Critical Involvement of TFIIB in Viral Pathogenesis

Michael J. O’Brien and Athar Ansari*
Department of Biological Science, Wayne State University, Detroit, MI, United States

Viral infections and the harm they cause to their host are a perpetual threat to living organisms. Pathogenesis and subsequent spread of infection requires replication of the viral genome and expression of structural and non-structural proteins of the virus. Generally, viruses use transcription and translation machinery of the host cell to achieve this objective. The viral genome encodes transcriptional regulators that alter the expression of viral and host genes by manipulating initiation and termination steps of transcription. The regulation of the initiation step is often through interactions of viral factors with gene specific factors as well as general transcription factors (GTFs). Among the GTFs, TFIIB (Transcription Factor IIB) is a frequent target during viral pathogenesis. TFIIB is utilized by a plethora of viruses including human immunodeficiency virus, herpes simplex virus, vaccinia virus, Thogoto virus, hepatitis virus, Epstein-Barr virus and gammaherpesviruses to alter gene expression. A number of viral transcriptional regulators exhibit a direct interaction with host TFIIB in order to accomplish expression of their genes and to repress host transcription. Some viruses have evolved proteins with a three-dimensional structure very similar to TFIIB, demonstrating the importance of TFIIB for viral persistence. Upon viral infection, host transcription is selectively altered with viral transcription benefitting. The nature of viral utilization of TFIIB for expression of its own genes, along with selective repression of host antiviral genes and downregulation of general host transcription, makes TFIIB a potential candidate for antiviral therapies.

Keywords: virus, TFIIB, transcription, RNA polymerase II, pathogenesis, gene expression

INTRODUCTION

Viruses have always been a threat to living creatures. Humans alone are the target of more than 200 viral species (Woolhouse et al., 2012; Knipe et al., 2013). The known viruses and the newly evolving strains, which are being discovered on a regular basis, have the potential to pose a global threat to humanity. They have caused pandemics in the past and the current COVID-19 pandemic is due to a recently evolved strain of coronavirus (Xie and Chen, 2020). It is necessary to identify, understand, and block replication of viruses to combat the hazards they pose. Viruses take advantage of their host to persist, replicate, and ultimately spread to a new host.

Necessary for viral infection is replication of the viral genome and production of viral proteins. Transcription of viral genes is the first step toward production of viral proteins (An et al., 2019; Liu et al., 2020). A number of DNA viruses and retroviruses use host transcription machinery to achieve this objective (Agostini et al., 1996; Gelev et al., 2014; Liu et al., 2020). Transcription is an essential biological process that results in production of RNA from the DNA template, a necessary step before the eventual production of proteins. At the center of transcription is the RNA
Viruses employ a two-pronged attack on host transcription machinery during pathogenesis. They exploit host transcription machinery to achieve expression of their own genes, and simultaneously downregulate transcription of host genes or gene products especially those linked to antiviral immune response (Gelev et al., 2014; Haas et al., 2018; Yang and You, 2020; Wang et al., 2020). A number of viruses use host transcription machinery to transcribe their protein-coding genes, and a number of them including herpes simplex virus-1 (HSV-1) target the general transcription factor TFIIIB to achieve this goal. With RNAi knockdown of TFIIIB, HeLa cells transfected with HSV-1 formed fewer plaques compared to the cells containing TFIIIB (Gelev et al., 2014). Viral replication and plaque formation were reduced more than sevenfold upon knockdown of TFIIIB. In the absence of TFIIIB, transcription of most of the herpes genes examined was reduced, while expression of only a subset of host genes was adversely affected (Gelev et al., 2014). Likewise, human immunodeficiency virus (HIV), hepatitis B virus (HBV), human cytomegalovirus (HCMV), equine herpesvirus type 1 (EHV), and Epstein-Barr viruses (EBV) use TFIIIB to enhance transcription of their genes (Figure 1; Caswell et al., 1993; Tong et al., 1995; Agostini et al., 1996; Haviv et al., 1998; Yang and You, 2020; Simmen et al., 2001).

