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Virus Association with Gastric Inflammation and Cancer: An Updated Overview

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ABSTRACT

Enteric viruses are the most common cause of gastroenteritis or infectious diarrhea worldwide. The genera *Rotavirus* (RoV), astrovirus (AstV), and *Norovirus* (NoV) are predominant viruses causing acute diarrhea in children and inflammation in the gastrointestinal tract. Apart from the enteric viruses, human papillomavirus (HPV), John Cunningham human polyomavirus (JCV), and human immunodeficiency viruses (HIV) are also significantly linked with gastrointestinal inflammation and gastric neoplasia. Moreover, recent studies demonstrated the direct induction of acute gut inflammation by *Norovirus* infection. Though mild inflammation occurs with astroviral infection, pro-inflammatory signaling pathways are also activated. Epstein-Barr virus (EBV), a significant tumor-causing pathogenic gammaherpesvirus, is also associated with diarrheal disease due to increased local and systemic inflammation. The association of EBV infection with ulcer colitis (UD), Crohn's disease (CD), inflammatory bowel syndrome (IBD), peptic ulcers, and chronic fatigue syndrome (CFS) indicates its potentiality for enhancing gut inflammation and gastric cancers. In the current scenario, extensive research is a prerequisite to understanding and achieving in-depth knowledge of the molecular mechanisms involved with enteric and tumor viral antigen-induced gut inflammation and cancer progression. This review represents new insights into the current research linking enteric and other pathogenic viruses as a trigger for gut inflammation and gastrointestinal malignancies.

INTRODUCTION

The most common cause of gastroenteritis worldwide is enteric virus infection [1]. There are several families of enteric viruses like family: *Adenoviridae* (Genus: *Mastadenovirus*, Species: *Human mastadenovirus A*), Family: *Astroviridae* (Genus: *Mamastrovirus*, Species: *Mamastrovirus 1*), Family: *Sedoreoviridae* (Genus: *Rotavirus*, Species: *Rotavirus A*), Family: *Caliciviridae* (Genus: *Norovirus*, Species: *Norwalk virus*) [2]. These viruses are well known for causing gastric inflammation in humans [3]. Several techniques were adopted to identify enteric and systemic viral infection by biosensing or nanotechnological approaches [3–6]. NoV, AstV, and RoV are associated with gut inflammation. These viruses are generally transmitted by the fecal-oral route and show strong tissue tropism to small intestinal epithelial cells, causing diarrhea [7]. Recent studies demonstrated that some of these enteric viruses, along with gammaherpesvirus members, EBV, may also play an essential role in the induction of gut inflammation leading to cancer [8]. In this comprehensive review, we have thoroughly discussed critical studies and recent scientific updates that link the pathological functions of viruses associated with gastric inflammation and cancer. The review primarily argues the case of the tumor virus EBV as a potential candidate in triggering gut inflammation-associated pathogenesis in connection with cancer progression.

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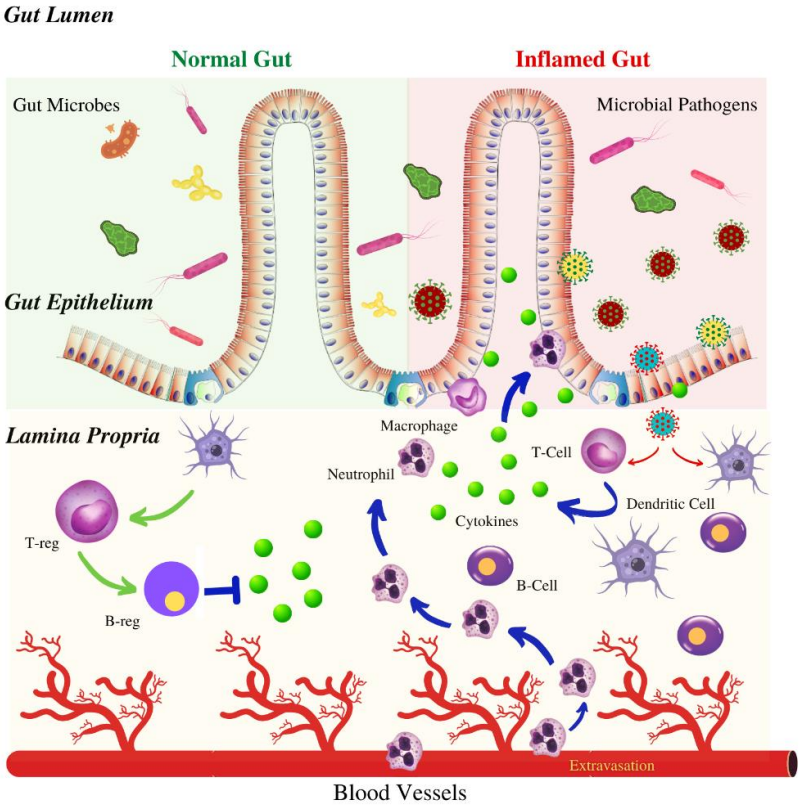

Fig. 1. Influence of microbial pathogens on inducing gut inflammation.

Inflammation is a complex physiological response of the body tissue towards various stimuli [9]. The inflammation of the gastrointestinal tract or alimentary canal is defined as 'gut

inflammation' manifested in gastroenteritis, inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC). Interestingly, CD and UC are the two clinical categories of IBD and are characterized as 'intestinal inflammation' and 'epithelial injury', respectively [10]. CD, which frequently affects the terminal ileum, is considered a transmural disease with deep ulceration spread from mouth to anus, whereas UC causes continuous and superficial inflammation involving the rectum and cecum. Gut inflammation generally involves numerous factors that disturb the normal functioning of the gut or the populations of normal gut microbiota (Fig. 1), a process that is also known as "gut dysbiosis" [11]. Several pathogens, such as bacteria (*Clostridium difficile*, *Shigella* sp.) [12], and viruses, including NoV and RoV, are directly involved in this pathogenic process [13]. Also, environmental factors, including stress, diet, drugs, and smoking, may trigger inflammation. Moreover, genetic susceptibility, Th1 and Th17 immune responses, and deregulated innate immune responses are the main factors for inducing gut inflammation [14]. Several studies have tried to delineate the general molecular mechanisms involved in gut inflammation, including infection-mediated or injury-mediated gut dysfunction, which causes activation of toll-like receptor (TLR) and NOD-like receptor (NLR) signaling leading to activation of NF-κB and apoptosis-inducing caspases [15]. Consequently, the initiation of the caspase cascade induces inflammatory reactions. These cytokines activate the immune cells, including DCs and macrophages in lamina propria, causing a large production of pro-inflammatory cytokines, prostaglandins, leukotrienes, and histamines leading to angiogenesis, hyper-vascularisation, increased microbicidal activities, and suppression of regulatory macrophages [16]. Previous studies reported that chemokines and cytokines produced during the inflammatory response could assist in recruiting effector

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cells (mainly monocyte and neutrophil populations) at the site of injury or pathogenic infection. Moreover, APCs (antigen-presenting cells) migrate to lymphoid tissue and activate naive T-cells, promoting large production of pro-inflammatory cytokines (INF-γ, TNF-α, and ILs) and aiding in the process of cell differentiation [17]. During this time, if the gut inflammation is not cured with anti-inflammatory therapeutics, chronic inflammation can develop and damage the gut epithelium, and consequently, fibrosis, fistulas, and gastric malignancies will appear [18].

