cancer cases are induced by human papillomavirus (HPV) infection. In about 95% of malignant cervical lesions, HPV DNA is identified.

Most HPV infections are evanescent and can be removed automatically. In some cases, however, a continuous infection can give rise to the progression of the premalignant conditions of cervical intraepithelial neoplasia or adenocarcinoma in situ. Without proper therapy, it takes years to decades to develop from dysplasia to invasive carcinoma in most women. In 2018, there are more than 570000 newly detected cases of cervical cancer, and approximately 51 percent of these cases were found in women in LMICs. The unfairness of CC occurrence is caused by the unequal offer of human papillomavirus (HPV) vaccination, as HPV vaccination offered in LMICs accounts for under 30%, whereas in countries with high income, this figure reached 85% [11].

3.2. The Relationship between HPV and Cervical Cancer Inflammation

3.2.1. Inflammation and HPV-induced Cervical Cancer.

Inflammation is a protective mechanism induced by numerous factors, such as diseases and infections. Inflammation can be divided into acute inflammation and chronic inflammation. The acute one continues for only several days or weeks. In order to minimize further injury to the individuals and promote tissue recovery, it stops instantly once the infection is eliminated. On the contrary, chronic inflammation establishes when the inflammation lasts over months or even years. There are two main reasons for chronic inflammation. One is that the host fails to eliminate the original stimulus. The other is that the host is unable to solve the inflammation program.

Progressive changes in different kinds of inflammatory cells caused by chronic inflammation, greatly increase the risk of getting chronic diseases, such as cervical cancer. An excessive inflammatory response is related to at least 15 to 20 percent of the total cancer mortalities. Furthermore, continuous infection with HPV is proved to trigger chronic inflammation in the cervix

and raise the risk of cervical cancer. Tumor progression without growth factors can be induced by cancer-related inflammation. This tumor can replicate illimitably, which means it can get rid of apoptosis and resist developmental suppression.

Long-term chronic inflammation caused by continuous HPV infection is an essential factor for the CC progression. It is a complicated process related to the impact of a series of factors: enzymes, reactive oxygen and nitrogen species, cytokines, and particular kinds of miRNAs. The shared influence of these factors contributes to CC development by making variations during expansion, decrepitude, cell death, and inducing mutation and DNA methylation [12].

3.2.2. Cytokines: A Cause of Inflammation in HPV-mediated CC.

Cytokines are the secreted regulators of cell-cell communication. It is one of the factors that contribute to the progression of HPV-induced CC, as its expression by tumor cells can promote tumor growth and development by attracting inflammatory cells. There are a variety of types of cytokines (IL-1, IL-6, IL-8, IL-18, TNF- α , etc.) that contribute to CC-related inflammation caused by the infection of HPV. This can eventually promote CC progression.

Tumor necrosis factor α (TNF- α), released by energized macrophages and monocytes, has a significant anticarcinogenic and procardiogenic function. It is an essential pro-inflammatory cytokine, as it can promote the activation and proliferation of naïve and effector T cells [13]. Besides, interleukin-12 (IL-12), an inflammation-promotion cytokine, resists tumors through the promotion of cytotoxic T cell responses and T-helper lymphocytes type 1 adaptive immunity. The different types of IL12 genes are likely to promote the risk of CC [14]. Furthermore, interleukin-6 (IL-6), another cytokine, influences the persistent HPV infection and the progression of CC. It promotes chronic inflammation, by activating the signal transducer and activator of transcription 3 (STAT3) oncogene, as abnormal STAT3 signaling contributes to tumor cell development, intrusion, metastasis, and inflammation [15]. Moreover, interleukin-8 (IL-8) is highly related to inflammation. IL-8 is negatively modulated by CCAR2 and its increase can trigger inflammation and development of CC. In CCAR2-deficient cells, the expression of IL-8 is upregulated by activating the transcription factor AP-1. This is also related to a shorter survival of CC patients [16].

