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Pathways involved in viral oncogenesis: New perspectives from virus-host protein interactomics

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ABSTRACT

Oncogenic viruses are among the apparent causes of cancer-associated mortality. It was estimated that 12% to 15% of human malignancies are linked to oncoviruses. Although modernist strategies and traditional genetic studies have defined host-pathogen interactions of the oncoviruses, their host functions which are critical for the establishment of infection still remain mysterious. However, over the last few years, it has become clear that infections hijack and modify cellular pathways for their benefit. In this context, we constructed the virus-host protein interaction networks of seven oncoviruses (EBV, HBV, HCV, HTLV-1, HHV8, HPV16, and HPV18), and revealed cellular pathways hijacking as a result of oncogenic virus infection. Several signaling pathways/processes such as TGF-β signaling, cell cycle, retinoblastoma tumor suppressor protein, and androgen receptor signaling were mutually targeted by viruses to induce oncogenesis. Besides, cellular pathways specific to a certain virus were detected. By this study, we believe that we improve the understanding of the molecular pathogenesis of viral oncogenesis and provide information in setting new targets for treatment, prognosis, and diagnosis.

1. Introduction

Oncogenic viruses can cause a global health burden: human cancer. It was estimated that infectious agents accounted for 13% of total new cancer cases worldwide in 2018, which corresponding to about 2.2 million new cancer cases [1]. According to the International Agency for Research on Cancer (IARC), seven oncogenic viruses are associated with human cancers. These include Epstein Bar virus (EBV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Human T-cell lymphotropic virus-1 (HTLV-1), Human Herpesvirus-8 (HHV8) also known as Kaposi's sarcoma herpesvirus (KSHV) and two Human Papillomaviruses (HPV16 and HPV18). It was estimated that oncogenic viruses are responsible for up to 12% of human cancer cases worldwide [2].

Among the oncogenic viruses, EBV infection is the most common infection among humans. EBV infecting approximately 90% of the world population [3], and, it is responsible for the development of about 1.5% of all cancers globally [4]. EBV pertains to both epithelial and B-lymphoid origin malignancies and induces nasopharyngeal cancer, gastric cancer, Burkitt lymphoma, and Hodgkin lymphoma [5]. Approximately 50% of malignancies attributed to EBV occurred in East Asia [6]. EBV has a linear double-stranded DNA genome and belonging to the gamma-herpesvirus group [7]. EBV is capable to infect B cells and epithelial cells. The EBV entry mechanisms are different for both cell types. For instance, the number of minimal viral glycoproteins and cellular proteins is different for the effective entry of the virus into B cells and epithelial cells [8]. The EBV life cycle can be divided into the two phases (i)lytic phase (EBV replication); (ii) latent phase (EBV obstruct most of its protein-encoding genes). All the EBV-associated cancers are related to the latent phase plus the viral protein expression. The viral proteins which are sort of reason for cancer development are the almost perfect targets for treatment. However, since these viral proteins are intracellular proteins or firmly embedded in the cell membrane, these EBV-specific treatment strategies were inadequate for EBV-related cancers [9].

The two unlinked viruses, HBV and HCV are both pertaining to the etiology of the primary malignancy of the liver, hepatocellular carcinoma, compromising 75–85% of liver cancer cases. Hepatocellular carcinoma is the fifth most encountered cancer type and the third cause of cancer deaths globally [10]. The prevalence of HBV and HCV infections varies according to the demographic factors; however, the most

Abbreviations: EBV, Epstein Bar virus; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HTLV-1, human T-cell lymphotropic virus-1; HHV8, Human Herpesvirus-8; KSHV, Kaposi's sarcoma herpesvirus; HPV, Human Papilloma virus; VHPI, virus-host protein interaction; pRB, retinoblastoma tumor suppressor protein; TSH, thyroid stimulating hormone

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affected regions for HBV infection are sub-Saharan Africa and East Asia, while Central and East Asia and North Africa for HCV infection [11]. It is estimated that HBV infection induces approximately 80% of the total virus-associated hepatocellular cases while HCV accounts for 20% [12]. HBV is composed of enveloped partially double-stranded, circular DNA. After HBV integrates its DNA to the host, the viral oncogene proteins such as HBX (crucial for HBV replication) are expressed. On the other hand, HCV is a single-stranded RNA virus that cannot integrate itself into the host genome [11]. HCV based malignancy is mediated by viral-induced factors and host-induced immunological responses [9]. Although the possibility of developing hepatocellular carcinoma can be decreased with current vaccination for HBV, it is still necessary to develop treatment strategies to complete vaccine implementation. Moreover, no vaccine is currently available for HCV infection; however, with the applied antiviral treatment carcinoma development risk was slightly decreased [11].

CD4 + /CD8 + T-cells, B- or dendritic cells represent the primary host cells for HTLV-1. Adult T-cell leukemia/lymphoma (ATLL) was the malignancy that arises as a result of the HTLV-1 infection [13] and it was estimated that about 4% to 7% of the infected individuals have a risk to develop ATLL [14]. The HTLV1 is endemic in south western Japan, Africa, the Caribbean Islands, and Australian aborigines. HTLV1 is an enveloped, single-stranded diploid RNA virus. Approximately more than 15 million individuals are infected with HTLV1 worldwide [15] and it was estimated that 12% of infections originate from a blood transfusion. After the HTLV1 infection, polyclonal proliferation, clinical latency, and oncogenesis formation occur for the development of cancer. The two proteins Tax and HBz play crucial roles in HTLV1 associated tumorigenesis development. Tax has a role in constitutive cell cycle progression and apoptosis resistance while HBz is necessary to stimulate T cell proliferation [16]. Unfortunately, there is no vaccine for the prevention of HTLV1 infection and no valid treatment methodologies [17].

The HHV-8 is associated with Kaposi sarcoma, a fatal malignancy that is widespread in certain regions such as Southern and Eastern Africa [9]. In 2018 approximately 42,000 new cases and 20,000 deaths were associated with Kaposi sarcoma [18]. Although HHV-8 infection is essential, it's inadequate alone, thus other contributing factors such as HIV infection came into prominence in disease formation. The Kaposi sarcoma incidence is 1 in 100,000 for HHV8 infected individuals and around 5% for individuals with both HHV8 and HIV positive [19]. HHV8 is an enveloped, double-stranded DNA virus infecting endothelial lineage cells. During most of the life cycle, the HHV8 exists in a latent form. Solely a few viral genes are expressed during the latent infection of HHV8. Among those genes, LANA has crucial roles like genome persistence and replication. Contemporarily, a vaccine was not developed for the infection and the virus-infected cancer cases are treated with simple chemotherapies [20,21].

The infection by highly oncogenic HPV is essential for cervical cancer, the fourth leading cause of death worldwide [22]. HPV16 and 18 are the two highly oncogenic HPV strains that are responsible for up to 70% of cervical cancer cases [23]. Besides, HPV is positive in about 30–60% of oropharyngeal carcinoma, 90% of anal cancer, and 40% of vulva, vagina, and penile cancer cases [24]. HPVs are non-enveloped double-stranded circular DNA viruses. To maintain productive infection, HPVs need to attain the host cells from the basal layer of the epithelium [24]. Cervical cancer was the primary cause of cancer-related deaths in women in Africa [25]. Despite the presently available screening tests and vaccines, nearly 311,000 deaths and 570,000 new cases of cervical cancer occur in 2018 around the world; this finding shows the inadequacy of existing screens and the need for effective screening strategies [22].

Oncogenic viruses represent a small part of all the viruses. To develop viral cancer, the associated virus infection is essential but inadequate. Therefore, other cancer-related risk factors such as genetic and environmental factors (i.e., gene and chromosome alterations/mutations, changes in levels of tumor suppressors and activators, suppressed immune system, harmful habit consumption, etc.) are necessary for cancer to develop. These viral cancers share common related risk factors, however, to disrupt proper cellular control to develop cancer, oncoviruses establish unique interactions with the host proteins which these interactions defined as virus-host protein interactions (VHPIs) [26].

Despite, VHPIs are detected and deposited in the public databases such as Host-Pathogen Interaction Database (HPIDB) [27] and Pathogen-Host Interaction Search Tool (PHISTO) [28], the reflection of these interactions in host cellular mechanisms remain mysterious. Over the last few years, it has become clear that infections hijack and modify cellular pathways for their benefit to promote replication, escape from the host immune systems, and construct a convenient environment for cancer development [29]. Considering these outcomes, in this study, the VHPI networks for above-mentioned seven oncoviruses (EBV, HBV, HCV, HTLV-1, HHV8, HPV16 and HPV18) were constructed, and cellular pathways hijacking as a result of oncogenic virus infection were revealed via analyzing the targeted host proteins within these networks.

2. Materials and methods

2.1. Data extraction: virus-host protein interactions

The VHPIs were obtained from three publicly available biological repositories (as available on May 2019) accumulating experimentally verified VHPIs: (i) Host-Pathogen Interaction Database (HPIDB v.2.0) [27], (ii) Pathogen-Host Interaction Search Tool (PHISTO) [28] and (iii) Hepatitis C Virus Protein Interaction Database (HCVpro) [30]. During data curation, only VHPIs that belong to *Homo sapiens* taxonomy were employed. Annotation and classification of host proteins were based on The Gene Ontology (GO) terminology [31], The Database for Annotation, Visualization, and Integrated Discovery (DAVID) Bioinformatics Resource (v.6.8) [32] and PANTHER database (v.14.0) [33]. The protein descriptions were obtained from The UniProt Knowledgebase (UniProtKB) [34], and the functional classification was performed through the PANTHER database (v.14.0) [33].

2.2. Reconstruction and topological analysis of virus-host protein interaction networks

The VHPI networks were reconstructed for each oncogenic virus strain and represented as undirected graphs where nodes represent the proteins and edges represent the interactions among the virus and host proteins. Graphs were visualized using Cytoscape (v.3.5.0) [35]. The topological features of each network (i.e., network size, the average number of neighbors, maximum characteristic path length, network centralization, network density, network diameter, network heterogeneity) were determined through the NetworkAnalyzer tool [36].

