1 YAP1 activation by human papillomavirus E7 promotes basal cell identity in squamous epithelia

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Abstract

Persistent human papillomavirus (HPV) infection of stratified squamous epithelial cells causes nearly five percent of cancer cases worldwide. HPV-positive oropharyngeal cancers harbor few mutations in the Hippo signaling pathway compared to HPV-negative cancers at the same anatomical site, prompting the hypothesis that an HPV-encoded protein inactivates the Hippo pathway and activates the Hippo effector YAP1. The HPV E7 oncoprotein is required for HPV infection and for HPV-mediated oncogenic transformation. We investigated the effects of HPV oncoproteins on YAP1 and found that E7 activates YAP1, promoting YAP1 nuclear localization in basal epithelial cells. YAP1 activation by HPV E7 required that E7 bind and degrade the tumor suppressor PTPN14. E7 required YAP1 transcriptional activity to extend the lifespan of primary keratinocytes, indicating that YAP1 activation contributes to E7 carcinogenic activity. Maintaining infection in basal cells is critical for HPV persistence, and here we demonstrate that YAP1 activation causes HPV E7 expressing cells to be retained in the basal compartment of stratified epithelia. We propose that YAP1 activation resulting from PTPN14 inactivation is an essential, targetable activity of the HPV E7 oncoprotein relevant to HPV infection and carcinogenesis.

Introduction

Human papillomaviruses (HPV) are non-enveloped viruses with circular double-stranded DNA genomes that infect keratinocytes in stratified squamous epithelia (Doorbar et al., 2015; Graham, 2017; McBride, 2017). Although most HPV infections are cleared by the immune system, some infections persist and form higher grade lesions that can lead to cancer (Koshiol et al., 2008; McBride, 2021; Radley et al., 2016; Rositch et al., 2013). HPV infection at mucosal epithelial sites causes cancers including oropharyngeal, cervical, vaginal, penile, and anal malignancies (de Martel et al., 2017; Gillison et al., 2015). Nearly 5% of human cancer cases are caused by persistent infection with one of the high-risk (oncogenic) human papillomavirus genotypes (de Martel et al., 2020).

Inactivation of host cell tumor suppressors by the high-risk HPV E6 and E7 oncoproteins modulates cellular processes that enable HPV persistence. Two well-characterized instances of tumor suppressor inactivation by HPV are high-risk HPV E6 proteins targeting p53 for proteasome-mediated degradation and high-risk HPV E7 proteins binding and degrading the retinoblastoma protein (RB1) (Heck et al., 1992; Münger et al., 1989; Scheffner et al., 1990; Werness et al., 1990). Both p53 degradation and RB1 inactivation are required for productive HPV infection (Collins et al., 2005; Flores et al., 2000; Kho et al., 2013; McLaughlin-Drubin et al., 2005; Wang et al., 2009). In addition to supporting productive infection, E7 is essential for HPV-mediated carcinogenesis (Mirabello et al., 2017). The impact of the HPV oncoproteins on cell growth control pathways is reflected in human cancer genomic data: genes in the p53 pathway and in the RB1-related cell cycle pathway are frequently mutated in HPV-negative head and neck squamous cell carcinoma (HNSCC) but infrequently mutated in HPV-positive HNSCC (Sanchez-Vega et al., 2018).

Although some of the growth-promoting activities of high-risk HPV E6 and E7 are well established, open questions remain. RB1 binding/degradation by high-risk HPV E7 is necessary but insufficient for E7 transforming activity (Balsitis et al., 2006, 2005; Banks et al., 1990;

Ciccolini et al., 1994; Helt and Galloway, 2002; Huh et al., 2005; Ibaraki et al., 1993; Jewers et al., 1992; Phelps et al., 1992; Strati and Lambert, 2007; White et al., 2015). Papillomavirus researchers have sought to identify one or more activities of HPV E7 that cooperate with RB1 inactivation to promote carcinogenesis and to identify the cellular pathway affected by such an activity. Human cancer genomic data indicates that like the p53 and cell cycle pathways, the Hippo signaling pathway is more frequently mutated in HPV-negative than in HPV-positive HNSCC. The core Hippo pathway consists of a kinase cascade upstream of the effector proteins Yes-Associated Protein (YAP1) and its paralogue TAZ. When the Hippo kinases are inactive, YAP1 and TAZ are activated and translocate to the nucleus. In stratified squamous epithelia YAP1 is primarily expressed in the basal layer, where YAP1 activation is regulated by contextual cues including cell density, tension in the extracellular matrix, and contact with the basement membrane (Elbediwy et al., 2016; Totaro et al., 2017; Zhang et al., 2011). In normal stratified squamous epithelia, activation of YAP1 and TAZ promotes expansion of the basal cell compartment and inhibition of YAP1 and TAZ allows keratinocytes to differentiate (Beverdam et al., 2013; Elbediwy and Thompson, 2018; Schlegelmilch et al., 2011; Totaro et al., 2017; Yuan et al., 2020; Zhang et al., 2011). Mutations in many of the tumor suppressors upstream of YAP1/TAZ are common in a variety of cancer types (Moroishi et al., 2015).

Non-receptor protein tyrosine phosphatase 14 (PTPN14) has been implicated as a tumor suppressor and negative regulator of YAP1 (Knight et al., 2018; Mello et al., 2017; Poernbacher et al., 2012; Wang et al., 2012). Diverse HPV E7 bind directly to PTPN14 and recruit the E3 ligase UBR4 to direct PTPN14 for proteasome-mediated degradation (Szalmás et al., 2017; White et al., 2016, 2012b; Yun et al., 2019). We have shown that PTPN14 degradation and RB1 binding/degradation are separable activities of HPV E7 that each contribute to E7 carcinogenic activity (Hatterschide et al., 2020, 2019; White et al., 2016). However, the downstream consequences of PTPN14 degradation are poorly understood, and so far we have not observed

that PTPN14 inactivation in human keratinocytes causes an increase in canonical YAP1 target genes *CTGF* and *CYR61*.

These observations regarding an additional transforming activity of HPV E7, the ability of E7 to inactivate PTPN14, and the relative paucity of mutations in the Hippo pathway in HPV-positive HNSCC led us to hypothesize that HPV E7-mediated activation of YAP1 is required for the transforming activity of high-risk HPV E7. Here we show that expression of high-risk HPV E7 is sufficient to activate YAP1 and that HPV E7 requires YAP1/TAZ-TEAD transcriptional activity to promote cell growth. We demonstrate that HPV E7 must bind PTPN14 to activate YAP1 and that PTPN14 inactivation alone is sufficient to activate YAP1. YAP1 activation by HPV E7 is restricted to the basal layer of the epithelium where we found *PTPN14* expression to be enriched.

Our finding that either HPV E7 or PTPN14 loss activated YAP1 specifically in basal epithelial cells led us to investigate the role of YAP1 activation during normal HPV infection. HPV infection begins in basal epithelial keratinocytes (Day and Schelhaas, 2014; Pyeon et al., 2009; Roberts et al., 2007) and infected basal cells are the site of persistent HPV infection (Doorbar et al., 2021). The basal cell compartment contains the only long-lived cells in the epithelium and the HPV genome can be maintained in dividing cells in a largely dormant state (Egawa et al., 2012; Parish et al., 2006; You et al., 2004). Activation of YAP1 and TAZ has been proposed to maintain the progenitor cell state in several different epithelia (Beverdam et al., 2013; Heng et al., 2020; Hicks-Berthet et al., 2021; Szymaniak et al., 2015; Yimlamai et al., 2014; Zhao et al., 2014). If YAP1 activation by E7 promotes the maintenance of a basal cell state in stratified squamous epithelia, YAP1 activation could facilitate the persistence of HPV-positive cells. Testing this hypothesis, we found that YAP1 activation and PTPN14 degradation by E7 both promote the maintenance of cells in the basal compartment of stratified epithelia. We propose that YAP1 activation facilitates HPV persistence and contributes to the carcinogenic activity of high-risk HPV E7.

Results

HPV E7 activates YAP1 in basal keratinocytes

A comprehensive analysis of somatic mutations and copy number variations in human tumor samples revealed that the cell cycle, p53, and Hippo pathways are the three pathways that exhibit the greatest difference in alteration frequency in HPV-negative vs HPV-positive HNSCC (Sanchez-Vega et al., 2018). We used data made available by The Cancer Genome Atlas (TCGA) through cBioPortal (Lawrence et al., 2015) to recapitulate the finding that genes in these pathways are altered at a lower frequency in HPV-positive than in HPV-negative HNSCC (Figure 1A and Figure 1—figure supplement 1). However, most HPV-positive HNSCC arise in the oropharynx. We repeated the analysis of pathway alteration rates using data only from HPV-positive and HPV-negative oropharyngeal squamous cell carcinomas (OPSCC) (Figure 1A and Figure 1—figure supplement 1). Consistent with previous findings, HPV-negative OPSCC were more frequently altered in the p53, cell cycle, and Hippo pathways than HPV-positive OPSCC. Hippo pathway alterations in HPV-negative HNSCC or OPSCC include amplification of the YAP1/TAZ oncogenes or inactivating mutations in one or more of the upstream inhibitors of YAP1/TAZ, including PTPN14. Either alteration type is consistent with a carcinogenic role for YAP1 activation in HNSCC.

To test whether an HPV-encoded protein activates YAP1, we grew three dimensional (3D) organotypic epithelial cultures to model the differentiation of keratinocytes into basal and suprabasal compartments. Organotypic cultures of primary human foreskin keratinocytes (HFK) harboring an HPV18 genome exhibited increased YAP1 staining and increased YAP1 nuclear localization, indicative of YAP1 activation, in the basal layer of the epithelium compared to HFK cultures (Figure 1B and Figure 1—figure supplement 2A-E). Proliferating cell nuclear antigen (PCNA) transcription increases upon RB1 inactivation and is a marker of HPV E7 expression (Cheng et al., 1995; Flores et al., 2000; Lee et al., 1995). Although YAP1 activation in the

HPV18 genome containing cells was restricted to the basal cells, PCNA levels were elevated in both the basal and suprabasal layers of the epithelium in the same cultures.

We next tested whether either high-risk HPV E6 or E7 alone was sufficient to activate YAP1. HFK transduced with retroviral expression vectors encoding HPV16 E6, HPV16 E7, or HPV18 E7 were used to grow organotypic cultures. YAP1 expression and nuclear localization were increased in the HPV16 E7 and HPV18 E7 expressing cells relative to parental HFK (Figure 1C, Figure 1—figure supplement 3A-C, and Figure 1—figure supplement 5A-C). Similar to our observation in the HPV18 genome-containing cells, YAP1 activation was restricted to the basal epithelial layer. YAP1 nuclear localization increased modestly in organotypic cultures of HPV16 E6 expressing cells (Figure 1D, Figure 1—figure supplement 4, and Figure 1—figure supplement 5A-C). Constitutive expression of either HPV16 E7 or HPV18 E7 induced PCNA expression in basal and suprabasal cells. We conclude that HPV promotes increased YAP1 expression and nuclear localization in basal keratinocytes and that E7 is sufficient for YAP1 activation.

HPV E7 activates YAP1 in keratinocytes through PTPN14 degradation

We previously discovered that HPV E7 binds and targets the YAP1 inhibitor PTPN14 for proteasome-mediated degradation (White et al., 2016, 2012b). We tested whether loss of PTPN14 expression in keratinocytes was sufficient to activate YAP1 in stratified epithelia by growing 3D organotypic cultures from existing control and PTPN14 knockout (KO) N/Tert-Cas9 keratinocytes (Hatterschide et al., 2019). We found that YAP1 levels and YAP1 nuclear localization were increased in PTPN14 KO cultures compared to controls (Figure 2A and Figure 2—figure supplement 1A-F). YAP1 activation in basal epithelial cells lacking PTPN14 was comparable to YAP1 activation in HPV E7 cells. We conclude that loss of PTPN14 expression activates YAP1 in basal keratinocytes.

A highly conserved C-terminal arginine in E7 makes a direct interaction with the C-terminus of PTPN14 and the HPV18 E7 R84S variant is unable to bind or degrade PTPN14 (Hatterschide et al., 2020; Yun et al., 2019). To test whether PTPN14 degradation by HPV E7 is required for activation of YAP1, we grew 3D organotypic cultures using primary HFK transduced with retroviral expression vectors encoding HPV18 E7 wild type (WT) or HPV18 E7 R84S. Indeed, YAP1 expression and nuclear localization in the basal layer of HPV18 E7 R84S cultures were reduced compared to HPV18 E7 WT controls (Figure 2B, Figure 1—figure supplement 5A-C, and Figure 2—figure supplement 2).

In addition to activating YAP1, PTPN14 loss increased basal cell density from an average of 5.5 cells per 100 μm in control cultures to 9.0 cells per 100 μm in PTPN14 KO cultures (Figure 2C). Basal cell density was higher in HPV18 E7 WT cultures (9.4 cells per 100 μm) than in HPV18 E7 R84S cultures (7.1 cells per 100 μm) (Figure 2E). No statistically significant difference in suprabasal cell density was observed in either comparison (Figure 2D,F). We conclude that E7 expression or PTPN14 loss in stratified squamous epithelia is sufficient to activate YAP1 in the basal layer of the epithelium and increase basal cell density.

***PTPN14* expression is enriched in basal keratinocytes**

YAP1 activation was restricted to basal epithelial cells in our organotypic cultures, leading us to hypothesize that PTPN14 may act as a basal layer specific inhibitor of YAP1. We therefore sought to determine whether *PTPN14* expression is restricted to a specific subset of cells in the stratified epithelium. In a recent single-cell RNA sequencing analysis of human neonatal foreskin epidermis, *PTPN14* mRNA expression was enriched in the basal-III cluster (Figure 3A,B) (S. Wang et al., 2020). The basal-III cell cluster was described to be non-proliferating, marked by COL17A1 expression, and predicted to differentiate directly into spinous cells based on pseudotime analysis. *PTPN14* expression was higher in basal-III cells than in the spinous or granular cell clusters. To measure *PTPN14* expression in basal and suprabasal cells in our

cultures, we used laser capture microdissection to isolate basal and suprabasal layers from 3D organotypic cultures grown from unmodified primary HFK (Figure 3C). We found that there was a ~5-fold enrichment of *PTPN14* mRNA in the basal epithelial layer compared to the suprabasal layers (Figure 3D). As expected, the basal integrins *ITGA6* and *ITGB4* were expressed in the basal layer (Figure 3E) and the differentiation markers *KRT1* and *IVL* were expressed in the suprabasal layers (Figure 3F). The same pattern of *PTPN14* mRNA expression was observed in an organotypic culture grown from primary HFK expressing HPV18 E7 WT (Figure 3—figure supplement 1A-C). We conclude that *PTPN14* mRNA is enriched in basal keratinocytes in the presence or absence of HPV E7. Our data support that PTPN14 acts as a YAP1 inhibitor specifically in the basal compartment of stratified epithelia.

YAP1/TAZ regulate differentiation downstream of PTPN14

In previous unbiased experiments we found that the primary effect of PTPN14 inactivation on transcription is to repress epithelial differentiation gene expression (Hatterschide et al., 2020, 2019). However, we also observed that PTPN14 inactivation did not increase expression of the canonical YAP1/TAZ targets *CTGF* and *CYR61*. Consistent with this difference there was minimal overlap between PTPN14-dependent differentially expressed genes and the genes listed in the MSigDB conserved YAP1 signature (Figure 4A). We therefore asked whether the ability of PTPN14 to regulate differentiation gene expression requires YAP1/TAZ as intermediates. Transduction of keratinocytes with a PTPN14 lentivirus induced the expression of the differentiation markers *KRT10* and *IVL* in a dose-dependent manner (Figure 4—figure supplement 1A-C). To test whether PTPN14 required YAP1/TAZ to increase differentiation marker gene expression, we transfected HFK with siRNAs targeting *YAP1* and *WWTR1* (the gene encoding TAZ) then transduced the cells with PTPN14 lentivirus (Figure 4B). HFK transfected with control siRNA exhibited the expected increase in *KRT1* and *IVL* after transduction with PTPN14 lentivirus (Figure 4C,D and Figure 4—figure supplement 2A,B).