Association of enteric viruses with gut inflammation

a. Norovirus

Norwalk virus, or winter vomiting virus, belongs to the *Caliciviridae* family. It is the prime cause of human viral gastroenteritis worldwide [19].

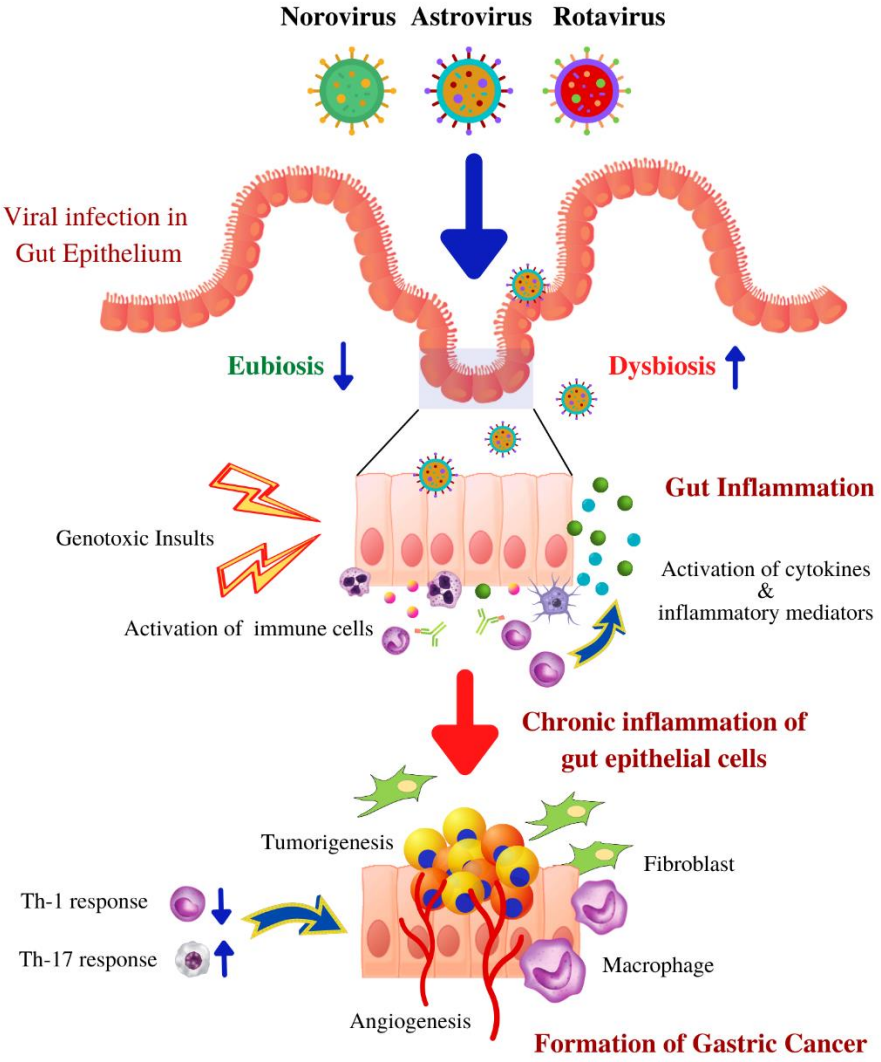

Fig. 2. The imbalance between eubyosis and dysbiosis causes gastric inflammation and viral infection.

NoV comprises six genogroups (GI-GVI). In particular, GI, GII, and GIV geneogroups cause infection in human. Transmission of this highly contagious virus through the fecal-oral route generally affects adults and children across the globe. Nausea, abdominal pain, vomiting, and non-bloody diarrhea are the symptoms of this infection. In severe cases, it may lead to copious watery diarrhea followed by dehydration, occasionally leading to death. The virus incubation period in the human host is 24-48 hours, while the associated symptoms last about 12-60

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hours. Virus elimination can continue for up to 2 weeks in asymptomatic and symptomatic infections. In infants and young children, NoV-induced enteric disease can be much more severe and long-lasting [20]. Very few patients with NoV infection require medical care, dehydration-related treatment, or hospitalization in extreme cases. Asymptomatic patients transmit the disease at a level lower than symptomatic patients. Interestingly, illness can be more severe in hospitalized patients than in otherwise healthy individuals [21].

The overall knowledge about the pathogenesis of NoV infection is relatively limited due to the lack of an *in-vitro* cell culture system to grow the virus [22]. With the development of medical research, we can reveal the significant pathogenic functions of NoV in the human intestine. NoV likely hampers the cellular processes crucial for absorption and barrier functional maintenance [23]. Decreased villi length, change in chloride (Cl) ion secretion, increased sodium-glucose transporter (SGLT1) activity, decrease in transepithelial resistance along with deduction in the level of occludin, claudins 4 and 5, and reduced activity of enterocytes enzymes, including alkaline phosphatase, sucrase, trehalase, and possibly lactase happen during NoV infection [13]. Still, the underlying mechanism is not yet precisely known. Interestingly, a new human NoV strain emerges every 2 to 3 years, partly due to mutations in the viral capsid that restrains the conformation of the antibody binding loop in the capsid, thus making it incompetent to be bound by antibodies and allowing it to dodge the antibody neutralization and herd immunity [24].

b. Astrovirus

Acute gastroenteritis is a common disease worldwide. Viruses have been suspected as the potential causes of gastroenteritis since the 1940s; however, enteric viruses were identified much later. Notably, acute viral gastroenteritis is more frequent than bacterial and intestinal parasite-induced diarrhea [25]. AstV is now recognized as a cause of gastroenteritis in children and adults.