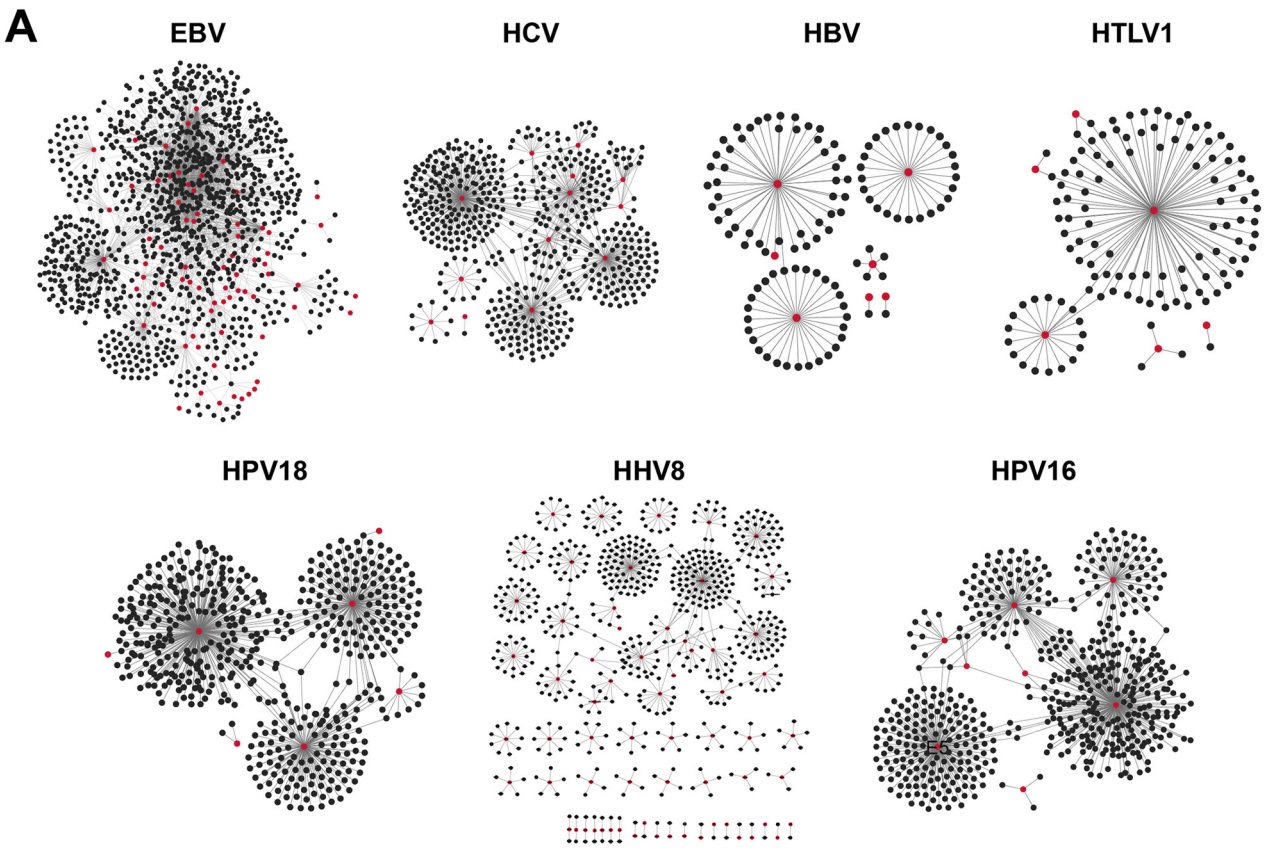
2.3. Overrepresentation analysis of host proteins

The overrepresentation analyses have been performed through ConsensusPathDB [37] to reveal host signaling pathways hijacked by oncogenic viruses. All the pathway database resources provided by ConsensusPathDB (including KEGG, Reactome, Biocarta, NetPath, and Wikipathways) were employed. p-Values were obtained via Fisher's Exact Test and false discovery rate (FDR) was applied to control p-values. In the overrepresentation analyses adjusted-p $< 10^{-5}$ were considered as statistically significant.

3. Results

3.1. Properties of virus-host proteins networks

The VHPIs were obtained from three publicly available repositories



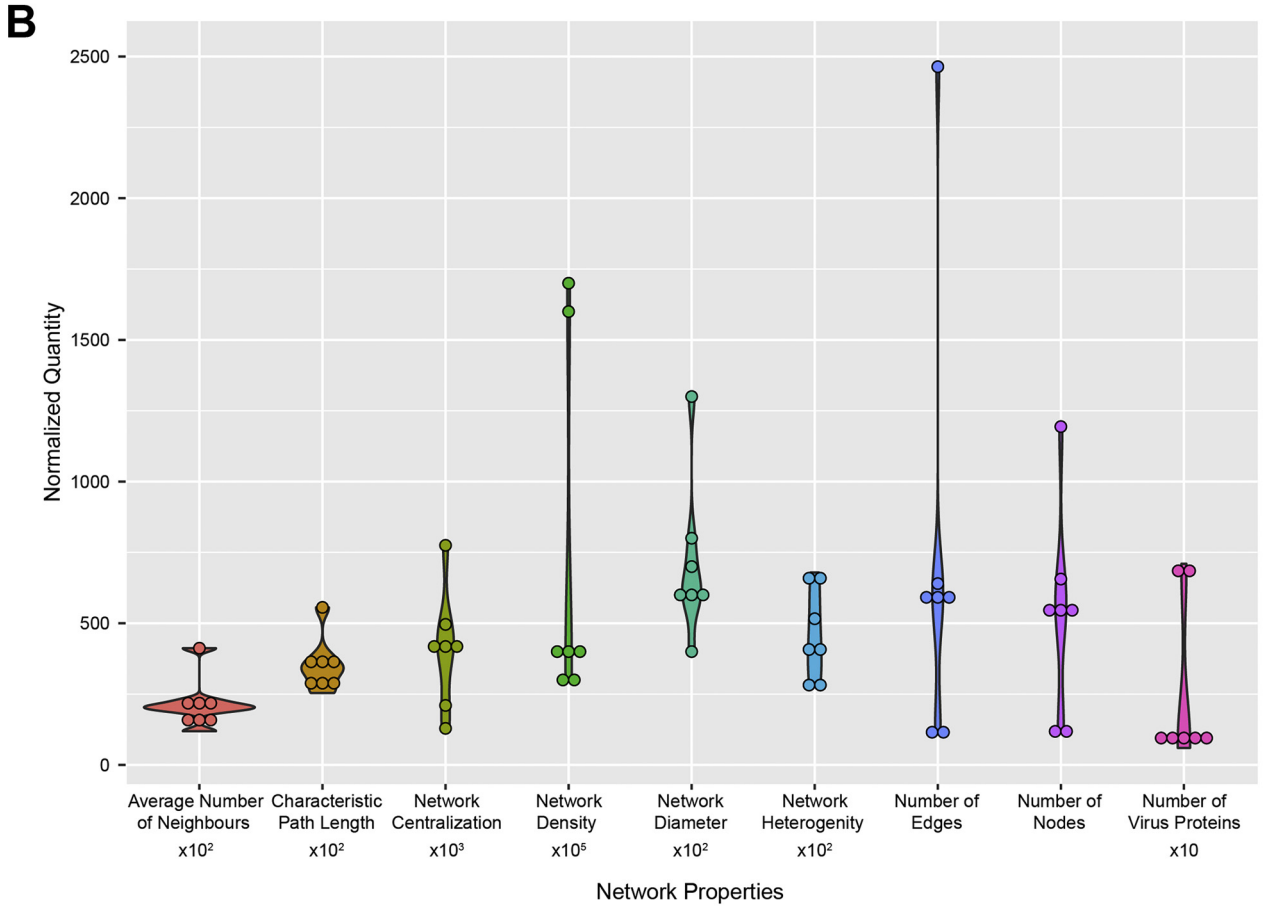


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Fig. 1. The topological properties of the reconstructed pathogen-host protein-protein interaction networks. (A) The graphs displaying the reconstructed pathogen-host protein-protein interaction networks for the seven oncoviruses. The red nodes represent the virus proteins while the dark gray nodes represent the host proteins. (B) The violin plot representing the topological metrics of the networks.

accumulating experimentally verified VHPIs. A total of 5164 VHPIs among 162 virus proteins and 2638 human proteins were gathered from the databases with the removal of duplicates, and strain-specific VHPI networks were reconstructed (Fig. 1A). VHPI networks displayed distinct network properties, and each one came into prominence with different characteristics (Table S1). For instance, the EBV network presented the highest number of virus proteins, the network size and the average number of neighbors, and the lowest network density. On the other hand, the lowest network size (in terms of the number of nodes), network diameter, network heterogeneity, and the average number of neighbors, and the highest network density were observed in HBV network. HTLV1 network displayed the lowest network size (in terms of the number of edges) and characteristic path length, and the highest network centralization, whereas HHV8 network presented the highest network diameter and characteristic path length, and the lowest network centralization and the network density (Fig. 1B).

When the biological processes associated with the 2638 host proteins represented in VHPI networks were analyzed, the metabolic processes were predominant (34%) followed by cellular component organization or biogenesis (13%), biological regulation (12%) and localization (10%), and cell communication (10%) processes. The host proteins were mainly located in the cytoplasm (26%), as a part of a protein complex (22%), nucleus (20%), or vacuole (12%), and exhibited mostly protein (29%) or nucleic acid (20%) binding, hydrolase (17%), transferase (14%), and transporter (8%) activities (Fig. 2A).

To compare the tendency of virus proteins in interacting with the highly connected host proteins and the tendency of host proteins in interacting with the central virus proteins, we analyzed the degree distribution profiles of virus and host proteins. We observed that the virus proteins appeared to have a strong tendency to interact with highly connected host proteins, and therefore, viruses generally target host proteins that are strikingly interconnected (Fig. 2B).

3.2. Pathways involved in viral oncogenesis mediated by oncogenic virus infections

Pathway information is fundamental for successful biological systems modeling. To solve the password that perdue behind the VHIPs, the overrepresentation analyses were performed for host proteins. As a result, a total of 27 different pathways were overrepresented (Fig. 3) Interestingly, TGF-β signaling was significantly associated with six viruses (i.e., EBV, HCV, HTLV1, HHV8, HPV16, and HPV18). Moreover, cell cycle (EBV, HTLV1, HHV8, HPV16, and HPV18), retinoblastoma tumor suppressor protein (pRB) (EBV, HTLV1, HHV8, HPV16, and HPV18) androgen receptor signaling (EBV, HTLV1, HHV8, and HPV16), EGFR (EBV, HCV, HTLV1, and HPV16) and p53 signaling pathway (HBV, HTLV1, HHV8, and HPV16) came into prominence for at least four viruses. The TNF-α signaling pathway (EBV, HCV, and HPV16), Notch signaling (HCV, HHV8, and HPV16) and thyroid-stimulating hormone (TSH) signaling pathways (HTLV1, HPV16, and HPV18) were the highlighted pathways for at least three viruses. Five pathways (i.e., NF-KB signaling, VEGFA-VEGFR2 signaling, ATF-2 transcription factor network, proteasome, and E2F transcription factor network) were associated with at least two viruses; however, eleven pathways (ATF6-Alpha activates chaperone genes, measles, focal adhesion, PDGFR- β signaling, PI3K-Akt signaling, apoptosis, FoxO signaling, AP-1 transcription factor network, nucleotide excision repair, Kit receptor, and N-Glycan biosynthesis) were specific to a certain virus.