However, keratinocytes depleted of YAP1/TAZ did not express relatively more *KRT1* or *IVL* when *PTPN14* was overexpressed than when it was not. We conclude that PTPN14 requires YAP1 and/or TAZ to regulate differentiation gene expression in keratinocytes. Both pairs of YAP1/TAZ siRNA had the same effect on differentiation in response to *PTPN14* overexpression yet only one pair efficiently depleted TAZ protein levels (Figure 4B), leading us to speculate that YAP1 is the key intermediate connecting PTPN14 levels to differentiation gene expression.

Next, we tested whether repression of keratinocyte differentiation occurs upon loss of LATS1 and LATS2, the core Hippo pathway kinases that phosphorylate and inhibit YAP1 and TAZ. We used siRNAs to deplete *PTPN14*, *LATS1*, or *LATS2* and measured the expression of the differentiation markers *KRT1* and *IVL* (Figure 4E,F). Depletion of *PTPN14*, *LATS1*, or *LATS2* all decreased differentiation gene expression to a similar degree. None of the three knockdowns significantly affected the levels of *CTGF* or *CYR61* (Figure 4G-H). Direct depletion of *YAP1* or *WWTR1* affected both differentiation gene expression and *CTGF/CYR61* levels. Other than siWWTR1-08, all siRNAs used in these experiments reduced the expression of their target genes by two-fold or greater (Figure 4I). *YAP1* knockdown always had a stronger effect than did *WWTR1* knockdown and our qRT-PCR analyses supported that *WWTR1* transcript levels were low in HFK. This result shows that inactivation of three different YAP1 inhibitors dampens differentiation gene expression even in the absence of a differentiation stimulus and does not increase canonical YAP1 target gene expression in keratinocytes. We have previously observed that *PTPN14* knockout or E7 expression reduces differentiation gene expression both in undifferentiated cells and in cells stimulated to differentiate (Hatterschide et al., 2020, 2019). Taken together, these data support that PTPN14 promotes differentiation through inhibition of YAP1/TAZ despite not affecting canonical YAP1/TAZ target genes.

HPV-positive HNSCC are less differentiated than HPV-negative HNSCC

We next asked whether the gene expression pattern observed downstream of PTPN14 loss is reflected in HPV-positive cancers. HPV-positive HNSCC have a strong propensity toward poorly differentiated, basaloid histology (Mendelsohn et al., 2010; Pai and Westra, 2009), which is reflected in their transcriptional profile (Hatterschide et al., 2019). We confirmed the relationship between HPV positivity and greater impairment of differentiation by immunohistochemical analysis of the differentiation marker KRT1 in sections of 14 HPV-negative tumors and 48 HPV-positive tumors (Figure 5A). 43% of HPV-negative tumors and 12.5% of HPV-positive tumors stained positive for KRT1. We also measured gene expression in patient-derived xenograft (PDX) models generated from human HNSCC. We measured *KRT1*, *KRT10*, and *IVL* levels using RNA extracted from 11 HPV-negative and 8 HPV-positive HNSCC PDX. Each differentiation marker was expressed at a lower level in HPV-positive PDX than in HPV-negative PDX (Figure 5B). We observed the same pattern of differentiation marker gene expression in an analysis of transcriptomic data from other cohorts (Figure 5—figure supplement 1A-C) (Lawrence et al., 2015). Having confirmed that HPV-positive HNSCC exhibit reduced expression of differentiation markers compared to HPV-negative HNSCC, we measured *CTGF* and *CYR61* levels. We found no significant difference in expression of these canonical YAP1/TAZ target genes in HPV-positive vs HPV-negative PDX, although there was a trend towards higher *CTGF* in the HPV-positive PDX (Figure 5C). In the transcriptomic analyses, *CTGF* and *CYR61* expression trended higher in the HPV-negative HNSCC (Figure 5—figure supplement 1D,E). The pattern of low expression of differentiation markers and unchanged canonical YAP1/TAZ target gene expression in HPV-positive versus HPV-negative patient samples is consistent with the effects of PTPN14 inactivation in cultured cells.

High-risk HPV E7 require YAP1/TAZ-TEAD transcriptional activity to extend the lifespan of primary keratinocytes.

High-risk but not low-risk HPV E7 proteins can extend the lifespan of primary keratinocytes (Halbert et al., 1991). The TEADi protein is a genetically encoded competitive inhibitor that prevents binding between YAP1/TAZ and TEAD transcription factors (Yuan et al., 2020). We used TEADi to test whether YAP1/TAZ-TEAD transcriptional activity was required for high-risk HPV E7 to extend the lifespan of primary HFK. We transduced HFK with retroviral vectors encoding GFP, HPV16 E7, or HPV18 E7 plus a lentiviral vector encoding doxycycline-inducible GFP-TEADi. As anticipated, HPV16 E7 or HPV18 E7 extended the lifespan of primary HFK based on cumulative population doublings (Figures 6A,B). TEADi induction upon doxycycline treatment decreased the lifespan of primary HFK in the presence or absence of E7, but the effect of YAP1/TAZ-TEAD inhibition was greater in the HPV16 E7 and HPV18 E7 cells, where E7 had minimal ability to promote growth in the presence of TEADi. We conclude that high-risk HPV E7 proteins require YAP1/TAZ-TEAD transcriptional activity for their lifespan extending capacity in primary keratinocytes.

PTPN14 loss and YAP1 activation promote basal cell retention in organotypic cultures

YAP1 overexpression impairs differentiation and promotes progenitor cell identity in squamous and non-squamous epithelia. HPV infection is maintained in a reservoir of infected basal cells and productive virus replication begins upon commitment to differentiation. To better understand how repression of differentiation downstream of YAP1 activation affects HPV viral biology, we developed an assay to measure cell retention in the basal epithelial layer. We hypothesized that YAP1 activation by HPV E7 might promote the adoption or maintenance of a basal cell identity in stratified squamous epithelia. In our cell fate monitoring assay, a small proportion of GFP-labeled cells were mixed with unmodified, parental HFK, and the pool was used to generate organotypic cultures in which normal labeled cells are randomly distributed throughout the epithelium.

Our initial experiment tested whether YAP1 activation altered cell fate in stratified squamous epithelia. We used GFP-labeled tracing cells that expressed doxycycline-inducible YAP1 WT, YAP1 S127A (hyperactive), or YAP1 S94A (cannot bind TEAD transcription factors) (Figure 7—figure supplement 1A,B). In organotypic cultures grown from a 1:25 mixture of GFP-labeled cells and unmodified HFK, about 20% of uninduced GFP+ cells were found in the basal layer. Induction of YAP1 WT or YAP1 S127A expression was sufficient to promote the retention of nearly 60% of labeled cells in the basal layer of the epithelium (Figure 7A,B). Only around 40% of GFP+ cells were found in the basal layer when YAP1 S94A was induced. These data indicate that YAP1 activation causes cells to be retained in the basal layer of a stratified squamous epithelium. The ability of YAP1 to bind TEAD transcription factors contributed to its activity in the cell fate assay.

We next tested whether loss of PTPN14 expression was sufficient to promote basal cell identity. We grew organotypic cultures from mixtures of unmodified primary HFK and GFP-labeled control or PTPN14 KO HFK (Figure 7—figure supplement 1C,D). 60-70% of PTPN14 KO tracer cells were found in the basal layer when either of two PTPN14 guide RNAs were used whereas about 20% of control tracer cells were retained in the basal layer (Figure 7C,D). Thus, PTPN14 knockout is sufficient to promote basal cell fate determination in keratinocytes.

Next, we tested whether HPV E7 promoted basal cell retention and if so, whether its cell retention activity required PTPN14 degradation. We grew organotypic cultures from mixtures of GFP-labeled HFK expressing HPV18 E7 WT, HPV18 E7 R84S, or the empty vector control diluted 1:50 into unmodified primary HFK (Figure 7—figure supplement 1E,F). We found that nearly 80% of GFP-labeled HPV18 E7 WT tracer cells were retained in the basal layer compared to about 10% of labeled control cells (Figure 7E,F). HPV18 E7 WT labeled cells were numerous and grouped in clusters in the basal layer, suggesting that E7 promoted the clonal expansion of labeled basal cells. Both effects were dampened in experiments using HPV18 E7 R84S tracer cells (cannot degrade PTPN14). Labeled HPV18 E7 R84S cells exhibited varying

degrees of basal cell expansion and basal cell retention and approximately 60% of labeled cells were in the basal layer. HPV18 E7 R84S retains the ability to inactivate RB1 and we interpret these data to mean that the proliferation of labeled basal cells resulted from RB1 inactivation. Finally, HPV18 E7 Δ DLLC cannot bind RB1 but can bind and degrade PTPN14. In a cell fate experiment using GFP-labeled HPV18 E7 Δ DLLC tracer cells, the labeled cells were present mainly as single cells in the basal layer (Figure 7—figure supplement 2A-B). The behavior of the two mutant HPV E7 proteins supports that PTPN14 degradation is required for basal cell retention and RB1 inactivation is required for basal cell expansion. We conclude that PTPN14 degradation and YAP1 activation by HPV18 E7 promote basal cell retention.

Discussion

YAP1 and TAZ are oncogenes that promote growth and inhibit differentiation in stratified squamous epithelia (Elbediwy et al., 2016; Schlegelmilch et al., 2011; Totaro et al., 2017; Yuan et al., 2020; Zhang et al., 2011). Here we report that HPV E7 activates YAP1 (Figure 1). YAP1/TAZ-TEAD transcriptional activity is required for the carcinogenic activity of HPV E7 (Figure 6) and YAP1 activation by E7 biases HPV E7-expressing cells to be retained in the basal epithelial layer (Figure 7). Based on these findings we propose that YAP1 activation by HPV E7 enables HPV-infected cells to persist in stratified epithelia. There is substantial evidence that RB1 inactivation is necessary but insufficient for the transforming activity of high-risk HPV E7 (Balsitis et al., 2006, 2005; Banks et al., 1990; Ciccolini et al., 1994; Helt and Galloway, 2002; Huh et al., 2005; Ibaraki et al., 1993; Jewers et al., 1992; Phelps et al., 1992; Strati and Lambert, 2007; White et al., 2015). We propose that YAP1 activation cooperates with RB1 inactivation to enable the transforming activity of HPV E7.

PTPN14 binding by HPV18 E7 was required for activation of YAP1 in the basal layer and PTPN14 KO was sufficient for the same effect (Figure 2). Highly conserved amino acids in E7 participate in binding to PTPN14 (Hatterschide et al., 2020; Yun et al., 2019), indicating that

YAP1 activation and maintenance of basal cell state is likely shared among diverse papillomavirus E7 proteins. Some minor genotype-specific differences were apparent. HPV18 E7 depletes PTPN14 protein levels more efficiently than HPV16 E7 (Hatterschide et al., 2020; White et al., 2016), which is consistent with the observed stronger effect of HPV18 E7 on YAP1 nuclear localization in basal cells (Figure 1). Genotype-specific differences could also explain the stronger effect of TEADi on HPV18 E7 in lifespan extension assays (Figure 6). Although other reports have suggested that HPV might activate YAP1 (He et al., 2015; Morgan et al., 2020; Olmedo-Nieva et al., 2020; Webb Strickland et al., 2018), no specific activity of an HPV protein has previously been shown to enable YAP1 activation. Other groups have proposed that HPV E6 activates YAP1 (He et al., 2015; Webb Strickland et al., 2018), and we observed modest YAP1 activation by HPV E6 compared to E7. We conclude that activation of YAP1 by HPV E7 is contingent upon its ability to bind and degrade PTPN14.

Even when HPV E7 was expressed in all layers of a stratified epithelium, YAP1 levels and nuclear localization increased only in basal epithelial cells. We found that E7 required PTPN14 degradation to activate YAP1 and that PTPN14 was expressed predominantly in basal keratinocytes (Figure 3). Basal cell-specific expression of *PTPN14* is consistent with the observation that it is regulated by p63, the master regulator of basal cell identity in stratified epithelia (Perez et al., 2007). We propose that PTPN14 inhibits YAP1 primarily in basal cells and that unlike the effects of E7 on RB1 in both differentiated and undifferentiated cells, E7 activates YAP1 primarily in basal cells.

Degradation of PTPN14 by HPV E7 represses keratinocyte differentiation but does not induce canonical Hippo pathway target genes (Hatterschide et al., 2020, 2019). Nonetheless, we found that PTPN14 overexpression required YAP1/TAZ to promote differentiation gene expression (Figure 4C,D). Few studies have tested how YAP1 inhibitor inactivation alters gene expression downstream of YAP1. Here we demonstrate that inactivation of LATS1 or LATS2, two well-characterized inhibitors of YAP1/TAZ, also decreased expression of differentiation

genes in unstimulated cells but did not induce canonical YAP1/TAZ targets (Figure 4E-I). Taken together, these experiments indicate that PTPN14 acts through YAP1/TAZ to regulate differentiation in keratinocytes. It is so far unclear why *CTGF* and *CYR61* expression is sensitive to large changes in total levels of YAP1 or TAZ yet is unaffected by alterations in regulators upstream of YAP1/TAZ. Nonetheless, the pattern of low differentiation gene expression and unchanged expression of canonical YAP1/TAZ target genes caused by PTPN14 loss is consistent with gene expression differences between HPV-positive and HPV-negative HNSCC.

PTPN14 knockout and knockdown reduced differentiation gene expression in monolayer culture. Even so, we did not observe reduced differentiation in suprabasal layers of organotypic cultures grown from PTPN14 knockout cells (Figure 2A and Figure 2—figure supplement 1A-C). Using our cell fate monitoring assay, we determined that instead, HPV18 E7 promotes basal cell retention and that either YAP1 overexpression or PTPN14 KO is sufficient for this activity (Figure 7). The HPV18 E7 R84S mutant that cannot degrade PTPN14 was impaired, but not completely deficient, in its ability to promote basal cell retention. We interpret these data to mean that E7 activities in addition to PTPN14 degradation might contribute to basal cell retention. GFP labeled basal cells in the HPV18 E7 R84S cell fate monitoring experiments were present in clusters, suggesting that cells that were able to remain in the basal layer had undergone clonal expansion. It is possible that RB1 inactivation by the mutant E7 drives an apparent increase in R84S mutant basal cells in this assay. The effect of YAP1 activation on cell fate in our assay resembles several experiments in which YAP1 promotes progenitor cell identity in airway and liver epithelia (Yimlamai et al., 2014; Zhao et al., 2014). Our findings demonstrate that YAP1 activation enables basal cell fate determination in stratified squamous epithelia and show that loss of an inhibitor of YAP1 has the same effect. We conclude that one consequence of YAP1 activation by HPV E7 is that E7-expressing cells are retained in the basal layer of stratified squamous epithelia.

Although persistent infection is a prerequisite for HPV-mediated carcinogenesis, the mechanisms used by papillomaviruses to establish persistent infections remain incompletely understood. Maintaining infection in the basal cell compartment is critical for papillomavirus persistence. Substantial effort has been devoted to the mechanistic understanding of how the papillomavirus genome is stably maintained in the basal layer upon cell division. However, much less is known about how papillomaviruses manipulate epithelial cell fate to establish and expand the pool of infected basal cells. Previously, HPV E7 was believed to be primarily required to establish a cellular environment conducive to HPV DNA replication in suprabasal cells (Cheng et al., 1995; Collins et al., 2005; Flores et al., 2000; McLaughlin-Drubin et al., 2005). We propose that a so far unappreciated role of E7 is that it activates YAP1 to facilitate HPV persistence by biasing infected cells to remain in the basal layer of the epithelium. Not every HPV E7-expressing cell was retained in the basal layer, so we do not anticipate that YAP1 activation would block differentiation-dependent HPV replication. HPV E6 also represses differentiation gene expression in keratinocytes and has been proposed to promote basal cell retention (Kranjec et al., 2017). Further research is needed to determine the extent to which different HPV genotypes depend on the activities of E6 or E7 for basal cell retention activity.

