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Original Article

Deregulation of the Hippo Signaling Pathway in Virus-Associated Cancer

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Abstract: *Hippo signaling has been recognized as a newly identified tumor suppressor signaling pathway that can regulate cellular processes including regeneration, cell death, differentiation, and development. Its dysregulation through overexpression of YAP (Yes-associated protein) and TAZ (PDZ-binding motif) as two main oncogenic factors of the Hippo pathway has a crucial role in several cancers. Because of the limited prognosis and therapeutic targets, further understanding of molecular pathways involved in tumorigenesis is one of the interesting issues in studies. Here, we demonstrated that some viruses, through dysregulation of the Hippo signaling pathway can be implicated in transformation, metastasis, and chemotherapeutic drug resistance in virus-related cancer and also help processes involved in the pathogenesis of viral infection such as persistence.*

Keywords: *Hippo signaling pathway, virus, cancer*

INTRODUCTION

The Hippo signaling pathway was discovered to be involved in controlling organ size and cell differentiation in Drosophila melanogaster for the first time, and it has recently been recognized as a critical tumor-suppressor network [1]. Consequently, the correlation of deregulated Hippo pathway signaling in several cancer types such as breast, liver, lung, prostate, gastric and colorectal tumors has been reported. In addition to this role, the Hippo pathway is involved in the conservation of tissue-specific stem cells, tissue renewal, and damage recovery [2,3].

The Hippo pathway is a kinase cascade that includes kinases MST1 and MST2 (also known as STK4 and STK3), large tumor suppressors 1 and 2 (LATS1 and LATS2) and adaptor proteins SAV1 (Salvador homolog 1), and MOB kinase activator 1A and 1B (MOB1A and MOB1B). MST1 and MST2 induce LATS1 and LATS2 phosphorylation, which in turn facilitates LATS-dependent phosphorylation of the homologous oncoproteins YAP (Yes-associated protein; encoded by YAP1) and TAZ (PDZ-binding motif, also known as WWTR1) that inhibit the activation of transcriptional co-activators Yorkie (Yki), YAP, and TAZ [4-6].

Hippo pathway main effectors YAP and TAZ, phosphorylation by the Hippo core complex can retain them in the cytoplasm where they expose to proteasomal degradation [7]. Since TAZ/YAP mutations rarely happen other mechanisms are more likely responsible for Hippo's relevance in cancer. Growing evidence suggests that a complex network of interactions with critical pathways can modulate YAP/TAZ activity such as TGFB, GPCR, Notch, EGFR, and angiogenesis [8].

In the case of modulation of Hippo signaling, stimulation of G protein-coupled receptors (GPCRs) associated with Gas might lead to phosphorylation of LATS and consequently down-regulation of YAP. GPCRs as integral membrane receptors activated by external ligands their binding leads to the activation of the alpha-subunits of subclasses of G proteins. In

contrast, stimulation of Ga12/13-coupled GPCRs is associated with suppression of LATS and up-regulation of YAP [9,10].

Other instances of membrane receptors that reported to modulate YAP expression are the receptor tyrosine kinases EGFR and ERBB4 [11]. The EGFR ligand amphiregulin (AREG) is an important YAP target that provides a positive cycle that mediates YAP and EGFR signaling and can stimulate intensifying proliferative signals from both pathways. Also, ERBB4 as a member of the EGFR family, via interaction of YAP and possibly TEAD1 with its intracellular domain in the nucleus, demonstrated either induction of YAP activation or increase expression of YAP target genes [12].

Oncoviruses are associated with about 12% of all human cancers. People carry at least one of these oncoviruses in their life, but these infections only a small proportion of these individuals go on to develop cancer [13]. The interaction between viral factors and the host is a complex process to provide a desirable microenvironment for oncogenesis [14]. The aim of this review is the improvement of our understanding of mechanisms of oncogenesis modulation by different viruses and a better understanding of tumorigenesis that may result in more effective targeted therapy in the future. By the recent rises in viral-related carcinomas and the link between Hippo and viruses, we assessed to determine if Hippo signaling is the main target in such cancers.

HEPATITIS B Virus

In recent decades human hepatocellular carcinoma (HCC) with approximately 746,000 deaths per year, identified as the sixth most common cancer and the third leading reason for cancer-related deaths in human populations [15].

Hepatocarcinogenesis, due to several genetic and epigenetic changes which occur through different stages of the disease is known as a complex process [16]. As regards the fact that hepatitis B virus (HBV) infection has a key role in the establishment of HCC, it is important to know its proteins' roles in Hepatocarcinogenesis. HBV encoded four proteins and among these proteins, the HBV X protein (HBx) is a multifunctional protein and has a critical role in hepatocellular carcinogenesis. Multiple signaling pathways are participating in the HCC progression [17,18].

Many studies are designed to assess the molecular and cellular mechanism of HCC because finding a suitable treatment for HCC is an immediate task for healing patients suffering from HCC. Recently, numerous researches have shown the role of the Hippo pathway in organ size control, cell proliferation, cell death, and tumor progression [19,20]. Although the role of YAP, which is a downstream factor of the Hippo signaling pathway in HCC, remains unclear, this review provides a vision for the regulation of YAP upstream and downstream effectors involved in hepatic cancer [21].

Interestingly, the hyperexpression of YAP can result in epithelial-to-mesenchymal transition (EMT) and may inhibit apoptosis, growth factor-independent proliferation, and anchorage-independent growth [22]. The liver has an amazing characterization that can lead to having unique features such as Growth control which in the liver has some unusual features. The liver has been known for its noticeable capacity to renew consequently to a two-third partial hepatectomy (PHx) or injury. The natural liver in an adult is composed of two parenchymal cell types — hepatocytes and cholangiocytes [23].

Dedifferentiated hepatocytes as multipotent stem cells are capable to be the source of tissue renovation in the damaged liver [24]. Factors of the Hippo signaling pathway including MST1 and MST2 have been demonstrated to have key roles in adjusting or restricting liver progenitor cells. Thus, it is predicted that the Hippo can be involved in the suppression of stem/progenitor cell proliferation in the mature liver [25]. Furthermore, some studies also showed that knocking out YAP resulted in hepatocyte and cholangiocyte injury and loss [26].

In synergy with the functional roles of Hippo signaling, any change of upstream effectors of the hippo pathway like Mst1/2 can result in over-proliferation and sometimes Hepatocarcinogenesis. Since HBV is commonly the major reason for HCC; YAP possibly has an important role in its carcinogenesis. Interestingly, YAP expression is frequently shown to be increased in HBV infections resulting in HCC, infected cell lines, and HBx transgenic mice. Through the CRE-dependent HBx attaching to the YAP promoter, HBx can increase YAP and follow stimulate YAP target genes which leads to the proliferation of hepatoma cells. Findings revealed the importance of the Hippo signaling pathway in cancer and suggested new treatments for HBV-infected patients to inhibit progression to HCC [27].

Studies have revealed that the loss of Mst1/2 may result in the promotion of several tumors in the liver of mice. The loss of both Mst1/2 is required to affect the liver since the loss of Mst1 or Mst2 is not effective on liver size or the number of liver tumors [28]. These findings firmly revealed the effect of Mst1/2 on YAP activity. Interestingly, lack of YAP phosphorylation and impairment of Mst1/2 activity that occurs in carcinogenesis have been reported in 30% of HCCs [29].

The liver-specific NF2/merlin inactivation may lead to an increase in hepatic stem cell number with a lack of any changes in differentiated hepatocytes [30]. The studies on Sav or Mst1/2 positive livers for assessment of the effectiveness of

YAP/TAZ and Lats1/2 phosphorylation in the hippo pathway displayed complex results regarding the need for Mst1/2 or Sav in Lats1/2 phosphorylation [29,31] and since in mouse fibroblasts, for YAP phosphorylation, presence of Mst1/2 was not crucial, it is considered that the pathway may be specific in hepatitis [29].