4. Discussion

The seven viruses including EBV, HBV, HCV, HTLV-1, HHV8, HPV16, and HPV18 are classified as “carcinogenic to humans” based on epidemiological and biological studies findings. These seven oncoviruses cause approximately 13% of all human cancers, and HPV was alone responsible for 690 000 new cases in 2018globally [1]. Therefore, to understand or get clues about how these viruses induce the cancer process will help to reduce the major part of the global human cancer burden.

Despite the adaptive immune system, oncogenic viruses can cause cancer. The adaptive immune system gives responses to the viruses and annihilates infected viruses as well as toxic molecules they generate. In humans, there are two types of adaptive immunity; (i) humoral and (ii) cell-mediated. One of the major differences between these adaptive responses is the stimulating white blood cells, which are B and T lymphocytes. The function of the humoral response is to produce antibodies, while the cell-mediated system reacts directly to a foreign antigen presented to the host cell. Therefore especially for oncogenic viruses, the cell-mediated adaptive responses have an important role, because antibodies cannot reach the virus, besides viral antigens on the surface can be acknowledged by T cells, thus with the cell-mediated systems infected host cell can be killed before it has a chance to proliferate [38,39].

Restrain viral infections, treating the infection that may have previously induced cancer or annihilate infected cancerous cells are the main steps for viral oncogenesis prevention and treatment [40]. In general, the influence of the clinical trials that developing day by day can assist and expedite these main steps development. Clinical trials are scientific studies which aim to find better ways to prevent, screen, diagnose, or treat the diseases. The clinicalTrials.gov is database which store privately and publicly funded clinical studies that conducted around the world [41]. The ongoing trials for investigated oncogenic viruses from clinicalTrials.gov were tabulated in the Table 1. Besides clinical trials, cancer immunoinformatics may induce new directions towards vaccine design from predicted potential epitope candidates [42]. For example in a study provides new information about HPV epitope- based vaccine development. Hereunder, they concluded that CD8 + epitopes from HPV45 proteins likely to significantly use to generate peptide vaccines against HPV infected cervical cancer cases [43]. Moreover, in another study the researchers designed a new chimeric vaccine for high oncogenic potential HPVs, including HPV16 and 18, using a variety of immunomic devices and the HPV58 sequence [44]. Apart from vaccine design, based on bioinformatics studies molecular docking was performed to found the inhibitors of HPV to support potent drug targets. According to many investigated curcuminoids, they purposed curcumin is a best inhibitor and is a potential target for oral and cervical cancers [45]. Except from the HPV based studies, HBV treatment model were established and based on this model the combination of forward and backward difference approximation were purposed via theoretical analysis and numerical simulations respectively [46].

All this to considered, this study gives information about which cell signaling machinery are regulated in humans as a result of viruses and host cells protein communications by using bioinformatic approaches. Hereby, in this study, the signaling mechanisms that are crucial for the suppressing host immune response or providing pathogen replication are highlighted which this information can predict therapeutic strategies for oncogenic viruses later on.

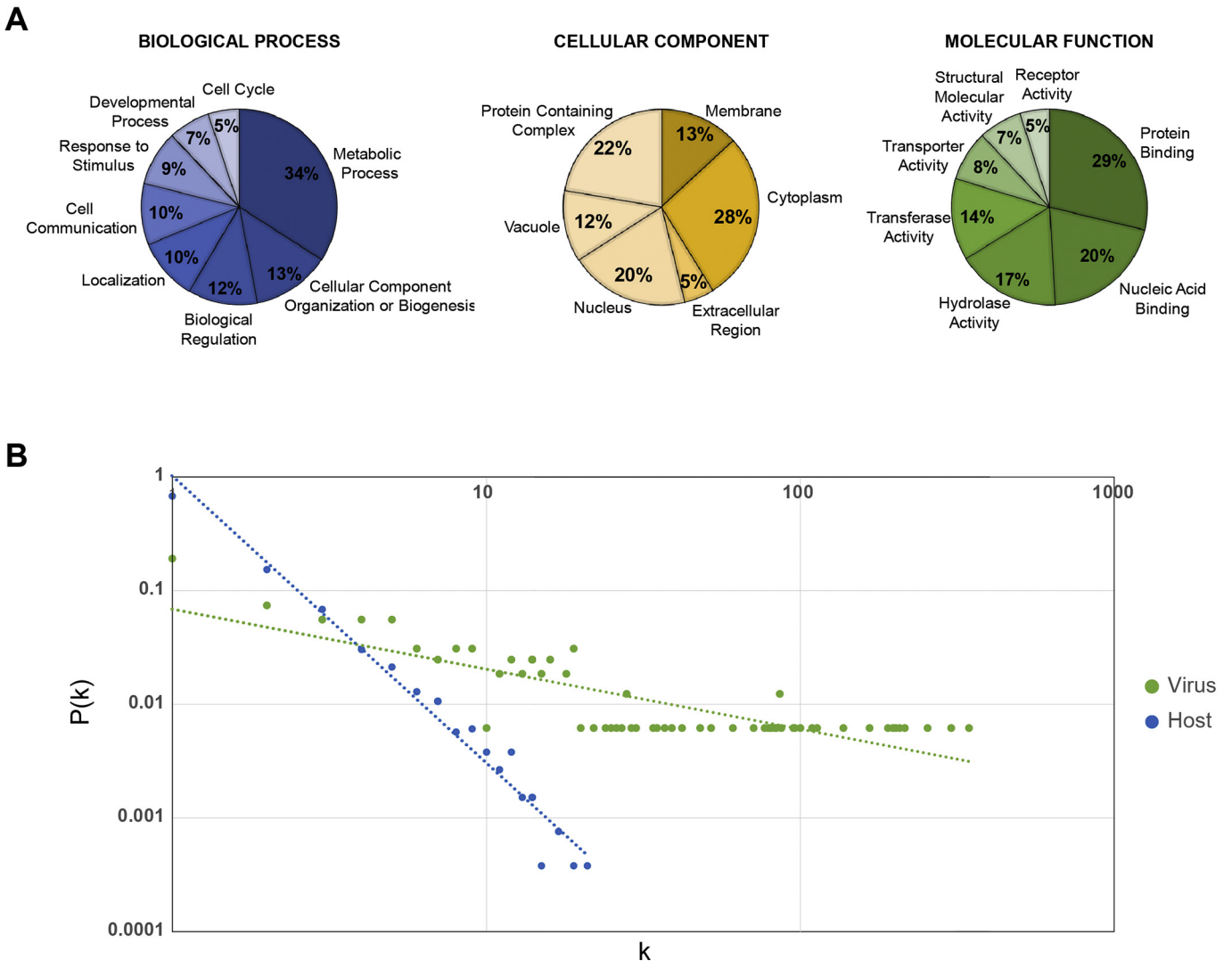


Fig. 2. Characterization of the host proteins and connectivity of host and virus proteins. (A) The distribution of host proteins into Gene Ontology (biological process, cellular component, and molecular function) categories. (B) The degree distribution plots for the virus and host proteins, where k represents the degree and P(k) is the fraction of the proteins with degree k.

4.1. TGF-β signaling pathway

Interestingly, depending on the stage of the tumor (in early stages) the TGF-β can act either as a tumor suppressor by preventing cell cycle and promoting apoptosis or as a tumor promoter by supporting metastasis (in late stages). This TGF-β variation during the tumorigenesis is known as “the TGF-β paradox” [47,48]. The 6 out of 7 oncogenic viruses: EBV, HCV, HTLV1, HHV8, HPV16 and HPV18 host target proteins were significantly enriched with the TGF-β signaling pathway (Fig. 4). In EBV positive and negative cancers the different TGF-β alterations were observed. In EBV positive cancerous cells the TGF-β components are highly expressed and TGF-β dependent apoptosis and growth inhibition have not occurred which can lead to more aggressive malignancies. However, in EBV negative cancerous cells these are just the opposite: the cells incline to pathway dependent apoptosis and growth inhibition [49]. The EBV host proteins that have a role in the TGF-β pathway generally (45%) have interactions with BRLF, EBNA6, and LMP2 virus proteins (Table S2). The association with three virus proteins and the TGF-β pathway has not been reported in the literature and to our knowledge it was reported here for the first time. Host proteins of NS5A, Core and HCVgp1 virus proteins; interact with a ratio 72% by pathway (Table S4). NS5A is one of the targets of TGF-β receptor 1 and by binding to the receptor the NS5A protein prevents the TGF-β pathway in hepatoma cell lines. Besides, it was reported that HCV infected patients have increased levels of TGF-β1 when compared to healthy subjects [50]. The tax and HBZ proteins are the two virus proteins that interact with enriched host proteins of the HTLV1 with a ratio of 57% and 35% respectively (Table S5). Tax virus protein is known as a repressor of the TGF-β pathway that contributes the cancer development [51]. Besides HBZ protein can able to interact with Smad2 and 3 which are the main signal transducers of the TGF-β signaling pathway. HBZ enhances TGF-β transcriptional responses via p300 transcription co-activator by interacting Smad2 and 3 [52]. The two latent virus proteins ORF72, ORF73 and two lytic virus proteins K-bZIP and vIRF are commonly (58%) interact with host proteins involved in this pathway (Table S6). The association between ORF72 and ORF73 with the TGF-β pathway has not been reported in the literature. The vIRF and K-bZIP can inhibit the TGF-β signaling pathway for the purpose of cell survival promotion during in both lytic and latent infection [53]. E7 virus protein for both HPV16 and 18 interacted with host proteins attended in this pathway by 75% and 60% respectively (Tables S7–S8). E7 oncoprotein can interact with SMAD2/3/4 and causes SMAD3 suppression which results with TGF-β signaling pathway inhibition [54].