To the best of our knowledge, no other viruses are recognized to modulate cell fate decisions in solid tissues in a way that facilitates persistence. Some herpesviruses impact the choice between progenitor/differentiated cell fates in infected immune cells, for example Epstein-Barr virus (EBV) and human herpesvirus 6B (HHV6B) restrict differentiation in infected cells (Knox and Carrigan, 1992; Niiya et al., 2006; Onnis et al., 2012; Romeo et al., 2019; Styles et al., 2017). Herpesviruses, polyomaviruses, and hepadnaviruses encode proteins proposed to activate YAP1/TAZ or alter Hippo signaling (Hwang et al., 2014; Liu et al., 2014, 2015; Nguyen et al., 2014; Shanzer et al., 2015; Tian et al., 2004; Z. Wang et al., 2020). Not all of the mechanisms used by these viruses to activate YAP1 nor the downstream consequences of YAP1 activation have been well defined. Our finding that HPV E7 activates YAP1 to manipulate

cell fate opens up an exciting new line of inquiry into how YAP1, TAZ, and the Hippo signaling pathway could impact viral infections by regulating tissue developmental processes.

YAP1 activation and PTPN14 are relevant to both viral and non-viral cancers. We found that a genetically encoded inhibitor of YAP1/TAZ-TEAD transcription inhibited the growth of high-risk HPV E7 expressing cells (Figure 6), indicating that high-risk HPV E7 proteins require YAP1 or TAZ for carcinogenesis. YAP1/TAZ activation is sufficient to drive carcinogenesis in mouse models of cervical and oral cancer (He et al., 2019; Nishio et al., 2020; Omori et al., 2020), and the YAP1 inhibitor verteporfin reduced the growth of HPV-positive tumors in a xenograft model (Liu et al., 2019). YAP1 activation correlates with the clinical stage of HPV infection (Nishio et al., 2020), and YAP1 localizes to the nucleus in HPV-positive cancers (Alzahrani et al., 2017). Basal cell carcinoma (BCC) is the non-viral cancer that is most clearly linked to PTPN14. Germline inactivating mutations in *PTPN14* are associated with a 4- to 8-fold increase in risk of BCC by age 70 (Olafsdottir et al., 2021) and somatic mutations in *PTPN14* are frequent in BCC (Bonilla et al., 2016). YAP1/TAZ-TEAD transcriptional activity also restricts differentiation in BCC cells (Yuan et al., 2021). We propose that the specific association of PTPN14 with BCC is related to our observation that PTPN14 loss activates YAP1 in basal epithelial cells. YAP1 inhibition is of major clinical interest for several cancer types, and it is appealing to speculate that targeting YAP1 could treat persistent HPV infection and/or HPV-positive cancers.

Key Resources Table				
Reagent type (species) or resource	Designation	Source or reference	Identifiers	Additional information
antibody	anti-Actin (Mouse monoclonal)	Sigma-Aldrich	Cat#: MAB1501; RRID:AB_2223041	WB (1:20,000)
antibody	anti-GFP (Rabbit polyclonal)	Invitrogen	Cat#: A6455; RRID:AB_221570	WB (1:1,000); IHC-P (1:2000)
antibody	anti-Mouse IgG Alexa Fluor 488 (Goat polyclonal)	Invitrogen	Cat#: A11001; RRID:AB_2534069	IHC-P (1:250)
antibody	anti-Mouse IgG HRP (Horse monoclonal)	Cell Signaling Technologies	Cat#: 7076; RRID:AB_330924	WB (1:2000)
antibody	anti-Rabbit IgG Alexa Fluor 594 (Goat polyclonal)	Invitrogen	Cat#: A11012; RRID:AB_2534079	IHC-P (1:250)
antibody	anti-Rabbit IgG HRP (Goat monoclonal)	Cell Signaling Technologies	Cat#: 7074; RRID:AB_2099233	WB (1:2000)
antibody	anti-HA-Peroxidase (Rat monoclonal)	Roche	Cat#: 12013819001; RRID:AB_390917	WB (1:500)
antibody	anti-ITGB4 (Rabbit polyclonal)	Sigma-Aldrich	Cat#: HPA036348; RRID:AB_2675077	IHC-P (1:100)
antibody	anti-IVL (Mouse monoclonal)	Santa Cruz Biotechnology	Cat#: sc-398952	IHC-P (1:100)

antibody	anti-KRT1 (Mouse monoclonal)	Enzo Life Sciences	Cat#: C34904; RRID:AB_2265594	
antibody	anti-PCNA	Santa Cruz Biotechnology	Cat#: sc-56; RRID:AB_628110	IHC-P (1:100)
antibody	Anti-PTPN14 (Rabbit monoclonal)	Cell Signaling Technology	D5T6Y; Cat#: 13808; RRID:AB_2798318	WB (1:500)
antibody	anti-TAZ (Rabbit monoclonal)	Cell Signaling Technology	D3I6D; Cat#: 70148; RRID:AB_2799776	WB (1:1000)
antibody	anti-V5 (Mouse monoclonal)	Invitrogen	Cat#: 46-0705	WB (1:1000)
antibody	anti-YAP1 (Rabbit monoclonal)	Cell Signaling Technology	D8H1X; Cat#: 14074; RRID:AB_2650491	WB (1:1000); IHC-P (1:50)
transfected construct (human)	nontargeting siRNA	Dharmacon	Cat#: D-001810-01	
transfected construct (human)	siRNA to YAP1 (OnTarget Plus)	Dharmacon	Cat#: J-012200-06	
transfected construct (human)	siRNA to YAP1 (OnTarget Plus)	Dharmacon	Cat#: J-012200-08	
transfected construct (human)	siRNA to WWTR1 (OnTarget Plus)	Dharmacon	Cat#: J-016083-06	
transfected construct (human)	siRNA to WWTR1 (OnTarget Plus)	Dharmacon	Cat#: J-016083-08	

transfected construct (human)	siRNA to PTPN14 (OnTarget Plus)	Dharmacon	Cat#: J-008509-05	
transfected construct (human)	siRNA to PTPN14 (OnTarget Plus)	Dharmacon	Cat#: J-008509-08	
transfected construct (human)	siRNA to LATS1 (OnTarget Plus)	Dharmacon	Cat#: J-004632-05	
transfected construct (human)	siRNA to LATS1 (OnTarget Plus)	Dharmacon	Cat#: J-004632-08	
transfected construct (human)	siRNA to LATS2 (OnTarget Plus)	Dharmacon	Cat#: J-003865-09	
transfected construct (human)	siRNA to LATS2 (OnTarget Plus)	Dharmacon	Cat#: J-003865-10	

439

440 **Plasmids and cloning.** pInducer20 EGFP-TEADi was a gift from Ramiro Iglesias-Bartolome
441 (Addgene plasmid # 140145) (Yuan et al., 2020). pQCXIH-Myc-YAP (Addgene plasmid #
442 33091), pQCXIH-Flag-YAP-S127A (Addgene plasmid # 33092), and pQCXIH-Myc-YAP-S94A
443 (Addgene plasmid # 33094) were gifts from Kun-Liang Guan (Zhao et al., 2007). Each YAP1
444 ORF was amplified by PCR from pQCXIH, cloned into pDONR223, and transferred into
445 pLIX_402 lentiviral backbone using Gateway recombination. pLIX_402 was a gift from David
446 Root (Addgene plasmid # 41394). pLenti CMV GFP Hygro (656-4) was a gift from Eric
447 Campeau & Paul Kaufman (Addgene plasmid # 17446) (Campeau et al., 2009). PHAGE-P-
448 CMVt N-HA GFP was previously described (Galligan et al., 2014). pNeo-loxP-HPV18 was the
449 kind gift of Thomas Broker and Louise Chow (Wang et al., 2009). The Δ DLLC mutation was

introduced into the pDONR HPV18 E7 vector using site-directed mutagenesis. HPV18 E7 Δ DLLC and GFP ORFs were cloned into MSCV-P C-FlagHA GAW or MSCV-Neo C-HA GAW destination vectors using Gateway recombination. The remaining MSCV-P C-FlagHA and MSCV-Neo C-HA HPV E6 and HPV E7 retroviral plasmids and pHAGE lentiviral plasmids have been previously described (Hatterschide et al., 2020; White et al., 2016, 2012a, 2012b). A complete list of all plasmids used in this study is in [Supplemental File 1](#).

Cell culture, retrovirus production, and lentivirus production. Deidentified primary human foreskin keratinocytes (HFK) and human foreskin fibroblasts (HFF) were provided by the University of Pennsylvania Skin Biology and Disease Resource-Based Center (SBDRC). N/Tert-1 cells are hTert-immortalized HFK (Dickson et al., 2000), and N/Tert-Cas9 mock and sgPTPN14-1 are N/Tert-1 cells further engineered to constitutively express Cas9 (Hatterschide et al., 2019). Keratinocytes for cell fate experiments were cultured in keratinocyte serum-free media (KSFM) (Life Technologies, Carlsbad, California) mixed 1:1 with Medium 154 (Thermo Fisher Scientific, Waltham, Massachusetts) with the human keratinocyte growth supplement (HKGS) (Thermo Fisher Scientific) (Ridky et al., 2010). Keratinocytes for all other experiments were cultured as previously described (White et al., 2012a). SBDRC-sourced primary HFK (Figures 1, 2B, 3, 4, 6, 7, Figure 1-Supplemental Figures 2, 3, 4, and 5 Figure 2-Supplemental Figures 1 and 2, Figure 3-Supplemental Figure 1, Figure 4-Supplemental Figure 2, and Figure 7-Supplemental Figures 1 and 2) were derived from independent donors and were used within the first 2-8 passages after isolation. N/Tert-1 keratinocytes (Figures 2A and Figure 4-Supplemental Figure 1) were obtained directly from the laboratory in which they were derived (Dickson et al., 2000) and were used in the first 2-4 passages post thawing. HFK are a short-lived source material that are not routinely STR profiled or tested for mycoplasma contamination. N/Tert-1 keratinocytes were observed at every passage to ensure that they retained keratinocyte morphology, displayed the cobblestone growth pattern characteristic of

human skin keratinocytes, and were immortalized, e.g. grew indefinitely past the time at which they were used in the experiments reported herein. These cells also express keratinocyte specific genes (e.g. KRT1 and IVL), and retain the capacity to stratify and differentiate in organotypic culture. HFF were cultured in Dulbecco's Modified Eagle Medium (DMEM) (Thermo Fisher Scientific) supplemented with antibiotic and antimycotic. HFK harboring the HPV18 genome were previously described (Hatterschide et al., 2020), and were generated by transfecting cells with the pNeo-loxP-HPV18 vector (Wang et al., 2009) along with NLS-Cre and selecting with G418 to generate a stable population. Lentiviruses and retroviruses were produced in 293T or 293 Phoenix cells respectively as previously described (White et al., 2016). Stable keratinocyte populations were generated following transduction by selection with puromycin, G418, or hygromycin alone or in combination.

Lifespan extension assay. Primary HFK were engineered and cultured as described in cell culture, retrovirus production, and lentivirus production. The growth of engineered HFK was monitored in culture for 38 days. Population doublings were calculated using the number of cells at the beginning and end of each passage.

Organotypic epithelial culture. Devitalized human dermis was provided as deidentified material from the University of Pennsylvania SBDRC. Stands for organotypic epithelial cultures were printed using high temperature, autoclavable resin at the University of Pennsylvania Biotech Commons 3D-printing facility. Organotypic cultures were generated as previously described (Duperret et al., 2015; Egolf et al., 2019). Devitalized dermis was seeded with primary HFF on the dermal side at a density of 3×10^4 cells per cm^2 of culturing area and cultured for four days. Dermis and fibroblasts were then stretched across 3D-printed stands. The epidermal side of the dermis was seeded with unmodified or engineered keratinocytes at a density of 1×10^6 cells per cm^2 . Organotypic cultures were cultured in E media (Fehrmann and Laimins, 2005)

with the dermal layer maintained at the air-liquid interface starting on the day of seeding keratinocytes. Cultures were allowed to stratify for 12-14 days, then trimmed and fixed in 10% neutral buffer formalin for 24 hours. Tissues were embedded in paraffin and sectioned by the SBDRC Core A. A complete list of all organotypic cultures used in this study is in [Supplemental File 2](#).

siRNA transfection. Primary HFK were transfected with siRNAs using the Dharmafect 1 transfection reagent. All siRNA experiments were collected 72 h post transfection. Two siRNAs were used to target each gene in an experiment. The siRNAs used in this study were all purchased from Dharmacon (Lafayette, Colorado): nontargeting siRNA, siYAP1-06, siYAP1-08, siWWTR1-06, siWWTR1-08, siPTPN14-05, siPTPN14-08, siLATS1-05, siLATS1-08, siLATS2-09, siLATS2-10.

Laser capture microdissection. Formalin-fixed paraffin-embedded (FFPE) organotypic cultures were sectioned onto polyethylene naphthalate (PEN) membrane glass slides by the SBDRC Core A. Laser capture microdissection was performed on a Leica LMD 7000 microscope. Hundreds of microdissections were made per sample amounting to ~1.5 mm² of total dissected area per sample. RNA was isolated using the RNeasy FFPE kit (Qiagen, Germantown, Maryland). RNA concentration was determined using Qubit RNA HS assay kit (Life Technologies).

Patient derived xenografts. The PDXs were previously established from surgical resections of treatment-naïve HPV-positive OPSCC as described (Facompre et al., 2020). Human tumors were engrafted subcutaneously in NSG mice and passaged at least twice before cryopreservation when they reached a volume of 0.5-1.0 cm³. Total tumor RNA was isolated using the QIAamp RNA Blood Mini Kit (Qiagen).

528

529 **Western blotting.** Western blots were performed using Mini-PROTEAN (Bio-Rad Laboratories,
530 Hercules, California) or Criterion (Bio-Rad) Tris/Glycine SDS-PAGE gels and transfers were
531 performed onto polyvinylidene difluoride (PVDF). Membranes were blocked with 5% nonfat dry
532 milk in Tris-buffered saline with 0.05% Tween 20 (TBST). Membranes were incubated with
533 primary antibodies as specified in [Supplemental File 1](#). Following TBST washes, membranes
534 were incubated with horseradish peroxidase-coupled secondary antibodies and imaged using
535 chemiluminescent substrate on an Amersham Imager 600 (GE Healthcare, Chicago, Illinois).

536

537 **qRT-PCR.** Unless otherwise specified, total cellular RNA was isolated using the NucleoSpin
538 RNA extraction kit (Macherey-Nagel/Takara, San Jose, California). cDNA was generated from
539 bulk RNA with the high-capacity cDNA reverse transcription kit (Applied Biosystems, Waltham,
540 Massachusetts). cDNAs were used as a template for qPCR using Fast SYBR green master mix
541 (Applied Biosystems) and a QuantStudio 3 system (Thermo Fisher Scientific). 18S rRNA qRT-
542 PCR primers were ordered from Integrated DNA Technologies (Integrated DNA Technologies,
543 Inc., Coralville, Iowa): FWD, 5- CGCCGCTAGAGGTGAAATTCT; REV, 5-
544 CGAACCTCCGACTTTCGTTCT (Roh et al., 2005). KiCqStart SYBR green primers for qRT-
545 PCR (MilliporeSigma, St. Louis, Missouri) were used for the remaining genes assayed in this
546 study: KRT1, KRT10, IVL, ITGB4, ITGA6, CYR61, CTGF, PTPN14, YAP1, WWTR1, LATS1,
547 LATS2, G6PD, and GAPDH.