Viral infection downregulates expression of a number of host genes related to anti-viral immune response. One such host gene normally induced upon viral infection is interferon regulatory factor 3 (IRF-3) (Lyles, 2000). IRF-3 along with IRF-7 are gene-specific transcription activators of type-I IFNs (IFN-α/β), which bind type-I IFN receptor present on the surface of the cell. Upon binding of IFN-α/β, the signal is transduced inside the cell by the signal transducer and activator of transcription STAT-1 and STAT-2. STATs translocate to the nucleus where they induce transcription of several hundred genes encoding proteins that protect the cell from viral infection. Viruses have evolved a variety of strategies to combat activity of such antiviral genes or gene products during pathogenesis. Polio and vesicular stomatitis viruses target TBP, while RVFV destabilizes the general transcription factor TFIIH to induce shut-off of host cell transcription (Yuan et al., 2001; Kundu et al., 2005; Kalveram et al., 2011). Gammaherpesviruses, including Kaposi’s sarcoma-associated herpesvirus (KSHV) and murine gammaherpesvirus 68 (MHV68), as well as orthomyxovirus Thogoto virus downregulate TFIIIB to repress host gene expression (Hartenian et al., 2020). Gammaherpesvirus adversely affects general host transcription (Hartenian et al., 2020), while Thogoto virus selectively represses transcription of antiviral genes without affecting general host transcription. Thogoto virus specifically inhibits transcription of type-I IFNs (IFN-α/β), inflammatory cytokines, and antiviral effector genes (Jennings et al., 2005; Vogt et al., 2008; Haas et al., 2018). Thus, TFIIIB is targeted in multiple ways during viral pathogenesis.
Viral transcriptional regulators target different general transcription factors, but TFIID and TFIIB are the prime targets. Viruses target general transcription factors such as TFIIB, TFIID, TFIIE and TFIIH in order to transcribe viral genes. TFIIB, however, is emerging as the most common target of many different viruses such as HIV, HSV, HCMV and HBV among others. Created with BioRender.com.

Evidence demonstrates that viruses accomplish this objective by physically interacting with TFIIB and recruiting it to the promoter of viral specific genes while preventing it from binding to selected host gene promoters. A number of viral transcriptional regulators like Vpr of HIV, HBx of Hepatitis B, VP16 and ICP4 of HSV, ML of Thogoto virus, IE2 of cytomegalovirus, E2TA of bovine papillomavirus type I, and IE of equine herpes virus exhibit a direct physical interaction with TFIIB (Table 1; Lin et al., 1991; Caswell et al., 1993; Rank and Lambert, 1995; Agostini et al., 1996; Haviv et al., 1998; Haas et al., 2018; Li et al., 2020). These viral transcription factors direct transcription of a subset of viral genes that are often vital to viability of the virus. Transcription of all viral genes, however, is not dependent on interaction of viral transcriptional factors with host TFIIB. The mechanism of regulation of transcription of viral and host genes by viral transcriptional regulators through their interaction with TFIIB is described in detail below.

Vpr and Tat: Vpr (Viral Protein R) is a highly conserved HIV-1 encoded protein required for replication, transcription and proliferation of the virus and is critical for viral pathogenicity. Vpr stimulates viral transcription, possibly due to its ability to interact with TFIIB (Agostini et al., 1996; Kino et al., 1999). In vitro studies have demonstrated a direct physical interaction of Vpr with TFIIB. Vpr binding brings about a change in the three-dimensional structure of TFIIB from “closed” to “open,” which is the transcriptionally active conformation (Agostini et al., 1996). Another HIV-1 protein Tat (Trans-Activator of Transcription), which drastically enhances viral transcription, also targets TFIIB to achieve its transactivation function (Yu et al., 1995). It forms a ternary complex with TFIIB and the human TAP protein. TAP protein binds strongly to a carboxy-terminal region of TFIIB as well as to the conserved activation domain of Tat. TAP acts as a bridge, facilitating interaction of the Tat transactivator with the host general transcription machinery through TFIIB (Yu et al., 1995). A direct protein-protein interaction has been observed between TFIIB and Tat (Veschambre et al., 1997).

VP16: Human herpes simplex virus 1 and 2 (HSV-1 and HSV-2) cause cold sores and genital herpes in humans. Both these viral species are common and contagious. Approximately 67% of the world population under the age of 50 has HSV-1 (James et al., 2020). Viral spread is dependent on the onset of the lytic cycle and reactivation. Viral tegument protein (VP16), which is the transcriptional activator of the immediate-early (IE) gene products (alpha genes), is the key activator of lytic infection (Mossman et al., 2000). VP16-induced transcription of IE genes acts as a regulatory switch; when it is on, it promotes lytic infection, and when it is off latent infection is favored. TFIIB is among several molecular targets of VP16 during transcription of IE genes. VP16 exhibits a physical interaction with both native and recombinant human TFIIB, but not with yeast or fly TFIIB (Lin et al., 1991; Gupta et al., 1996). A mutation in the VP16
only mild symptoms, but occasionally it causes serious disorders that infects people of all ages. Normally the infected people show virus that targets TFIIB during pathogenesis. It is a common virus RNA transcription.

One of the host proteins that HBx interacts with to enable viral replication and prevent antiviral response. HBx: Hepatitis B virus (HBV), which causes inflammation of the liver, also manipulates TFIIB during pathogenesis. HBV causes fatal liver infection and chronically infects more than 250 million people worldwide. The HBV minigenome persists in the nucleus of infected cells and is the template for production of four viral proteins. One of these proteins, HBx, is crucial for viral pathogenesis as it interacts with a number of host factors to facilitate viral replication and prevent antiviral response. One of the host proteins that HBx interacts with to enable viral transcription is TFIIB (Turton et al., 2020). HBx directly interacts with TFIIB through its B-finger motif (Haviv et al., 1998; Zhou et al., 2015). This interaction is critical for the coactivator function of HBx. TFIIB-HBx interaction facilitates recruitment of RNAPII on viral promoters leading to upregulation of viral RNA transcription.