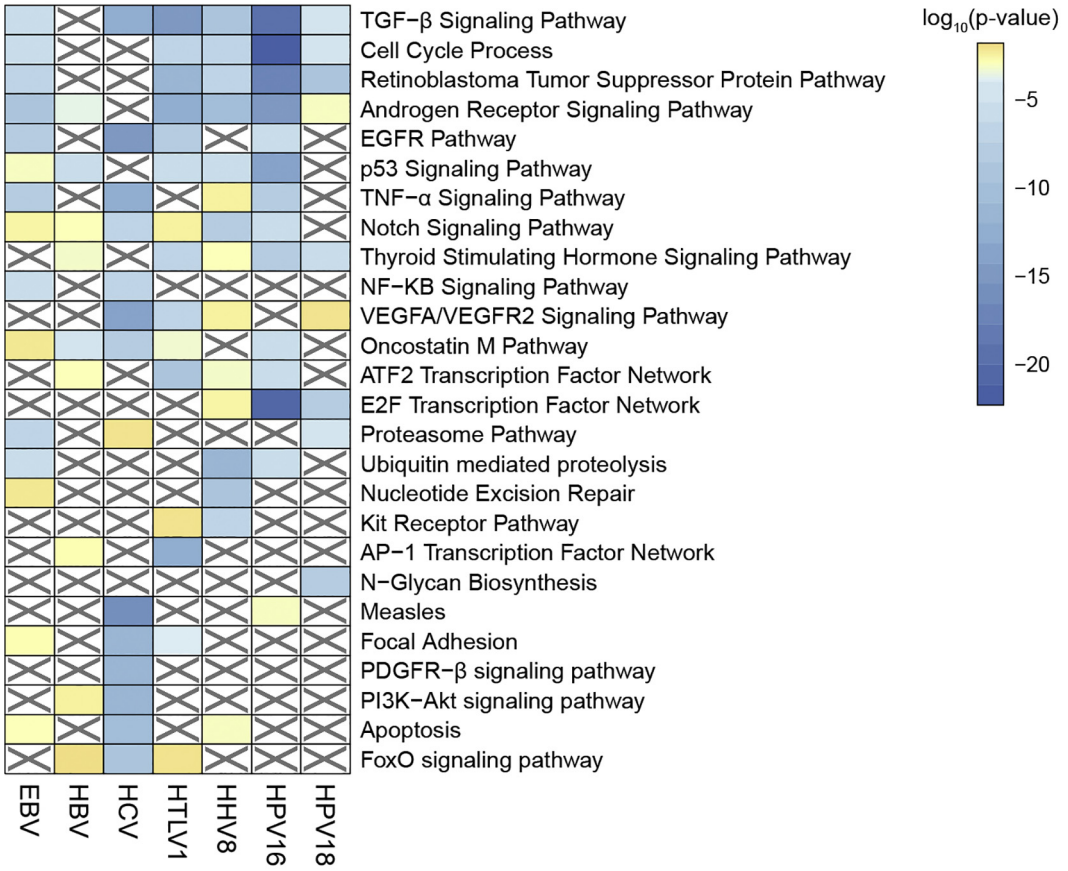


Fig. 3. The heat-map representing the host proteins targeted pathways. The color key represents the statistical significance in the logarithmic scale.

Table 1
Ongoing clinical studies that are currently on recruiting participants.

Virus	Identifier	Cancer type	Intervention/treatment	Phase
EBV	NCT03923842	Nasopharyngeal carcinoma	Denosumab	Phase 2
	NCT00181220	Nasopharyngeal carcinoma	Valproic acid	Phase 1
	NCT03769467	Nasopharyngeal carcinoma	Combination of tabelecleucel with pembrolizumab	Phase 1/2
	NCT03682055	Nasopharyngeal carcinoma	VK-2019	Phase 1/2
HBV	NCT03086564	Hepatocellular carcinoma	Activated Dendritic-cells combined Cyclophosphamide combining with transarterial chemoembolization	Phase 1/2
	NCT02650271	Hepatocellular carcinoma	Entecavir and Lamivudine	Phase 2/3
	NCT04032860	Hepatocellular carcinoma	Entecavir and Tenofovir Disoproxil	Phase 4
	NCT03591965	Hepatocellular carcinoma	ATG-008	Phase 2
	NCT04233840	Hepatocellular carcinoma	P1101 and Nivolumab	Phase 1/2
HCV	NCT03775798	Hepatocellular carcinoma	Direct antiviral agents for hepatitis C	–
	NCT03551444	Hepatocellular carcinoma	Administration of direct-acting antiviral based treatment	Phase 3
HTLV-1	NCT01712659	Adult T-cell leukemia/lymphoma	Ruxolitinib	Phase 2
HHV8	NCT01419561	Kaposi sarcoma	Zidovudine, Liposomal Doxorubicin, Valganciclovir, and Rituximab	Phase 2
	NCT00092222	Kaposi sarcoma	Etoposide, interferon-alpha, Rituximab, Zidovudine, Liposomal Doxorubicin, Bortezomib, Valganciclovir, Doxorubicin, Vincristine, Cyclophosphamide, Filgrastim, Prednisone and Sirolimus	Phase 2
HPV16	NCT02659930	Cervical cancer	TA-CIN vaccine	Phase 1
	NCT04001413	Oropharynx cancer	Durvalumab and MEDI0457	Phase 2
	NCT04180215	HPV 16+ cancers	HB-201 intravenous administration and intratumoral administration	Phase 1/2
	NCT03669718	Oropharynx cancer	ISA101b vaccine combination with Cemiplimab	Phase 2
	NCT03912831	HPV 16+ cancers	KITE-439, Cyclophosphamide and Fludarabine	Phase 1
HPV16 and 18	NCT03439085	Cervical, vulvar, vaginal, anal, penile cancers	Combination of MEDI0457 vaccine and Durvalumab	Phase 2
	NCT03444376	Cervical cancer	Combination of GX-188E vaccination and Pembrolizumab	Phase 1/2
	NCT02866006	Cervical cancer	BVAC-C vaccine	Phase 1/2
	NCT02379520	Oropharyngeal, cervical, anal, vulvar, penile	Cytoxan, Fludarabine, Nivolumab	Phase 1

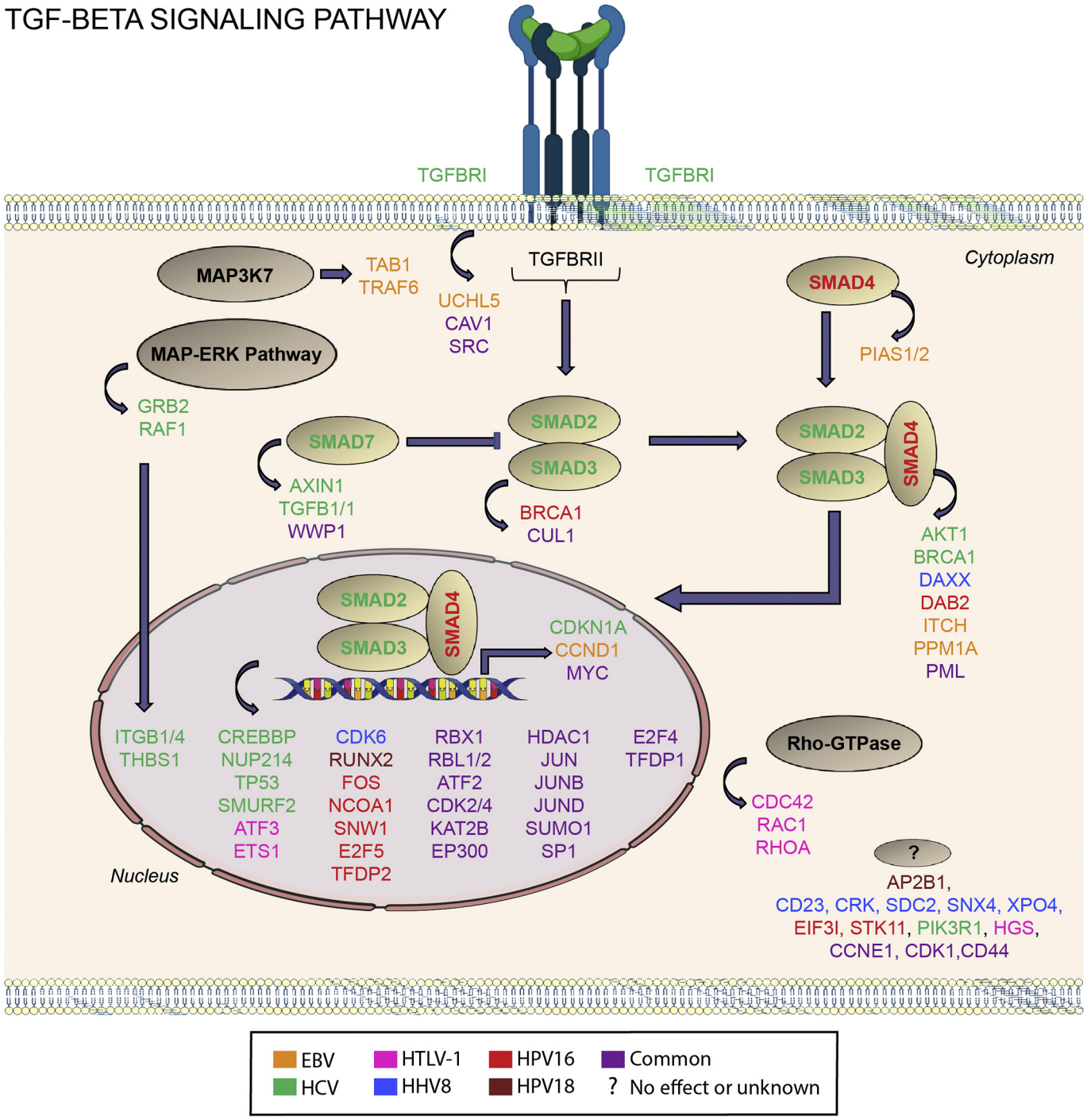


Fig. 4. The six oncoviruses host proteins targeted the TGF-β signaling pathway. In TGF-β signaling pathway, TGF-β ligand binds to type II receptor, this recruits the type I receptor and type II receptor phosphorylation and receptor I activation. The phosphorylated receptor I (interacting with UCHL5, CAV1 and SRC) phosphorylate Smad2/3 (interacting with BRCA1 and CUL1) and phosphorylated Smad2/3 binds to Smad4 (interacting with PIAS1 and 2) and composed complex (interacting with AKT1, BCAR1, DAXX, DAB2, ITCH, PPM1A and PML). This complex migrates to the nucleus. In the nucleus, the complex binds to their transcription factors and co-factors (CREBBP to SP1) to initiate the target genes transcription (CDKN1A, CCND1 and MYC). Despite the presence of the ligand, the pathway activation can be suppressed by the inhibitory Smad; Smad7 (interacting AXIN, TGFBI1 and WWP1). In addition, the ITGB1/4 and THBS1 proteins initiate the target genes transcription by MAP-ERK pathway (GRB2 and RAF1 components). Moreover, there are Rho-GTPases (CDC42, RAC1, and RHOA) that regulate the rapid and long-term actin reorganization. The orange host proteins represent EBV, the green HCV, the pink HTLV-1, the blue HHV8, the red HPV16, the brown HPV18 and the purple common. The question mark represents the host protein has no effect or is unknown.