548

549 **Immunofluorescence, immunohistochemistry, and microscopy.** FFPE sections were
550 prepared for immunofluorescence by deparaffinization with xylene washes, rehydration through
551 an ethanol gradient, and heat induced epitope retrieval (HIER). Tissue sections were blocked
552 with PBS containing 1% bovine serum albumin, 10% normal goat serum, and 0.3% Triton X-
553 100. Tissue sections were incubated with primary antibodies at 4°C overnight, washed with PBS

with 0.05% Tween 20, and incubated with fluorescently labeled secondary antibodies and Hoechst 33342 at room temperature. Antibody dilutions and HIER conditions are specified in [Supplemental File 1](#). Fluorescent micrographs were captured using an Olympus IX81 microscope. All fluorescent micrograph images within the same figure panels were captured using the same exposure time and batch processed using the same contrast settings.

YAP1 localization in basal epithelial cells was quantified by visual classification of the YAP1 staining in each cell as predominantly nuclear, predominantly cytoplasmic, or comparably distributed between the nucleus and cytoplasm using Hoechst stain to demarcate the nucleus. Basal or suprabasal cell identity in the cell fate monitoring assays was determined by visual classification based on co-staining of GFP+ with the suprabasal cell marker IVL. All image analysis was performed using deidentified images with codified names.

The TMA was constructed from surgical resection specimens of 120 HNSCC that vary by TNM stage and HPV status ([Supplemental File 3](#)). Archival FFPE tumors of the oral cavity and oropharynx were identified retrospectively and oropharyngeal tumors were evaluated for HPV status as per College of American Pathologists criteria (Lewis et al., 2018) using IHC for p16. When present, lymph node metastases were included in association with the primary tumor of origin. All FFPE specimens were represented in the TMA by at least three tissue cores that incorporate both non-necrotic central tumor regions and invasive margins. Staining for KRT1 was performed by the Clinical Services Laboratory in the University of Pennsylvania Department of Pathology and Laboratory Medicine. Antibody information can be found in [Supplemental File 1](#). The KRT1 stained slides were reviewed with a standard light microscope, and evaluation was based on the presence or absence of staining in the cytoplasm of tumor cells.

All patient-derived materials and clinical data in this study were obtained from patients who underwent surgery to remove an oral cavity or oropharyngeal cancer. Patients were counseled preoperatively and provided informed consent under University of Pennsylvania IRB-approved protocol #417200 “Head and Neck Cancer Specimen Bank” (PI: D. Basu) by signing a

combined informed consent and HIPAA form for use of tissue for research. Consent under this longstanding and currently active protocol explicitly provides permission to access surgically removed fresh tumor tissue that is not needed for pathologic analysis as well as to access FFPE tumor tissue in the pathology archive at a later date. It also provides explicit permission to publish deidentified analyses of these resources. Patient care is not altered under this protocol, which carries minimal risk. Minors and other vulnerable populations are not included in the study.

Bioinformatic analysis. Genomic mutation and copy number variation data as well as tumor RNA-seq gene expression data from TCGA (Lawrence et al., 2015) were analyzed using the cBioPortal.org graphical interface (Cerami et al., 2012; Gao et al., 2013). RNA-seq V2 RSEM (RNA-Seq by Expectation Maximization) normalized expression values for individual genes were downloaded directly from cBioPortal.org. OPSCC were distinguished from HNSCC by clinical annotation of primary tumor site and HPV-positive and HPV-negative status was assigned based on previously reported HPV transcript status (Chakravarthy et al., 2016). Genes included as a part of each pathway analysis are listed in [Supplemental File 4](#). Missense, truncating, and splice mutations of unknown significance as well as amplifications of tumor suppressor genes and deletion of oncogenes were excluded from total alteration tallies.

Single cell-RNA sequencing dataset derived from the human neonatal foreskin epidermis and subsequent clustering analysis were retrieved from GitHub (S. Wang et al., 2020) and reanalyzed with MATLAB. PTPN14 expression was calculated by averaging mRNA expression for all cells by cluster and donor.

603 **Acknowledgments**

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606 processing and sectioning. Stands for organotypic cultures were printed courtesy of the
607 University of Pennsylvania Libraries' Biotech Commons.

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Figure Legends

Figure 1 | HPV E7 activates YAP1 in basal epithelial keratinocytes. (A) cBioPortal analysis for total genomic mutations and copy number alterations in HPV+/- OPSCC and HNSCC. Graph displays the percent of tumors with alterations in each pathway. Statistical significance was determined by Fisher's exact test (** $p < 0.01$, **** $p < 0.0001$). (B-D) Organotypic cultures were grown from primary HFK, HFK harboring the HPV18 genome, or HFK transduced with retroviral expression vectors encoding HPV E6 or E7 proteins. FFPE sections of cultures grown from (B) HFK or HFK harboring the HPV18 genome, (C) HFK or HFK expressing HPV16 E7 or HPV18 E7, or (D) HFK or HFK expressing HPV16 E6 or HPV16 E7 were stained for YAP1 (magenta), PCNA (green), and Hoechst (gray). White dashed lines indicate the basement membrane. White boxes indicate the location of insets in main images. Main image scale bars = 100 μm . Inset scale bars = 25 μm .

Figure 2 | HPV E7 activates YAP1 in basal keratinocytes through PTPN14 degradation. Organotypic cultures were grown from N/Tert-Cas9 keratinocytes or primary HFK transduced with retroviral expression vectors encoding HPV18 E7 WT or R84S. (A) FFPE sections of cultures grown from mock or sgPTPN14 transfected N/Tert-Cas9 keratinocytes were stained for YAP1 (magenta), IVL (green), and Hoechst (Gray). (B) FFPE sections of cultures grown from parental HFK, HPV18 E7 WT or HPV18 E7 R84S expressing HFK were stained for YAP1 (magenta), PCNA (green), and Hoechst (Gray). White dashed lines indicate the basement membrane. White boxes indicate the location of insets in main images. Main image scale bars = 100 μm . Inset scale bars = 25 μm . (C-F) Quantification of the number of (C and D) basal cells and (E and F) suprabasal cells per 100 μm of epidermis. Graphs display the mean $\pm$ standard deviation (SD) and each individual data point (independent organotypic cultures). (C and E) Statistical significance was determined by t-test. (D and F) Statistical significance was

determined by ANOVA using the Holm-Sídák correction for multiple comparisons (* $p < 0.05$, *** $p < 0.001$).

Figure 3 | PTPN14 expression is enriched in basal keratinocytes. (A-B) Single-cell RNA sequencing data and clustering analysis from Wang et al. was reanalyzed to assess PTPN14 expression in different subsets of epidermal cells. (A) Diagram of epidermis; shading depicts tissue localization of cell clusters. (B) For each donor, the mean of PTPN14 mRNA expression was calculated for each cell cluster. Graphs display the mean of PTPN14 mRNA expression for each donor (circles) as well as the mean of all five donors $\pm$ SEM (bars and error bars). Statistical significance was determined by ANOVA using the Holm-Sídák correction for multiple comparisons (* $p < 0.05$, ** $p < 0.01$). (C-F) Basal and suprabasal layers from organotypic cultures were dissected using laser capture microdissection. (C) Representative images of HFK cultures before and after individual laser dissections. Hundreds of such cuts were performed per sample. (D-F) RNA was purified from isolated layers and qRT-PCR was used to assess the expression of PTPN14 (D), basal cell markers ITGA6 and ITGB4 (E), and differentiation markers KRT1 and IVL (F). Graphs display the mean and each individual data point.

Figure 4 | YAP1/TAZ regulate differentiation downstream of PTPN14. (A) Venn diagram comparing the MSigDB YAP conserved signature to the differentially expressed genes (DEG) from our two published experiments that reflect PTPN14 loss in keratinocytes. (B-D) *YAP1* and *WWTR1* were simultaneously knocked down by siRNA transfection in HFK. Transfected HFK were then transduced with PTPN14 lentivirus at 24h post transfection. Cells were lysed for protein and total cellular RNA at 72h post transfection. (B) Cell lysates were subjected to SDS-PAGE/Western blot analysis and probed with antibodies to PTPN14, YAP1, TAZ, and Actin (Figure 4—source data 1). (C and D) qRT-PCR was used to measure the expression of the differentiation markers *KRT1* and *IVL* relative to *G6PD*. Graphs display fold change in gene

expression relative to the mock transduced cells. (E-I) Primary HFK were transfected with siRNAs targeting *YAP1*, *WWTR1* (TAZ), *PTPN14*, *LATS1*, and *LATS2*. Two siRNAs were used per target. qRT-PCR was used to measure gene expression for: the differentiation markers *IVL* (E) and *KRT1* (F), and the canonical YAP1/TAZ targets *CTGF* (G) and *CYR61* (H). Data confirming that individual siRNA transfections depleted intended transcripts is summarized in a heatmap of $\log_2$ (fold-change) levels (I). Bar graphs display the mean $\pm$ SD of three independent replicates. Statistical significance of each treatment compared to siC was determined by ANOVA using the Holm-Sídák correction for multiple comparisons (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$).

Figure 5 | HPV-positive HNSCC are less differentiated than HPV-negative HNSCC. (A) Human HNSCC tumor samples were stained for KRT1 (left). Scale bar = 100 μ m. Graph displays the percentage of tumors that were KRT1⁺ (right). Statistical significance was determined by Fisher's exact test. (B-C) Total RNA was purified from PDX samples and qRT-PCR was used to assess gene expression of (B) the differentiation markers KRT1, KRT10, and IVL and (C) the canonical YAP1/TAZ targets CTGF and CYR61. Statistical significance was determined by Mann-Whitney nonparametric test (* $p < 0.05$, ** $p < 0.01$).

Figure 6 | High-risk HPV E7 requires YAP1/TAZ-TEAD transcriptional activity to extend the lifespan of primary keratinocytes. Primary HFK were transduced with retroviruses encoding HPV16 E7, HPV18 E7, or GFP, plus pInducer20 TEADi lentivirus. Each cell population was cultured with or without 1 μ g/mL doxycycline in the media for 38 days and population doublings were tracked with each passage. Graph displays the mean $\pm$ SD of two independently transduced cell populations per condition. Statistical significance when

comparing cell growth with and without doxycycline was determined by two-way ANOVA using the Sídák correction for multiple comparisons (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$).

Figure 7 | PTPN14 loss and YAP1 activation by HPV E7 promote basal cell retention in organotypic cultures. Organotypic cultures were grown from GFP-labeled HFK mixed with unmodified HFK. (A-B) GFP-labeled HFK were transduced with lentiviral vectors encoding YAP1 WT, YAP1 S127A, or YAP1 S94A under the control of a doxycycline inducible promoter. GFP-labeled YAP1 cells were mixed 1:25 into unmodified HFK and organotypic cultures were grown from the mixture. Cultures were grown +/- 1 $\mu\text{g/mL}$ doxycycline. (C-D) GFP-labeled HFK were transduced with LentiCRISPR v2 vectors encoding control or PTPN14 targeting sgRNAs. GFP-labeled cells were mixed 1:25 into unmodified HFK and organotypic cultures were grown from the mixture. (E-F) GFP-labeled HFK were transduced with HPV18 E7 WT, HPV18 E7 R84S, or the empty vector (EV). GFP-labeled HPV18 E7 cells were mixed 1:50 into unmodified HFK and organotypic cultures were grown from the mixture. Two different images for 18E7 R84S reflect cases in which all tracer cells migrated to the suprabasal layers (*Differentiated*) or in which some tracer cells remained in the basal layer (*Basal*). (A, C, E) FFPE sections of cultures were stained for GFP (green), IVL (grey), and Hoechst (blue). Scale bar = 100 μm . (B, D, F) Quantification of the percentage of GFP+ cells found in the basal layer. Graphs display the mean $\pm$ SD and each individual data point (independent organotypic cultures). Shapes indicate cultures grown from different HFK donors. Statistical significance was determined by ANOVA using the Holm-Sídák correction for multiple comparisons (* $p < 0.05$, ** $p < 0.01$).

Figure 1—figure supplement 1 | HPV-positive HNSCC have fewer Hippo pathway alterations and lower expression of differentiation genes. cBioPortal analysis for genomic mutations and copy number alterations in HPV+/- HNSCC and OPSCC. Oncoprint displays specific genomic alterations in individual tumor samples.

Figure 1—figure supplement 2 | HPV18 E7 activates YAP1 in basal keratinocytes. (A-B) Additional replicates of organotypic cultures grown from primary HFK or HFK harboring the HPV18 genome. FFPE sections were stained for YAP1 (magenta), PCNA (green), and Hoechst (gray). White dashed lines indicate the basement membrane. White boxes indicate the location of insets in main images. Main image scale bars = 100 μ m. Inset scale bars = 25 μ m. (C-E) Quantification of the percentage of basal cells in which YAP1 is predominantly localized to the nucleus (C), comparably distributed between the nucleus and cytoplasm (D), or predominantly localized to the cytoplasm (E). Graphs display the mean $\pm$ SD and each individual data point (independent organotypic cultures). Statistical significance was determined by t-test (* $p < 0.05$).

Figure 1—figure supplement 3 | HPV E7 activates YAP1 in basal keratinocytes. Additional replicates of organotypic cultures grown from primary HFK or HFK transduced with retroviral expression encoding HPV E7 proteins. FFPE sections of cultures grown from (A) HFK or HFK expressing HPV16 E7 or HPV18 E7, (B) HFK or HFK expressing HPV16 E7, or (E) HFK and HFK expressing HPV18 E7 were stained for YAP1 (magenta), PCNA (green), and Hoechst (gray). White dashed lines indicate the basement membrane. White boxes indicate the location of insets in main images. Main image scale bars = 100 μ m. Inset scale bars = 25 μ m.

Figure 1—figure supplement 4 | HPV E6 does not activate YAP1 in basal keratinocytes. Additional replicates of organotypic cultures grown from primary HFK or HFK transduced with retroviral expression encoding HPV E6 or E7 proteins. FFPE sections were stained for YAP1 (magenta), PCNA (green), and Hoechst (gray). White dashed lines indicate the basement membrane. White boxes indicate the location of insets in main images. Main image scale bars = 100 μ m. Inset scale bars = 25 μ m.

Figure 1—figure supplement 5 | Quantification of YAP1 activation by HPV E7 in basal keratinocytes. (A-C) Quantification of the percentage of basal cells in which YAP1 is predominantly localized to the nucleus (A), comparably distributed between the nucleus and cytoplasm (B), or predominantly localized to the cytoplasm (C). Graphs display the mean $\pm$ SD and each individual data point (independent organotypic cultures). Statistical significance was determined by ANOVA using the Holm-Sídák correction for multiple comparisons (* $p < 0.05$, ** $p < 0.01$).

Figure 2—figure supplement 1 | PTPN14 knockout activates YAP1 in basal keratinocytes. Additional replicates of organotypic cultures grown from N/Tert-Cas9 keratinocytes (A-C) FFPE sections from mock or sgPTPN14 transfected N/Tert-Cas9 keratinocytes were stained for YAP1 (magenta), IVL (green), and Hoechst (Gray). White dashed lines indicate the basement membrane. White boxes indicate the location of insets in main images. Main image scale bars = 100 μ m. Inset scale bars = 25 μ m. (D-F) Quantification of the percentage of basal cells in which YAP1 is predominantly localized to the nucleus (D), comparably distributed between the nucleus and cytoplasm (E), or predominantly localized to the cytoplasm (F). Graphs display the mean $\pm$ SD and each individual data point (independent organotypic cultures). Statistical significance was determined by t-test (* $p < 0.05$).

Figure 2—figure supplement 2 | HPV E7 activates YAP1 in basal keratinocytes through PTPN14 degradation. Additional replicates of organotypic cultures grown from primary HFK transduced with retroviral expression vectors encoding HPV18 E7 WT or R84S. FFPE sections from parental HFK, HPV18 E7 WT or HPV18 E7 R84S expressing HFK were stained for YAP1 (magenta), PCNA (green), and Hoechst (Gray). White dashed lines indicate the basement membrane. White boxes indicate the location of insets in main images. Main image scale bars = 100 μ m. Inset scale bars = 25 μ m.

Figure 3—figure supplement 1 | PTPN14 expression is enriched in basal keratinocytes in HPV 18 E7 expressing organotypic cultures. Basal and suprabasal layers from a 3D organotypic culture grown from HFK transduced with a retroviral expression vector encoding HPV18 E7 were dissected using laser capture microdissection. RNA was purified from isolated layers and qRT-PCR was used to assess the expression of PTPN14 (A), the basal cell markers ITGA6 and ITGB4 (B), and the differentiation marker IVL (C). Graphs display individual data points.