In a study on transgenic mice, it was shown that YAP induction can lead to abnormal hepatocyte expansion after 2 months and consequently several nodes have been reported in hepatitis [32]. The nodes were reported to be a collection of hepatocytes in a generative condition that condensed the near parenchyma and revealed severe HCC. Also, this liver-specific loss of either Mst1/2 in hepatocytes leads to noticeable liver growth because of its deregulated cell proliferation [28].

On the other hand, when transgenic mice models with YAP hyperactivity crossed with mice lost its DNA-binding domain TEAD2 do not promote HCC. Lacking YAP overexpression may lead to having mice with livers deficiency in Nf2/merlin after crossing with mice that have the defective TEAD2 gene, confirming the therapeutic concept of using the TEAD with YAP in the complex. Verteporfin injection has been demonstrated to reduce liver mass in YAP transgenic animal models and also has no side effect on the wild mice tissue homeostasis, defining the potency of compounds for therapeutic administration in patients with HCC. Verteporfin displayed numerous important features that make its clinical execution for HCC promising [32].

In HCC cell lines induction of YAP results in further resistance to doxorubicin-induced apoptosis; while, inhibition of YAP expression by RNA interference has been reported to reverse YAP-increased chemoresistance. These processes are mediated by the MAP kinase signaling pathway induction rather than an AKT-dependent mechanism of chemoresistance [33]. This process of chemoresistance occurs after treatment by the MEK1/2 suppressor U0126 before doxorubicin injection, which noticeably reduces cell vitality in YAP overexpressing HCC lines [34].

Survivin is accepted as an antiapoptotic protein and in HCC patients identified to be associated with a weak prognosis. Recent studies have shown YAP overexpression is in associate with survivin induction in patients with HCC. It seems that YAP has this oncogenic capacity on the cell with a survivin increase leading to carcinogenesis [35].

HUMAN PAPILLOMAVIRUS

Cervical cancer considers the most important cancer in women because it is the fourth leading reason of cancer-related death in women. Due to the detection of human papillomavirus (HPV) DNA in the majority of cervical cancer patients, high-risk HPV types recognize as the cause of cervical cancer [2].

In a study by Chunbo He et al results implicated that YAP1, one of the main oncogenic effectors of the Hippo pathway, was (11%) amplified several times, whereas LATS1/2, MST1, and FATs, that identified as upstream tumor inhibitors of the Hippo pathway, were not detectable or mutated in cervical cancer patients. YAP1 induction in cervical cancer cells noticeably triggers the expression of EGFR and its related ligands AREG and TGFa. On the other hand, TGFa and AREG, through EGFR signaling, can block the Hippo pathway and induce YAP protein (dephosphorylated LATS1, MOB1, and YAP1) to promote cervical cancer cell growth. Recognition of this circumstance between Hippo/YAP and EGFR in human cervical cancer provides an opportunity to combine targeting of the Hippo/YAP and EGFR pathways to have an efficient way to treat cervical cancer [36].

In addition, hyperactivation of YAP1 can be an important mediator to the persistence of HPV infection. First, studies report that hyperactivated YAP1 increases the expression of HPV receptor molecules such as ITGRA6, SDC1, and EGFR, which through the early stage of HPV infection can help the HPV entry process. Second, is that hyperactivation of YAP1 in cervical epithelial cells may reduce viral pattern recognition by the innate immune system. Some studies report that TLR2 and TLR4 and adaptor proteins MYD88 and TRIF were suppressed, which could facilitate HPV infection. Third, there is evidence that ectopic expression of YAP may suppress the activation of transcriptional factors that are essential for the production of type I IFNs, including IRF1, IRF3, and IRF7, leading to the reduction of IFNA1, IFNB1, and IFNE in hers. IFNs can activate antiviral factors of the immune system and play their role in the progress of innate and adaptive immune responses. Also, some studies showed that the expression and activation of main components of the type I IFN pathway, like IFNAR2, STAT1, JAK1, and IRF9, are suppressed by the expression of YAPS127A in the epithelium of the cervix. Suppression of the IFNAR2/JAK1/STAT1 signaling pathway leads to decreasing of antiviral ISGs, such as MX1, CH25H, and IFITMs (blockers of virus entry), and APOBEC3G, OAS1, ISG15, and IFI44L (suppressors of virus translation and replication) [37].

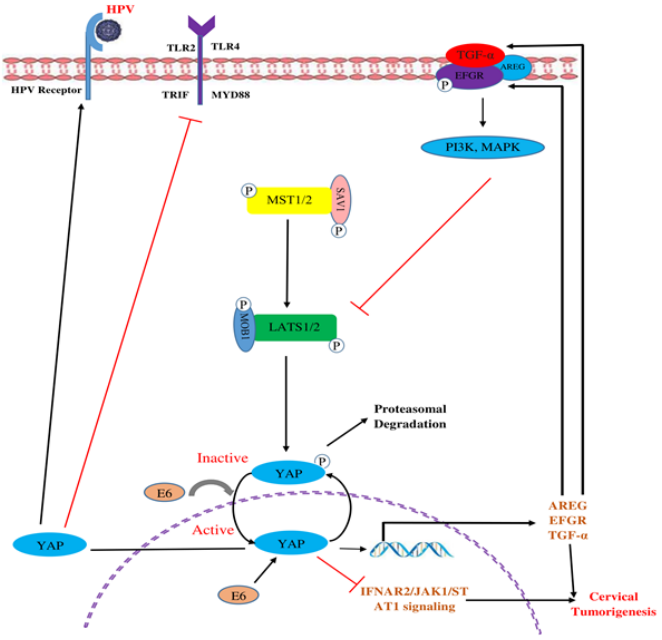
The HPV oncoproteins E6 and E7 expression can result in the suppression of some essential tumor inhibitors such as TP53 and RB1 in many types of cells [38,39]. Suppression of TP53 and RB1 extends cell life (by inhibition of death) and may lead to immortality in cervical epithelial cells, facilitating malignancy of HPV-infected cells by an oncogenic signal (including hyperactivation of YAP1) [40,41].

In epithelial cell cultures, cell-cell contact development is a key step in differentiation before the formation of distinguished apicobasal surfaces. The transcriptional co-activator YAP plays a key role in this event [42,43]. Numerous reports have shown that cell-cell contacts activate the LATS1/2 serine/threonine kinases which can phosphorylate YAP [44,45]. During phosphorylation, YAP restricts from the nucleus and it inhibits the transcription of key genes in the cell cycle [42,46]. A cervical cancer study recently demonstrated that in high-grade cervical lesions levels of nuclear YAP are increased [47].

There are some studies demonstrating that HPV16-E6 or HPV16-E6/E7 double-transgenic mice treated with estrogen may promote cervical cancer [48,49]. Related to that result, other studies report that YAP was increased in the E6 and E6/E7-induced cervical tumor cells, and YAP was localized in the nucleus of these cells [36]. The human foreskin keratinocyte(HFK) "raft" culture infected with HPV16 makes a unique model for the assessment of the HPV16 proliferation cycle [48,50].

YAP can be inactivated by two mechanisms: first, the Ser127 phosphorylation-mediated spatial adjustment (system of nuclear-cytoplasmic shuttling); and second, the Ser397 (Ser381 in YAP protein isoform 2) phosphorylation-mediated adjustment (the phosphodegron-induced degradation). These two mechanisms are applicable directly to prevent YAP oncogenic activity [51,52]. It has been observed that CK1d/ε and SOCS6 proteins are crucial for YAP degradation [52,53]. Although expression of HPV E6 in HT3 cells causes a noticeable increase in CK1d/ε and a reduction in p-YAP (S397), it suggests that the CK1d/ε pathway may not participate in the HPV E6-mediated YAP protein turning [40]. HPV E6 increases YAP protein levels, but also it upregulates the expression and activation of AREG protein in the cell culture. These observations showed a possibility that HPV E6 protein may be associated with the Hippo-ERBB signaling circle and also implicating the transformation and development of cervical cancer. Interestingly, HPV16 E6 and E7 could transcriptionally activate EGFR expression [40,54]. The HPV16 E6 makes receptor protein tyrosine kinase to signaling and facilitates the internalization of phosphorylated receptors [55] (Figure 1).