4.2. Cell cycle process

Host proteins of five of the seven carcinogenic viruses were associated with the cell cycle process (EBV, HTLV1, HHV8, HPV16 and 18). Viruses manipulate cell cycle machinery of the infected cells and they need to duplicate their genomes quite a lot in the infected host cell [55] therefore, it's plausible to encounter the cell cycle process in our results. Cell cycle process enriched host proteins mostly interact with EBNA-LP, EBNA1 and EBNA6 (37%). It was reported that EBNA-LP promotes G1/S transition as a result of phosphorylation of protein kinase CDC2 [56].

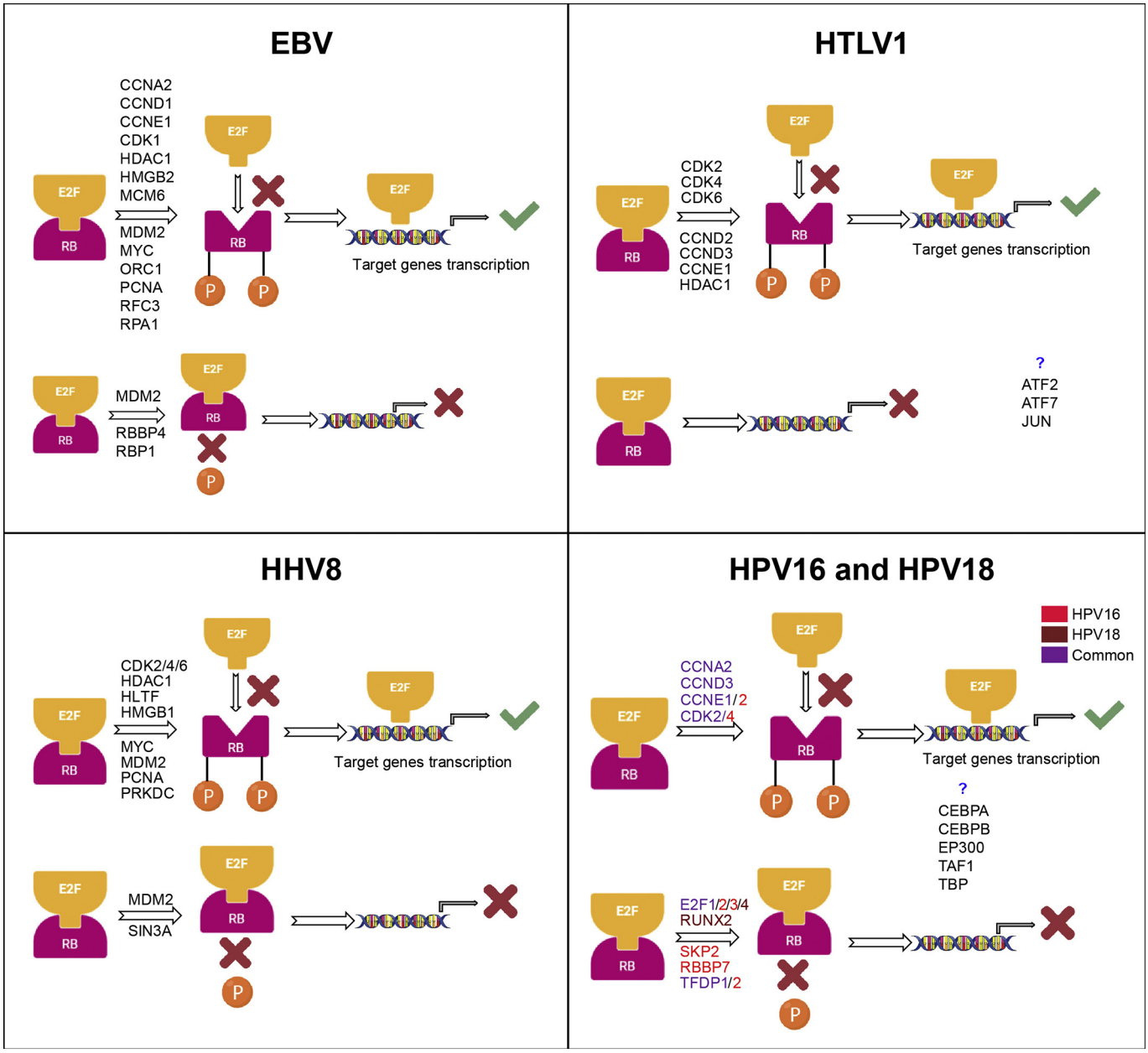


Fig. 5. The five oncoviruses host proteins targeted the retinoblastoma tumor suppressor protein (pRB) pathway. Target genes of the E2F transcription factors are controlled by pRB interactions. The pRB binds to E2F. The molecules phosphorylate pRB and make pRB inactivated. Therefore, pRB leaves E2F and releases. As a result, the E2F associated target genes transcription can occur. If pRB phosphorylation is inhibited by molecules, E2F remains attached to pRB, and transcription of E2F target genes does not occur. The host proteins that provide pRB phosphorylation and the host proteins that have no effect on pRB phosphorylation have been shown in the figure. In the HPV 16 and 18 section, the red host proteins belong to HPV16, the brown ones belong to HPV18 and the purples both. The question mark means that the host protein has no effect or is unknown.

In another report it was demonstrated that the of EBNA1 mRNA was regulated by the cell cycle. For instance, EBNA1 expression is lowest during G1 phase while highest during S phase [57]. HTLV1's Tax protein commonly interacts with host proteins (75%) attended in this process and impresses cell cycle and DNA repair [58]. Although the HHV8's host proteins that take place in the cell cycle process interact with ORF73 and 72 virus proteins generally (35%), their associations between virus proteins and the process has not been reported. The two HPV oncoproteins which are E6 and E7 participate in cell cycle based processes to provide to sustain the viral genome replication [59]. E7 is the first viral protein that interacted with HPV host proteins (HPV16 interacted with 83% of host proteins and HPV18–75%) that involved in the cell cycle.

4.3. Retinoblastoma tumor suppressor protein pathway

pRB and its pathway have essential roles in supervising cell division and death by coordinating the family of E2F transcription factors. pRB inactivation supports cell proliferation and cell cycle control escape and it is an indispensable event in cancer cases [60]. EBV, HTLV1, HHV8 and both HPV host proteins that are highly oncogenic were associated with the pRB pathway (Fig. 5). A study was conducted by Al-Salam et al., suggested that EBV infection had an inverse correlation with pRB. They reported that in EBV infected samples, the pRB expression decreased [61]. EBV's; EBNA1, EBNA6 and EBNA-LP virus proteins interacted with host proteins (65%) that participated in this pathway. pRB can represses the EBNA-1 promoter via E2F binding regions [62]

Table 2
The host proteins of the EBV, HTLV1, HHV8 and HPV16 that function as co-activators and co-repressors in the androgen signaling pathway.

Protein	Description	EBV	HTLV1	HHV8	HPV16
Co-activator					
KAT5	Lysine acetyltransferase 5	+	−	+	+
CCNE1	Cyclin E1	+	+	−	+
EP300	E1A binding protein p300	+	−	+	+
JUN	Jun proto-oncogene, AP-1 transcription factor subunit	−	+	−	+
FHL2	Four and a half LIM domains 2	+	−	−	−
RNF4	Ring finger protein 4	+	−	−	−
SP1	Sp1 transcription factor	+	+	−	−
SUMO1	Small ubiquitin-like modifier 1	+	−	−	−
CARM1	Coactivator associated arginine methyltransferase 1	−	+	−	−
CREB1	cAMP responsive element binding protein 1	−	+	−	−
RHOA	ras homolog family member A	−	+	−	−
RAC1	ras-related C3 botulinum toxin substrate 1	−	+	−	−
CDC37	Cell division cycle 37	−	−	+	−
NCOA2	Nuclear receptor coactivator 2	−	−	+	−
KDM3A	Lysine demethylase 3A	−	−	+	−
PELP1	Proline, glutamate and leucine rich protein 1	−	−	+	−
STAT3	Signal transducer and activator of transcription 3	−	−	+	−
BRCA1	BRCA1, DNA repair associated	−	−	−	+
CAV1	Caveolin 1	−	−	−	+
FLNA	Filamin A	−	−	−	+
HSPB1	Heat shock protein family B	−	−	−	+
KAT2B	Lysine acetyltransferase 2B	−	−	−	+
RAN	RAN, member RAS oncogene family	−	−	−	+
TMF1	TATA element modulatory factor 1	−	−	−	+
Co-repressor					
HDAC1	Histone deacetylase 1	+	+	+	+
DAXX	Death domain associated protein	+	−	+	−
MDM2	MDM2 proto-oncogene	+	−	+	−
CALR	Calreticulin	+	+	−	−
AES	Amino-terminal enhancer of split	+	−	−	+
CASP8	Caspase 8	−	−	+	+
CCND1	Cyclin D1	+	−	−	−
PIAS1	Protein inhibitor of activated STAT 1	+	−	−	−
PIAS2	Protein inhibitor of activated STAT 2	+	−	−	−
ATF2	Activating transcription factor 2	−	−	+	−
CCND3	Cyclin D3	−	−	−	+
CEBPA	CCAAT/enhancer binding protein alpha	−	−	−	+
FLNA	Filamin A	−	−	−	+
NCOA1	Nuclear receptor coactivator 1	−	−	−	+
PATZ1	POZ/BTB and AT hook containing zinc finger 1	−	−	−	+

and EBNA6 can regulate cyclin–CDKs complexes including pRB [63]. The majority (58%) of HTLV1's host proteins were enriched with this pathway interacted with tax virus protein. When the tax and pRB association investigated, it was found that tax protein causes decreased pRB and increased expression of E2F1 [64]. Correlatively it was pointed out that HHV8 encodes pRBs [65]. ORF72 and 73 were the two proteins which HHV8's host proteins interacted most (63%). Although there has not been any association with ORF72 and pRB pathway, it was reported that ORF73 can modulate pRB [66]. One of the key targets of the HPV16 and HPV18 virus, E7 protein, is a binding target of pRB thus, as expected, the host proteins mostly interact with E7 (HPV16's host proteins that enriched in this pathway interacted with E7 with the ratio of 89% and HPV18–46%). As a consequence of interaction, the E7 can inhibit pRB's function; thus, pRB can't suppress the deviant cell proliferation in cancerous cells [67].