Figure 4—figure supplement 1 | PTPN14 overexpression promotes differentiation in keratinocytes. NTert-Cas9 Mock and sgPTPN14-1 keratinocytes were transduced with lentiviruses encoding GFP or PTPN14 or the empty vector control. (A) Cell lysates were subjected to SDS-PAGE/Western blot analysis and probed with antibodies to PTPN14, V5-tag, Involucrin, and Actin (Figure 4—figure supplement 1—source data 1). (B) qRT-PCR was used to measure the expression of the differentiation markers IVL and KRT10 relative to G6PD. Graphs display the mean $\pm$ SD of two independent replicates.

Figure 4—figure supplement 2 | YAP1 and TAZ are required for PTPN14 to promote keratinocyte differentiation. Primary HFK were transfected with control or YAP1 and WWTR1 targeting siRNAs then transduced with PTPN14 encoding lentivirus. qRT-PCR was used to measure the expression of the differentiation markers (A) KRT1 and (B) IVL relative to G6PD. Graphs portray the change in gene expression relative to siC. Graphs display the mean $\pm$ SD of three independent replicates. Statistical significance was determined by ANOVA using the Holm-Sídák correction for multiple comparisons (** $p < 0.01$, *** $p < 0.001$).

Figure 5—figure supplement 1 | HPV-positive HNSCC express lower levels of differentiation genes. RNA-seq data from TCGA were accessed through cBioPortal. Violin plots display the distribution in log₂ mRNA expression of differentiation markers (A) KRT1, (B) KRT10, and (C) IVL, and the canonical YAP1/TAZ targets (D) CTGF and (E) CYR61. Statistical significance was determined by Mann-Whitney nonparametric test (**p<0.01, ***p<0.001, ****p<0.0001).

Figure 7—figure supplement 1 | PTPN14 degradation by HPV E7 promotes basal cell retention. (A-B) GFP-labeled HFK were transduced with YAP1 WT, YAP1 S127A, or YAP1 S94A under the control of a doxycycline inducible promoter. (A) GFP expression was confirmed by fluorescence microscopy. Scale bar = 100 µm. (B) Total RNA was purified from monolayer cells +/- treatment with 1 µg/mL doxycycline for 72h. qRT-PCR was used to assess gene expression of YAP1 and CTGF. (C-D) GFP-labeled HFK were transduced with LentiCRISPR v2 sgNT-1, sgPTPN14-3, or sgPTPN14-4 vectors. (C) GFP expression was confirmed by fluorescence microscopy. Scale bar = 100 µm (D) Cell lysates were subjected to SDS-PAGE/Western blot analysis and probed with antibodies to PTPN14 and Actin (Figure 7—figure supplement 1—source data 1). (E-F) GFP-labeled HFK were transduced with retroviral vectors encoding HPV18 WT, HPV18 ΔDLLC, HPV18 E7 R84S, or the empty vector control (EV). (E) GFP expression was confirmed by fluorescence microscopy. Scale bar = 100 µm. (F) Cell lysates were subjected to SDS-PAGE/Western blot analysis and probed with antibodies to PTPN14, RB1, and Actin (Figure 7—figure supplement 1—source data 2).

Figure 7—figure supplement 2 | HPV18 E7 can promote basal cell retention in the absence of RB1 binding. Organotypic cultures were grown from GFP-labeled cells mixed with unmodified HFK. GFP-labeled HFK were transduced with HPV18 E7 ΔDLLC or the empty vector (EV). GFP-labeled cells were mixed 1:50 into unmodified HFK. (A) FFPE sections were

817 stained for GFP (green), IVL (grey), and Hoechst (blue). Scale bar = 100 μ m (B) Quantification
818 of the percentage of GFP+ cells found in the basal layer. Graphs display the mean $\pm$ SD and
819 each individual data point (independent cultures). Statistical significance was determined by t-
820 test. (**p<0.01).

821

Supplementary File Legends

Supplementary File 1 | Plasmids and antibodies used in this study. Sheet 1 includes a list of all plasmids used in this study including details on the encoded genes, sgRNAs, promoters, bacterial resistances, tags, tag locations, selectable markers as well as addgene numbers and citations of the original sources. Sheet 2 includes a list of all antibodies used in this study including details on the company, product number, and experimental conditions in which they were used.

Supplementary File 2 | Organotypic cultures used in this study. Lists all organotypic cultures analyzed in this study and includes details on the expression vectors employed, the cell backgrounds used, and all figures and panels that portray each culture.

Supplementary File 3 | Tumor microarray specimen information. Lists the characteristics of the tumors included in the tumor microarray including the primary tumor site, HPV-positive/negative status, primary tumor T-stage, presence of nodal metastasis, and overall pathological stage.

Supplementary File 4 | Gene lists used for pathway mutational analyses. Lists the genes included in each pathway used in the pathway mutational analyses.

Source Data File Legends

Figure 4—Source Data 1 | Original images for Western blots in Figure 4B. Original uncropped images from YAP1, TAZ, V5, and actin Western blots presented in Figure 4B are included as individual image files and as a compiled summary document.

Figure 4—Figure Supplement 1—Source Data 1 | Original images for Western blots in Figure 4—Figure Supplement 1A. Original uncropped images from PTPN14, Involucrin, V5, and actin Western blots presented in Figure 4—Figure Supplement 1A are included as individual image files (cropped to individual gels and uncropped versions) and as a compiled summary document.

Figure 7—Figure Supplement 1—Source Data 1 | Original images for Western blots in Figure 7—Figure Supplement 1D. Original uncropped images from PTPN14 and actin Western blots presented in Figure 7—Figure Supplement 1D are included as individual image files and as a compiled summary document.

Figure 7—Figure Supplement 1—Source Data 2 | Original images for Western blots in Figure 7—Figure Supplement 1F. Original uncropped images from PTPN14, RB1, and actin Western blots presented in Figure 7—Figure Supplement 1F are included as individual image files and as a compiled summary document.

References

- Alzahrani F, Clattenburg L, Muruganandan S, Bullock M, MacIsaac K, Wigerius M, Williams BA, Graham MER, Rigby MH, Trites JRB, Taylor SM, Sinal CJ, Fawcett JP, Hart RD. 2017. The Hippo component YAP localizes in the nucleus of human papilloma virus positive oropharyngeal squamous cell carcinoma. *Journal of Otolaryngology - Head and Neck Surgery* **46**. doi:10.1186/s40463-017-0187-1
- Balsitis S, Dick F, Dyson N, Lambert PF. 2006. Critical Roles for Non-pRb Targets of Human Papillomavirus Type 16 E7 in Cervical Carcinogenesis. *Cancer Res* **66**:9393–400. doi:10.1158/0008-5472.CAN-06-0984
- Balsitis S, Dick F, Lee D, Farrell L, Hyde RK, Griep AE, Dyson N, Lambert PF. 2005. Examination of the pRb-Dependent and pRb-Independent Functions of E7 In Vivo. *Journal of Virology* **79**:11392–11402. doi:10.1128/jvi.79.17.11392-11402.2005
- Banks L, Edmonds C, Vousden KH. 1990. Ability of the HPV16 E7 protein to bind RB and induce DNA synthesis is not sufficient for efficient transforming activity in NIH3T3 cells. *Oncogene* **5**:1383–9.
- Beverdam A, Claxton C, Zhang X, James G, Harvey KF, Key B. 2013. Yap Controls Stem/Progenitor Cell Proliferation in the Mouse Postnatal Epidermis. *Journal of Investigative Dermatology* **133**:1497–1505. doi:10.1038/JID.2012.430
- Bonilla X, Parmentier L, King B, Bezrukov F, Kaya G, Zoete V, Seplyarskiy VB, Sharpe HJ, McKee T, Letourneau A, Ribaux PG, Popadin K, Basset-Seguín N, Chaabene R ben, Santoni FA, Andrianova MA, Guipponi M, Garieri M, Verdan C, Grosdemange K, Sumara O, Eilers M, Aifantis I, Michielin O, de Sauvage FJ, Antonarakis SE, Nikolaev SI. 2016. Genomic analysis identifies new drivers and progression pathways in skin basal cell carcinoma. *Nature Genetics* **48**:398–406. doi:10.1038/ng.3525
- Campeau E, Ruhl VE, Rodier F, Smith CL, Rahmberg BL, Fuss JO, Campisi J, Yaswen P, Cooper PK, Kaufman PD. 2009. A Versatile Viral System for Expression and Depletion of Proteins in Mammalian Cells. *PLOS ONE* **4**:e6529. doi:10.1371/JOURNAL.PONE.0006529
- Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, Jacobsen A, Byrne CJ, Heuer ML, Larsson E, Antipin Y, Reva B, Goldberg AP, Sander C, Schultz N. 2012. The cBio Cancer Genomics Portal: An Open Platform for Exploring Multidimensional Cancer Genomics Data. *Cancer Discovery* **2**:401–404. doi:10.1158/2159-8290.CD-12-0095
- Chakravarthy A, Henderson S, Thirdborough SM, Ottensmeier CH, Su X, Lechner M, Feber A, Thomas GJ, Fenton TR. 2016. Human Papillomavirus Drives Tumor Development Throughout the Head and Neck: Improved Prognosis Is Associated With an Immune Response Largely Restricted to the Oropharynx. <https://doi.org/10.1200/JCO.2016.68.2955> **34**:4132–4141. doi:10.1200/JCO.2016.68.2955
- Cheng S, Schmidt-Grimminger DC, Murrant T, Broker TR, Chow LT. 1995. Differentiation-dependent up-regulation of the human papillomavirus E7 gene reactivates cellular DNA replication in suprabasal differentiated keratinocytes. *Genes & development* **9**:2335–49. doi:10.1101/GAD.9.19.2335

903 Ciccolini F, di Pasquale G, Carlotti F, Crawford L, Tommasino M. 1994. Functional studies of E7
904 proteins from different HPV types. *Oncogene* **9**:2633–8.

905 Collins AS, Nakahara T, Do A, Lambert PF. 2005. Interactions with pocket proteins contribute to
906 the role of human papillomavirus type 16 E7 in the papillomavirus life cycle. *J Virol*
907 **79**:14769–80. doi:10.1128/JVI.79.23.14769-14780.2005

908 Day PM, Schelhaas M. 2014. Concepts of papillomavirus entry into host cells. *Current Opinion*
909 *in Virology* **4**:24–31. doi:10.1016/J.COVIRO.2013.11.002

910 de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. 2020. Global burden of cancer
911 attributable to infections in 2018: a worldwide incidence analysis. *The Lancet Global Health*
912 **8**:e180–e190. doi:10.1016/S2214-109X(19)30488-7/ATTACHMENT/BC543EDD-015D-
913 48D3-A3FB-6DFCF0BCDE7F/MMC1.PDF

914 de Martel C, Plummer M, Vignat J, Franceschi S. 2017. Worldwide burden of cancer attributable
915 to HPV by site, country and HPV type. *International Journal of Cancer* **141**:664–670.
916 doi:10.1002/ijc.30716

917 Dickson MA, Hahn WC, Ino Y, Ronfard V, Wu JY, Weinberg RA, Louis DN, Li FP, Rheinwald
918 JG. 2000. Human Keratinocytes That Express hTERT and Also Bypass a p16INK4a-
919 Enforced Mechanism That Limits Life Span Become Immortal yet Retain Normal Growth
920 and Differentiation Characteristics. *Molecular and Cellular Biology* **20**:1436–1447.
921 doi:10.1128/mcb.20.4.1436-1447.2000

922 Doorbar J, Egawa N, Griffin H, Kranjec C, Murakami I. 2015. Human papillomavirus molecular
923 biology and disease association. *Reviews in Medical Virology* **25**:2–23.
924 doi:10.1002/rmv.1822

925 Doorbar J, Zheng K, Aiyenuro A, Yin W, Walker CM, Chen Y, Egawa N, Griffin HM. 2021.
926 Principles of epithelial homeostasis control during persistent human papillomavirus
927 infection and its deregulation at the cervical transformation zone. *Current Opinion in*
928 *Virology* **51**:96–105. doi:10.1016/J.COVIRO.2021.09.014

929 Duperret EK, Dahal A, Ridky TW. 2015. Focal-adhesion-independent integrin-av regulation of
930 FAK and c-Myc is necessary for 3D skin formation and tumor invasion. *Journal of Cell*
931 *Science* **128**:3997–4013. doi:10.1242/jcs.175539

932 Egawa N, Nakahara T, Ohno S -i., Narisawa-Saito M, Yugawa T, Fujita M, Yamato K, Natori Y,
933 Kiyono T. 2012. The E1 Protein of Human Papillomavirus Type 16 Is Dispensable for
934 Maintenance Replication of the Viral Genome. *Journal of Virology*. doi:10.1128/JVI.06450-
935 11

936 Egolf S, Aubert Y, Doepner M, Anderson A, Maldonado-Lopez A, Pacella G, Lee J, Ko EK, Zou
937 J, Lan Y, Simpson CL, Ridky T, Capell BC. 2019. LSD1 Inhibition Promotes Epithelial
938 Differentiation through Derepression of Fate-Determining Transcription Factors. *Cell*
939 *Reports* **28**:1981–1992.e7. doi:10.1016/j.celrep.2019.07.058

940 Elbediwy A, Thompson BJ. 2018. Evolution of mechanotransduction via YAP/TAZ in animal
941 epithelia. *Current Opinion in Cell Biology*. doi:10.1016/j.ceb.2018.02.003

942 Elbediwy A, Vincent-Mistiaen ZI, Spencer-Dene B, Stone RK, Boeing S, Wculek SK, Cordero J,
 943 Tan EH, Ridgway R, Brunton VG, Sahai E, Gerhardt H, Behrens A, Malanchi I, Sansom
 944 OJ, Thompson BJ. 2016. Integrin signalling regulates YAP and TAZ to control skin
 945 homeostasis. *Development (Cambridge, England)* **143**:1674–87. doi:10.1242/dev.133728

946 Facompre ND, Rajagopalan P, Sahu V, Pearson AT, Montone KT, James CD, Gleber-Netto FO,
 947 Weinstein GS, Jalaly J, Lin A, Rustgi AK, Nakagawa H, Califano JA, Pickering CR, White
 948 EA, Windle BE, Morgan IM, Cohen RB, Gimotty PA, Basu D. 2020. Identifying predictors of
 949 HPV-related head and neck squamous cell carcinoma progression and survival through
 950 patient-derived models. *International Journal of Cancer* **147**:3236–3249.
 951 doi:10.1002/IJC.33125

952 Fehrmann F, Laimins LA. 2005. Human Papillomavirus Type 31 Life Cycle Methods for
 953 Studying Using Tissue Culture Models. *Methods in Molecular Biology* **292**:317–330.

954 Flores ER, Allen-Hoffmann BL, Lee D, Lambert PF. 2000. The human papillomavirus type 16 E7
 955 oncogene is required for the productive stage of the viral life cycle. *Journal of virology*
 956 **74**:6622–31. doi:10.1128/JVI.74.14.6622-6631.2000

957 Galligan JT, Martinez-Noël G, Arndt V, Hayes S, Chittenden TW, Harper JW, Howley PM. 2014.
 958 Proteomic Analysis and Identification of Cellular Interactors of the Giant Ubiquitin Ligase
 959 HERC2. *Journal of Proteome Research* **14**:953–966. doi:10.1021/PR501005V

960 Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, Sun Y, Jacobsen A, Sinha R,
 961 Larsson E, Cerami E, Sander C, Schultz N. 2013. Integrative Analysis of Complex Cancer
 962 Genomics and Clinical Profiles Using the cBioPortal. *Science Signaling* **6**:1–1.
 963 doi:10.1126/SCISIGNAL.2004088

964 Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. 2015. Epidemiology of Human
 965 Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. *J Clin Oncol* **33**:3235–
 966 3242. doi:10.1200/JCO.2015.61.6995

967 Graham S v. 2017. The human papillomavirus replication cycle, and its links to cancer
 968 progression: a comprehensive review. *Clinical Science* **131**:2201–2221.
 969 doi:10.1042/CS20160786

970 Halbert CL, Demers GW, Galloway DA. 1991. The E7 gene of human papillomavirus type 16 is
 971 sufficient for immortalization of human epithelial cells. *Journal of virology* **65**:473–8.