Figure 1: Schematic presentation of reciprocal interactions between HPV and Hippo signaling pathway



POLYOMAVIRUSES

Through identification of SV40 tumorigenesis in specific laboratory animals and transforms several types of cultured cells offered an opportunity to discover the molecular basis of the tumor. Viral oncogenes were introduced as key tools in the recognition of tumor inhibitor pathways in human primary cells. The p53 and p16/pRb tumor inhibitor pathways have been introduced as targets of SV40 large T. Hahn's study indicates a transformation model [56], expressed HRas V12, and a construct encoding SV40 large T to target the p14ARF/p53 and p16INK4A/pRb pathways. Recently it is discovered that SV40 small T (ST) (encoded in the large T construct) is needed without requiring large T to enhance anchorage-independent growth [57].

Murine polyomavirus also has frequently presented visions into tumorigenesis by demonstrating important modulation

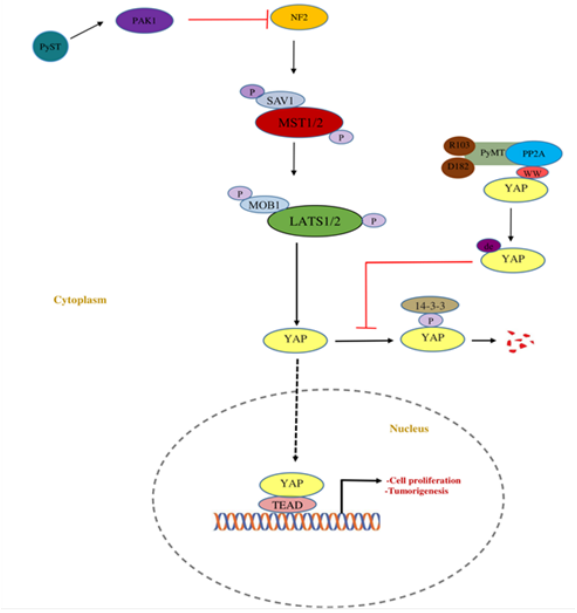
mechanisms including tyrosine phosphorylation and phosphoinositide 3-kinase (PI3K) signaling. Previous studies showed that polyomavirus small T antigen (ST) associates with YAP, an effector of the Hippo pathway, to modulate differentiation. Other studies introduced YAP as a target of middle T antigen (MT) required for transformation [58,59]. Wild-type MT via a surface containing residues R103 and D182 binds to the YAP WW domains. Mutation in each one of R103 or D182 of MT disrupts YAP binding. This happens without disturbing bindings to other signaling factors or the strength of PI3K or Ras signaling. One of the other genetic disruptions of MT binding to YAP or stopping of YAP via short hairpin RNA (shRNA) decreased MT transformation, offering that YAP has an important participation in the transformed phenotype. MT targets YAP via triggering signaling pathways that affect it and consequently bind to it. The signaling of either wild-type MT or the YAP associate MT mutant develops YAP phosphorylation at S127 and S381/397 (YAP2/YAP1) [58]. In addition to previous roles of these phosphorylated serines, MT signaling results in the reduction of YAP from the nucleus and degradation. When MT Binds to YAP, it associates YAP with protein phosphatase 2A (PP2A), resulting in the YAP dephosphorylation together with the MT complex. Furthermore, this process results in the increase of YAP in membranes. Overall, these data demonstrate that YAP develops MT transformation by mechanisms that may be due to YAP's established major transcriptional activation functions [60].

The capability of ST to discuss anchorage-independent growth brings with it its ability to inactivate the PP2A function. Suppression of PP2A may bypass the need for ST in cellular transformation models, and mutations inactivating PP2A subunits have been recognized in tumors [61,62]. PP2A has several substrates including, AKT, b-catenin, and c-Myc which are defined to be activated by ST. Although the total overexpression of these proteins only incompletely replaced ST in cellular transformation, it suggests that undefined PP2A effector pathways may be involved [62].

Hippo/MST kinase acts by a membrane-associated complex including the tumor inhibitor NF2/Merlin [63]. MST kinases enhance activating LATS kinases, which subsequently phosphorylation of the transcriptional coactivators YAP and TAZ, resulting in their inactivation of them via cytoplasmic isolation and increased degradation [64-66]. Suppression of YAP and TAZ restricts proliferation and triggers apoptosis [67].

Interestingly, it is observed that overexpression of YAP is enough to result in tumorigenesis in mice. Both SV40 ST and the Merkel cell polyomavirus ST induce endogenous YAP. Some studies provide data that ST acts through PAK1 to inactivate the NF2 tumor suppressor to alleviate the inactivation of YAP. Activation of PAK1 at the cell membrane is sufficient to bypass the requirement for ST. Restricting PAK1 activity disrupts the transforming capability of the ST protein. Therefore, ST detaches YAP from modulation via the Hippo tumor inhibitor pathway. Induction of Active YAP is required and enough to replace ST in cellular transformation. Therefore, the YAP proto-oncogene is an important mediator of the transforming properties of the ST oncoproteins [68] (Figure 2).

Figure 2: Schematic presentation of reciprocal interactions between Polyomaviruses and Hippo signaling pathway



EPSTEIN-BARR VIRUS

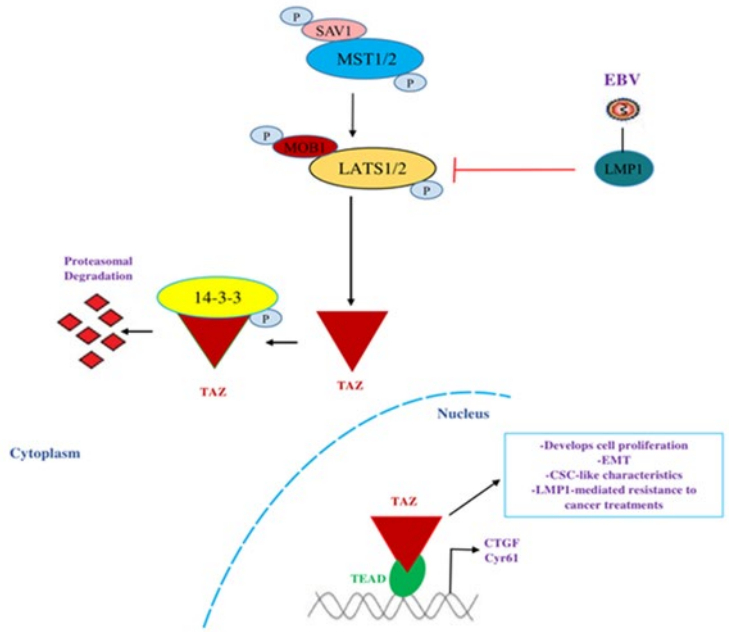
Epstein-Barr virus (EBV) is recognized as a linear dsDNA virus and a member of the human gamma-herpesvirus family that observed to correlate with various B-cell lymphomas, such as Burkitt's lymphoma, Hodgkin's lymphoma, and other tumors like nasopharyngeal carcinoma, T-cell non-Hodgkin lymphomas, and gastric carcinomas. These cancers are firmly correlated with latent Epstein-Barr virus (EBV) infection, genetic factors, and environmental factors thus EBV can regulate mechanisms affecting carcinogenesis, proliferation, death, migration of cells, epigenetic changes in lymphocyte-specific development, and induce cell immortalization. The main mechanisms related to the carcinogenic effectors of EBV consist of LMP1, LMP2, and microRNA that we will introduce bellow [69-71].

The capacity of LMP1 to immortalize and transform cells possibly depends on simultaneously regulating cellular signaling pathways which suppress apoptosis or mediate proliferative, growth factor-like effects. Furthermore, LMP1 can induce a cancer progenitor cells (CPC)-like appearance in epithelial cells, offering that LMP1-induced phenotypic alterations can be related to the promotion of cancer [72]. Therefore, the mechanism and role of LMP1 in immortalizing and transforming cells is complex and several important questions remain to be answered.

