Oncogenic viruses: DUBbing their way to cancer

Nehul Saxena and Vijay Kumar*
*Correspondence: vijay@icgeb.res.in
Virology Group, International centre for genetic engineering and biotechnology, Aruna Asaf Ali Marg, New Delhi-110067, India.

Abstract
Ubiquitination is one of the most important post-translational modifications of proteins with a profound effect on their intracellular stability and activity. Deubiquitinases (DUBs), on the other hand, act by removing the ubiquitin moiety from proteins and thereby reverse their stability and/or activity. Besides, DUBs play a major role in maintenance of free ubiquitin pool, histone modification, vesicular trafficking and receptor recycling. The revelation of DUB interactome by Sowa et al., [1] highlighted the importance of DUBs in key cellular pathways. While the role of E3 ubiquitin ligases in the virus biology is well documented, the involvement of DUBs in viral life cycle is still being probed. Recent findings suggest DUBs could play a central role in invasion and pathogenesis of oncogenic viruses. Viral oncoproteins such as E6 and E7 of human papilloma virus and Tax of human T-cell leukemia virus type 1 are now known to target cellular DUBs such as cyclindromatosis tumor suppressor, ubiquitin-specific proteases 7, 11, 15 and 20, A-20 and signal-transducing adaptor molecule binding protein-like-1 in order to improve their intracellular stability and/or subjugate cellular signaling pathways. The viral oncoprotein-DUB interactions create an ambience leading to unbridled proliferation of virus-infected cells and drive cell transformation. Interestingly, some viruses like herpes simplex virus-1, Epstein-Barr virus, human cytomegalovirus and Kaposi’s Sarcoma-associated herpes virus also encode their own DUBs such as UL36, UL48, BPLF1 and ORF64 to support viral invasion, replication, and persistence and even subvert host immune responses. Efforts are also underway to find specific inhibitors that can abrogate the interaction between cellular DUB and viral oncoproteins or inhibit viral DUBs as this might result in the development of next generation cancer chemotherapeutic agents. This review showcases the relevance of the viral DUBs and the cellular DUBs with interacting viral partners in virus-triggered cancer development.

Keywords: Deubiquitinase, interactome, oncogenic viruses, ubiquitination, ubiquitin proteasome system

Introduction
Ubiquitin is a highly conserved 76-amino acid polypeptide that is encoded by at least four different genes in mammalian cells, viz., UBA52, UBB, UBC and RPS27a. While the UBB and UBC genes code for poly-ubiquitin precursors, UBA52 and RPS27A genes encode fusion proteins L40 and S27a, respectively. These precursor proteins are processed by the cellular endopeptidases to release identical mono-ubiquitins [2].

Ubiquitination is a process of conjugation of a monoubiquitin moiety or polyubiquitin moieties to lysine residues in a target molecule [3,4]. Ubiquitination of proteins could affect their stability, intracellular localization, conformation and activity, protein-protein interaction and even chromatin modification [5]. Thus, ubiquitination has profound effect on different cellular processes including protein turnover, transcription, cell cycle progression, signal transduction pathways, host defense, endocytosis, receptor recycling, chromatin remodeling, apoptosis, angiogenesis, DNA repair, nuclear export of mRNA, phospholipid balance, etc [3,5,6].

The process of ubiquitination is dependent on the action of three main enzymes - E1 universal ubiquitin activating enzyme, E2 ubiquitin conjugating enzyme and E3 ubiquitin ligase [3,4]. The E4 ubiquitin ligase often acts in association with E3 ubiquitin ligase to increase E3 Ligases processivity or to facilitate ubiquitin chain extension on mono-ubiquitylated substrates [7]. Ubiquitination involves nucleating monoubiquitin moiety or polyubiquitin chains on single or multiple lysine residues of substrate such as Lys 6, Lys 11, Lys 27, Lys 29, Lys 33, Lys-48 and Lys 63. Of these, ubiquitination at Lysine 11 (K-11), Lysine 48 (K-48) and lysine 63 (K-63) are the most studied ubiquitination. While the ubiquitination at K-63 usually regulates the intracellular localization and the activity of substrates, poly-ubiquitination at K-11 and K-48 are invariably involved in the degradation of target proteins [8].