4.4. Androgen receptor signaling pathway

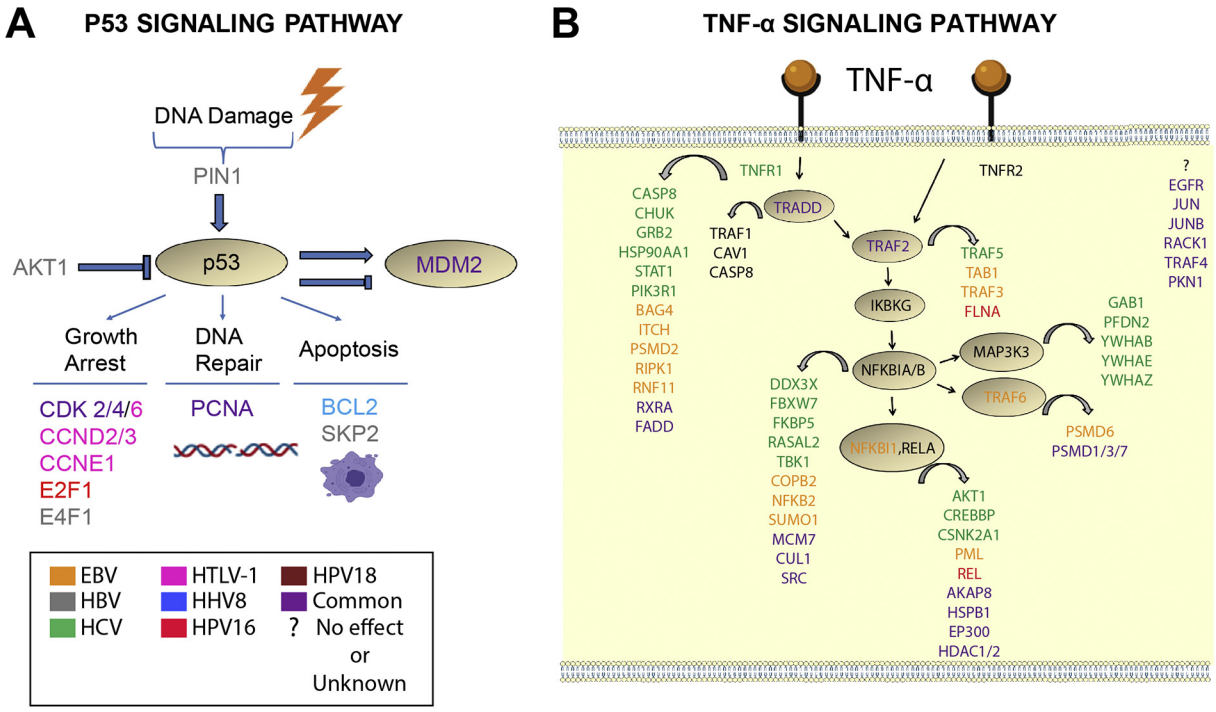
The significant association between androgen receptor alterations and prostate cancer is accepted by the authorities [68]. The four oncogenic viruses; EBV, HTLV1, HHV8 and HPV16's host target proteins enriched with the androgen receptor signaling pathway. In this pathway, the transcriptional activity of the androgen is mainly regulated by many co-regulators (co-activators and co-repressors) in different cell compartments. The functions of four viruses host proteins (as a co-activator or co-repressor) are given in Table 2. It was reported that infection of HHV8 supports androgen-independent prostate cancer growth via disrupting androgen receptor signaling pathway under androgen destitute situations [69]. It has been also suggested that HPV16 encoding proteins E6 and E7 (pathway-related host proteins interact by 46%) supported the differentiation process in the immortalized prostate epithelial cell line [70]. BRLF1, EBNA6 and BNLF2a for EBV (32%), tax for HTLV1 (66%) and ORF73 (35%) for HHV8 are the primary virus proteins that interact with the host proteins that have roles in androgen receptor signaling pathway. However, the association of the androgen signaling pathway with these virus proteins has not been previously reported in the literature and, to our knowledge was reported here for the first time.

4.5. EGFR pathway

The EGFR pathway came into prominence for EBV, HCV, HTLV1 and HPV16 viruses. BALF1, BHRF1, BNLF2a and tax are the major virus proteins of EBV and HTLV1 respectively, and these were the primary virus proteins that associated the pathway (34% for EBV and 83% for HTLV1). However, there has been no information that shows virus proteins and pathway relationships. Nevertheless, the activation of EGFR is essential for HCV viral entry and it increases HCV infectivity. Although the mechanism of how EGFR effects the HCV functions couldn't reveal, Diao and co-workers demonstrated that HCV was binding to CD81 and its induced EGFR activation and this activation was critical for HCV viral internalization and entry [71]. The virus proteins NS5A and Core generally (53%) had interactions with the host proteins that have a role in EGFR signaling pathway. The relation between EGFR and NS5A virus protein was reported and defined as EGFR degradation can be blocked by NS5A [72]. As well as, excessive EGFR can overcome the mechanisms that shorten the life of normal human keratinocytes, that's why E6 and E7 (E7 is a viral protein that interacted with host proteins involved in this pathway as a ratio of 89%) collaborate to increase EGFR mRNA levels [73].

4.6. p53 signaling pathway

The p53 signaling pathway was associated with host proteins of HBV, HTLV1, HHV8 and HPV16 (Fig. 6A). Under normal (stress-free) conditions, the p53 level is substantially low, but when the cell receives any stress signal, the p53 expression increases significantly. Mutations causing p53 suppression are present in > 50% of human malignancies. If there isn't mutation the p53 activity is obstructed by up-regulation of its negative regulators (i.e. MDM2) [47]. HBV encoding oncoprotein X which interacted with all host proteins (Table S3) that enriched with p53, can modulate the p53's crucial activities such as apoptosis [74]. As mentioned the HTLV1 infection causes ATLL and in these patients the p53 activity is repressed like other cancers. Interestingly in ATLL patients the incidence of mutated p53 is considerably lower when compared to other human malignancies which shows that the loss of p53 activity can be promoted via a variety of unknown mechanisms instead of mutation. Moreover, despite the mechanism of how the Tax (the host proteins attended in this pathway commonly interacts with, with a ratio of 71%) binds to p53 has not been reported, it was only pointed out that the protein Tax inactivates p53 [75]. Moreover, host proteins included in this pathway binded to ORF72 (40%), but the path and virus protein



(caption on next page)

association has not been demonstrated in the literature yet. The only virus protein E7 which interacted with host proteins enriched in this pathway, disrupts the control of the cell cycle control points of p53 [76].

4.7. TNF-α signaling pathway

TNF-α is synthesized by any inflammation, infection or injury. TNF-α signaling induces a caspase cascade and causes cell death. Moreover, the AP-1 and NF-KB are the two main transcription factors that become activated as a result of TNF-α pathway signaling [77]. EBV, HCV and HPV16 were the three oncoviruses that their host proteins associated with TNF-α (Fig. 6B). The EBV's virus proteins; LMP-1, LMP-2 and gB interacted (25%) with host proteins that attended this pathway. LMP-1 down-regulates TNF-α receptor 1 and offers capacitance to the TNF-α induced cell death [78,79]. Besides, in HCV, the TNF-α blood levels are

Fig. 6. The oncoviruses host proteins targeted p53, TNF-α a and thyroid stimulating hormone signaling pathways. (A) In the p53 signaling pathway, MDM2 is a cellular antagonist of the p53. AKT1 inactivates p53. DNA damage enhances the interaction between PIN1 and p53. The CDK 2/4/6, CCND2/3, CCNE1, E2F1 and E4F1 modulate the growth arrest under the effect of p53. PCNA attends in p53 influenced DNA repair. The SKP2 and BCL2 suppress p53 dependent apoptosis. (B) Upon binding of the ligand (TNF-α) to the receptors TNFR1 (interacts with CASP8, CHUK, GRB2, HSP90AA1, STAT1, PIK3R1, BAG4, ITCH, PSMD2, RIPK1, RNF11, RXRA and FADD) and TNFR2 the adaptor proteins such as TRADD (TRAF1, CAV1 and CASP8) and TRAF2 (interacts with TRAF5, TAB1, TRAF3 and FLNA) become activated which this activation enables the signaling cascade to be initiated. TRAF2 recruits and activates the IKBKG and NFKBIA/B complexes respectively. The ubiquitin of the IKBKG can be mediated by TRAF6 (interacts with PSMD1/3/7). Also the NFKBIA/B interacts with MAP3K3 and MAP3K3 interacts with GAB1, PFDN2, YWHAB, YWHAE and YWHAZ. The activated IKBKG and NFKBIA/B (interacts with DDX3X, FBXW7, FKBP5, RASAL2, TBK1, COPB2, NFKB2, SUMO1, MCM7, CUL1 and SRC) activates the transcription regulator NFKB1 and the transcription factor RELA (interacts with AKT1, CREBBP, CSNK2A1, PML, REL, AKAP8, HSPB1, EP300 and HDAC1/2). (C) The thyroid stimulating hormone (TSH) signaling pathway begins with the binding of TSH to the TSH receptor (TSHR). The TSHR can interact with JAK1 and SCRIB. The TSH exerts its action through various signaling cascades protein kinase cAMP-dependent cascades. Moreover, the PIK3R1/2, PIK3CA, HRAS, RAF1, BRAF and MAP Kinases become activated. The cAMP can interact with RAP1A and the Protein Kinase with CDK2/4, CCNE1, CCND3 and CREB1. MAPK1 induced FOS, JUN, MYC expression and CREB1 induce TTF1. Then these induced protein expression can initiate cell proliferation. Moreover, the CDK4 and CCND3 transported to the nucleus they phosphorylate RB1 and regulates the E2F1. The orange host proteins represent EBV, the gray HBV, the green HCV, the pink HTLV-1, the blue HHV8, the red HPV16, the brown HPV18 and the purple common. The question mark represents the host protein has no effect or is unknown.

up-regulated in HCV patients and the increased TNF-α levels are positively associated with the HCV related disease development [80]. The treatment of HCV patients with TNF-α inhibitors still have been under debate, due to there have not been any sufficient data about the trustworthiness in the long-term use [81]. The Core protein, which inhibits TNF-α -mediated apoptosis [82], was the viral protein that HCV's hosts interacted with (33%). A recent study was conducted by Cabeça demonstrated that TNF receptor 1 was under-expressed in the HPV16 positive keratinocytes [83]. E7 is the virus protein of HPV16, which usually associated with host proteins (42%) enriched in this pathway, reduces apoptosis caused by TNF [84].