Previous studies demonstrated that LMP1 could induce actin remodeling [73]. The actin cytoskeleton is a key factor for the modulation of the Hippo pathway. These data make us investigate How LMP1 can upregulate TAZ expression by inhibition of the Hippo pathway. In a study, findings determined that the LMP1-targeted CNE1-LMP1 cells decreased TAZ expression. The target genes of TAZ are CTGF and Cyr61. Other researches demonstrate that LMP1 can trigger the mRNA expression of CTGF and Cyr61 [74]. There is the possibility that TAZ may be involved in the positive modulation of cell proliferation and survival associated with the obtaining of cancer stem cell (CSC) properties and epithelial-to-mesenchymal transition (EMT) [75, 76]. Previously, some studies have been done to determine if LMP1 can develop EMT by TAZ and define if the morphology alters. The result of these studies has shown some morphological variations from epithelial to mesenchymal phenotypes. LMP1 can develop cell proliferation, EMT, and CSC-like characteristics by TAZ and give us some visions and rationales for the LMP1-mediated resistance to cancer treatments [74].

On the other hand, it has been shown that phosphorylation of the WW domain of the transactivator TAZ by activated LATS1/2, leads to TAZ degradation [77]. Studies have shown that LMP1 can elevate the level of TAZ and increase TAZ nucleus translocation. Thus, it is possible that LMP1 could suppress LATS1/2 activation, resulting in the enhancement of TAZ stability [74] (Figure 3).

Figure 3: Schematic presentation of reciprocal interactions between EBV and Hippo signaling pathway



KAPOSI'S SARCOMA-ASSOCIATED HERPESVIRUS

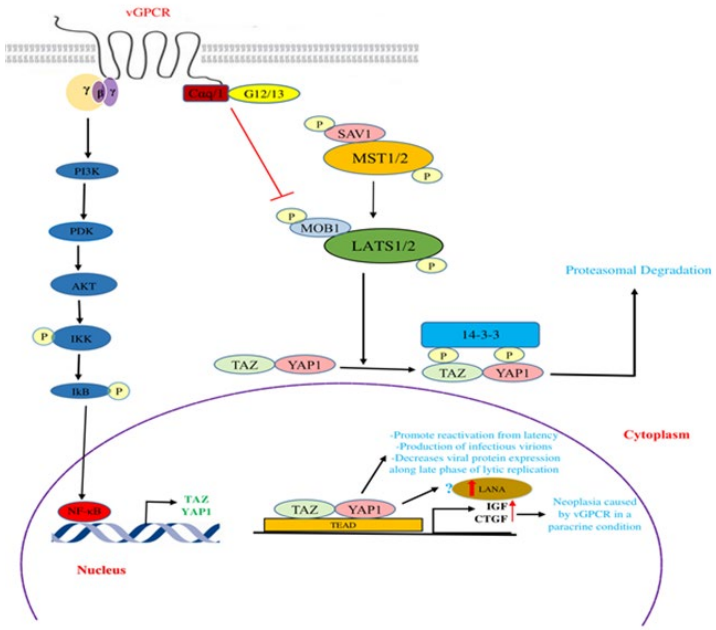
Kaposi sarcoma-associated herpesvirus (KSHV) is a double-stranded linear DNA virus of the human gamma-herpesvirus family from rhadinovirals and also an oncogenic virus that is responsible for human Kaposi sarcoma (KS) and is associated with an AIDS-defining malignancy. One of the main viral proteins of KSHV is a viral G-protein-coupled receptor (vGPCR). KSHV encodes vGPCR which is essential for the initiation and progression of Kaposi sarcoma [78-80]. Previous studies identified that YAP/TAZ, two homologous oncoproteins that can be suppressed by the Hippo tumor inhibitor pathway, activates in KSHV-infected cells in in vitro conditions, KS-like tumors in mice, and clinical human KS samples [81].

The molecular process to which vGPCR contributes in KSHV-induced oncogenesis remained uncertain but it is suggested to be involving both direct and paracrine oncogenic effects, that are activated by growth factors including VEGF and PDGF induced by vGPCR [82,83]. The KSHV protein (vGPCR) activity is via Gq/11 and G12/13 to suppress the Hippo pathway kinases Lats1/2, enhancing the activation of YAP/TAZ. Also, clearance of YAP/TAZ inhibits vGPCR-induced cell proliferation and tumorigenesis in a xenograft mice model. The transformation of cells mediated by vGPCR is sensitive to pharmacological blockers of YAP [84,85].

It is demonstrated that the Knockdown of YAP or TAZ can inhibit the vGPCR-induced CTGF expression, offering that YAP/TAZ enhances the biological functions of vGPCR. In addition to the Hippo pathway, studies have shown other signaling pathways that have also been related to the oncogenic effect of vGPCR [85]. For instance, PI3Kγ is activated by vGPCR and has a key role in vGPCR-induced sarcomas, whereas NFkB has an indirect role in vGPCR-induced paracrine neoplasia. It seems the activation of YAP/TAZ is associated with other vGPCR downstream signaling events, including PI3K and NFkB, which generally participates in KS tumorigenesis in KSHV-infected patients. It is noticeable that YAP/TAZ also upregulates the expression of several growth factors, including CTGF and insulin-like growth factor (IGF) [86,87], that can be associated with neoplasia caused by vGPCR in a paracrine condition [81, 88].

Some studies revealed that Hippo pathway activation has a key role in the promotion of the lytic cycle and transition from latency. Inactivation of the Hippo pathway modulator YAP1 may promote reactivation from latency, lytic protein increase, and production of infectious virions. Interestingly, expression of the YAP1-inactivating kinase LATS1 consequently induces reactivation from latency. Conversely, LATS1 silencing decreases viral protein expression along the late phase of lytic replication. However the detailed mechanism of switching of KSHV latent/lytic by the Hippo signaling pathway is still unclear, increased amounts of nuclear centers containing the viral latency-associated nuclear antigen (LANA) have been reported in YAP1-silenced cells [89] (Figure 4).

Figure 4: Schematic presentation of reciprocal interactions between KSHV and Hippo signaling pathway

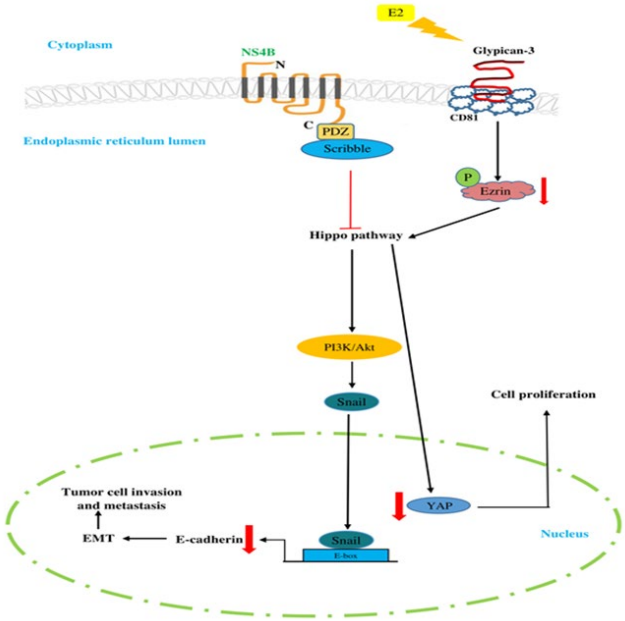


HEPATITIS C VIRUS

Hepatitis C virus (HCV), a member of the Flaviviridae family, is an enveloped RNA virus with a positive sense single-strand RNA genome [90]. Chronic HCV infection is one of the main risk factors for disease progression to metabolic disorders, fibrosis, cirrhosis, and HCC [91]. Epithelial-to-mesenchymal transition (EMT) is a physiological process by which epithelial cells lose their cell polarity and cell-to-cell junctions, and achieve migratory and invasive properties to become mesenchymal cells [92]. Previous literature reviews have shown that EMT plays a crucial role in promoting metastasis in various human cancers including HCC [93]. During the process of EMT, loss of epithelial markers, especially E-cadherin is mediated by transcriptional repressor SNAIL that binds to the E-box motif on the promoter region of E-cadherin [94]. HCV non-structural 4B (NS4B) protein is a 27kDa hydrophobic protein that role in HCC pathogenesis mediate interaction networks with cellular host proteins [95]. A study recently showed that interaction NS4B with scribble protein, a scaffold protein involved in regulating cell polarity and cell proliferation in epithelial cells, suppresses the Hippo signal pathway that subsequently results in the induction of the PI3K/AKT pathway. Induction of the PI3K-Akt pathway upregulates Snail expression via translocation to the nucleus. Finally, the up-regulation of Snail induces EMT progression by reducing E-cadherin expression which contributes to HCV-caused HCC progression, invasion, and metastasis [96].