The process of ubiquitination can be subverted by an inventory of proteases called deubiquitinases or DUBs that can either cleave the isopeptide bond between the ε-amino group of lysine side chains or α-amino acid of substrates and the C-terminal group of ubiquitin [9]. These proteases play a key role: a) in maintenance of free ubiquitin pool, b) histone modification, c) protein stability or activity, d) vesicular trafficking, and e) receptor recycling. Further, by effecting the proteins stability or activity, DUBs can also modulate the cell signaling pathways, cell cycle progression, DNA damage repair pathways, immune responses and apoptosis (Figure 1) [10]. Apart from their normal cellular functions, mutations or altered expression levels of DUBs and the perturbation caused by DUBs in a repertoire of pathways and physiological processes (viz., Chromatin remodeling, signaling pathways, immune response, cell cycle progression, angiogenesis, apoptosis and stress response)
underlie the development of numerous cancers and disorders with predisposition to various cancers in humans (Table 2). Of late, DUBs are reported to play a central role in the life cycle of many human pathogens including some oncogenic viruses. These viruses not only engage cellular DUBs but also encode their own DUBs to support virus invasion, replication, and persistence or to subvert host immune responses [11]. The human genome encodes for atleast 98 known DUBs which have been classified into 6 different families (Table 1)- (i) ubiquitin-specific proteases (USPs), (ii) ubiquitin carboxy-terminal hydrolases (UCHs), (iii) ovarian-tumor proteases (OTUs), (iv) Machado–Joseph disease protein domain proteases (MJD), (v) Jab1/Mov34/Mpr1 (JAMM) metalloprotease deubiquitinase and (vi) monocyte chemotactic protein-induced protein (MCPIP) family. Most of the DUBs are typical cysteine proteases (USPs, UCH and Josephin family of proteases) with a few exceptions that are metalloproteases viz., JAMMs and anomalous cysteine proteases, viz., OTUs and MCPIP [9,12-14].

USP's form the largest and the most diverse family of DUBs characterized by ubiquitin specific protease domain; domain in ubiquitin specific protease (DUSP); ubiquitin interaction Motifs (UIMs); ubiquitin associated domains (UAD); B-box; Zn finger domain and Exonuclease III domain. Some vegetative homologues lack the catalytically active cysteine and histidine boxes, yet retain the ubiquitin binding activity. The tumor suppressor cylindramatosis(CYLD) and C19-papain family of proteases are the bona-fide members of USPs. Many USPs are reported to play a role in carcinogenesis [9,12,14].

UCHs were the first structurally characterized DUBs with a ubiquitin carboxy-terminal hydrolases domain. They include four known members in humans- UCHL1, UCHL3, UCHL5/UCH37 and BAP1. UCHs can efficiently process short ubiquitin chains due to a constricting loop in catalytic site of its members. They are actively involved in maintaining the intracellular ubiquitin pool. They are known to play a significant role in Parkinson's disease and cancer [9,12,14].

OTUs constitute a 15 member strong family of proteases in humans. Apart from the ovarian tumor domain, the members also have UIMs, UAD and Zn fingers. The members are divided into 3 sub-classes- Otubains, A20 like OTUs and OTUDs. Unlike typical cysteine proteases, they lack a complete catalytic triad. Some OTUs are regulated in tumorigenesis [9,12,14]. The Josephin family of DUBs includes cysteine proteases with a single cysteine box, double histidine box and UIM domain. Four members of this family are encoded by humans. They have been implicated in diseases like spino-cerebellar ataxia, Machado-Joseph disease and cancer [9,12,14]. The JAMM family of proteases is the most conserved family of DUBs. They are zinc-metalloproteases by nature. So far, just 12 members of JAMMs have been reported in humans. These are recruited for vesicle trafficking and receptor recycling. They have also been implicated in some cancers [9,12,14]. The MCPIP family of DUBs are unique cysteine protease which lack histidine box inside the N-terminal catalytic triad. These are characterized by the presence of a UAD and a conserved N-terminal domain, a Zn-finger domain in the middle region and a C-terminal proline-rich domain. With seven known members, these are reported to play a role in cancer related pathways [9,12,13].