IE1 and IE2: Human cytomegalovirus (HCMV) is another virus that targets TFIIB during pathogenesis. It is a common virus that infects people of all ages. Normally the infected people show only mild symptoms, but occasionally it causes serious disorders like mononucleosis and hepatitis. During viral pathogenesis, IE1 and IE2 proteins, which are the product of immediate early genes, transactivate a number of homologous (HCMV) and heterologous (non-HCMV) promoters. Transcription activation potential of IE2 is dependent on its interaction with two GTFs, TBP and TFIIB. IE2 exhibits a direct physical interaction with TFIIB (Caswell et al., 1993). The region of IE2 that mediates binding to TFIIB overlaps with that required for TBP binding. This is also the region linked to the transcriptional regulatory function of the protein. The IE2 gene produces three IE2 protein isoforms, IE2-86, IE2-60, IE2-40, late in infection. IE2-86 is essential for viral replication. An independent study demonstrated binding of IE2-86 to TFIIB under in vitro conditions (Xu and Ye, 2002). IE2-86-TFIIB interaction could be crucial for transcriptional regulation of viral early promoters, by facilitating downregulation of its own promoter and activating expression of many host cellular genes necessary for progression of viral infection.

ML: Thogoto virus is an orthomyxovirus that is transmitted to vertebrates through ticks. Thogoto virus targets TFIIB to repress transcription of host antiviral genes linked to innate immunity by a unique mechanism (Vogt et al., 2008; Haas et al., 2018). The ML (Matrix Long) protein of the virus physically interacts with TFIIB and relocalizes it to the cytoplasm (Haas et al., 2018). ML-mediated nuclear depletion of TFIIB represses transcription of genes that require de novo recruitment of RNAPII, while transcription of genes with paused polymerases continues unabated (Haas et al., 2018). Among host genes that require de novo recruitment of polymerases are antiviral immune

| Virus | Viral protein | Mechanism of transcriptional regulation |
|-------|--------------|----------------------------------------|
| Herpes Simplex Virus I (HSV-I) | VP16 | Direct interaction with TFIIB; TFIIB knockdown decreases HSV1 gene transcription, viral replication, and plaque formation |
| Equine Herpesvirus 1 (EHV-1) | IE | Direct interaction with TFIIB; IE utilizes TFIIB to activate EHV-1 promoters |
| Thogoto Virus (THOV) | ML | Direction interaction with TFIIB; Downregulates TFIIB, represses antiviral gene transcription, and relocalizes TFIIB from nucleus to cytoplasm |
| Hepatitis B Virus (HBV) | HBx | Interacts with TFIIB to recruit RNAPII on viral promoters. |
| African Swine Fever Virus (ASFV) | ASFV-RNAP | Encodes a viral homolog similar to TFIIB |
| Human Immunodeficiency Virus Type 1 (HIV-1) | Vpr/Tat | Vpr: Direct interaction with TFIIB and induces transcriptionally active form of TFIIB. Tat: Forms ternary complex with TFIIB and human TAP protein facilitating interaction with transcriptional machinery |
| Epstein-Barr virus (EBV) | EBNA-2 | Specific interaction with TFIIB crucial for transcription activation potential of EBNA-2 |
| Murine gammaherpesvirus 68 (MHV68) | N/A | Reduced promoter occupancy of RNAPII due to viral induced degradation of RNAPII subunits and TFIIB |
| Kaposi's sarcoma-associated herpesvirus (KSHV) | N/A | Reduced promoter occupancy of RNAPII due to viral induced degradation of RNAPII subunits and TFIIB |
| Poxviruses | vRNA | Viral RNAP contains a subunit with homology to TFIIB. |
| Canine parvovirus (CBPV) | N/A | Sequesters TFIIB to viral induced nuclear compartment which is site of viral mRNA transcription |
| Simian virus 40 (SV40) | LSF | Increases rate of association of TFIIB to viral promoters leading to efficient PIC assembly |
| Cytomegalovirus | IE2 | Direct interaction with TFIIB and likely crucial for transcriptional regulation of viral early promoters. |
| Coronavirus | N/A | TFIIB is a high confidence transcriptional target |
response genes like pro-inflammatory cytokines, IRF3 and its regulated genes, as well as NFκB regulated genes. Sequestration of TFII B by the ML protein therefore facilitates viral infection by selectively inhibiting host antiviral genes without affecting the bulk of general host transcription.

IE: In addition, equine herpesvirus type 1 (EHV-1) also targets TFII B during pathogenesis (Jang et al., 2001). At least six viral transcriptional regulators including the IE (Immediate Early) protein regulates the coordinated expression of EH V-1 genes. The transcription activation potential of IE is dependent on its ability to interact with TFII B. The IE interaction domain of TFII B spans residues 125–174 in the first direct repeat of the protein. Transient transfection assays demonstrated that exogenous native TFII B did not perturb transcription activation potential of the IE protein, but a TFII B mutant that lacked the IE interactive domain adversely affected the ability of the IE protein to activate EHV-1 promoters (Albrecht et al., 2003). These results demonstrate that direct interaction of IE with TFII B is essential for its ability to activate EHV-1 promoters.