972 Hatterschide J, Bohidar AE, Grace M, Nulton TJ, Kim HW, Windle B, Morgan IM, Munger K,
 973 White EA. 2019. PTPN14 degradation by high-risk human papillomavirus E7 limits
 974 keratinocyte differentiation and contributes to HPV-mediated oncogenesis. *Proceedings of*
 975 *the National Academy of Sciences of the United States of America* **116**:7033–7042.
 976 doi:10.1073/pnas.1819534116

977 Hatterschide J, Brantly AC, Grace M, Munger K, White EA. 2020. A Conserved Amino Acid in
 978 the C Terminus of Human Papillomavirus E7 Mediates Binding to PTPN14 and Repression
 979 of Epithelial Differentiation. *Journal of Virology* **94**. doi:10.1128/jvi.01024-20

980 He C, Lv X, Huang C, Angeletti PC, Hua G, Dong J, Zhou J, Wang Z, Ma B, Chen X, Lambert
 981 PF, Rueda BR, Davis JS, Wang C. 2019. A Human Papillomavirus-Independent Cervical

982 Cancer Animal Model Reveals Unconventional Mechanisms of Cervical Carcinogenesis.
983 *Cell Reports* **26**. doi:10.1016/j.celrep.2019.02.004

984 He C, Mao D, Hua G, Lv X, Chen X, Angeletti PC, Dong J, Remmenga SW, Rodabaugh KJ,
985 Zhou J, Lambert PF, Yang P, Davis JS, Wang C. 2015. The Hippo/YAP pathway interacts
986 with EGFR signaling and HPV oncoproteins to regulate cervical cancer progression. *EMBO*
987 *molecular medicine* **7**:1426–49. doi:10.15252/emmm.201404976

988 Heck D v, Yee CL, Howley PM, Münger K. 1992. Efficiency of binding the retinoblastoma protein
989 correlates with the transforming capacity of the E7 oncoproteins of the human
990 papillomaviruses. *Proceedings of the National Academy of Sciences of the United States of*
991 *America* **89**:4442–6. doi:10.1073/PNAS.89.10.4442

992 Helt A-MA-M, Galloway DA. 2002. Destabilization of the Retinoblastoma Tumor Suppressor by
993 Human Papillomavirus Type 16 E7 Is Not Sufficient To Overcome Cell Cycle Arrest in
994 Human Keratinocytes. *JOURNAL OF VIROLOGY* **75**:6737–6747.
995 doi:10.1128/JVI.75.15.6737-6747.2001

996 Heng BC, Zhang X, Aubel D, Bai Y, Li X, Wei Y, Fussenegger M, Deng X. 2020. Role of
997 YAP/TAZ in Cell Lineage Fate Determination and Related Signaling Pathways. *Frontiers in*
998 *Cell and Developmental Biology* **0**:735. doi:10.3389/FCELL.2020.00735

999 Hicks-Berthet J, Ning B, Federico A, Tilston-Lunel A, Matschulat A, Ai X, Lenburg ME, Beane J,
1000 Monti S, Varelas X. 2021. Yap/Taz inhibit goblet cell fate to maintain lung epithelial
1001 homeostasis. *Cell Reports* **36**. doi:10.1016/J.CELREP.2021.109347

1002 Huh KW, DeMasi J, Ogawa H, Nakatani Y, Howley PM, Münger K. 2005. Association of the
1003 human papillomavirus type 16 E7 oncoprotein with the 600-kDa retinoblastoma protein-
1004 associated factor, p600. *Proceedings of the National Academy of Sciences of the United*
1005 *States of America* **102**:11492–11497. doi:10.1073/pnas.0505337102

1006 Hwang JH, Pores Fernando AT, Faure N, Andrabi S, Adelmant G, Hahn WC, Marto JA,
1007 Schaffhausen BS, Roberts TM. 2014. Polyomavirus small T antigen interacts with yes-
1008 associated protein to regulate cell survival and differentiation. *Journal of virology*
1009 **88**:12055–64. doi:10.1128/JVI.01399-14

1010 Ibaraki T, Satake M, Kurai N, Ichijo M, Ito Y. 1993. Transacting activities of the E7 genes of
1011 several types of human papillomavirus. *Virus Genes* **7**:187–196. doi:10.1007/BF01702398

1012 Jewers RJ, Hildebrandt P, Ludlow JW, Kell B, McCance DJ. 1992. Regions of human
1013 papillomavirus type 16 E7 oncoprotein required for immortalization of human keratinocytes.
1014 *Journal of virology* **66**:1329–35.

1015 Kho E-Y, Wang H-K, Banerjee NS, Broker TR, Chow LT. 2013. HPV-18 E6 mutants reveal p53
1016 modulation of viral DNA amplification in organotypic cultures. *Proceedings of the National*
1017 *Academy of Sciences* **110**:7542–7549. doi:10.1073/PNAS.1304855110

1018 Knight JF, Sung VYC, Kuzmin E, Couzens AL, de Verteuil DA, Ratcliffe CDH, Coelho PP,
1019 Johnson RM, Samavarchi-Tehrani P, Gruosso T, Smith HW, Lee W, Saleh SM, Zuo D,
1020 Zhao H, Guiot MC, Davis RR, Gregg JP, Moraes C, Gingras AC, Park M. 2018. KIBRA
1021 (WWC1) Is a Metastasis Suppressor Gene Affected by Chromosome 5q Loss in Triple-
1022 Negative Breast Cancer. *Cell Reports* **22**:3191–3205. doi:10.1016/j.celrep.2018.02.095

1023 Knox KK, Carrigan DR. 1992. In Vitro Suppression of Bone Marrow Progenitor Cell
1024 Differentiation by Human Herpesvirus 6 Infection. *The Journal of Infectious Diseases*
1025 **165**:925–928. doi:10.1093/INFDIS/165.5.925

1026 Koshiol J, Lindsay L, Pimenta JM, Poole C, Jenkins D, Smith JS. 2008. Persistent human
1027 papillomavirus infection and cervical neoplasia: A systematic review and meta-analysis.
1028 *American Journal of Epidemiology*. doi:10.1093/aje/kwn036

1029 Kranjec C, Holleywood C, Libert D, Griffin H, Mahmood R, Isaacson E, Doorbar J. 2017.
1030 Modulation of basal cell fate during productive and transforming HPV-16 infection is
1031 mediated by progressive E6-driven depletion of Notch. *The Journal of Pathology* **242**:448–
1032 462. doi:10.1002/path.4917

1033 Lawrence MS, Sougnez C, Lichtenstein L, Cibulskis K, Lander E, Gabriel SB, Getz G, Ally A,
1034 Balasundaram M, Birol I, Bowlby R, Brooks D, Butterfield YSN, Carlsen R, Cheng D, Chu
1035 A, Dhalla N, Guin R, Holt RA, Jones SJM, Lee D, Li H, Marra MA, Mayo M, Moore RA,
1036 Mungall AJ, Robertson AG, Schein JE, Sipahimalani P, Tam A, Thiessen N, Wong T,
1037 Protopopov A, Santoso N, Lee S, Parfenov M, Zhang Jianhua, Mahadeshwar HS, Tang J,
1038 Ren X, Seth S, Haseley P, Zeng D, Yang Lixing, Xu AW, Song X, Pantazi A, Bristow CA,
1039 Hadjipanayis A, Seidman J, Chin L, Park PJ, Kucherlapati R, Akbani R, Casasent T, Liu W,
1040 Lu Y, Mills G, Motter T, Weinstein J, Diao L, Wang J, Hong Fan Y, Liu J, Wang K, Auman
1041 JT, Balu S, Bodenheimer T, Buda E, Hayes DN, Hoadley KA, Hoyle AP, Jefferys SR,
1042 Jones CD, Kimes PK, Liu Yufeng, Marron JS, Meng S, Mieczkowski PA, Mose LE, Parker
1043 JS, Perou CM, Prins JF, Roach J, Shi Y, Simons J v., Singh D, Soloway MG, Tan D,
1044 Veluvolu U, Walter V, Waring S, Wilkerson MD, Wu J, Zhao N, Cherniack AD,
1045 Hammerman PS, Tward AD, Peadamallu CS, Saksena G, Jung J, Ojesina AI, Carter SL,
1046 Zack TI, Schumacher SE, Beroukhir R, Freeman SS, Meyerson M, Cho J, Noble MS,
1047 DiCara D, Zhang H, Heiman DI, Gehlenborg N, Voet D, Lin P, Frazer S, Stojanov P, Liu
1048 Yingchun, Zou L, Kim J, Muzny D, Doddapaneni HV, Kovar C, Reid J, Morton D, Han Y,
1049 Hale W, Chao H, Chang K, Drummond JA, Gibbs RA, Kakkar N, Wheeler D, Xi L, Ciriello
1050 G, Ladanyi M, Lee W, Ramirez R, Sander C, Shen R, Sinha R, Weinhold N, Taylor BS,
1051 Aksoy BA, Dresdner G, Gao J, Gross B, Jacobsen A, Reva B, Schultz N, Sumer SO, Sun
1052 Y, Chan TA, Morris LG, Stuart J, Benz S, Ng S, Benz C, Yau C, Baylin SB, Cope L,
1053 Danilova L, Herman JG, Bootwalla M, Maglinte DT, Laird PW, Triche T, Weisenberger DJ,
1054 van den Berg DJ, Agrawal N, Bishop J, Boutros PC, Bruce JP, Byers LA, Califano J, Carey
1055 TE, Chen Z, Cheng H, Chiosea SI, Cohen E, Diergaarde B, Egloff AM, El-Naggar AK,
1056 Ferris RL, Frederick MJ, Grandis JR, Guo Y, Haddad RI, Harris T, Hui ABY, Lee JJ,
1057 Lippman SM, Liu FF, McHugh JB, Myers J, Ng PKS, Perez-Ordóñez B, Pickering CR,
1058 Prystowsky M, Romkes M, Saleh AD, Sartor MA, Seethala R, Seiwert TY, Si H, van Waes
1059 C, Waggott DM, Wiznerowicz M, Yarbrough WG, Zhang Jiexin, Zuo Z, Burnett K, Crain D,
1060 Gardner J, Lau K, Mallery D, Morris S, Paulauskis J, Penny R, Shelton C, Shelton T,
1061 Sherman M, Yena P, Black AD, Bowen J, Frick J, Gastier-Foster JM, Harper HA, Leraas K,
1062 Lichtenberg TM, Ramirez NC, Wise L, Zmuda E, Baboud J, Jensen MA, Kahn AB, Pihl TD,
1063 Pot DA, Srinivasan D, Walton JS, Wan Y, Burton RA, Davidsen T, Demchok JA, Eley G,
1064 Ferguson ML, Mills Shaw KR, Ozenberger BA, Sheth M, Sofia HJ, Tarnuzzer R, Wang Z,
1065 Yang Liming, Zenklusen JC, Saller C, Tarvin K, Chen C, Bollag R, Weinberger P,
1066 Golusiński W, Golusiński P, Ibbs M, Korski K, Mackiewicz A, Suchorska W, Szybiak B,
1067 Curley E, Beard C, Mitchell C, Sandusky G, Ahn J, Khan Z, Irish J, Waldron J, William WN,

1068 Egea S, Gomez-Fernandez C, Herbert L, Bradford CR, Chepeha DB, Haddad AS, Jones
1069 TR, Komarck CM, Malakh M, Moyer JS, Nguyen A, Peterson LA, Prince ME, Rozek LS,
1070 Taylor EG, Walline HM, Wolf GT, Boice L, Chera BS, Funkhouser WK, Gulley ML,
1071 Hackman TG, Hayward MC, Huang M, Rathmell WK, Salazar AH, Shockley WW, Shores
1072 CG, Thorne L, Weissler MC, Wrenn S, Zanation AM, Brown BT, Pham M. 2015.
1073 Comprehensive genomic characterization of head and neck squamous cell carcinomas.
1074 *Nature* 2015 517:7536 **517**:576–582. doi:10.1038/nature14129

1075 Lee H-H, Chiang W-H, Chiang S-H, Liu JY-C, Hwang J, Ng S-Y. 1995. Regulation of Cyclin D I,
1076 DNA Topoisomerase I, and Proliferating Cell Nuclear Antigen Promoters During the Cell
1077 Cycle. *Gene Expression* **4**:95–109.

1078 Lewis JS, Beadle B, Bishop JA, Chernock RD, Colasacco C, Lacchetti C, Moncur JT, Rocco
1079 JW, Schwartz MR, Seethala RR, Thomas NE, Westra WH, Faquin WC. 2018. Human
1080 Papillomavirus Testing in Head and Neck Carcinomas: Guideline From the College of
1081 American Pathologists. *Archives of Pathology & Laboratory Medicine* **142**:559–597.
1082 doi:10.5858/ARPA.2017-0286-CP

1083 Liu G, Yu F-X, Kim YC, Meng Z, Naipauer J, Looney DJ, Liu X, Gutkind JS, Mesri EA, Guan K-
1084 L. 2014. Kaposi sarcoma-associated herpesvirus promotes tumorigenesis by modulating
1085 the Hippo pathway. *Oncogene* 2015 34:27 **34**:3536–3546. doi:10.1038/onc.2014.281

1086 Liu K, Du S, Gao P, Zheng J. 2019. Verteporfin suppresses the proliferation, epithelial-
1087 mesenchymal transition and stemness of head and neck squamous carcinoma cells via
1088 inhibiting YAP1. *Journal of Cancer* **10**:4196–4207. doi:10.7150/jca.34145

1089 Liu P, Zhang H, Liang X, Ma H, Luan F, Wang B, Bai F, Gao L, Ma C. 2015. HBV preS2
1090 promotes the expression of TAZ via miRNA-338-3p to enhance the tumorigenesis of
1091 hepatocellular carcinoma. *Oncotarget* **6**:29048. doi:10.18632/ONCOTARGET.4804

1092 McBride AA. 2021. Human papillomaviruses: diversity, infection and host interactions. *Nature*
1093 *Reviews Microbiology*. doi:10.1038/s41579-021-00617-5

1094 McBride AA. 2017. Mechanisms and strategies of papillomavirus replication. *Biological*
1095 *Chemistry* **398**:919–927. doi:10.1515/hsz-2017-0113

1096 McLaughlin-Drubin ME, Bromberg-White JL, Meyers C. 2005. The role of the human
1097 papillomavirus type 18 E7 oncoprotein during the complete viral life cycle. *Virology* **338**:61–
1098 68. doi:10.1016/j.virol.2005.04.036

1099 Mello SS, Valente LJ, Raj N, Seoane JA, Flowers BM, McClendon J, Bieging-Rolett KT, Lee J,
1100 Ivanochko D, Kozak MM, Chang DT, Longacre TA, Koong AC, Arrowsmith CH, Kim SK,
1101 Vogel H, Wood LD, Hruban RH, Curtis C, Attardi LD. 2017. A p53 Super-tumor Suppressor
1102 Reveals a Tumor Suppressive p53-Ptpn14-Yap Axis in Pancreatic Cancer. *Cancer Cell*
1103 **32**:460-473.e6. doi:10.1016/j.ccell.2017.09.007

1104 Mendelsohn AH, Lai CK, Shintaku IP, Elashoff DA, Dubinett SM, Abemayor E, st. John MA.
1105 2010. Histopathologic findings of HPV and p16 positive HNSCC. *The Laryngoscope*
1106 **120**:1788–1794. doi:10.1002/lary.21044

1107 Mirabello L, Yeager M, Yu K, Clifford GM, Xiao Y, Zhu B, Cullen M, Boland JF, Wentzensen N,
1108 Nelson CW, Raine-Bennett T, Chen Z, Bass S, Song L, Yang Q, Steinberg M, Burdett L,

1109 Dean M, Roberson D, Mitchell J, Lorey T, Franceschi S, Castle PE, Walker J, Zuna R,
1110 Kreimer AR, Beachler DC, Hildesheim A, Gonzalez P, Porras C, Burk RD, Schiffman M.
1111 2017. HPV16 E7 Genetic Conservation Is Critical to Carcinogenesis. *Cell* **170**:1164-
1112 1174.e6.