AstVs are positive-sense single-stranded RNA viruses discovered in 1975 and associated with gastroenteritis outbreaks in infants [26]. These viruses were first recognized by electron microscopic examination of diarrheal stool samples from infants. To describe the shape of small round viruses with a characteristic star-like appearance, Madeley and Cosgrove (1975) used the term 'astrovirus' derived from the ancient Greek word `Astron', which means star. Members of the *Astroviridae* family have been described to cause diarrhea and enteritis in several mammalian and avian host species, and thus they are divided into two genera *Mamastrovirus* (mammalian astrovirus) and *Avastrovirus* (avian astrovirus) [27]. Based on molecular techniques developed in the past two decades, human astroviruses (HAstv) were identified as one of the leading causes of pediatric gastroenteritis. Eight serotypes of HAstv are currently known; among them, type-I is the most prevalent worldwide [1].

Little data on AstV pathogenesis or the host factors involved in virus clearance and disease resolution is available. Of the non-human AstVs, only bovine, ovine, and turkey AstVs have been studied experimentally [28]. Most children are infected with human AstV and develop antibodies very young, which might protect them from future viral infections. The elderly and immune-compromised people are at a higher risk of infection [29]. Diarrhea caused by AstV infection is mild and generally linked with fever, vomiting, anorexia, watery stool, and abdominal pain. While this virus's mean incubation period is 4-5 days, the symptoms usually last for 2-3 days. Infections caused by AstV are usually less severe than RoV or NoV infections, and it also resolves spontaneously. The prevalence of AstV as asymptomatic pathogens remains to be investigated, but studies have shown that classic human AstV infection can spread systemically and cause severe lethal infections in highly immuno-compromised children [30]. The AstV-infected intestinal tissues show minor histopathological changes and inflammation, suggesting that diarrhea caused by the infection is not directly immune-mediated and the loss of fluids and electrolytes may occur due to inhibition of the usual absorptive functions of the intestine, activation of secretory processes, or loss of intestinal epithelial barrier permeability [28]. Studies on Caco-2 cells infected with HAstV have shown F-actin rearrangements alongside cell barrier disruption and occludin redistribution. The effect of HAstV infection on epithelial barrier permeability occurs independently of viral replication, suggesting that the capsid protein of HAstV may act as an enterotoxin [31]. However, the study did not report a significant amount of cell death at the time of loss of barrier function upon HAstV infection, suggesting that the HAstV-induced enterocyte death may occur at a late stage of the infection. Other studies using Caco-2 cell lines have shown that HAstV infection induces cell death by apoptosis [32]. Based on this information, it can be concluded that the virions released from infected cells may occur through a non-lytic mechanism [33].

c. Rotavirus

Rotaviruses are responsible for gastrointestinal diseases, primarily in children under five [34]. Diarrhea is the primary clinical manifestation of RoV infection in infants and young children. It may lead to life-threatening diarrheal disease among infants and young children and accounts for 82% of deaths among children in the poorest countries. This virus is a non-enveloped, complex, triple-layered capsid structure surrounding a genome composed of eleven segments of double-stranded RNA and belongs to the order *Reoviriales*. The RoV genus is divided into five serological groups (A-E), out of which groups A-C infect humans, and all groups infect animals [35]. The VP7 and VP4 proteins of the RoV that form the capsid and the spikes induce neutralizing antibody responses

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and, thus, are the basis of a binary classification system for viral serotypes [36]. Human RoV were discovered a decade after visualizing the first animal RoVs [37].

RoV diarrhea is attributed to several different mechanisms, including malabsorption secondary to enterocyte destruction, a virus-encoded toxin, stimulation of the enteric nervous system (ENS), and villus ischemia [34]. Rotaviruses are responsible for around 6% of acute gastroenteritis (AGE) episodes and 20% of AGE-related deaths among children in developing countries [38]. Type A rotavirus (RVA) is the frequent etiologic agent of gastroenteritis in children under five years old [39]. Each year RVA causes around 100 million cases in children under five years old, of which around 3.5-6 hundred thousand children die [40]. Most studies on the role of RoV as an etiologic cause of gastroenteritis have revealed that rotavirus-associated illness (Figure 2) tends to be more severe than gastroenteritis caused by other enteric pathogens [41].

Of note, RoV infection can result in both asymptomatic and symptomatic infections. The clinical outcome of rotaviral infection is affected by not only viral factors but also host factors (age being one of the most prominent host factors). The incubation period for RoV diarrhea is usually less than 48 hours, and clinical manifestation depends on whether it is the first infection or reinfection. To understand rotavirus-mediated gastric inflammation, we need to comprehend the intestinal damage caused by rotavirus infection. The enterocytes lining the small intestine are divided into villus enterocytes and crypt cells. RoV primarily infects the intestinal villus enterocytes while the crypt cells get spared. Binding to the enterocytes is mainly mediated by its sequential interaction with a series of sialic acid-containing and non-sialylated receptor molecules [42].

Experiments with specific agents that block the function of ENS showed that RoV infection induces epithelial secretion of fluids via stimulation of the ENS [43]. Moreover, the pathogenesis of the disease is multifactorial, and diarrhea is considered malabsorptive due to the virus-mediated destruction of the absorptive enterocytes. The virus-induced downregulation of the absorptive enzyme's expression levels and functional changes in the tight junctions between the enterocytes lead to paracellular leakage. A secretory component of the RoV diarrhea was suggested based on the elevated levels of prostaglandin E2 in the infected gut (probably due to the activation of the enteric nervous system) and the effects of NSP4 (the first described virus-encoded enterotoxin). Studies on animal models and cultured cells have shown that rotavirus-induced diarrhea results partly because of the activation of cellular Cl^- channels leading to increased secretion of Cl^- ions and, consequently, water [37].

Chronic inflammation was known as a crucial factor for the cancer progression and pathogenesis. [44]. Today, the causal relationship between inflammation, innate immunity, and cancer is more widely accepted in humans and animals [45].

However, to understand the role of inflammation in cancer development, it is crucial to understand how inflammation contributes to physiological and pathological processes such as wound healing and infection [46]. It is assumed that many malignancies arise from areas of infection and inflammation simply as part of the normal host response (Fig. 3). Various studies have given data and information about how the inflammations caused by enteric viruses may lead to cancer (Table 1). Here, we provide more examples of links between enteric viruses and cancer.

1. The link between hepatitis C virus (HCV) and gut inflammation

The Hepatitis C virus (HCV) virus was identified in 1989 (Family: *Flaviviridae*, Genus: *Hepacivirus*, Species: *Hepacivirus A*) [2]. The viral genome consists of positive-sense single-stranded RNA about 9.7 Kb long. HCV is mainly a bloodborne virus affecting liver cells [47]. HCV is the primary cause of acute and chronic hepatitis, eventually leading to hepatocellular carcinoma, which currently affects about 170 million people worldwide [48]. More than 200 million people live with HCV infection, and about 3.3% of the world's population suffers from hepatitis-associated complications. HAV, HEV and HFV are indeed enteric viruses, whereas HBV, HCV, HDV, and HGV are parenterally transmitted viruses [49]. It is interesting to explore that although HCV is responsible for liver cell infection and damage, the virus is indirectly associated with gastric inflammation and cancer progression [50].