HCVs entry to hepatocytes is recognized to be mediated by CD81 [97]. Ezrin is a member of a membrane-cytoskeleton linking protein that increases in HCC and is identified in correlation with malignant HCC [98]. In normal hepatocytes, CD81 overexpression results in the phosphorylation of ezrin and increasing nuclear YAP. As the CD81-SYK-ezrin complex causes signals to modify cell construction through protein interactions, gene expression is mediated by YAP via downstream regulation of the Hippo signaling pathway [99]. Also deregulation of the Hippo signaling pathway and increased YAP activity have been demonstrated in 50% of HCC cases [100]. In contrast since Glypican (GPC)-3 is one of the main ligands for CD81, it upregulates the expression of CD81 in HCC cells enhances activation of Hippo, a reduction in ezrin phosphorylation, and a reduction in YAP. Interestingly HCV E2 protein mimics the function of GPC3, enhances the activation of the Hippo signaling pathway, and subsequently reduces YAP and cell proliferation. Consequently, although any hepatocytes which have missing CD81 expression are considered to be resistant to HCV infection but can expand faster than the normal hepatocytes, loss of CD81 is a usual event in the promotion of hepatic neoplasia [101] (Figure 5).

Figure 5: Schematic presentation of reciprocal interactions between HCV and Hippo signaling pathway



CONCLUSION

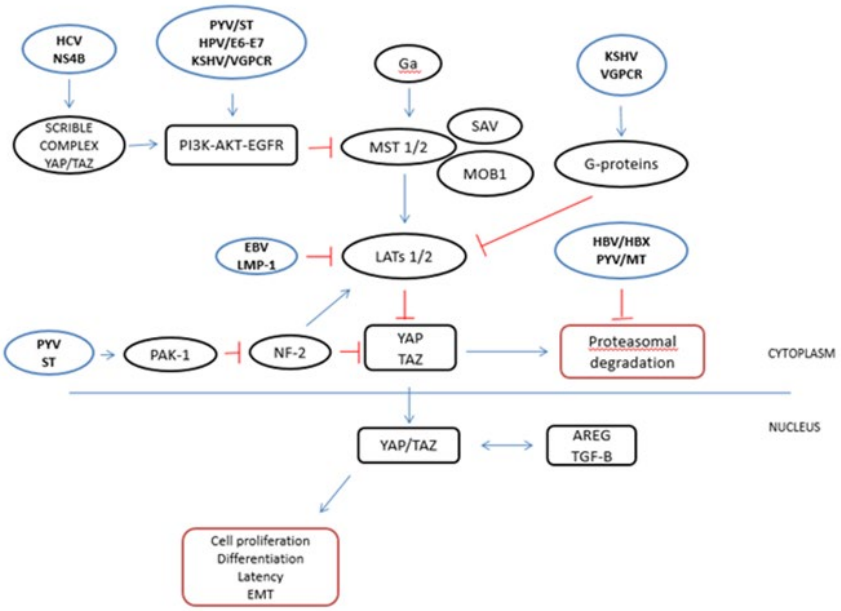
The Hippo signaling is an emerged evolutionarily conserved tumor suppressor pathway that regulates proliferation, apoptosis, differentiation, and development, whose dysregulation overexpresses YAP and TAZ as two major oncogenic downstream effectors of Hippo pathways that play a crucial role in multiple human pathological diseases, such as cancer (Table 1).

Table 1: The summary of the deregulation of the hippo signaling pathway by oncoviruses

Virus	Viral protein	Component of hippo signaling	Mechanism/Effect	References
HBV	HBx	YAP	HBx can increases YAP via the CRE-dependent HBx binding to the YAP promoter and following stimulation of YAP target genes	[27]
HPV	-	YAP1	Hyperactivation of YAP1 can be an important mediator in the persistence of HPV infection	[37]
	-	YAP1	Hyperactivation YAP1 increases the expression of HPV receptor molecules such as ITGRA6, SDC1, and EGFR	[37]
	-	YAP1	Hyperactivation of YAP1 in cervical epithelial cells may reduce viral patterns recognition TLR2 and TLR4 and adaptor proteins MYD88 and TRIF of the innate immune system	[37]
	-	YAP1	Expression of YAP may suppress the activation of transcriptional factors that are essential for the production of type I IFNs, including IRF1, IRF3, and IRF	[37]
	E6/E7	YAP	Expression and activation of main components of the type I IFN pathway, like IFNAR2, STAT1, JAK1, and IRF9, suppressed by expression of $YAPS^{127A}$	[37]
		YAP	YAP was increased in the E6 and E6/E7-induced cervical tumor cells and YAP was localized in the nucleus of these cells	[36]
PyVs		ST YAP	Polyomavirus small T antigen (ST) associates with YAP, an effector of the Hippo pathway, to modulate differentiation	[58]
		MT YAP	MT Binds to YAP, it associates YAP with protein phosphatase 2A (PP2A), resulting in the YAP dephosphorylation together with the MT complex	[60]
		ST YAP	ST acts through PAK1 to inactivate the NF2 tumor suppressor to alleviate the inactivation of YAP	[68]
EBV		LMP1 TAZ	LMP1 can upregulate TAZ expression by inhibition of Hippo pathway proteins	[74]
		LMP1 TAZ	LMP1 can develop cell proliferation, EMT, and CSC-like characteristics by TAZ	[74]
		LMP1 LATS1/2	LMP1 could suppress LATS1/2 activation, resulting in the enhancement of TAZ stability	[74]
KSHV		vGPCR Lats1/2	The KSHV protein (vGPCR) activity is via Gq/11 and G12/13 to suppress the Hippo pathway kinases Lats1/2, enhancing the activation of YAP/TAZ	[85]
		vGPCR YAP/TAZ	Activation of YAP/TAZ is associated with other vGPCR downstream signaling events, including PI3K and NF-kB	[86,87]
		- YAP1	Inactivation of the Hippo pathway modulator YAP1 may promote reactivation from latency, lytic protein increasing, and production of infectious virions	[89]
		LATS1	Expression of the YAP1-inactivating kinase LATS1 consequently induces reactivation from latency	[89]
HCV	*NS5B*	-	*Interaction NS4B with scribble protein suppresses the Hippo signal pathway that subsequently resulting in the induction of PI3K/AKT pathway*	[96]
	E2	YAP	HCV E2 protein mimics the function of GPC3, enhances the activation of the Hippo signaling pathway, and subsequently reduces YAP	[101]

The activation of YAP and TAZ contributes to cancer initiation, metastasis, and anticancer drug resistance via interactions with several signaling pathways in many human tumors. Oncoviruses either directly or indirectly by modulating a variety of cellular signaling pathways lead to the dysregulation of the Hippo signaling pathway to increase the expression of the downstream effectors TAZ and YAP which can be implicated in transformation, metastasis, and chemotherapeutic drug resistance in virus-related cancer and also to facilitate some processes involved in the pathogenesis of viral infection such as entry, persistence, escape from the immune system, and latency. However, in some cases inactivation of YAP can aid the pathogenesis of KSHV and HCV. (Figure 6).