**VIRUSES TARGET TFII B OVER TFII D AND OTHER GENERAL TRANSCRIPTION FACTORS**

Since transcription by RNAPII requires at least six GTFs, it is likely that GTFs other than TFII B are also targeted during viral pathogenesis. There are reports of viruses interacting with the TFII D subunit TBP, TFII E and TFII H to achieve transcription of viral genes and turn off host transcription. TBP and TFII B, however, have emerged as the preferred target of viral transcriptional regulators (Sundseth and Hansen, 1992; Tong et al., 1995; Ihalainen et al., 2012). Transcription regulators of some viruses like SV40, Epstein-Barr virus and canine parvovirus (CPV) interact with both TFII B and TBP. TFII B, however, is more critical for viral pathogenesis. In the case of gammaherpesvirus, despite both TFII B and TFII A being the viral targets, TFII B is the key factor for viral transcription (Hartenian et al., 2020).

LSF (Late Simian virus 40 transcription Factor) is a cellular transcriptional activator of SV40 that dramatically increases transcription from viral major late promoters. LSF enhances transcription by facilitating assembly of the PIC on major late promoters. LSF, however, does not affect binding of TFII D to the promoter. Instead, it increases the rate of association of TFII B, which leads to efficient PIC assembly and increased transcription of SV40 genes (Sundseth and Hansen, 1992). Similarly, Epstein-Barr virus nuclear antigen 2 (EBNA-2) has an acidic domain, which is essential for the transcription activation potential of EBNA-2 (Tong et al., 1995). EBNA-2 exhibits specific interaction with TFII B, while its binding affinity for TBP is much less (Tong et al., 1995). The EBNA-2-TFII B interaction is crucial for transcription activation potential of EBNA-2 during the viral life cycle.

Canine parvovirus (CPV) infection leads to formation of a proteinaceous sub-compartment within the nucleus, which is the site of transcription of viral mRNA. Fluorescence recovery after photobleaching (FRAP) revealed accumulation of both TBP and TFII B in the nuclear sub-compartment during viral infection. TBP and TFII B, however, exhibited different kinetics of diffusion and binding affinities to the nuclear sub-compartment (Ihalainen et al., 2012). The binding affinity of TBP to the nuclear body area decreased upon viral infection while that of TFII B slightly increased. The measured binding time of TFII B reflected the time scale of TFII B association with the PIC and recruitment of RNAPII to the promoter, indicating selective usefulness of TFII B over TBP for transcription of CPV genes in the nuclear body area.

Kaposi’s sarcoma-associated herpesvirus (KSHV) and murine gammaherpesvirus 68 (MHV68) infection leads to mRNA-decay induced repression of transcription of antiviral genes and overall general transcription of host cells. Viral induced downregulation of host transcription was due to the genomewide decrease in RNAPII promoter occupancy (Hartenian et al., 2020). Reduced promoter occupancy was attributed to viral induced degradation of subunits of RNAPII and TFII B. The amount of TFII A also registered a slight decline upon viral infection. There was, however, absolutely no decrease in the level of TBP in the cell. Clearly, SV40, Epstein-Barr virus, canine parvovirus and gammaherpesviruses target TFII B over TBP or TFII A during viral pathogenesis.

**VIRUSES HAVE EVOLVED PROTEINS SIMILAR TO TFII B**

Some viruses have evolved proteins with a structure and function similar to that of TFII B, resulting in less reliance upon the host. Vaccinia virus, which is a prototype poxvirus, encodes its own RNAP (vRNAP). The vRNAP is a multi-subunit protein capable of carrying out transcription in the cytoplasm, not reliant upon host RNAPII to transcribe viral genes (Moss, 2013; Grimm et al., 2019). Replication in the cytoplasm not only rules out the utilization of host RNAPII, but of natively localized host TFII B as well. The vRNAP complex consists of eight subunits with varying degrees of homology to RNAPII and one subunit, Rap94, displays homology to TFII B (Grimm et al., 2019; Hillen et al., 2019; Liu et al., 2020). A central region of Rap94 possesses a “B-homology region” containing elements homologous to eukaryotic TFII B B-ribbon, B-cyclin, and B-reader domains. These regions allow Rap94 to interact with RNAPII, bind to DNA, and determine start site selection in a manner similar to host TFII B (Nikolov and Burley, 1997; Bushnell et al., 2004; Weinzierl and Wiesler, 2011; Sainsbury et al., 2013; Grimm et al., 2019; Hillen et al., 2019). These similarities suggest that Rap94 likely functions in transcription initiation, bypassing the need to utilize host TFII B (Grimm et al., 2019). African Swine Fever Virus (ASFV) also encodes a vRNAP with subunits exhibiting homology to RNAPII subunits and TBP. One of the subunits also exhibits remarkable structural and functional similarities to TFII B (Cackett et al., 2020). For such viruses like vaccinia virus and ASFV, which assemble a viral PIC using a vRNAP complex, the critical usage of host TFII B is bypassed, as they have evolved TFII B-like proteins. Concerning the gammaherpesvirus, host TFII B is used in conjunction with the TFII B-like viral protein for transcribing
viral genes. Host TFIIB is required for early transcription of viral genes that produces components of the vPIC. Once vPIC proteins are synthesized, the requirement of host TFIIB for transcription of late viral genes is bypassed (Nandakumar and Glaunsinger, 2019). Thus, early transcription during viral life cycle is vPIC-independent, while late transcription is vPIC-dependent. The presence of these TFIIB-like proteins in viral transcription complexes simply reflects the vital role of TFIIB in viral gene expression.