4.8. Notch signaling pathway

The Notch signaling pathway is widely active in cancer and the association of the Notch pathway with leukemia, breast, esophageal, prostate, colorectal, lung cancer and central nervous system malignancies has been demonstrated in the literature [47]. The Notch signal was associated with the host target proteins of HCV, HHV8 and HPV16. The virus proteins such as NS5A, Core, and HCVgp1 were commonly (81%) interacted with the HCV's host proteins that attended in this pathway. The other HCV virus protein NS3 modulates the Notch signaling pathway through the targeting SRCAP transcription factor and it is known that SRCAP is also affected by NS5A and Core proteins [85]. Host targets of HHV8 involved in this pathway generally interacted with ORF73, K-bZIP and vIRF-3 virus proteins (69%). Although there has been no association in the literature between these virus proteins and the pathway, the association of HHV8 infection and the Notch signaling pathway has been specified. The expression of Notch is up-regulated in HHV8 infected cells. In addition, the expression of Notch receptor 4, JAG1 and DLL3/4 (Notch ligands) and Hes-1 and Hey-1 (Notch targets) is up-regulated in HHV8-infected lymphatic endothelial cells [86]. E7 was the virus protein of HPV16, which often contained host proteins that interacted with this pathway (70%). It was shown that both E6 and E7 up-regulate Notch1 expression and activity which may support the impairment of regular cell growth in cervical cancer [87]. Moreover, recently in a study, a y-secretase inhibitor that provides suppression of Notch signaling was proposed as a potential drug target for cervical cancer cells [88].

4.9. Thyroid stimulating hormone signaling pathway

TSH signaling resulted in relation to host target proteins of HTLV1, HPV16 and HPV18 (Fig. 6C). Any disorders of the TSH signaling pathway can cause thyroid associated disorders such as hypo- or hyperthyroid [89]. Although there has not been any certain argument about the TSH pathway and HTLV1 infection, there is evidence that in the autoimmune thyroid disorders, is a probable pathogenic factor of the HTLV1 infection [90]. The host proteins of the HTLV1 that attended in this pathway generally interacted with tax virus protein (56%). It was reported that silencing mediator of thyroid receptor especially stimulates Tax-mediated activation of the HTLV1 promoter [91]. In one study, the expression of TSH in cervical epithelial cells was investigated and as a result of the study, it was concluded that there was a feasible association between HPV positive cells and thyroid-stimulating hormone expression [92]. For both HPV oncogenic viruses host proteins that had a major role in this pathway were primarily interacted with E7 virus protein (83% for HPV16 and 67% for HPV18).

4.10. NF-KB signaling pathway

NF-KB composed of transcription factors that can regulate the pro-inflammatory genes, especially those attend in inflammatory and immune processes. Therefore, NF-KB deregulation can lead to development of chronic inflammatory diseases. In addition, this pathway is one of the significant targets for viral pathogens. Viruses induce the NF-KB transcription factors to escape antiviral responses [93,94]. NF-KB pathway was associated with EBV and HCV's host proteins. These host proteins interacted with EBV's gB and LMP1 (37%) and HCV's NS5A and Core (61%) virus proteins. It was reported that in EBV infection NF-KB becomes activated during latency to provide oncogenic transformation [95]. It was shown that LMP1 constitutively activates NF-κB [96]. In addition, NF-KB activation was shown in HCV positive liver tissues [95]. NS5A stimulates cell proliferation, also via the NF-KB signaling pathway [97].

4.11. VEGFA/VEGFR2 signaling pathway

VEGFA/VEGFR2 signaling pathway is vital for endothelial cells functions that relevant to angiogenesis [98]. HCV and HTLV1 were the two oncoviruses whose their host proteins were associated with the VEGFA/VEGFR2 signaling pathway (Fig. 7A). In a study, it was purposed that VEGFA expression can induce HCV infection. Its expression causes hepatocyte depolarization and promotes viral entry. Moreover, in this study researchers suggested that a VEGFA inhibitor suppresses the viral infection, therefore, they emphasized that VEGFA inhibitors may have therapeutic potential for HCV infection [99]. The VEGF pathway regulation can contribute pathogenesis of HTLV1 induced diseases such as ATLL via formation and development of new blood vessels, therefore in ATLL patients increased levels of VEGF were observed [100]. The host proteins that attended this pathway generally interacted with NS5A, Core (ratio of 54%) and tax (ratio of 75%) virus proteins. However, there has not been any available information in the literature that shows the relationship between these virus proteins and pathway.

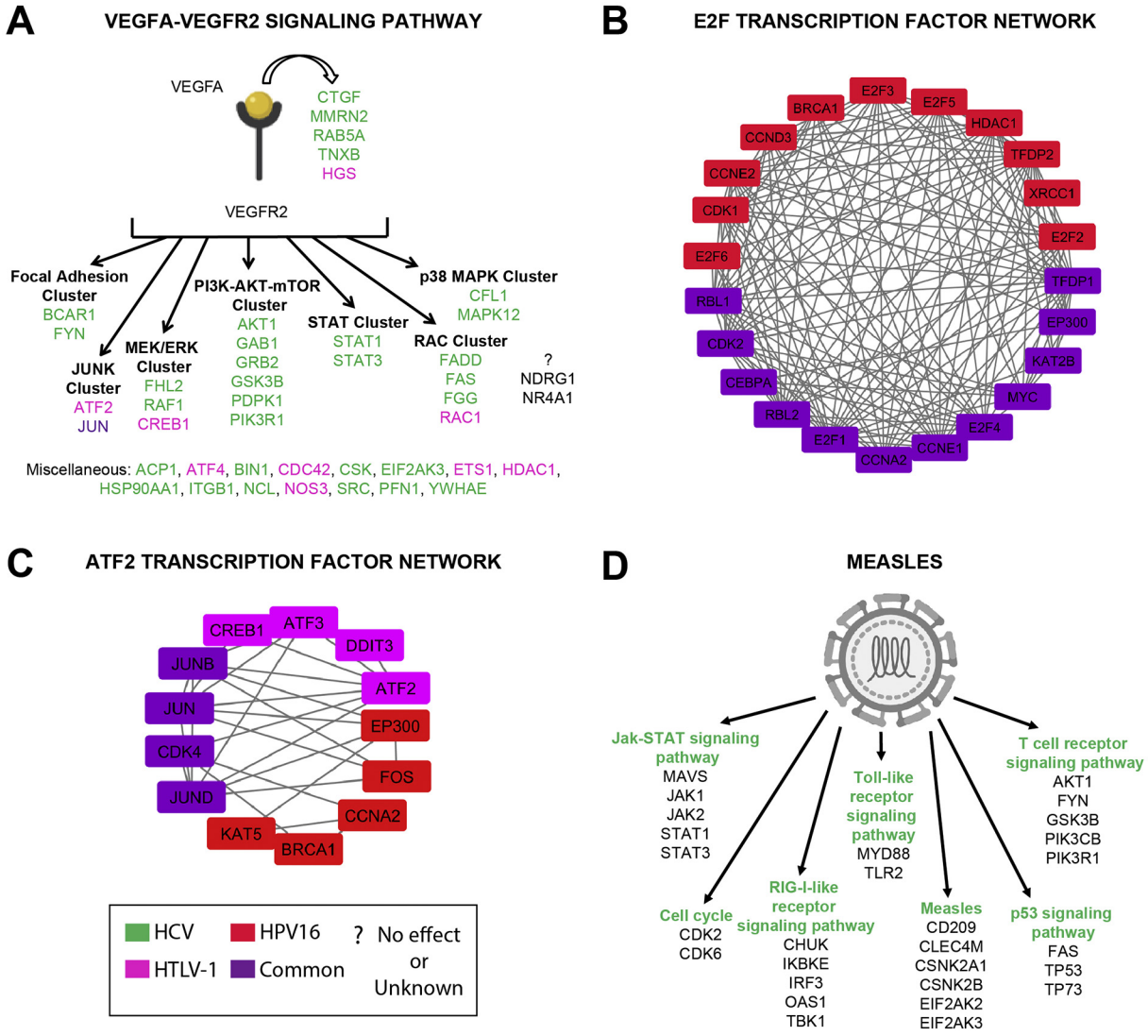


Fig. 7. The oncoviruses host proteins targeted the VEGFA-VEGFR2 signaling pathway, ATF2 transcription factor network, E2F transcription factor network and Measles. (A) VEGFA-VEGFR2 signaling pathway is initiated by the interaction of the VEGFA (interact with CTGF, MMRN2, RAB5A, TNXB and HGS) ligand to VEGFR2. It leads to activation of multiple downstream signaling cascades including focal adhesion (BCAR1 and FYN), JNK (ATF2 and JUN), MEK/ERK (FHL2, RAF1 and CREB1), PI3K-AKT-mTOR (AKT1, GAB1, GRB2, GSK3B, PDPK1 and PIK3R1), STAT (STAT1 and 3), p38 MAPK (CFL1 and MAPK12) and RAC (FADD, FAS, FGG and RAC1). Also some of the host proteins have miscellaneous functions in this pathway. The green host proteins represent HCV, the pink HTLV-1 and the purple common. The question mark represents the host protein has no effect or is unknown. (B) The host proteins interaction that have attended in ATF2 transcription factor network were obtained from STRING: functional protein association networks [117] and the interaction score was identified as > 0.90. The pink host proteins represent HTLV-1, the red HPV16, and the purple common in both viruses. The question mark represents the host protein has a no effect or is unknown. (C) The host proteins interaction that have attended in E2F transcription factor network were obtained from STRING: functional protein association networks [117] and the interaction score was identified as > 0.90. The red host proteins represent HPV16, and the purple common in HPV16 and 18. The question mark represents the host protein has no effect or is unknown. (D) The measles pathway can be activated from multiple downstream signaling pathways such as Jak-STAT (MAVS, JAK1/2, STAT1/3), RIG-I-like receptor (CHUK, IKBKE, IRF3, OAS1, and TBK1), Toll-like receptor (MYD88 and TLR2), T cell receptor (AKT1, FYN, GSK3B, PIK3CB and PIK3R1), p53 signaling (FAS, TP53 and TP73), cell cycle (CDK2 and CDK6). Also some elements have specific roles in the measles pathway (CD209, CLLEC4M, CSNK2A1, CSNK2B, EIF2AK2 and EIF2AK3).