1113 Morgan EL, Patterson MR, Ryder EL, Lee SY, Wasson CW, Harper KL, Li Y, Griffin S, Blair GE,
1114 Whitehouse A, Macdonald A. 2020. MicroRNA-18a targeting of the STK4/MST1 tumour
1115 suppressor is necessary for transformation in HPV positive cervical cancer. *PLOS*
1116 *Pathogens* **16**:e1008624. doi:10.1371/journal.ppat.1008624

1117 Moroishi T, Hansen CG, Guan K-L. 2015. The emerging roles of YAP and TAZ in cancer.
1118 *Nature Reviews Cancer* **15**:73–79. doi:10.1038/nrc3876

1119 Münger K, Werness BA, Dyson N, Phelps WC, Harlow E, Howley PM. 1989. Complex formation
1120 of human papillomavirus E7 proteins with the retinoblastoma tumor suppressor gene
1121 product. *The EMBO Journal* **8**:4099–4105. doi:10.1002/j.1460-2075.1989.tb08594.x

1122 Nguyen HT, Hong X, Tan S, Chen Q, Chan L, Fivaz M, Cohen SM, Voorhoeve PM. 2014. Viral
1123 Small T Oncoproteins Transform Cells by Alleviating Hippo-Pathway-Mediated Inhibition of
1124 the YAP Proto-oncogene. *Cell Reports* **8**:707–713. doi:10.1016/J.CELREP.2014.06.062

1125 Niiya H, Lei J, Guo Y, Azuma T, Yakushijin Y, Sakai I, Hato T, Tohyama M, Hashimoto K,
1126 Yasukawa M. 2006. Human herpesvirus 6 impairs differentiation of monocytes to dendritic
1127 cells. *Experimental Hematology* **34**:642–653. doi:10.1016/J.EXPHEM.2006.02.001

1128 Nishio M, To Y, Maehama T, Aono Y, Otani J, Hikasa H, Kitagawa A, Mimori K, Sasaki T,
1129 Nishina H, Toyokuni S, Lydon JP, Nakao K, Mak TW, Kiyono T, Katabuchi H, Tashiro H,
1130 Suzuki A. 2020. Endogenous YAP1 activation drives immediate onset of cervical
1131 carcinoma in situ in mice. *Cancer Science* **111**:3576. doi:10.1111/CAS.14581

1132 Olafsdottir T, Stacey SN, Sveinbjornsson G, Thorleifsson G, Norland K, Sigurgeirsson B,
1133 Thorisdottir K, Kristjansson AK, Tryggvadottir L, Sarin KY, Benediktsson R, Jonasson JG,
1134 Sigurdsson A, Jonasdottir A, Kristmundsdottir S, Jonsson H, Gylfason A, Oddsson A,
1135 Fridriksdottir R, Gudjonsson SA, Zink F, Lund SH, Rognvaldsson S, Melsted P,
1136 Steinthorsdottir V, Gudmundsson J, Mikaelisdottir E, Olason PI, Stefansdottir L, Eggertsson
1137 HP, Halldorsson B v., Thorsteinsdottir U, Agustsson TT, Olafsson K, Olafsson JH, Sulem
1138 P, Rafnar T, Gudbjartsson DF, Stefansson K. 2021. Loss-of-Function Variants in the
1139 Tumor-Suppressor Gene PTPN14 Confer Increased Cancer Risk. *Cancer Research*
1140 **81**:1954–1964. doi:10.1158/0008-5472.CAN-20-3065

1141 Olmedo-Nieva L, Muñoz-Bello JO, Manzo-Merino J, Lizano M. 2020. New insights in Hippo
1142 signalling alteration in human papillomavirus-related cancers. *Cellular Signalling* 109815.
1143 doi:10.1016/j.cellsig.2020.109815

1144 Omori H, Nishio M, Masuda M, Miyachi Y, Ueda F, Nakano T, Sato K, Mimori K, Taguchi K,
1145 Hikasa H, Nishina H, Tashiro H, Kiyono T, Mak TW, Nakao K, Nakagawa T, Maehama T,
1146 Suzuki A. 2020. YAP1 is a potent driver of the onset and progression of oral squamous cell
1147 carcinoma. *Science Advances* **6**:eaay3324. doi:10.1126/sciadv.aay3324

1148 Onnis A, Navari M, Antonicelli G, Morettini F, Mannucci S, de Falco G, Vigorito E, Leoncini L.
1149 2012. Epstein-Barr nuclear antigen 1 induces expression of the cellular microRNA hsa-

1150 miR-127 and impairing B-cell differentiation in EBV-infected memory B cells. New insights
 1151 into the pathogenesis of Burkitt lymphoma. *Blood Cancer Journal* 2012 2:8 2:e84–e84.
 1152 doi:10.1038/bcj.2012.29

1153 Pai SI, Westra WH. 2009. Molecular Pathology of Head and Neck Cancer: Implications for
 1154 Diagnosis, Prognosis, and Treatment. *Annual Review of Pathology: Mechanisms of*
 1155 *Disease* 4:49–70. doi:10.1146/annurev.pathol.4.110807.092158

1156 Parish JL, Bean AM, Park RB, Androphy EJ. 2006. ChIR1 Is Required for Loading
 1157 Papillomavirus E2 onto Mitotic Chromosomes and Viral Genome Maintenance. *Molecular*
 1158 *Cell* 24:867–876. doi:10.1016/j.molcel.2006.11.005

1159 Perez CA, Ott J, Mays DJ, Pietenpol JA. 2007. p63 consensus DNA-binding site: identification,
 1160 analysis and application into a p63MH algorithm. *Oncogene* 26:7363–7370.
 1161 doi:10.1038/sj.onc.1210561

1162 Phelps WC, Munger K, Yee CL, Barnes JA, Howley PM. 1992. Structure-function analysis of the
 1163 human papillomavirus type 16 E7 oncoprotein. *Journal of Virology* 66:2418–2427.
 1164 doi:10.1128/jvi.66.4.2418-2427.1992

1165 Poernbacher I, Baumgartner R, Marada SK, Edwards K, Stocker H. 2012. Drosophila Pez acts
 1166 in Hippo signaling to restrict intestinal stem cell proliferation. *Current biology : CB* 22:389–
 1167 96. doi:10.1016/j.cub.2012.01.019

1168 Pyeon D, Pearce SM, Lank SM, Ahlquist P, Lambert PF. 2009. Establishment of human
 1169 papillomavirus infection requires cell cycle progression. *PLoS Pathogens* 5:e1000318.
 1170 doi:10.1371/journal.ppat.1000318

1171 Radley D, Saah A, Stanley M. 2016. Persistent infection with human papillomavirus 16 or 18 is
 1172 strongly linked with high-grade cervical disease. *Human Vaccines & Immunotherapeutics*
 1173 12:768–772. doi:10.1080/21645515.2015.1088616

1174 Ridky TW, Chow JM, Wong DJ, Khavari PA. 2010. Invasive three-dimensional organotypic
 1175 neoplasia from multiple normal human epithelia. *Nature Medicine* 2010 16:12 16:1450–
 1176 1455. doi:10.1038/nm.2265

1177 Roberts JN, Buck CB, Thompson CD, Kines R, Bernardo M, Choyke PL, Lowy DR, Schiller JT.
 1178 2007. Genital transmission of HPV in a mouse model is potentiated by nonoxynol-9 and
 1179 inhibited by carrageenan. *Nature Medicine* 2007 13:7 13:857–861. doi:10.1038/nm1598

1180 Roh M, Song C, Kim J, Abdulkadir SA. 2005. Chromosomal Instability Induced by Pim-1 Is
 1181 Passage-dependent and Associated with Dysregulation of Cyclin B1 *. *Journal of Biological*
 1182 *Chemistry* 280:40568–40577. doi:10.1074/JBC.M509369200

1183 Romeo MA, Gilardini Montani MS, Falcinelli L, Gaeta A, Nazzari C, Faggioni A, Cirone M. 2019.
 1184 HHV-6B reduces autophagy and induces ER stress in primary monocytes impairing their
 1185 survival and differentiation into dendritic cells. *Virus Research* 273:197757.
 1186 doi:10.1016/J.VIRUSRES.2019.197757

1187 Rositch AF, Koshiol J, Hudgens MG, Razzaghi H, Backes DM, Pimenta JM, Franco EL, Poole
 1188 C, Smith JS. 2013. Patterns of persistent genital human papillomavirus infection among

1189 women worldwide: A literature review and meta-analysis. *International Journal of Cancer*
1190 **133**:1271–1285. doi:10.1002/ijc.27828

1191 Sanchez-Vega F, Mina M, Armenia J, Chatila WK, Luna A, La KC, Dimitriadou S, Liu DL,
1192 Kantheti HS, Saghafein S, Chakravarty D, Daian F, Gao Q, Bailey MH, Liang WW, Foltz
1193 SM, Shmulevich I, Ding L, Heins Z, Ochoa A, Gross B, Gao J, Zhang Hongxin, Kundra R,
1194 Kandoth C, Bahceci I, Dervishi L, Dogrusoz U, Zhou W, Shen H, Laird PW, Way GP,
1195 Greene CS, Liang H, Xiao Y, Wang C, Iavarone A, Berger AH, Bivona TG, Lazar AJ,
1196 Hammer GD, Giordano T, Kwong LN, McArthur G, Huang C, Tward AD, Frederick MJ,
1197 McCormick F, Meyerson M, Caesar-Johnson SJ, Demchok JA, Felau I, Kasapi M,
1198 Ferguson ML, Hutter CM, Sofia HJ, Tarnuzzer R, Wang Z, Yang L, Zenklusen JC, Zhang J
1199 (Julia), Chudamani S, Liu J, Lolla L, Naresh R, Pihl T, Sun Q, Wan Y, Wu Y, Cho J,
1200 DeFreitas T, Frazer S, Gehlenborg N, Getz G, Heiman DI, Kim J, Lawrence MS, Lin P,
1201 Meier S, Noble MS, Saksena G, Voet D, Zhang Hailei, Bernard B, Chambwe N, Dhankani
1202 V, Knijnenburg T, Kramer R, Leinonen K, Liu Y, Miller M, Reynolds S, Shmulevich I,
1203 Thorsson V, Zhang W, Akbani R, Broom BM, Hegde AM, Ju Z, Kanchi RS, Korkut A, Li J,
1204 Liang H, Ling S, Liu W, Lu Y, Mills GB, Ng KS, Rao A, Ryan M, Wang Jing, Weinstein JN,
1205 Zhang J, Abeshouse A, Armenia J, Chakravarty D, Chatila WK, de Bruijn I, Gross BE,
1206 Heins ZJ, Kundra R, La K, Ladanyi M, Luna A, Nissan MG, Ochoa A, Phillips SM, Reznik
1207 E, Sanchez-Vega F, Sander C, Schultz N, Sheridan R, Sumer SO, Sun Y, Taylor BS,
1208 Wang Jioajiao, Zhang Hongxin, Anur P, Peto M, Spellman P, Benz C, Stuart JM, Wong
1209 CK, Yau C, Hayes DN, Parker JS, Wilkerson MD, Ally A, Balasundaram M, Bowlby R,
1210 Brooks D, Carlsen R, Chuah E, Dhalla N, Holt R, Jones SJM, Kasaian K, Lee D, Ma Y,
1211 Marra MA, Mayo M, Moore RA, Mungall AJ, Mungall K, Robertson AG, Sadeghi S, Schein
1212 JE, Sipahimalani P, Tam A, Thiessen N, Tse K, Wong T, Berger AC, Beroukhir R,
1213 Cherniack AD, Cibulskis C, Gabriel SB, Gao GF, Ha G, Meyerson M, Schumacher SE,
1214 Shih J, Kucherlapati MH, Kucherlapati RS, Baylin S, Cope L, Danilova L, Bootwalla MS, Lai
1215 PH, Maglinte DT, van den Berg DJ, Weisenberger DJ, Auman JT, Balu S, Bodenheimer T,
1216 Fan C, Hoadley KA, Hoyle AP, Jefferys SR, Jones CD, Meng S, Mieczkowski PA, Mose
1217 LE, Perou AH, Perou CM, Roach J, Shi Y, Simons J v., Skelly T, Soloway MG, Tan D,
1218 Veluvolu U, Fan H, Hinoue T, Laird PW, Shen H, Zhou W, Bellair M, Chang K, Covington
1219 K, Creighton CJ, Dinh H, Doddapaneni HV, Donehower LA, Drummond J, Gibbs RA, Glenn
1220 R, Hale W, Han Y, Hu J, Korchina V, Lee S, Lewis L, Li W, Liu X, Morgan M, Morton D,
1221 Muzny D, Santibanez J, Sheth M, Shinbrot E, Wang L, Wang M, Wheeler DA, Xi L, Zhao F,
1222 Hess J, Appelbaum EL, Bailey M, Cordes MG, Ding L, Fronick CC, Fulton LA, Fulton RS,
1223 Kandoth C, Mardis ER, McLellan MD, Miller CA, Schmidt HK, Wilson RK, Crain D, Curley
1224 E, Gardner J, Lau K, Mallery D, Morris S, Paulauskis J, Penny R, Shelton C, Shelton T,
1225 Sherman M, Thompson E, Yena P, Bowen J, Gastier-Foster JM, Gerken M, Leraas KM,
1226 Lichtenberg TM, Ramirez NC, Wise L, Zmuda E, Corcoran N, Costello T, Hovens C,
1227 Carvalho AL, de Carvalho AC, Fregnani JH, Longatto-Filho A, Reis RM, Scapulatempo-
1228 Neto C, Silveira HCS, Vidal DO, Burnette A, Eschbacher J, Hermes B, Noss A, Singh R,
1229 Anderson ML, Castro PD, Ittmann M, Huntsman D, Kohl B, Le X, Thorp R, Andry C, Duffy
1230 ER, Lyadov V, Paklina O, Setdikova G, Shabunin A, Tavobilov M, McPherson C, Warnick
1231 R, Berkowitz R, Cramer D, Feltmate C, Horowitz N, Kibel A, Muto M, Raut CP, Malykh A,
1232 Barnholtz-Sloan JS, Barrett W, Devine K, Fulop J, Ostrom QT, Shimmel K, Wolinsky Y,
1233 Sloan AE, de Rose A, Giulianti F, Goodman M, Karlan BY, Hagedorn CH, Eckman J, Harr
1234 J, Myers J, Tucker K, Zach LA, Deyarmin B, Hu H, Kvecher L, Larson C, Mural RJ, Somiari