DISCUSSION

TFIIB is a general transcription factor that is essential for initiation of transcription from a majority of RNAPII-transcribed genes in eukaryotes. Viruses can target any general transcription factor to inhibit transcription of antiviral genes for successful pathogenesis. The general target of most viruses, however, are TFIID and TFIIB. The preferential targeting of these GTFs prevents assembly of PICs at an early stage prior to the recruitment of RNAPII. Recent studies have uncovered rather unexpected novel roles of TFIIB in the transcription cycle. The studies have revealed that TFIIB is not merely an initiation factor but plays pleiotropic roles in the transcription cycle (Wang et al., 2010; Medler et al., 2011; Tan-Wong et al., 2012). TFIIB affects gene architecture by facilitating interaction of the terminator with the promoter of the cognate gene during transcription (Medler et al., 2011). The promoter-terminator interaction results in the formation of a looped gene architecture (Ansari and Hampsey, 2005). Gene looping affects termination, reinitiation and promoter directionality (Grzechnik et al., 2014; Al-Husini et al., 2020). Thus, viruses have the potential to affect multiple aspects of the transcription cycle by targeting TFIIB. This could be one of the reasons why viral transcriptional regulators prefer TFIIB over TBP and more so than other GTFs during viral pathogenesis. Future research must focus on which of the TFIIB-dependent processes described above are the target of viral transcriptional regulators during pathogenesis.

The importance of TFIIB in completion of the viral life cycle is corroborated by the fact that multiple viruses have evolved proteins with structural and functional similarity to host TFIIB. Bypassing the need for host TFIIB, these viruses are now self-sufficient in terms of their TFIIB requirement, thus demonstrating the critical role of TFIIB in viral transcription. It is not surprising that TFIIB was also identified along with a number of other proteins as a high confidence transcriptional target (HCT) during infection by the current coronavirus (Ochsner et al., 2020). Taken together, selective downregulation of viral transcription without compromising host gene expression, specific viral targeting of TFIIB over other GTFs, and evolution of viral TFIIB-like proteins are compelling evidence for the critical role of TFIIB in viral pathogenesis. Involvement of TFIIB in pathogenicity of multiple human viruses by altering viral and host gene expression makes TFIIB a potential target of antiviral therapies. Future research concerning the extent of abrogation or inhibition of TFIIB necessary to invoke negative viral responses while maintaining normal host function would further foretell how TFIIB may be targeted to control viral infection. This is likely to be accomplishable as organisms or cells with mutant or inhibited TFIIB have been shown to be viable for study (Gelev et al., 2014). A three-dimensional structure of viral transcription regulators with TFIIB will elucidate the region of TFIIB essential for viral pathogenesis. The regions of TFIIB targeted by virus but not critical for host transcription may be the ideal drug target for future antiviral therapies. The viral TFIIB-like proteins of gammaherpesvirus and ASFV are also the potential drug targets for stopping the lifecycle of these viruses as selective inhibition of vPIC-dependent transcription may stop viral replication without adversely affecting host cell functions.

AUTHOR CONTRIBUTIONS

AA conceptualized and edited the manuscript. MJO wrote the original draft. Both authors contributed to the article and approved the submitted version.

FUNDING

This research was supported by NSF grant MCB-1936030.

ACKNOWLEDGMENTS

We would like to thank Dr. Haidong Gu for critical reading of the manuscript.

REFERENCES

Agostini, I., Navarro, J. M., Rey, F., Bouhamdani, M., Spire, B., Vigne, R., et al. (1996). The human immunodeficiency virus type 1 Vpr transactivator: cooperation with promoter-bound activator domains and binding to TFIIB. J. Mol. Biol. 261, 599–606. doi: 10.1006/jmbi.1996.0485

Albrecht, R. A., Jang, H. K., Kim, S. K., and O’Callaghan, D. J. (2003). Direct interaction of TFIIB and the IE protein of equine herpesvirus 1 is required for maximal trans-activation function. Virology 316, 302–312. doi: 10.1016/j.virol.2003.08.017

Albrecht, R. A., Jang, H. K., and O’Callaghan, D. J. (2003). Direct interaction of TFIIB and the IE protein of equine herpesvirus 1 is required for maximal trans-activation function. Virology 316, 302–312. doi: 10.1016/j.virol.2003.08.017