The molecular mechanism for how HCV infects and replicates in targeted cells while evading the immune system is still not clearly understood [51]. However, HCV-associated inflammation, progression of cirrhosis, and related complications have been associated with systemic pro-inflammatory milieu abetted by microbial dysbiosis of the gut [52], even though it is associated with cancer cell migration and metastasis [53,54]. Studies have shown that despite sustained virological response (SVR), there is no significant change in gut dysbiosis and related systemic inflammation. Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory conditions of the gastrointestinal tract collectively referred to as inflammatory bowel diseases (IBD) [55]. It is a chronic disease affecting around 1 million people in the USA and about 2.5 million in Europe. It is commonly caused due to convergence of genetic, environmental, and microbial factors triggering an aberrant immune response and leading to intestinal inflammation [56]. The gut and liver are the two crucial organs in nutrient absorption and metabolism. A healthy gut can mediate optimal interaction and functioning of the gut-liver axis, which is further critical in preventing systemic inflammation [57]. Studies of patients with IBD have shown that even when

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the inflammation is in remission, the altered enteric nerves, and abnormal microbiota can generate IBD-like symptoms [58].

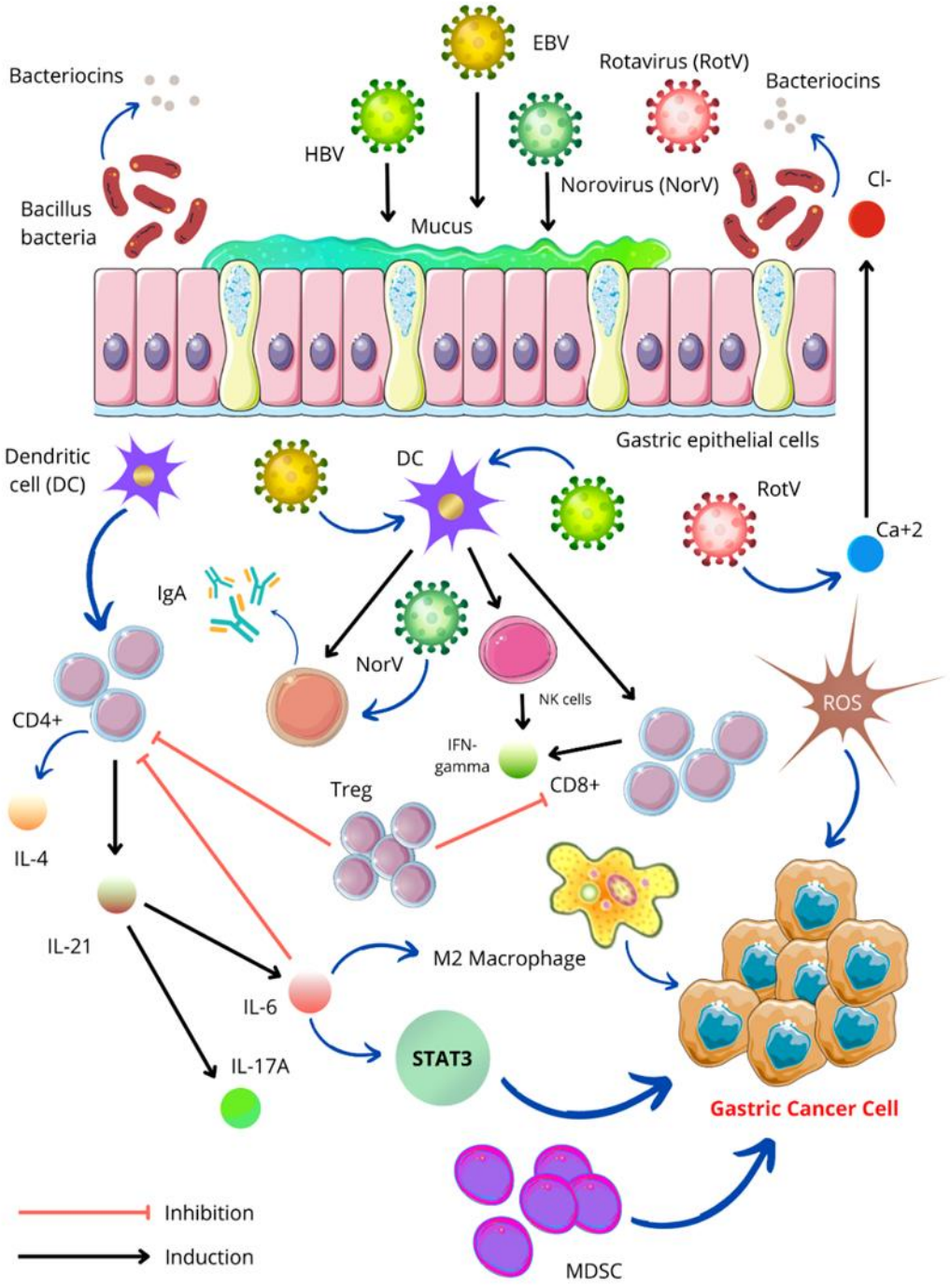

Fig. 3. Enteric and tumor virus infection induce the inflammatory response pathways towards gastric cancer progression.