Table 2. The influence of cytokines in cervical cancer inflammation

Cytokine	Effect on inflammatory	Mechanism	reference
IL-6	Induced	Activating STAT3 oncogene	[15]
IL-8	Induced	Activating AP-1	[16]
IL-12	Induced	Promoting cytotoxic T cell responses and T-helper lymphocytes type 1 adaptive immunity	[14]
TNF- α	Induced	promoting the activation and proliferation of naïve and effector T cells	[13]

3.3. The Role and Function of APOBEC3 in HPV-associated Cervical Cancer

3.3.1. APOBECs: Function as endogenous mutators.

Most somatic mutations that occur in a cell are biologically neutral, which means they will not trigger cancer progression. In contrast, some mutations can induce tumor adaptation, escape from immunosurveillance, and provide treatment resistance. A series of exogenous factors, such as ultraviolet rays, ionizing radiation, hydroxylamine, and nitrite chemicals, can result in carcinogenic mutation. Apart from these factors, APOBEC activation is an endogenous mutational factor.

APOBEC function as endogenous mutators, promoting the development of CC. For instance, missense mutations in APOBEC3B, APOBEC3F, and APOBEC3G are discovered in cervical cancers, exacerbating the mutational burden. These abnormal expressions of APOBEC can give rise to C > T mutations in tumour suppressor genes. Besides, mutations in APOBEC also arise in non-coding regions, inducing the expression of oncogenic driver genes. Additionally, mutations promoted by

APOBEC increase the differences in the genome that can raise mutations resulting in drug resistance, and immunosurveillance escape [17].

3.3.2. HPV-related APOBEC3 expression.

APOBECs usually act as a part of the immune system, and APOBEC3 genes can resist both exogenous and endogenous retroviruses. Once cells are infected with HPV, APOBEC expression is activated. They induce the inflammatory response, in which cytokines promote the production of APOBEC proteins. Consequently, APOBEC3A, APOBEC3B, and APOBEC3H expressing levels increase, which promotes off-target injury of cellular DNA. The expression of APOBEC3B is upregulated due to the decline of p53 activity. Meanwhile, the mutagenic ability of normal and cancer cells is enhanced [17]. Moreover, the interaction between APOBEC3A and HPV16 E7 and CUL2 indicates that the formation of the E7-CUL2 complex can mediate the expression of APOBEC3A with unharmed enzyme activity, and APOBEC3A expression is deregulated by HPV E7. Besides, APOBEC3 expression can cause host nucleotide changes. This is corresponding to the finding that APOBEC3A expression is upregulated when HPV sequence integration occurs. Furthermore, HPV16 infections in somatic cells can lead to mutations caused by APOBEC3. However, the infections have a large possibility of being removed. This means that mutations led by APOBEC3 in somatic cells contribute to the removal of HPV.

4. Conclusion

Hepatocellular carcinoma (HCC) and cervical cancer (CC) are two common human cancers induced by viruses. Chronic hepatitis B infection induces HCC through various mechanisms. HBV genomic integration plays a critical part in HCC development. In chronic B infections, HBV DNA integration breaks liver cells' double-stranded DNA, and the clonal HBV DNA-integrated hepatocytes can survive cytotoxic T-cell responses. In acute B infection, HBV DNA integration takes place in the initial stage of the infection, and the integration of HBV sequences can assist infected hepatocytes to escape from immune damage. miRNAs also regulate the liver regeneration led by HBV infection. HBV replication can be mediated by many miRNAs, such as HBV-miR-3, miR-199-3p, miR-122, and miR-99 family, through assorted mechanisms.

As for cervical cancer (CC), most cases of them are caused by human papillomavirus (HPV) infection. Chronic inflammation raised by continuous HPV infection is one factor in the occurrence of CC. A variety of types of cytokines are related to CC-related inflammation. Furthermore, the expression of APOBECs is stimulated by a viral infection and is highly linked to HPV-induced cervical cancer. APOBEC activity is generated from cells infected by the virus, while its DNA-editing proteins can also trigger tumor mutation.

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