4.12. Oncostatin M pathway

Oncostatin M is a cytokine that belongs to interleukin-6 families. HBV, HCV and HPV16 were the three oncoviruses that their host proteins associated with Oncostatin M pathway. HBV's virus protein X interacted with all host proteins. Moreover, for this pathway NS5A, Core virus proteins mostly interacted with host proteins of HCV (70%) and E7 virus proteins mostly interacted with host proteins of HPV16 (62%). Although Oncostatin M has many functions a few of the functions of it is hepatocyte differentiation and liver regeneration. In a study, it was reported that together with the interferon-α, the HCV genome replication can be suppressed by Oncostatin M. In the same study, cells were treated with Oncostatin M in combination with IFN-α and it was reported that Oncostatin M inhibited Core and NS5A expression in a dose-dependent manner. As a result, in this study Oncostatin M was proposed as a potential anti-HCV marker [101]. Oncostatin M has a clinical significance in cervical cancer and represents a potential target for the disease. Oncostatin M's receptor is up-regulated in cervical cancer patients and associated with worse clinical outcomes [102]. Also in another study, it was demonstrated that that E6 and E7 expression up-regulates the Oncostatin M receptor [103].

4.13. ATF2 transcription factor network

ATF2 is one of the members of the AP1 transcription factor family. The latest evidence has been shown that the ATF-2 has roles in inflammation. The multiple genes which interfering in inflammation based processes (e.g. chemokines, pro-inflammatory cytokines, and cell adhesion molecules) transcription are stimulated as a result of ATF2 transcription factor activation [104]. HTLV1 and HPV16 were the two oncoviruses that their host target proteins associated with ATF-2 transcription factor network. During the viral replication, HTLV1 encoded protein Tax, binds to CREB/ATF complexes to activate ATF1–4 transcription factors [105] (Fig. 7B). HBZ is the HTLV1's other virus protein in which the host proteins enriched (the ratio was 66%). The only association of ATF2 and HBZ virus protein has been demonstrated in the literature in vitro [106]. The association between ATF2 and E7 virus protein (host proteins participating in this path were 72% related to this virus protein) has not been reported in the literature until now as far as we know.

4.14. E2F transcription factor network

The key role of E2F transcription factors is that its members regulate cell cycle processes especially G1/S transition and S phase entry. These members are positive regulators of the genes that have functions in DNA synthesis. The key target of the E2F is a well-known tumor suppressor protein which is pRB and its pathway as mentioned. This pathway is also known as pRB-E2F pathway and has an essential role in cell division control [107]. In this study, both onco-HPV host proteins enriched with E2F transcription network. The HPV16 and 18's virus proteins, E7, which host proteins generally interacted with, can to bind and make pRB unstable (HPV16–78% and HPV18–71%). This instability results in inactivating pRB-E2F repressor complexes and provides uncontrolled cell cycle progression [108] (Fig. 7C).

4.15. Proteasome and ubiquitin mediated proteolysis pathway

The proteasome resulted in an important pathway for EBV and HPV18 host proteins. These host proteins generally interacted with EBV's LMP2 and BVLF1 (57%) and HPV18's E6 (100%) virus proteins. Carcinogenic viruses use the proteasome systems to support their replication, suppress cell death and to handle immune responses. Like other oncoviruses, deviation in proteasome activity appears in EBV infected cells [109]. It was reported that HPV18 E6 can interact with multiple proteasome subunits [110]. The ubiquitin mediated proteolysis came into prominence for EBV, HHV8 and HPV16 host proteins. The BPLF1, LMP2 (35%) for EBV, ORF73 (40%) for HHV8 and E7 (60%) for HPV16 are the virus proteins that associated host proteins that interacted with this pathway. In a study, it was reported that E7 is regulated by the ubiquitin proteasome pathway in HPV positive cervical carcinoma cells [111].

4.16. Nucleotide excision repair and kit receptor pathways

HHV8 host proteins resulted specifically to nucleotide excision repair and Kit Receptor pathways. The host proteins that enriched with nucleotide excision repair commonly (50%) interacted with ORF73 while the host proteins enriched with Kit receptor pathway interacted with K15-M and gM with a ratio of 50%. Nucleotide excision repair pathway is accountable for the repair of five nitrogen-containing bases. It was encountered that the repair pathways are activated in herpes viruses [112]. A study was conducted by Kerr et al., was demonstrated that the over-expression of c-Kit signaling pathway constituents in multiple human Kaposi sarcoma patients [113].

4.17. AP-1 transcription factor network

The AP-1 transcription factor network resulted in enrichment of HTLV1 host proteins. The AP-1 transcription factor has binding sites for most of the inflammatory mediators; therefore, it's generally become activated in any bacterial or viral infections. The transcription factor, AP-1, has subunits of JUN and FOS proto-oncogenes and they are generally acting as positive regulators while regulating the inflammation [83]. In HTLV1 infection or ATLL development, it was suggested that AP-1 demonstrates the aberrant function and contributed the HTLV1 phenotype occurrence. Moreover, high levels of JUN, FOS and AP-1 binding activity were observed in ATLL patients in this study [114]. The host proteins enriched in this pathway generally interact with HBz (61%) virus protein. HBZ interacts and regulates transcriptional properties of the JUN family and sequestration of JunB and c-Jun in HBZ nuclear bodies obstructs their transcriptional activities [115].

4.18. N-glycan biosynthesis

The N-glycan biosynthesis specifically associated with HPV18 host proteins. These host proteins with a ratio of 70% interacted with E5's virus proteins, however there hasn't been any association reported in the literature between the pathway and the E5. On the other hand, the viruses and host cell surfaces are encrusted by various glycan compounds. These compounds have versatile functions on both viruses and hosts. The glycans assist the viral genome entry to the host and viral proteins proteolysis for the viruses. Besides the host proteins, the glycans function as primary or co-receptors and attachment factors that can be identified by the glycans of the viral surface [116].

4.19. Other signaling pathways

HCV host proteins were associated with the measles (Fig. 7D), focal adhesion, PDGFR-β signaling, PI3K-Akt signaling, apoptosis, and FoxO signaling pathways. Besides the apoptosis pathway, NS5A was the virus protein that host proteins mostly interacted with. The host proteins associated with apoptosis pathway interacted with Core virus protein. In addition, ATF6-α activates chaperone genes pathway resulted specific to HBV host proteins. Measles is known as a childhood infection which is caused by the rubeola virus and it has a vaccine today. Due to the measles vaccine is very safe to use and the virus has the ability to be engineered recently it become a potential candidate to be used in malignant cells therapy. In cancers such as ovarian and myeloma the engineered measles virus gives promising results [118]. In addition, the researchers tried to develop the HCV vaccine by using two recombinant measles viruses and emphasized the benefits of measles virus vectors for the HCV vaccine [119]. It was pointed out that via focal adhesion activation pro-oncogenic and fibrogenic phenotype induction occurs in HCV positive hepatic stellate cells [120]. Although there isn't a relationship between HCV infection and PDGFR-β signaling it was reported that, the up-regulation of PDGFR-β induced the liver carcinogenesis development [121]. PI3K-Akt pathway becomes activated in HCV infected cells to promote cell entry and reproduction. Moreover, researchers indicated the pathway can also enhance HCV translation via regulatory proteins [122]. The host cells protect themselves against virus infections by apoptosis. It is widely accepted by the researchers that, apoptosis occurs in the liver of HCV-infected patients; however, the certain mechanism how apoptosis mediated has not been clear. A study showed that, HCV infection induces apoptosis via Bax-triggered, mitochondrion-mediated, caspase 3-dependent pathway [123]. As a result of HCV infection FOXO activity is increasing and this may lead to HPV-induced insulin resistance and the persistent infection [124].

5. Conclusions

VHPIs are liable for every aspect of infection including viral

infections therefore these interactions are the building block of oncoviruses because they improve our overall understanding of the molecular basis of pathogenicity. The analysis of VHPIs represents the root of the viral cancers establishment and crucial for developing better prediction and treatment approaches. In this study, by analyzing VHPIs, we aimed to deeply understand the general signal events involved in viral oncogenesis mediated by seven oncogenic virus infections and found the basis of targeted therapeutic development. The study revealed that the TGF-β signaling pathway, cell cycle process, pRB pathway, and androgen receptor signaling pathway were targeted with several viruses. Besides several pathways including measles, focal adhesion, and N-glycan biosynthesis were identified as virus-specific targeted processes. We believe that this study created a map of systems for these seven oncoviruses that could represent the milestones of future advances. The resulting pathways and their component inhibitors can contribute to the development of anti-viral vaccines and drugs and enable new drivers of viral malignancies to be discovered in future studies.

VHPIs support the enormous potential for the development of antiviral molecules. However, small inhibitor molecules or drugs that disrupt VHPIs have been studied for various viruses, but it should not be forgotten that there is still much to done. In this study, the viral proteins that interacted with host proteins of the significant pathways were discussed which this information opens new horizons for the discovery of virus- or host-oriented drugs. These viral or host proteins can be countable as potential therapeutic targets that can be manipulated by existing small inhibitor molecules. Moreover, the drugs that used today can reposition as new antiviral agents. Namely, in this study beyond the discovery of which oncogenic viruses hijacked which pathways, we tried to offer identification and development of drugs and small inhibitors against host and VHPIs to the research field. The construction virus host interactomes and investigating the hijacking pathway is a starting point to support this field. We believe that all these will help the scientific community to succeed in the decisive goal of better prevention and treatment of virus- related cancers.

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CRediT authorship contribution statement

Medi Kori:Conceptualization, Methodology, Data curation, Visualization, Writing - original draft.**Kazim Yalcin Arga**:Conceptualization, Supervision, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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