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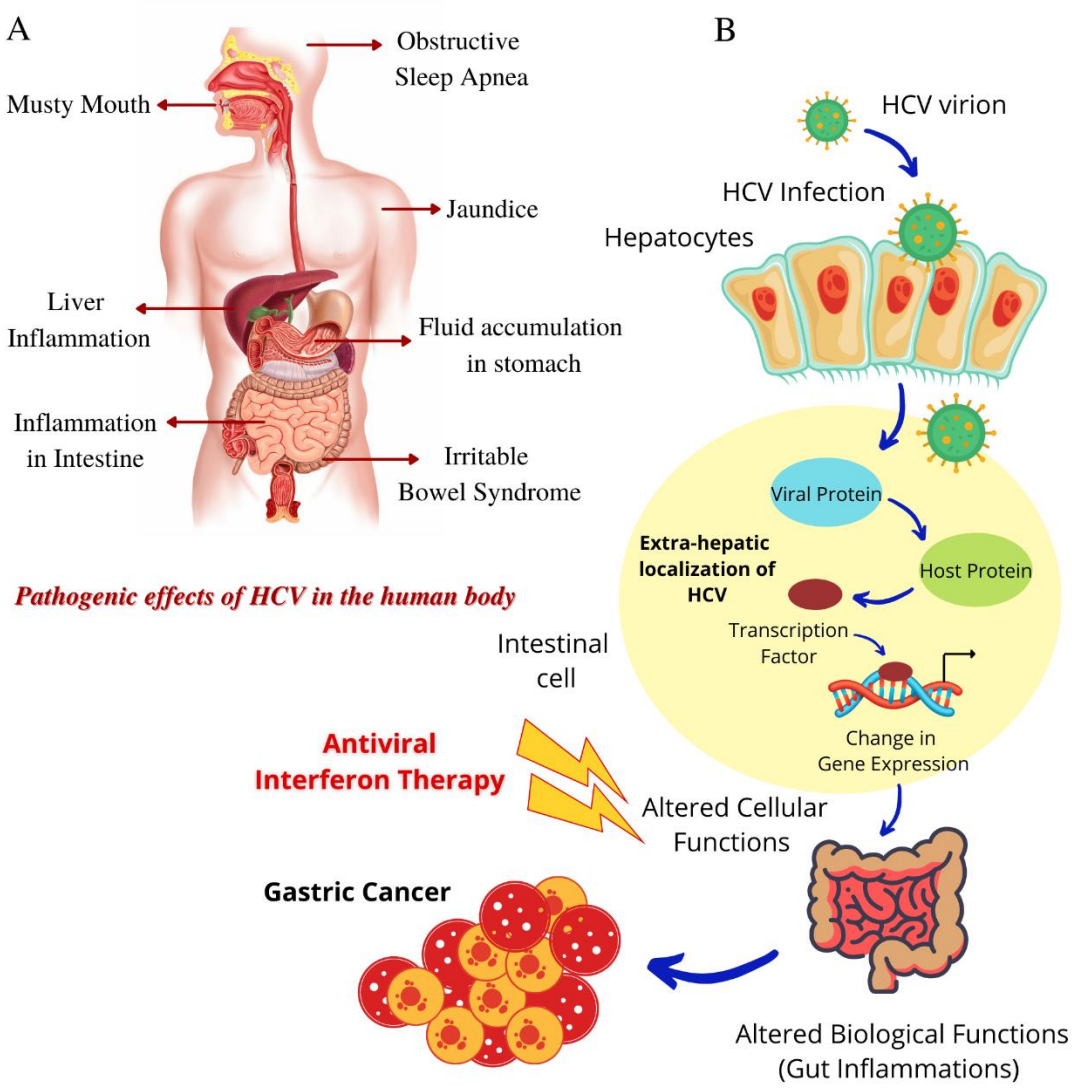

Fig. 4. Pathogenic effects of HCV in gastric inflammation and cancer.

Moreover, any damage to the gut barrier could increase intestinal permeability, followed by bacteria translocation and LPS accumulation [59]. Increased intestinal permeability, bacterial overgrowth, or impaired clearance of microbial products by Kupffer cells may increase the translocation of gut microbiota. Microbiota and its components can pass through the gut barrier, enter the portal circulation, and then be transported to the liver [60]. Within the liver, Kupffer cells, hepatic stellate cells (HSCs), and hepatocytes express TLR4 and thus might be a target for bacterial LPS, which is an essential step in the development and progression of hepatitis [61].

Of note, patients with inflammatory bowel disease (IBD) are at an increased risk of HBV and HCV infection due to the elevated frequency of endoscopic, surgical, and transfusion procedures needed to control the disease effectively [62]. Moreover, immunosuppressive therapies and immune-modulatory action with the IFN therapy for HCV infection is a crucial concern as it can worsen the clinical course of IBD and potentially lead to a more rapid progression of fibrosis in HCV-infected patients. Another aspect underlying the reluctance to treat HCV is the potential for serious adverse events, such as pancytopenia or hepatotoxicity, resulting from the interaction between HCV and IBD-specific agents [63]. Although the prevalence has decreased in recent years, the risk of viral hepatitis C has long increased in patients with IBD, even gastric cancer (Fig. 4). Blood transfusion and surgery have been identified as the two main risk factors. However, recent epidemiologic studies indicated that HCV prevalence in IBD patients is similar to or even lower than in the general population [64].

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2. Role of Human papilloma-virus (HPV) in gastric inflammation and cancers

The link between human papillomavirus (HPV) and cancers was well established (Family: *Pleolipoviridae*, Genus: *Alphapleolipovirus*, Species: *Alphapleolipovirus HHPV1*) [2, 65]. The progression of cancers could be related to HPV-induced chronic inflammations and the development of mutations that result in repeated tissue damage [66]. Earlier studies have established the vital role of HPV oncogenes in upregulating pro-inflammatory cytokine genes during HPV infections [67]. Interestingly, such an event expedites the inflammation process. Research has also demonstrated the role of microRNAs and aging in increasing the levels of pro-inflammatory cytokines, which are crucial to accelerating the HPV-induced inflammation in the cervix and, consequently, the onset of malignancies [68]. In addition to patients with Crohn's disease (CD), inflammatory bowel diseases (IBD), and ulcerative colitis (UC) at higher risk of HPV infection, a range of HPV infections can be located in different regions of the gastrointestinal tract as well as the stomach of gastric cancer patients [69]. Possibly the immunosuppression and alterations in cancer patients' mucosal immunity during the chemotherapy for gastric cancers make them susceptible to HPV infections [70].

Interestingly, several studies proved that the intricate association for HPV-related malignancies is significantly higher among individuals with IBD symptoms [71]. Although the effect of inflammation on cancer progression is well established [72], further analysis of the clinical and epidemiological data showed that 15%-20% of the human body's solid tumors might result from chronic inflammation [73]. Of note, recent studies showed that HPV infection in diseased vs. normal tissues is significantly correlated with chronic inflammation and linked with the progression of pre-malignant lesions of the oropharyngeal region, strongly suggesting an important role of chronic inflammation in HPV-associated oropharyngeal cancers [74]. Delineating the vital roles of HPV E6 and E7 proteins in the inflammatory pathways for progressing cervical cancers [75] indicated that after HPV infection, E6/E7-mediated enhancement of COX-2 transcription activities induces the EGFR/Ras/MAP kinase pathway, as well as PI3K/Akt signaling axis [76]. Both of these signaling axes increase the binding affinity of activator protein-1 (AP-1) with the cyclic AMP (cAMP) responsive element (CRE) of the COX-2 promoter. CRE activation induces a set of corepressor or coactivator genes to modulate inflammatory pathways. Moreover, while E6 and E7 increase vascular endothelial growth factor (VEGF) expression through hypoxia-inducible factor-1 alpha (HIF-1a), viral antigen E5 facilitates the overexpression of VEGF, which sequentially activates MAPK/PI3K–Akt signaling to enhance inflammatory signaling [77].