Albrecht, R. A., Jang, H. K., Kim, S. K., and O’Callaghan, D. J. (2003). Direct interaction of TFIIB and the IE protein of equine herpesvirus 1 is required for maximal trans-activation function. Virology 316, 302–312. doi: 10.1016/j.virol.2003.08.017

An, P., Guo, J. T., and Winkler, C. A. (2019). Host genetics in viral pathogenesis and control. Front. Genet. 10.1038. doi: 10.3389/genet.2019.01038

Ansari, A., and Hampsey, M. (2005). A role for the CPF 3′-end processing machinery in RNAP II-dependent gene looping. Genes Dev. 19, 2969−2978. doi: 10.1101/gad.1362305

Bushnell, D. A., Westover, K. D., Davis, R. E., and Kornberg, R. D. (2004). Structural basis of transcription: an RNA polymerase II-TFIIB cocrystal at 4.5 Å. Science 303, 983–988. doi: 10.1126/science.1090838

Gelev, S. G., Drane, D. W., and Funk, D. R. (2014). A novel role for TFIIB in the antiviral response. Biochim. Biophys. Acta Gene Regul. Mech. 1863:194657. doi: 10.1101/jbbagrm.2020.194657

Hampsey, M., et al. (1996). The human immunodeficiency virus type 1 Vpr transactivator: cooperation with promoter-bound activator domains and binding to TFIIB. J. Mol. Biol. 261, 599–606. doi: 10.1006/jmbi.1996.0485

Medler, S., and Ansari, A. (2020). Crosstalk of promoter and terminator during RNA polymerase II transcription cycle. Biochim. Biophys. Acta Gene Regul. Mech. 1863:194657. doi: 10.1101/jbbagrm.2020.194657

Ochsner, P., et al. (2020). A role for the CPF 3′-end processing machinery in RNAP II-dependent gene looping. Genes Dev. 19, 2969–2978. doi: 10.1101/gad.1362305

An, P., Guo, J. T., and Winkler, C. A. (2019). Host genetics in viral pathogenesis and control. Front. Genet. 10.1038. doi: 10.3389/genet.2019.01038

Ansari, A., and Hampsey, M. (2005). A role for the CPF 3′-end processing machinery in RNAP II-dependent gene looping. Genes Dev. 19, 2969–2978. doi: 10.1101/gad.1362305

Albrecht, R. A., Jang, H. K., Kim, S. K., and O’Callaghan, D. J. (2003). Direct interaction of TFIIB and the IE protein of equine herpesvirus 1 is required for maximal trans-activation function. Virology 316, 302–312. doi: 10.1016/j.virol.2003.08.017

Al-Husini, N., Medler, S., and Ansari, A. (2020). Crosstalk of promoter and terminator during RNA polymerase II transcription cycle. Biochim. Biophys. Acta Gene Regul. Mech. 1863:194657. doi: 10.1101/jbbagrm.2020.194657

An, P., Guo, J. T., and Winkler, C. A. (2019). Host genetics in viral pathogenesis and control. Front. Genet. 10.1038. doi: 10.3389/genet.2019.01038

Ansari, A., and Hampsey, M. (2005). A role for the CPF 3′-end processing machinery in RNAP II-dependent gene looping. Genes Dev. 19, 2969–2978. doi: 10.1101/gad.1362305

Bushnell, D. A., Westover, K. D., Davis, R. E., and Kornberg, R. D. (2004). Structural basis of transcription: an RNA polymerase II-TFIIB cocrystal at 4.5 Å. Science 303, 983–988. doi: 10.1126/science.1090838

Al-Husini, N., Medler, S., and Ansari, A. (2020). Crosstalk of promoter and terminator during RNA polymerase II transcription cycle. Biochim. Biophys. Acta Gene Regul. Mech. 1863:194657. doi: 10.1101/jbbagrm.2020.194657

An, P., Guo, J. T., and Winkler, C. A. (2019). Host genetics in viral pathogenesis and control. Front. Genet. 10.1038. doi: 10.3389/genet.2019.01038

Ansari, A., and Hampsey, M. (2005). A role for the CPF 3′-end processing machinery in RNAP II-dependent gene looping. Genes Dev. 19, 2969–2978. doi: 10.1101/gad.1362305

Bushnell, D. A., Westover, K. D., Davis, R. E., and Kornberg, R. D. (2004). Structural basis of transcription: an RNA polymerase II-TFIIB cocrystal at 4.5 Å. Science 303, 983–988. doi: 10.1126/science.1090838
Ihalainen, T. O., Willman, S. F., Niskanen, E. A., Paloheimo, O., Smolander, James, C., Harfouche, M., Welton, N. J., Turner, K. M., Abu-Raddad, L. J., Gottlieb, di Valentin, E., Bontems, S., Habran, L., Jolois, O., Markine-Goriaynoff, N., Dion, V., and Coulombe, B. (2003). Interactions of a DNA-bound transcriptional regulator of the basal transcription machinery by disorganizing the pre-initiation complex. *Biochim. Biophys. Acta Gene Expr. Struct.* 1627, 101–110. doi: 10.1016/s0167-4781(03)00080-0