Figure 6: Schematic presentation of reciprocal interactions between oncoviruses and Hippo signaling pathway



With these interpretations, we recommend that the overexpression of the major downstream effectors of the Hippo pathway, TAZ, and YAP can be used as prognosis markers in cancers caused by oncoviruses. Overall, Hippo signaling is a new pathway in viral infection, and in this way, better understanding interaction between oncoviruses with Hippo signaling can be used as a new therapeutic target in virus-caused cancers.

Conflicts of interest and sources of funding
The authors declare no conflict of interest.

References:

1. Choi K-W. Upstream paths for Hippo signaling in Drosophila organ development. BMB Rep. 2018;51(3):134-42.

2. Lin KC, Park HW, Guan K-L. Deregulation and Therapeutic Potential of the Hippo Pathway in Cancer. Annual Review of Cancer Biology. 2018;2:59-79.

3. Wang Y, Yu A, Yu F-X. The Hippo pathway in tissue homeostasis and regeneration. Protein Cell. 2017;8(5):349-59.

4. Zhao B, Li L, Guan K-L. Hippo signaling at a glance. J Cell Sci. 2010;123(23):4001-6.

5. Sebio A, Lenz H-J. Molecular pathways: Hippo signaling, a critical tumor suppressor. Clinical Cancer Research. 2015;21(22):5002-7.

6. Wei C, Wang Y, Li X. The role of Hippo signal pathway in breast cancer metastasis. OncoTargets and therapy. 2018;11:2185.

7. Ardestani A, Lupse B, Maedler K. Hippo signaling: key emerging pathway in cellular and whole-body metabolism. Trends in Endocrinology & Metabolism. 2018;29(7):492-509.

8. Bae JS, Kim SM, Lee H. The Hippo signaling pathway provides novel anti-cancer drug targets. Oncotarget. 2016;8(9):16084-98.

9. Luo J, Yu F-X. GPCR-Hippo Signaling in Cancer. Cells. 2019;8(5):426.

10. Meng Z, Moroishi T, Guan KL. Mechanisms of Hippo pathway regulation. Genes & development. 2016;30(1):1-17.

11. Haskins JW, Nguyen DX, Stern DF. Neuregulin 1-activated ERBB4 interacts with YAP to induce Hippo pathway target genes and promote cell migration. Sci Signal. 2014;7(355):ra116-ra.

12. Boopathy GT, Hong W. Role of Hippo pathway-YAP/TAZ signaling in angiogenesis. Frontiers in cell and developmental biology. 2019;7.

13. Mui UN, Haley CT, Tyring SK. Viral Oncology: Molecular Biology and Pathogenesis. J Clin Med. 2017;6(12):111.

14. Subramani C, Nair VP, Anang S, Mandal SD, Pareek M, Kaushik N, et al. Host-Virus Protein Interaction Network Reveals the Involvement of Multiple Host Processes in the Life Cycle of Hepatitis E Virus. mSystems. 2018;3(1):e00135-17.

15. Golabi P, Fazel S, Otgonsuren M, Sayiner M, Locklear CT, Younossi ZM. Mortality assessment of patients with hepatocellular carcinoma according to underlying disease and treatment modalities. Medicine (Baltimore). 2017;96(9):e5904-e.

16. Li C-W, Chang P-Y, Chen B-S. Investigating the mechanism of hepatocellular carcinoma progression by constructing genetic and epigenetic networks using NGS data identification and big database mining method. Oncotarget. 2016;7(48):79453.

17. Mani SKK, Andrisani O. Hepatitis B Virus-Associated Hepatocellular Carcinoma and Hepatic Cancer Stem Cells. Genes (Basel). 2018;9(3):137.

18. Cheng J, Zhong Y, Chen S, Sun Y, Huang L, Kang Y, et al. Gab2 mediates hepatocellular carcinogenesis by integrating multiple signaling pathways. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2017;31(12):5530-42.

19. Li H, Wolfe A, Septer S, Edwards G, Zhong X, Bashar Abdulkarim A, et al. Deregulation of Hippo kinase signalling in human hepatic malignancies. Liver International. 2012;32(1):38-47.

20. Apte U, Gkretsi V, Bowen WC, Mars WM, Luo JH, Donthamsetty S, et al. Enhanced liver regeneration following changes induced by hepatocyte-specific genetic ablation of integrin-linked kinase. Hepatology. 2009;50(3):844-51.

21. Shi C, Cai Y, Li Y, Li Y, Hu N, Ma S, et al. Yap promotes hepatocellular carcinoma metastasis and mobilization via governing cofilin/F-actin/lamellipodium axis by regulation of JNK/Bnip3/SERCA/CaMKII pathways. Redox Biol. 2017;14:59-71.

22. Overholtzer M, Zhang J, Smolen GA, Muir B, Li W, Sgroi DC, et al. Transforming properties of YAP, a candidate oncogene on the chromosome 11q22 amplicon. Proceedings of the National Academy of Sciences. 2006;103(33):12405-10.

23. Lim SK, Orhant-Prioux M, Toy W, Tan KY, Lim YP. Tyrosine phosphorylation of transcriptional coactivator WW-domain binding protein 2 regulates estrogen receptor α function in breast cancer via the Wnt pathway. The FASEB Journal. 2011;25(9):3004-18.

24. Mishra L, Banker T, Murray J, Byers S, Thenappan A, He AR, et al. Liver stem cells and hepatocellular carcinoma. Hepatology. 2009;49(1):318-29.

25. Song JY, Lee J-H, Joe CO, Lim D-S, Chung JH. Retrotransposon-specific DNA hypomethylation and two-step loss-of-imprinting during WW45 haploinsufficiency-induced hepatocarcinogenesis. Biochemical and biophysical research communications. 2011;404(2):728-34.

26. Oka T, Schmitt A, Sudol M. Opposing roles of angiomotin-like-1 and zona occludens-2 on pro-apoptotic function of YAP. Oncogene. 2012;31(1):128.

27. Zhang T, Zhang J, You X, Liu Q, Du Y, Gao Y, et al. Hepatitis B virus X protein modulates oncogene Yes-associated protein by CREB to promote growth of hepatoma cells. Hepatology. 2012;56(6):2051-9.

28. Lu L, Li Y, Kim SM, Bossuyt W, Liu P, Qiu Q, et al. Hippo signaling is a potent in vivo growth and tumor suppressor pathway in the mammalian liver. Proceedings of the National Academy of Sciences. 2010;107(4):1437-42.

29. Zhou D, Conrad C, Xia F, Park J-S, Payer B, Yin Y, et al. Mst1 and Mst2 maintain hepatocyte quiescence and suppress hepatocellular carcinoma development through inactivation of the Yap1 oncogene. Cancer cell. 2009;16(5):425-38.

30. Benhamouche S, Curto M, Saotome I, Gladden AB, Liu C-H, Giovannini M, et al. Nf2/Merlin controls progenitor homeostasis and tumorigenesis in the liver. Genes & development. 2010;24(16):1718-30.

31. Lee JH, Kim TS, Yang TH, Koo BK, Oh SP, Lee KP, et al. A crucial role of WW45 in developing epithelial tissues in the mouse. The EMBO journal. 2008;27(8):1231-42.

32. Liu-Chittenden Y, Huang B, Shim JS, Chen Q, Lee S-J, Anders RA, et al. Genetic and pharmacological disruption of the TEAD–YAP complex suppresses the oncogenic activity of YAP. Genes & development. 2012;26(12):1300-5.

33. Huo X, Zhang Q, Liu AM, Tang C, Gong Y, Bian J, et al. Overexpression of Yes-associated protein confers doxorubicin resistance in hepatocellullar carcinoma. Oncol Rep. 2013;29(2):840-6.