3. Contribution of John Cunningham virus (JCV) in the progression of inflammation and malignancies

Virologists have classified the John Cunningham virus (JCV) as a neurotropic polyomavirus (Family: *Polyomaviridae*, Genus: *Betapolyomavirus*, Species: *Betapolyomavirus secuhominis*), a significant contributor to progressive multifocal leukoencephalopathy (PML) in HIV patients [2, 78], a causal factor for tumor progression in the central nervous system (CNS) [79]. Recently, the crucial role of JCV in gastrointestinal carcinoma and colorectal cancers was discovered [80]. JCV infects children during their early childhood, and the antibodies against JCV infection increase with age and reach 50% within a few years (within 9-11 years) [81]. The site of infection was identified in the gastrointestinal tract, but infection could also be located in the respiratory tract indicating the possibility of an oral-fecal transmission route for the virus [82]. JCV infection is asymptomatic initially, but the virus may adopt a persistent infection throughout life [83]. As previously discussed, significant JCV infection can occur in the CNS, which can be responsible for initiating encephalitis [84]. Immunomodulatory treatments, e.g., immune reconstitution, can destroy the virus-infected neurons but manifest clinical exacerbation like PML with immune reconstitution inflammatory syndrome or PML–IRIS [85].

JCV expresses viral antigens during infections. From the pathophysiological point of view, antibodies used to detect infection mainly focus against large 'T-antigen Simian Virus 40' (SV40), which shows cross-reactivity with JCV [86]. Different capsid proteins are also expressed, which can be identified using specific antibodies. JCV T-antigen (T-Ag) was found to be potential enough to transform mammalian cells by binding and deactivating two major tumor suppressors, proteins P53 and pRb, which are critically involved in cell-cycle progression as well as apoptosis [87]. Approximately 50% of all human cancers are identified with loss of p53 functions [88]. The studies indicated that T-Ag-mediated inhibition of p53 causes cell cycle deregulation and apoptotic cell death inhibition leading to the onset of human malignancies [89]. On the other hand, impediment of the pRb protein family members by T-Ag can result in the dysregulation of the E2F transcription factor and the expression patterns of E2F downstream effectors, namely, c-fos and c-myc. As a result of the events mentioned earlier, abnormal cell proliferation can be observed [90].

4. Human immunodeficiency virus (HIV) Role in gastric inflammation and cancers

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Several studies have demonstrated the typical association of human immunodeficiency virus (HIV) (Family: *Retroviridae*, Subfamily: *Orthoretrovirinae*, Genus: *Lentivirus*, Species: *Human immunodeficiency virus 1*) [2] infections with upper gastrointestinal disorders, ranging from dysphagia to odynophagia [91]. Most clinical symptoms in AIDS patients are identified as a consequence of secondary opportunistic infections due to the patient's immunosuppressed and intensity [92]. A study showed that the alterations in the gut microbiome could cause chronic inflammations in HIV-infected individuals [93]. The gut microbiome environment is further changed during chronic HIV infection; as a result, *Prevotella* sp. (gut flora bacterial species) becomes a causal factor for gut inflammation [94]. During inflammation, upregulated pro-inflammatory cytokines are not capable enough to initiate sepsis or systemic inflammatory response syndrome (SIRS) but can induce chronic inflammation in the gut even with effective antiretroviral therapy (ART) [95]. Systemic inflammation during HIV infection is strongly related to the upregulation of pro-inflammatory cytokines (mainly TNFα and IL-6) [96]. In the case of acute infections, an increased level of IL-1β also occurs, which functions as pyrogen [97]. Several reports have suggested that elevated inflammation may turn into a cytokine storm, although not as severe as sepsis [98]. Elevated levels of different serum proteins, including C-reactive protein (CRP), coagulation factors, and D-dimer, have also been detected in HIV-infected patients [99]. In the context of immune cell activation, augmented T-cell response was connected with higher levels of TNFα, soluble CD14, IL-18, IL-15, IL-6, IL-12p70, and CD163 in plasma, signifying an inflammatory state found during HIV infection. Of note, HIV-mediated immune dysfunction and coagulation may eventually perform as a higher risk factor for different epithelial cancers including colorectal, breast, prostate cancers, and inflammatory response was already known to be an important etiologic factor [100].

5. Epstein Barr Virus (EBV), the potential instigator candidate for gut inflammation

Epstein Barr Virus (EBV), a ubiquitous oncogenic γ-human herpesvirus (Family: *Herpesviridae*, Subfamily: *Gammaherpesvirinae*, Genus: *Lymphocryptovirus*, Species: *Human gammaherpesvirus 4*) [2], is associated with both lymphoid and epithelial tumors that include Burkitt's lymphoma, nasopharyngeal carcinoma (EBV), Hodgkin disease, a subset of gastric carcinoma (GC), along with the development of lymphomas in immunosuppressed patients [101–104]. EBV infection is generally involved in gastrointestinal lymphomas characterized by the monoclonal proliferation of cancer cells with the expression of latent EBV antigens [105]. Although the direct role of EBV as a gastroenteritis instigator was not adequately investigated earlier, over the past few years, several studies have significantly related EBV with gastric inflammation, increased gastric acids, or disorders like inflammatory bowel disorder (IBD), peptic ulcers, and colitis [106]. EBV is associated with 15-20% of chronic fatigue syndrome (CFS) cases [107].

Table. 1 Virus relationship with gastrointestinal inflammation and malignancies.

Sl No.	Virus name	Role in cancer/gastric inflammation	References
1.	Norovirus (NoV)	Norovirus (NoV) was considered the leading cause of viral-linked diarrhea in cancer patients with chronic gastrointestinal inflammation.	[114]
2.	Rotavirus (RoV)	Rotavirus infection was demonstrated as clinically significant but preventable in pediatric cancer patients.	[115]
3.	Astrovirus (AstV)	Astrovirus infection was found responsible for causing chronic gastrointestinal inflammation, but its relation with cancer is not proven yet.	[116]
4.	Hepatitis C Virus (HCV)	Chronic Hepatitis Virus infections were associated with Gastric Cancer progression and inflammation.	[117]
5.	Human papilloma virus (HPV)	The human papillomavirus potency in the pathogenesis and progression of gastric cancer.	[118]
6.	JC Polyomavirus (JCV)	JC Polyomavirus antigen was detected in gastric carcinoma samples.	[80]
7.	Human Immuno Deficiency Virus (HIV)	HIV was found to be related to gastrointestinal Cancers.	[119]
8.	Epstein-Barr Virus (EBV)	EBV-Positivity was detected in Gastric Cancers.	[120]