Deng, W., and Roberts, S. G. (2005). A core promoter element downstream of the TATA box that is recognized by TFIIIB. *Genes Dev.* 19, 2418–2423. doi: 10.1101/gad.342405

di Valentin, E., Bontems, S., Habran, L., Jolois, O., Markine-Goriaynoff, N., Vendrell, S., et al. (2005). Varicella-zoster virus IE63 protein represses the basal transcription machinery by disinorganizing the pre-initiation complex. *Biocell.* 38, 255–267. doi: 10.1515/bc.2005.031

Dion, V., and Glaunsinger, B. (2013). Interactions of a DNA-bound transcriptional activator with the TBP-TFIIA-TFIIIB-promoter quaternary complex. *J. Biol. Chem.* 278, 11495–11501. doi: 10.1074/jbc.m211938200

Gelev, V., Zabolotny, J. M., Lange, M., Hiromura, M., Yu, S. W., Orlando, J. S., et al. (2014). A new paradigm for transcription factor TFIIH functionality. *Sci. Rep.* 4.16:e1008402. doi: 10.1371/journal.ppat.1008402

Lin, Y. S., Li, H., Maldonado, E., Reiner, D., and Green, M. R. (1991). Binding of general transcription factor TFIIB to an acidic activating region. *Nature* 353, 569–571. doi: 10.1038/353569a0

Liu, X., Hong, T., Paremswaran, S., Ernst, K., Marazzi, I., Weirauch, M. T., et al. (2020). Human virus transcriptional regulators. *Cell* 182, 24–37. doi: 10.1016/j.cell.2020.06.023

Luse, D. S. (2014). The RNA polymerase II preinitiation complex: what pathway is the complex assembled? *Transcription* 5:e27050. doi: 10.4161/trans.27050

Lyles, D. S. (2000). Cytopathogenesis and inhibition of host gene expression by RNA viruses. *Microbiol. Mol. Biol. Rev.* 64, 709–724. doi: 10.1128/mmbr.64.4.709-724.2000

Maldonado, E., Cabrejos, M. E., Banks, L., and Allende, J. E. (2002). Human papillomavirus-16 E7 protein inhibits the DNA interaction of the TATA binding transcription factor. *J. Cell. Biol.* 158, 663–669. doi: 10.1083/jcb.158.7.663

Medler, S., Al Husini, N., Raghunayakula, S., Mukundan, B., Aldea, A., and Ansari, A. (2011). Evidence for a complex of transcription factor IIB (TFIIB) with poly (A) polymerase and cleavage factor 1 subunits required for gene looping. *J. Cell. Biol.* 193, 1525–1536. doi: 10.1083/jcb.201007.028

Medler, S., Al Husini, N., Raghunayakula, S., Mukundan, B., Aldea, A., and Ansari, A. (2011). Evidence for a complex of transcription factor IIB (TFIIB) with poly (A) polymerase and cleavage factor 1 subunits required for gene looping. *J. Cell. Biol.* 193, 1525–1536. doi: 10.1083/jcb.201007.028

Moss, B. (2013). "Poxviridae," in Fields Virology, 6th edition, Vol. 2, eds D. M. Knipe, and P. M. Howley (Philadelphia, PA: Lippincott Williams & Wilkins), 2129–2159.

Mossman, K. L., Sherburne, R., Lavery, C., Duncan, J., and Smiley, R. J. (2000). Evidence that herpes simplex virus VP16 is required for viral egress downstream of the initial envelopment event. *J. Virol.* 74, 6287–6299. doi: 10.1128/jvi.74.10.6287-6299.2000

Nandakumar, D., and Glaunsinger, B. (2019). An integrative approach identifies direct targets of the late viral transcription complex and an expanded promoter recognition motif in Kaposi’s sarcoma-associated herpesvirus. *PLoS Pathog.* 15, e1007774. doi: 10.1371/journal.ppat.1007774

Nikolov, D. B., and Burley, S. K. (1997). RNA polymerase II transcription initiation: a structural view. *Proc. Natl. Acad. Sci. U.S.A.* 94, 15–22. doi: 10.1073/pnas.94.1.15

Ochsner, S. A., Lillic, R. T., and McKenna, N. J. (2020). Consensus transcriptional regulators of coronavirus-infected human cells. *Sci. Data* 7:314.