34. Bai H, Gayyed MF, Lam-Himlin DM, Klein AP, Nayar SK, Xu Y, et al. Expression of Yes-associated protein modulates Survivin expression in primary liver malignancies. Human pathology. 2012;43(9):1376-85.

35. Huo X, Zhang Q, Liu AM, Tang C, Gong Y, Bian J, et al. Overexpression of Yes-associated protein confers doxorubicin resistance in hepatocellullar carcinoma. Oncology reports. 2013;29(2):840-6.

36. He C, Mao D, Hua G, Lv X, Chen X, Angeletti PC, et al. The Hippo/YAP pathway interacts with EGFR signaling and HPV oncoproteins to regulate cervical cancer progression. EMBO Mol Med. 2015;7(11):1426-49.

37. He C, Lv X, Huang C, Angeletti PC, Hua G, Dong J, et al. A Human Papillomavirus-Independent Cervical Cancer Animal Model Reveals Unconventional Mechanisms of Cervical Carcinogenesis. Cell reports. 2019;26(10):2636-50. e5.

38. Shamir ER, Devine WP, Pekmezci M, Umetsu SE, Krings G, Federman S, et al. Identification of high-risk human papillomavirus and Rb/E2F pathway genomic alterations in mutually exclusive subsets of colorectal neuroendocrine carcinoma. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2019;32(2):290-305.

39. Yeo-Teh NSL, Ito Y, Jha S. High-Risk Human Papillomaviral Oncogenes E6 and E7 Target Key Cellular Pathways to Achieve Oncogenesis. Int J Mol Sci. 2018;19(6):1706.

40. He C, Mao D, Hua G, Lv X, Chen X, Angeletti PC, et al. The Hippo/YAP pathway interacts with EGFR signaling and HPV oncoproteins to regulate cervical cancer progression. EMBO Mol Med. 2015;7(11):1426-49.

41. Liu X-l, Ding J, Meng L-h. Oncogene-induced senescence: a double edged sword in cancer. Acta Pharmacologica Sinica. 2018;39(10):1553.

42. Hiemer SE, Zhang L, Kartha VK, Packer TS, Almershed M, Noonan V, et al. A YAP/TAZ-regulated molecular signature is associated with oral squamous cell carcinoma. Molecular Cancer Research. 2015;13(6):957-68.

43. Wei Z, Wang Y, Li Z, Yuan C, Zhang W, Wang D, et al. Overexpression of Hippo pathway effector TAZ in tongue squamous cell carcinoma: correlation with clinicopathological features and patients' prognosis. Journal of Oral Pathology & Medicine. 2013;42(10):747-54.

44. Piccolo S, Dupont S, Cordenonsi M. The biology of YAP/TAZ: hippo signaling and beyond. Physiological reviews. 2014;94(4):1287-312.

45. Gumbiner BM, Kim N-G. The Hippo-YAP signaling pathway and contact inhibition of growth. J Cell Sci. 2014;127(4):709-17.

46. Hergovich A. YAP-Hippo signalling downstream of leukemia inhibitory factor receptor: implications for breast cancer. Breast Cancer Research. 2012;14(6):326.

47. Xiao H, Wu L, Zheng H, Li N, Wan H, Liang G, et al. Expression of Yes-associated protein in cervical squamous epithelium lesions. International Journal of Gynecologic Cancer. 2014;24(9):1575-82.

48. Brake T, Lambert PF. Estrogen contributes to the onset, persistence, and malignant progression of cervical cancer in a human papillomavirus-transgenic mouse model. Proceedings of the National Academy of Sciences. 2005;102(7):2490-5.

49. Shai A, Brake T, Somoza C, Lambert PF. The human papillomavirus E6 oncogene dysregulates the cell cycle and contributes to cervical carcinogenesis through two independent activities. Cancer research. 2007;67(4):1626-35.

50. Wang H-K, Duffy AA, Broker TR, Chow LT. Robust production and passaging of infectious HPV in squamous epithelium of primary human keratinocytes. Genes & development. 2009;23(2):181-94.

51. Zhao B, Li L, Tumaneng K, Wang C-Y, Guan K-L. A coordinated phosphorylation by Lats and CK1 regulates YAP stability through SCFβ-TRCP. Genes & development. 2010;24(1):72-85.

52. Mo JS, Park HW, Guan KL. The Hippo signaling pathway in stem cell biology and cancer. EMBO reports. 2014;15(6):642-56.

53. Hong X, Nguyen HT, Chen Q, Zhang R, Hagman Z, Voorhoeve PM, et al. Opposing activities of the Ras and Hippo pathways converge on regulation of YAP protein turnover. The EMBO journal.

2014;33(21):2447-57.

54. Akerman GS, Tolleson WH, Brown KL, Zyzak LL, Mourateva E, Engin TS, et al. Human papillomavirus type 16 E6 and E7 cooperate to increase epidermal growth factor receptor (EGFR) mRNA levels, overcoming mechanisms by which excessive EGFR signaling shortens the life span of normal human keratinocytes. Cancer research. 2001;61(9):3837-43.

55. Spangle JM, Munger K. The HPV16 E6 oncoprotein causes prolonged receptor protein tyrosine kinase signaling and enhances internalization of phosphorylated receptor species. PLoS pathogens. 2013;9(3):e1003237.

56. Hahn WC, Counter CM, Lundberg AS, Beijersbergen RL, Brooks MW, Weinberg RA. Creation of human tumour cells with defined genetic elements. Nature. 1999;400(6743):464.

57. Hahn WC, Dessain SK, Brooks MW, King JE, Elenbaas B, Sabatini DM, et al. Enumeration of the simian virus 40 early region elements necessary for human cell transformation. Molecular and cellular biology. 2002;22(7):2111-23.

58. Rouleau C, Pores Fernando AT, Hwang JH, Faure N, Jiang T, White EA, et al. Transformation by Polyomavirus Middle T Antigen Involves a Unique Bimodal Interaction with the Hippo Effector YAP. J Virol. 2016;90(16):7032-45.

59. Whitman M, Downes CP, Keeler M, Keller T, Cantley L. Type I phosphatidylinositol kinase makes a novel inositol phospholipid, phosphatidylinositol-3-phosphate. Nature. 1988;332(6165):644.

60. Shanzer M, Ricardo-Lax I, Keshet R, Reuven N, Shaul Y. The polyomavirus middle T-antigen oncogene activates the Hippo pathway tumor suppressor Lats in a Src-dependent manner. Oncogene. 2015;34(32):4190-8.

61. Sablina AA, Hahn WC. SV40 small T antigen and PP2A phosphatase in cell transformation. Cancer and Metastasis Reviews. 2008;27(2):137-46.

62. Sablina AA, Hector M, Colpaert N, Hahn WC. Identification of PP2A complexes and pathways involved in cell transformation. Cancer research. 2010;70(24):10474-84.

63. Yin F, Yu J, Zheng Y, Chen Q, Zhang N, Pan D. Spatial organization of Hippo signaling at the plasma membrane mediated by the tumor suppressor Merlin/NF2. Cell. 2013;154(6):1342-55.

64. Zhao B, Wei X, Li W, Udan RS, Yang Q, Kim J, et al. Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. Genes & development. 2007;21(21):2747-61.

65. Dong J, Feldmann G, Huang J, Wu S, Zhang N, Comerford SA, et al. Elucidation of a universal size-control mechanism in Drosophila and mammals. Cell. 2007;130(6):1120-33.

66. Zhao B, Li L, Lei Q, Guan K-L. The Hippo–YAP pathway in organ size control and tumorigenesis: an updated version. Genes & development. 2010;24(9):862-74.

67. Barry ER, Camargo FD. The Hippo superhighway: signaling crossroads converging on the Hippo/Yap pathway in stem cells and development. Current opinion in cell biology. 2013;25(2):247-53.

68. Nguyen HT, Hong X, Tan S, Chen Q, Chan L, Fivaz M, et al. Viral small T oncoproteins transform cells by alleviating hippo-pathway-mediated inhibition of the YAP proto-oncogene. Cell reports. 2014;8(3):707-13.