Besides EBV associations with the inflammation in gastric mucosa, severe colitis, and gastritis, the elevation of anti-EBV antibody titer in gastritis [108] and progression of gastritis to GC in post-transplanted *Helicobacter pylori* patients involving EBV have been reported [109]. The role of EBV in gastritis to GC progression might be via direct or indirect mechanisms involving tissue damage by favoring chronic inflammatory responses [110]. The association between EBV reactivation antibodies and severe inflammatory responses in the gastric mucosa of gastritis patients has also been demonstrated. In addition, active EBV infections could be found within the gut tissue of Crohn's disease (63%) and ulcerative colitis patients (60%) [111]. Interestingly, it may influence the overall content of inflammatory infiltrates and can lead to autoimmune diseases and cancer development. Studies have also shown that the frequent presence of EBV-infected

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lymphocytes in inflamed gastric and colonic mucosa has a potential role in mucosal and gastrointestinal inflammations [112]. DNA levels of EBV in the gastritis samples were also higher than expected, suggesting that the role of EBV may be more than just a mere presence due to random B lymphocytes infiltrating the inflamed tissue. Wakefield *et. al*. (1992) found high levels of EBV-encoded EBER-1 and EBV-DNA in tissue specimens, EBV-positive lymphocytes accumulation under and within the epithelium, and the presence of PCR-amplifiable EBV-DNA in inflammatory bowel disease [111]. In addition, clinical case studies have found an association of EBV not only with IBD but also with diarrhea indicating the role of EBV in the pathogenesis of gut inflammation [113]. Considering all these recent findings and studies, EBV can be a potential instigator of gut inflammation (Fig. 5). A majority of these findings show no direct relation between EBV and chronic gastritis pathogenesis, necessitating further studies and investigation into the role of EBV.

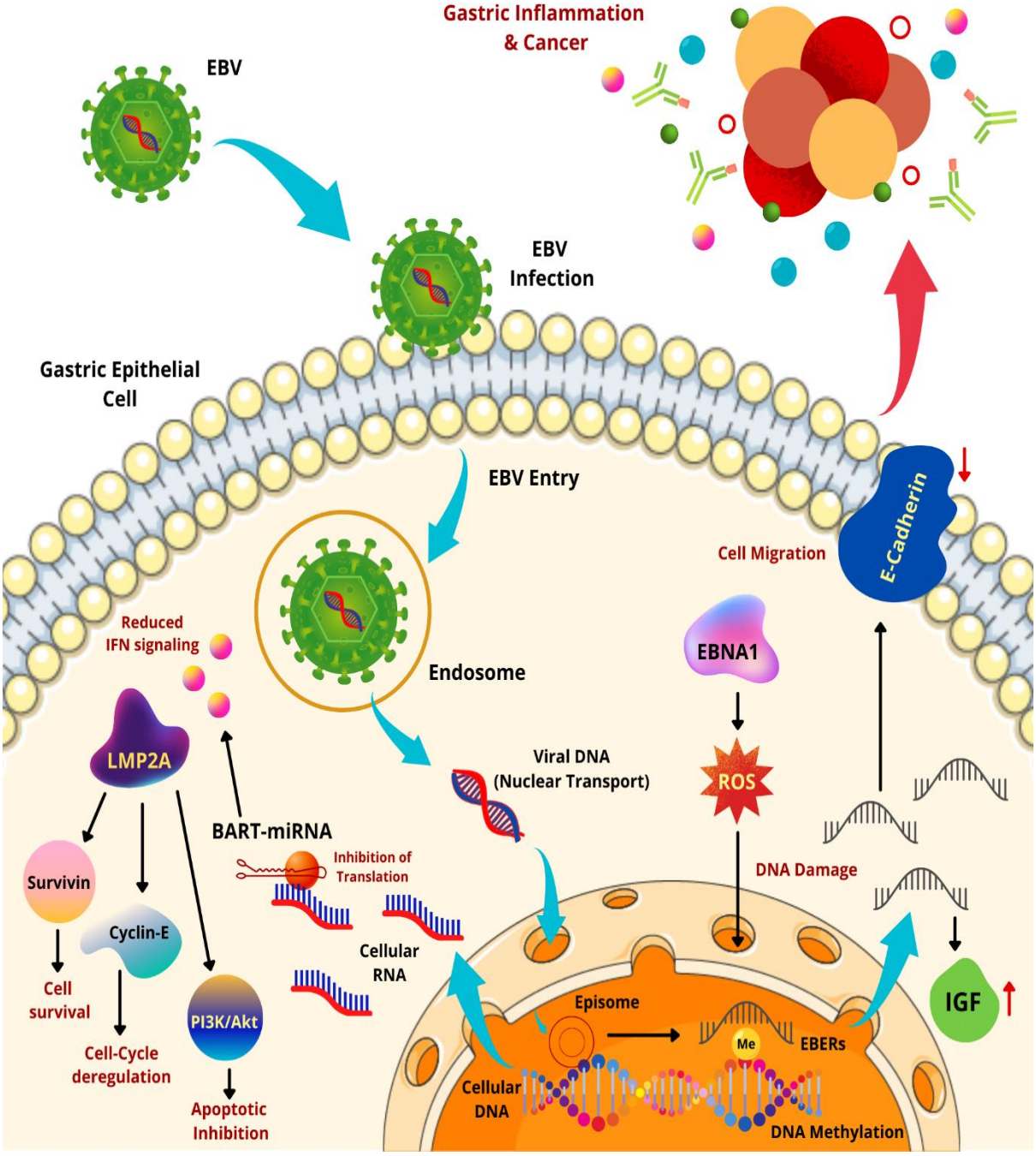

Fig. 5. Major Epstein-Barr virus antigens deregulate cellular signaling in the progression of gastric cancer.

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Antiviral therapeutics for virus-associated gastric inflammation and cancers

Astroviral infections are well known to initiate gastroenteritis, especially in infants and the elderly. Although these infections are mild extra care and precautionary measures are required for patients having immunosuppressive disorders or advanced HIV infection [121]. Unfortunately, earlier, no frontline-prescribed drugs or vaccines were available to prevent astrovirus infection. Nevertheless, recent advances in developing neutralizing monoclonal antibodies might effectively prevent astroviral infections soon. RotaTeq® has a worldwide license as an effective vaccine against RoV.

Table. 2 Antiviral therapies for virus-induced gastric infections within this review.