Rank, N. M., and Lambert, P. F. (1995). Bovine papillomavirus type 1 E2 protein-binding transcription regulators directly bind two cellular transcription factors, TFIIH and TFIIE. *J. Virol.* 69, 6332–6334. doi: 10.1128/jvi.69.10.6332-6334.1995

Sainsbury, S., Niesser, J., and Cramer, P. (2013). Structure and function of the initially transcribing RNA polymerase II–TFIIH complex. *Nature* 493, 437–440. doi: 10.1038/nature11715
Simmen, K. A., Singh, J., Luukkonen, B. M., Lopper, M., Bittner, A., Miller, N. E., et al. (2001). Global modulation of cellular transcription by human cytomegalovirus is initiated by viral glycoprotein B. Proc. Natl. Acad. Sci. U.S.A. 98, 7140–7145. doi: 10.1073/pnas.121177598

Smith, C. A., Bates, P., Rivera-Gonzalez, R., Gu, B., and Deluca, N. A. (1993). ICP4, the major transcriptional regulatory protein of herpes simplex virus type 1, forms a tripartite complex with TATA-binding protein and TFIIIB. J. Virol. 67, 4676–4687. doi: 10.1128/jvi.67.8.4676-4687.1993

Sundseth, R., and Hansen, U. (1992). Activation of RNA polymerase II transcription by the specific DNA-binding protein LSF. Increased rate of binding of the basal promoter factor TFIIH. J. Biol. Chem. 267, 7845–7855. doi: 10.1016/0021-9258(92)81823-O

Tan-Wong, S. M., Zaugg, J. B., Camblong, J., Xu, Z., Zhang, D. W., Mischo, H. E., et al. (2012). Gene loops enhance transcriptional directionality. Science 338, 671–675. doi: 10.1126/science.1224350

Turton, K. L., Meier-Stephenson, V., Badmalia, M. D., Coffin, C. S., and Patel, T. R. (2020). Host transcription factors in hepatitis B virus RNA synthesis. Viruses 12, 160. doi: 10.3390/v120160160

Veschembre, P., Roisin, A., and Jalinot, P. (1997). Biochemical and functional interaction of the human immunodeficiency virus type 1 Tat transactivator with the general transcription factor TFIIB. J. Gen. Virol. 78, 2235–2245. doi: 10.1099/0022-1317-78-9-2235

Vogt, C., Preuss, E., Mayer, D., Weber, F., Schwemmle, M., and Kochs, G. (2008). The interferon antagonist ML protein of Thogoto virus targets general transcription factor IIB. J. Virol. 82, 11446–11453. doi: 10.1128/jvi.01284-08

Wang, X., Hennig, T., Whisnant, A. W., Erhard, F., Prusty, B. K., Friedel, C. C., et al. (2020). Herpes simplex virus blocks host transcription termination via the bimodal activities of ICP27. Nat. Commun. 11:293.

Wang, Y., Fairley, J. A., and Roberts, S. G. (2010). Phosphorylation of TFIIIB links transcription initiation and termination. Curr. Biol. 20, 548–553. doi: 10.1016/j.cub.2010.01.052

Weinzierl, R. O., and Wiesler, S. C. (2011). Revealing the functions of TFIIIB. Transcription 2, 254–257. doi: 10.4161/trns.2.6.18076

Woolhouse, M., Scott, F., Hudson, Z., Howey, R., and Chase-Topping, M. (2012). Human viruses: discovery and emergence. Philos. Trans. R. Soc. B Biol. Sci. 367, 2864–2871. doi: 10.1098/rstb.2011.0354

Woychik, N. A., and Hampsey, M. (2002). The RNA polymerase II machinery: structure illuminates function. Cell 108, 453–463. doi: 10.1016/s0092-8674(02)00646-3

Xie, M., and Chen, Q. (2020). Insight into 2019 novel coronavirus—an updated interim review and lessons from SARS-CoV and MERS-CoV. Int. J. Infect. Dis. 94, 119–124. doi: 10.1016/j.ijid.2020.03.071

Xu, J., and Ye, L. (2002). Human cytomegalovirus IE2 protein interacts with transcription activating factors. Sci. China Ser. C Life Sci. 45, 604–612. doi: 10.1360/02yc9067

Yang, J. F., and You, J. (2020). Regulation of polymavirus transcription by viral and cellular factors. Viruses 12:1072. doi: 10.3390/v12101072

Yu, L., Loewenstein, P. M., Zhang, Z., and Green, M. (1995). In vitro interaction of the human immunodeficiency virus type 1 Tat transactivator and the general transcription factor TFIIH with the cellular protein TAP. J. Virol. 69, 3017–3023. doi: 10.1128/jvi.69.5.3017-3023.1995

Yuan, H., Puckett, S., and Lyles, D. S. (2001). Inhibition of host transcription by vesicular stomatitis virus involves a novel mechanism that is independent of phosphorylation of TATA-binding protein (TBP) or association of TBP with TBP-associated factor subunits. J. Virol. 75, 4453–4458. doi: 10.1128/jvi.75.9.4453-4458.2001

Zhou, Q., Huang, F., Chen, L., Chen, E., Bai, L., Cheng, X., et al. (2015). RBPS-mediating protein suppresses hepatitis B virus (HBV) transcription and replication by counteracting the transcriptional activation of hepatitis B virus X protein in HBV replication mouse model. Jundishapur J. Microbiol. 8:e21936.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 O’Brien and Ansari. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.