69. Myers JS. Review complementary and integrative interventions for cancer-related cognitive changes. Asia-Pacific journal of oncology nursing. 2015;2(4):215.

70. Lung RW-M, Tong JH-M, Sung Y-M, Leung P-S, Ng DC-H, Chau S-L, et al. Modulation of LMP2A expression by a newly identified Epstein-Barr virus-encoded microRNA miR-BART22. Neoplasia. 2009;11(11): 1174-84.

71. Yoshizaki T, Kondo S, Endo K, Nakanishi Y, Aga M, Kobayashi E, et al. Modulation of the tumor microenvironment by Epstein-Barr virus latent membrane protein 1 in nasopharyngeal carcinoma. Cancer science. 2018;109(2):272-8.

72. Kondo S, Wakisaka N, Muramatsu M, Zen Y, Endo K, Murono S, et al. Epstein-Barr virus latent membrane protein 1 induces cancer stem/progenitor-like cells in nasopharyngeal epithelial cell lines. J Virol. 2011;85(21):11255-64.

73. Liu H-P, Chen C-C, Wu C-C, Huang Y-C, Liu S-C, Liang Y, et al. Epstein-Barr virus-encoded LMP1 interacts with FGD4 to activate Cdc42 and thereby promote migration of nasopharyngeal carcinoma cells. PLoS pathogens. 2012;8(5):e1002690.

74. He J, Tang F, Liu L, Chen L, Li J, Ou D, et al. Positive regulation of TAZ expression by EBV-LMP1 contributes to cell proliferation and epithelial-mesenchymal transition in nasopharyngeal carcinoma. Oncotarget. 2016;8(32):52333-44.

75. Cordenonsi M, Zanconato F, Azzolin L, Forcato M, Rosato A, Frasson C, et al. The Hippo transducer TAZ confers cancer stem cell-related traits on breast cancer cells. Cell. 2011;147(4):759-72.

76. Shao DD, Xue W, Krall EB, Bhutkar A, Piccioni F, Wang X, et al. KRAS and YAP1 converge to regulate EMT and tumor survival. Cell. 2014;158(1):171-84.

77. Salah Z, Aqeilan RI. WW domain interactions regulate the Hippo tumor suppressor pathway. Cell Death Dis. 2011;2(6):e172-e.

78. Ganem D. KSHV and the pathogenesis of Kaposi sarcoma: listening to human biology and medicine. The Journal of clinical investigation. 2010;120(4):939-49.

79. Montaner S, Sodhi A, Molinolo A, Bugge TH, Sawai ET, He Y, et al. Endothelial infection with KSHV genes in vivo reveals that vGPCR initiates Kaposi's sarcomagenesis and can promote the tumorigenic potential of viral latent genes. Cancer cell. 2003;3(1):23-36.

80. Hunte R, Alonso P, Thomas R, Bazile CA, Ramos JC, van der Weyden L, et al. CADM1 is essential for KSHV-encoded vGPCR-and vFLIP-mediated chronic NF-kappaB activation. PLoS Pathog. 2018;14(4):e1006968.

81. Mesri EA, Cesarman E, Boshoff C. Kaposi's sarcoma and its associated herpesvirus. Nature reviews Cancer. 2010;10(10):707-19.

82. Cavallin LE, Ma Q, Naipauer J, Gupta S, Kurian M, Locatelli P, et al. KSHV-induced ligand mediated activation of PDGF receptor-alpha drives Kaposi's sarcomagenesis. PLoS pathogens. 2018;14(7):e1007175-e.

83. Purushothaman P, Uppal T, Sarkar R, Verma SC. KSHV-Mediated Angiogenesis in Tumor Progression. Viruses. 2016;8(7):198.

84. Yu F-X, Zhao B, Panupinthu N, Jewell JL, Lian I, Wang LH, et al. Regulation of the Hippo-YAP pathway by G-protein-coupled receptor signaling. Cell. 2012;150(4):780-91.

85. Liu G, Yu FX, Kim YC, Meng Z, Naipauer J, Looney DJ, et al. Kaposi sarcoma-associated herpesvirus promotes tumorigenesis by modulating the Hippo pathway. Oncogene. 2015;34(27):3536-46.

86. Zhao B, Ye X, Yu J, Li L, Li W, Li S, et al. TEAD mediates YAP-dependent gene induction and growth control. Genes & development. 2008;22(14):1962-71.

87. Straßburger K, Tiebe M, Pinna F, Breuhahn K, Teleman AA. Insulin/IGF signaling drives cell proliferation in part via Yorkie/YAP. Developmental biology. 2012;367(2):187-96.

88. Cavallin LE, Goldschmidt-Clermont P, Mesri EA. Molecular and cellular mechanisms of KSHV oncogenesis of Kaposi's sarcoma associated with HIV/AIDS. PLoS Pathog. 2014;10(7):e1004154.

89. O'Brien S. Hippo pathway control of KSHV latency. 2018.

90. Morozov VA, Lagaye S. Hepatitis C virus: Morphogenesis, infection and therapy. World journal of hepatology. 2018;10(2):186.

91. Bandiera S, Billie Bian C, Hoshida Y, Baumert TF, Zeisel MB. Chronic hepatitis C virus infection and pathogenesis of hepatocellular carcinoma. Curr Opin Virol. 2016;20:99-105.

92. Das V, Bhattacharya S, Chikkaputtaiah C, Hazra S, Pal M. The basics of epithelial-mesenchymal transition (EMT): A study from a structure, dynamics, and functional perspective. Journal of cellular physiology. 2019.

93. Yamanaka C, Wada H, Eguchi H, Hatano H, Gotoh K, Noda T, et al. Clinical significance of CD13 and epithelial mesenchymal transition (EMT) markers in hepatocellular carcinoma. Japanese journal of clinical oncology. 2018;48(1):52-60.

94. Kaufhold S, Bonavida B. Central role of Snail1 in the regulation of EMT and resistance in cancer: a target for therapeutic intervention. J Exp Clin Cancer Res. 2014;33(1):62-.

95. Li S, Yu X, Guo Y, Kong L. Interaction networks of hepatitis C virus NS4B: Implications for antiviral therapy2012. 994-1002 p.

96. Hu B, Xie S, Hu Y, Chen W, Chen X, Zheng Y, et al. Hepatitis C virus NS4B protein induces epithelial-mesenchymal transition by upregulation of Snail. Virol J. 2017;14(1):83-.

97. Vieyres G, Thomas X, Descamps V, Duverlie G, Patel AH, Dubuisson J. Characterization of the envelope glycoproteins associated with infectious hepatitis C virus. J Virol. 2010;84(19):10159-68.

98. Bakheet AMH, Mahmoud SA, Huang Y, Zhang J, Wang J, Wei Y, et al. Ezrin as a possible diagnostic and/or prognostic biomarker in mice lymphatic metastatic hepatocellular carcinoma in vivo. BioFactors (Oxford, England). 2017;43(5):662-72.

99. Xue Y, Bowen W, Koral K, Orr A, Mars W, Michalopoulos G. Glypican 3 (GPC3)-CD81 axis regulates spleen tyrosine kinase (Syk)-Ezrin mediated Hippo pathway via cross talking with HGF/c-Met axis in hepatocytes and hepatocellular carcinoma (HCC). The FASEB Journal. 2017;31(1_supplement):805.2-.2.

100.Johnson R, Halder G. The two faces of Hippo: targeting the Hippo pathway for regenerative medicine and cancer treatment. Nature reviews Drug discovery. 2014;13(1):63.

101.Xue Y, Mars WM, Bowen W, Singhi AD, Stoops J, Michalopoulos GK. Hepatitis C Virus Mimics Effects of Glypican-3 on CD81 and Promotes Development of Hepatocellular Carcinomas via Activation of Hippo Pathway in Hepatocytes. The American journal of pathology. 2018;188(6):1469-77.