Antivirals	Virus	Types	Molecular Target	Mechanism of action
2′-C-methylcytidine (2CMC)	Rotavirus	Cytidine Nucleoside analog	RNA-dependent RNA polymerase (RdRp)	Inhibits viral RdRp to stop replication
Nitazoxanide	Rotavirus	Thiazolide	Viral Proteins (VPs)	Inhibits VP7 processing & viral component assembly
7-deaza-2'-C-methyladenosine (7DMA)	Rotavirus	Adenosine nucleoside analog	RNA-dependent RNA polymerase (RdRp)	Inhibits viral RdRp to stop replication
ML-60218	Rotavirus	RNA Pol-III inhibitor	Double-layer virus particles (DLPs)	Inhibits VP6 formation
NITD008	Norovirus	Adenosine nucleoside analog	RNA-dependent RNA polymerase (RdRp)	Inhibits viral RdRp & creates lethal mutagenesis
Rupintrivir	Norovirus	Irreversible 3C protease inhibitor	Viral Protease	Inhibits viral protein formation
Ribavirin	Norovirus	Guanosine Nucleoside analogue	RNA-dependent RNA polymerase (RdRp)	Inhibits viral RdRp & creates lethal mutagenesis
Suramin	Norovirus	Non-nucleoside analogue	RNA-dependent RNA polymerase (RdRp)	Inhibits viral RdRp
Favipiravir	Astrovirus	Pyrazine Nucleoside analog	RNA-dependent RNA polymerase (RdRp)	Inhibits viral RdRp functions
Cidofovir	Adenovirus	Cytosine Nucleoside analog	Viral DNA-Pol	Inhibits viral DNA-Pol to stop replication
Brincidofovir	Adenovirus	Cytosine Nucleoside analog	Viral DNA-Pol	Inhibits viral DNA-Pol to stop replication
Chymostatin	Norovirus	Protease Inhibitor	Viral Protease	Inhibits viral protease (Geno groups- I & II)
Naphthalene di-sulfonate (NAF2)	Norovirus	Non-nucleoside inhibitor	RNA-dependent RNA polymerase (RdRp)	Inhibits viral RdRp functions
Ginseng	Norovirus	Steroid glycoside	Host proteins	Induces Interferon (IFN) signaling

Moreover, various vaccines are in pre-clinical, early, and advanced clinical developmental phases, such as RV388/UK re-assortment and subunit vaccines for RoV or intramuscular bivalent vaccine candidate GI.1 and GII.4 VLPs and multivalent alphavirus replicon particles, for NoVs [122]. Research results provided direct evidence that an AstV spike protein is the prime target of a neutralizing antibody [123]. *In vitro* study showed that the FDA-approved drug, nitazoxanide, which is a broad-spectrum anti-infective agent, inhibits AstV replication effectively [124]. For preventing NoV infections, some antiviral compounds are prescribed, including, ribavirin [125], B-D-N(4) hydroxycytidine [126], suramin [127], cyclosulfamide derivatives [128], Chymostatin [129], human IFNα [130]. The situation is slightly different for RoV infection, as oral rotavirus vaccine solutions are available to prevent rotavirus-induced diarrhea and gastroenteritis [131]. Of note, scientists have discovered therapeutic remedies for HCV-related gastric disorders by using combinations of antiviral drugs, including sofosbuvir, ledipasvir, and ribavirin [132]. There are no specific antiviral drugs to cure the symptoms of HPV-mediated cancer. However, three types of vaccines are available to control the virus propagation, gastrointestinal inflammation, and infections and probably prevent HPV-associated cancers, i.e., bivalent vaccine (HPV2), quadrivalent vaccine (HPV4), and nonavalent vaccine. In the context of HIV-induced gut inflammation and gastroenteritis, antiretroviral therapy (ART) could be the most recommended option for treatment. Along with ART, some specific antiviral drugs were found effective for preventing infection-related illness, including lopinavir and fosamprenavir, but diarrhea may occur as a side effect of taking these medications [133]. Several safer new antivirals like darunavir and atazanavir were developed to reduce gastric disorders [134]. In the search for potential antiviral therapeutics for EBV-associated gut inflammation and carcinoma, nucleoside analogs, acyclovir, and ganciclovir could effectively inhibit EBV infection *in-vitro* [135]. The response of anti-program cell death-1 (PD-1) inhibitors in EBV-positive gastric cancers is under assessment [136]. In addition, antivirals

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pembrolizumab and nivolumab were reported as effective for inhibiting EBV-positive gastric carcinoma in phase II trials NCT03257163 and NCT02951091, respectively [137,138]. There are reports on the therapeutic effects of phytochemicals like cranberry bioactive, pomegranate bioactive, blueberry bioactive, black raspberry bioactive, grape seed bioactive, and other plant flavonoids against enteric virus infections (Table 2). These compounds have anti-inflammatory, anticarcinogenic, cardioprotective, and antimicrobial properties [139] and are inexpensive, sustainable, and safe as antivirals.

CONCLUSION

viruses can be harbored in the gastrointestinal tract without showing any clinical symptoms. Apart from the xenobiotic insult, gut mucosa often faces infections from different enteric viruses that may harm the host. Moreover, pathogenic virus-induced gut inflammation and gastric disorders occur due to interaction with other gut microbes and host factors. In particular, enteric viruses may alter the normal gut microbiome to induce inflammatory responses in the gastrointestinal tract. Such inflammatory responses may modulate the cellular signalings toward chronic gastric disorders and inflammation in the host. Long-term pathogenic exposure to tumor viruses and gut inflammations may lead to gastric malignancies. Recent advancements in diagnostic techniques, proper preventive measures, and treatment strategies for infectious gastrointestinal diseases have shown profound patient benefits. Therefore, in-depth research on new therapeutic interventions is needed to control infectious gastroenteritis. Compared with available antibiotic groups that are highly effective against bacterial infections in the gut, only a few antivirals are available to combat virus-induced gastric infections. The gut microbiome appears as an intricate 'signaling hub' crucial for affecting host metabolism and immunological responses upon infection. Effective vaccination programs, development of safe small-molecule antiviral drugs, use of protease inhibitors, and combinatorial application of natural antiviral phytochemicals may control the incidence of virus-associated gut inflammatory diseases and cancers. Currently, no therapy is effective against these enteric virus infections other than proper hygiene and cleanliness. The main challenges with vaccines will be to improve effectiveness and access in resource-limited regions, increase vaccine usage, and reduce the risk of intestinal intussusceptions. Although TNF-alpha inhibitors in gut inflammation treatment may benefit the inflammations, they can activate latent EBV and severe gut problems. On the other hand, Quercetin-induced apoptosis can be a future candidate as an antiviral against EBV and gastric carcinoma.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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