1235 S, Vicha A, Zelinka T, Bennett J, Iacocca M, Rabeno B, Swanson P, Latour M, Lacombe L,
 1236 Têtu B, Bergeron A, McGraw M, Staugaitis SM, Chabot J, Hibshoosh H, Sepulveda A, Su
 1237 T, Wang T, Potapova O, Voronina O, Desjardins L, Mariani O, Roman-Roman S, Sastre X,
 1238 Stern MH, Cheng F, Signoretti S, Berchuck A, Bigner D, Lipp E, Marks J, McCall S,
 1239 McLendon R, Secord A, Sharp A, Behera M, Brat DJ, Chen A, Delman K, Force S, Khuri F,
 1240 Magliocca K, Maithel S, Olson JJ, Owonikoko T, Pickens A, Ramalingam S, Shin DM, Sica
 1241 G, van Meir EG, Zhang Hongzheng, Eijckenboom W, Gillis A, Korpershoek E, Looijenga L,
 1242 Oosterhuis W, Stoop H, van Kessel KE, Zwarthoff EC, Calatuzzolo C, Cuppini L, Cuzzubbo
 1243 S, DiMeco F, Finocchiaro G, Mattei L, Perin A, Pollo B, Chen C, Houck J, Lohavanichbutr
 1244 P, Hartmann A, Stoehr C, Stoehr R, Taubert H, Wach S, Wullich B, Kyler W, Murawa D,
 1245 Wiznerowicz M, Chung K, Edenfield WJ, Martin J, Baudin E, Bubley G, Bueno R, de
 1246 Rienzo A, Richards WG, Kalkanis S, Mikkelsen T, Noushmehr H, Scarpacci L, Girard N,
 1247 Aymerich M, Campo E, Giné E, Guillermo AL, van Bang N, Hanh PT, Phu BD, Tang Y,
 1248 Colman H, Evason K, Dottino PR, Martignetti JA, Gabra H, Juhl H, Akeredolu T, Stepa S,
 1249 Hoon D, Ahn K, Kang KJ, Beuschlein F, Breggia A, Birrer M, Bell D, Borad M, Bryce AH,
 1250 Castle E, Chandan V, Cheville J, Copland JA, Farnell M, Flotte T, Giana N, Ho T, Kendrick
 1251 M, Kocher JP, Kopp K, Moser C, Nagorney D, O'Brien D, O'Neill BP, Patel T, Petersen G,
 1252 Que F, Rivera M, Roberts L, Smallridge R, Smyrk T, Stanton M, Thompson RH, Torbenson
 1253 M, Yang JD, Zhang L, Brimo F, Ajani JA, Gonzalez AMA, Behrens C, Bondaruk J,
 1254 Broaddus R, Czerniak B, Esmaeli B, Fujimoto J, Gershenwald J, Guo C, Logothetis C,
 1255 Meric-Bernstam F, Moran C, Ramondetta L, Rice D, Sood A, Tamboli P, Thompson T,
 1256 Troncso P, Tsao A, Wistuba I, Carter C, Haydu L, Hersey P, Jakrot V, Kakavand H,
 1257 Kefford R, Lee K, Long G, Mann G, Quinn M, Saw R, Scolyer R, Shannon K, Spillane A,
 1258 Stretch J, Synott M, Thompson J, Wilmott J, Al-Ahmadie H, Chan TA, Ghossein R,
 1259 Gopalan A, Levine DA, Reuter V, Singer S, Singh B, Tien NV, Broudy T, Mirsaidi C, Nair P,
 1260 Drwiega P, Miller J, Smith J, Zaren H, Park JW, Hung NP, Kebebew E, Linehan WM,
 1261 Metwalli AR, Pacak K, Pinto PA, Schiffman M, Schmidt LS, Vocke CD, Wentzensen N,
 1262 Worrell R, Yang H, Moncrieff M, Goparaju C, Melamed J, Pass H, Botnariuc N, Caraman I,
 1263 Cernat M, Chemencedji I, Clipca A, Doruc S, Gorincioi G, Mura S, Pirtac M, Stancul I,
 1264 Tcaciuc D, Albert M, Alexopoulou I, Arnaout A, Bartlett J, Engel J, Gilbert S, Parfitt J,
 1265 Sekhon H, Thomas G, Rassl DM, Rintoul RC, Bifulco C, Tamakawa R, Urba W, Hayward
 1266 N, Timmers H, Antenucci A, Facciolo F, Grazi G, Marino M, Merola R, de Krijger R,
 1267 Gimenez-Roqueplo AP, Piché A, Chevalier S, McKercher G, Birsoy K, Barnett G, Brewer
 1268 C, Farver C, Naska T, Pennell NA, Raymond D, Schilero C, Smolenski K, Williams F,
 1269 Morrison C, Borgia JA, Liptay MJ, Pool M, Seder CW, Junker K, Omberg L, Dinkin M,
 1270 Manikhas G, Alvaro D, Bragazzi MC, Cardinale V, Carpino G, Gaudio E, Chesla D,
 1271 Cottingham S, Dubina M, Moiseenko F, Dhanasekaran R, Becker KF, Janssen KP, Slotta-
 1272 Huspenina J, Abdel-Rahman MH, Aziz D, Bell S, Cebulla CM, Davis A, Duell R, Elder JB,
 1273 Hilty J, Kumar B, Lang J, Lehman NL, Mandt R, Nguyen P, Pilarski R, Rai K, Schoenfield
 1274 L, Senecal K, Wakely P, Hansen P, Lechan R, Powers J, Tischler A, Grizzle WE, Sexton
 1275 KC, Kastl A, Henderson J, Porten S, Waldmann J, Fassnacht M, Asa SL, Schadendorf D,
 1276 Couce M, Graefen M, Huland H, Sauter G, Schlomm T, Simon R, Tennstedt P, Olabode O,
 1277 Nelson M, Bathe O, Carroll PR, Chan JM, Disaia P, Glenn P, Kelley RK, Landen CN,
 1278 Phillips J, Prados M, Simko J, Smith-McCune K, VandenBerg S, Roggin K, Fehrenbach A,
 1279 Kendler A, Sifri S, Steele R, Jimeno A, Carey F, Forgie I, Mannelli M, Carney M,
 1280 Hernandez B, Campos B, Herold-Mende C, Jungk C, Unterberg A, von Deimling A, Bossler
 1281 A, Galbraith J, Jacobus L, Knudson M, Knutson T, Ma D, Milhem M, Sigmund R, Godwin

1282 AK, Madan R, Rosenthal HG, Adebamowo C, Adebamowo SN, Boussioutas A, Beer D,
 1283 Giordano T, Mes-Masson AM, Saad F, Bocklage T, Landrum L, Mannel R, Moore K,
 1284 Moxley K, Postier R, Walker J, Zuna R, Feldman M, Valdivieso F, Dhir R, Luketich J,
 1285 Pinero EMM, Quintero-Aguilo M, Carlotti CG, dos Santos JS, Kemp R, Sankarankuty A,
 1286 Tirapelli D, Catto J, Agnew K, Swisher E, Creaney J, Robinson B, Shelley CS, Godwin EM,
 1287 Kendall S, Shipman C, Bradford C, Carey T, Haddad A, Moyer J, Peterson L, Prince M,
 1288 Rozek L, Wolf G, Bowman R, Fong KM, Yang I, Korst R, Rathmell WK, Fantacone-
 1289 Campbell JL, Hooke JA, Kovatich AJ, Shriver CD, DiPersio J, Drake B, Govindan R, Heath
 1290 S, Ley T, van Tine B, Westervelt P, Rubin MA, Lee J il, Aredes ND, Mariamidze A, van
 1291 Allen EM, Cherniack AD, Ciriello G, Sander C, Schultz N. 2018. Oncogenic Signaling
 1292 Pathways in The Cancer Genome Atlas. *Cell* **173**:321-337.e10.
 1293 doi:10.1016/J.CELL.2018.03.035

1294 Scheffner M, Werness BA, Huibregtse JM, Levine AJ, Howley PM. 1990. The E6 oncoprotein
 1295 encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. *Cell*
 1296 **63**:1129–1136. doi:10.1016/0092-8674(90)90409-8

1297 Schlegelmilch K, Mohseni M, Kirak O, Pruszek J, Rodriguez JR, Zhou D, Kreger BT, Vasioukhin
 1298 V, Avruch J, Brummelkamp TR, Camargo FD. 2011. Yap1 acts downstream of α -catenin to
 1299 control epidermal proliferation. *Cell* **144**:782–795. doi:10.1016/j.cell.2011.02.031

1300 Shanzer M, Ricardo-Lax I, Keshet R, Reuven N, Shaul Y. 2015. The polyomavirus middle T-
 1301 antigen oncogene activates the Hippo pathway tumor suppressor Lats in a Src-dependent
 1302 manner. *Oncogene* **34**:4190–4198. doi:10.1038/onc.2014.347

1303 Strati K, Lambert PF. 2007. Role of Rb-dependent and Rb-independent functions of
 1304 papillomavirus E7 oncogene in head and neck cancer. *Cancer Research* **67**:11585–11593.
 1305 doi:10.1158/0008-5472.CAN-07-3007

1306 Styles CT, Bazot Q, Parker GA, White RE, Paschos K, Allday MJ. 2017. EBV epigenetically
 1307 suppresses the B cell-to-plasma cell differentiation pathway while establishing long-term
 1308 latency. *PLOS Biology* **15**:e2001992. doi:10.1371/JOURNAL.PBIO.2001992

1309 Szalmás A, Tomaić V, Basukala O, Massimi P, Mittal S, Kónya J, Banks L. 2017. The PTPN14
 1310 Tumor Suppressor Is a Degradation Target of Human Papillomavirus E7. *Journal of*
 1311 *Virology* **91**:e00057-17. doi:10.1128/jvi.00057-17

1312 Szymaniak AD, Mahoney JE, Cardoso W v., Varelas X. 2015. Crumbs3-Mediated Polarity
 1313 Directs Airway Epithelial Cell Fate through the Hippo Pathway Effector Yap. *Developmental*
 1314 *Cell* **34**:283–296. doi:10.1016/J.DEVCEL.2015.06.020

1315 Tian Y, Li D, Dahl J, You J, Benjamin T. 2004. Identification of TAZ as a Binding Partner of the
 1316 Polyomavirus T Antigens. *Journal of Virology* **78**:12657–12664.
 1317 doi:10.1128/jvi.78.22.12657-12664.2004

1318 Totaro A, Castellan M, Battilana G, Zanconato F, Azzolin L, Giulitti S, Cordenonsi M, Piccolo S.
 1319 2017. YAP/TAZ link cell mechanics to Notch signalling to control epidermal stem cell fate.
 1320 *Nature Communications* **8**:1–13. doi:10.1038/ncomms15206

1321 Wang H-K, Duffy AA, Broker TR, Chow LT. 2009. Robust production and passaging of
 1322 infectious HPV in squamous epithelium of primary human keratinocytes. *Genes &*
 1323 *development* **23**:181–94. doi:10.1101/gad.1735109

1324 Wang S, Drummond ML, Guerrero-Juarez CF, Tarapore E, MacLean AL, Stabell AR, Wu SC,
 1325 Gutierrez G, That BT, Benavente CA, Nie Q, Atwood SX. 2020. Single cell transcriptomics
 1326 of human epidermis identifies basal stem cell transition states. *Nature Communications*
 1327 *2020 11:1* **11**:1–14. doi:10.1038/s41467-020-18075-7

1328 Wang W, Huang J, Wang X, Yuan J, Li X, Feng L, Park J il, Chen J. 2012. PTPN14 is required
 1329 for the density-dependent control of YAP1. *Genes and Development* **26**:1959–1971.
 1330 doi:10.1101/gad.192955.112

1331 Wang Z, Lu W, Zhang Y, Zou F, Jin Z, Zhao T. 2020. The Hippo Pathway and Viral Infections.
 1332 *Frontiers in Microbiology* **0**:3033. doi:10.3389/FMICB.2019.03033

1333 Webb Strickland S, Brimer N, Lyons C, vande Pol SB. 2018. Human Papillomavirus E6
 1334 interaction with cellular PDZ domain proteins modulates YAP nuclear localization. *Virology*
 1335 **516**:127–138. doi:10.1016/J.VIROL.2018.01.003

1336 Werness BA, Levine AJ, Howley PM. 1990. Association of human papillomavirus types 16 and
 1337 18 E6 proteins with p53. *Science* **248**:76–79. doi:10.1126/science.2157286

1338 White EA, Kramer RE, Hwang JH, Pores Fernando AT, Naetar N, Hahn WC, Roberts TM,
 1339 Schaffhausen BS, Livingston DM, Howley PM. 2015. Papillomavirus E7 Oncoproteins
 1340 Share Functions with Polyomavirus Small T Antigens. *Journal of Virology* **89**:2857–2865.
 1341 doi:10.1128/jvi.03282-14

1342 White EA, Kramer RE, Tan MJA, Hayes SD, Harper JW, Howley PM. 2012a. Comprehensive
 1343 Analysis of Host Cellular Interactions with Human Papillomavirus E6 Proteins Identifies
 1344 New E6 Binding Partners and Reflects Viral Diversity. *Journal of Virology* **86**:13174–13186.
 1345 doi:10.1128/JVI.02172-12

1346 White EA, Münger K, Howley PM. 2016. High-Risk Human Papillomavirus E7 Proteins Target
 1347 PTPN14 for Degradation. *mBio* **7**:e01530-16. doi:10.1128/mBio.01530-16

1348 White EA, Sowa ME, Tan MJA, Jeudy S, Hayes SD, Santha S, Münger K, Harper JW, Howley
 1349 PM. 2012b. Systematic identification of interactions between host cell proteins and E7
 1350 oncoproteins from diverse human papillomaviruses. *Proceedings of the National Academy*
 1351 *of Sciences of the United States of America* **109**:E260-7. doi:10.1073/pnas.1116776109

1352 Yimlamai D, Christodoulou C, Galli GG, Yanger K, Pepe-Mooney B, Gurung B, Shrestha K,
 1353 Cahan P, Stanger BZ, Camargo FD. 2014. Hippo Pathway Activity Influences Liver Cell
 1354 Fate. *Cell* **157**:1324–1338. doi:10.1016/J.CELL.2014.03.060

1355 You J, Croyle JL, Nishimura A, Ozato K, Howley PM. 2004. Interaction of the bovine
 1356 papillomavirus E2 protein with Brd4 tethers the viral DNA to host mitotic chromosomes.
 1357 *Cell* **117**:349–360. doi:10.1016/S0092-8674(04)00402-7

1358 Yuan Y, Park J, Feng A, Awasthi P, Wang Z, Chen Q, Iglesias-Bartolome R. 2020. YAP1/TAZ-
 1359 TEAD transcriptional networks maintain skin homeostasis by regulating cell proliferation

1360 and limiting KLF4 activity. *Nature Communications* **11**:1–14. doi:10.1038/s41467-020-
1361 15301-0

1362 Yuan Y, Salinas Parra N, Chen Q, Iglesias-Bartolome R. 2021. Oncogenic Hedgehog-
1363 Smoothened Signaling Depends on YAP1–TAZ/TEAD Transcription to Restrain
1364 Differentiation in Basal Cell Carcinoma. *Journal of Investigative Dermatology*.
1365 doi:10.1016/J.JID.2021.06.020

1366 Yun H-Y, Kim MW, Lee HS, Kim W, Shin JH, Kim H, Shin H-C, Park H, Oh B-H, Kim WK, Bae
1367 K-H, Lee SC, Lee E-W, Ku B, Kim SJ. 2019. Structural basis for recognition of the tumor
1368 suppressor protein PTPN14 by the oncoprotein E7 of human papillomavirus. *PLOS Biology*
1369 **17**:e3000367. doi:10.1371/journal.pbio.3000367

1370 Zhang H, Pasolli HA, Fuchs E. 2011. Yes-associated protein (YAP) transcriptional coactivator
1371 functions in balancing growth and differentiation in skin. *Proceedings of the National*
1372 *Academy of Sciences* **108**:2270–2275. doi:10.1073/pnas.1019603108

1373 Zhao B, Wei X, Li W, Udan RS, Yang Q, Kim J, Xie J, Ikenoue T, Yu J, Li L, Zheng P, Ye K,
1374 Chinnaiyan A, Halder G, Lai Z-C, Guan K-L. 2007. Inactivation of YAP oncoprotein by the
1375 Hippo pathway is involved in cell contact inhibition and tissue growth control. *Genes &*
1376 *Development* **21**:2747–2761. doi:10.1101/GAD.1602907

1377 Zhao R, Fallon TR, Saladi SV, Pardo-Saganta A, Villoria J, Mou H, Vinarsky V, Gonzalez-
1378 Celeiro M, Nunna N, Hariri LP, Camargo F, Ellisen LW, Rajagopal J. 2014. Yap Tunes
1379 Airway Epithelial Size and Architecture by Regulating the Identity, Maintenance, and Self-
1380 Renewal of Stem Cells. *Developmental Cell* **30**:151–165. doi:10.1016/j.devcel.2014.06.004

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