USP6 was the first DUB to be identified as an oncoprotein
Table 1. DUB's implicated in various cancers and cancer related pathways.

| A. Cancer associated DUBs (CAD)- DUBs with altered expression or inherent mutations in cancers | References |
|---|---|
| CYLD | Cylindromatosis, Brooke Spieglider Syndrome, Trichoepithelioma, hepatocellular carcinoma, colon cancer, kidney cancer, uterine cervix carcinoma, and malignant melanoma |
| USP1 | Fanconi Anemia and Gastric cancer |
| USP2 | Breast tumor, Glioma, oral squamous cell carcinoma, Ovarian Carcinoma and prostrate carcinomas |
| USP4 | Small-cell lung carcinoma |
| USP6 | Benign bone tumor and Neoplastic aneurismal bone cysts |
| USP7 | Multiple myeloma, prostrate cancer, non-small cell lung carcinomas, renal carcinoma and colon cancer |
| USP9X | Breast cancer, pancreatic-duetal adenocarcinoma, cervical carcinoma |
| USP10 | Breast cancer, glioblastoma multiforme, Multiple melanoma |
| USP11 | Malignant melanoma |
| USP14 | Cholangiocarcinoma |
| USP15 | Placitaxel resistant ovarian cancer and Glioblastoma |
| USP17 | Primary lung, colon, esophagus and cervix tumor |
| USP20 | Von Hippel-Lindau cancer syndrome |
| USP22 | Papillary thyroid carcinoma, Non-small cell lung carcinoma, Oral squamous cell carcinoma, human esophageal squamous cell carcinoma, Malignant melanoma and colorectal carcinomas, Gastric carcinoma, breast cancer |
| USP25 | Breast Cancer |
| USP28 | Lobular breast carcinoma and colon cancer |
| USP32 | Breast Cancer |
| USP33 | Von Hippel-Lindau cancer syndrome and B cell-acute lymphoblastic leukemia |
| USP42 | Acute Myeloid leukemia |
| USP44 | Human T-cell leukemia |
| USP48 | Malignant melanoma |
| UCHL1 | Meningiomas, Prostrate cancer, non-small cell lung carcinomas and Breast cancer |
| UCHL5 | Human esophageal squamous cell carcinoma |
| BAP1 | Breast cancer, pleural mesotheliomas, uveal melanomas, cutaneous melanoma and Non-small cell lung cancer |
| A20 | Lymphomas- including B cell lymphomas, Hodgkin lymphoma, mantle cell lymphoma, MALT lymphoma, marginal zone lymphoma |
| JOSD1 | Nonsmall cell lung carcinoma |
| CSN5 | Nonsmall cell lung carcinomas, Nasopharyngeal Carcinoma, malignant melanoma |

| B. Cancer related redundant pathway associated DUBs (CRRPAD) | References |
|---|---|
| Chromatin associated DUBs | DUBs participating in Chromatin remodelling |
| USP3, USP7, USP10, USP11, USP16, USP21, USP22, BAP1, BRCC36, MYSM1 and UCHL5 |
| DNA Damage repair related DUBs | USP1, USP3, USP7S, USP11, USP16, USP24, USP28, USP47, BRCC36, OTUB1 and P0H1 |

| DUBs manipulating the Signalling pathways | Innate immune response and Inflammatory pathways – JAK-STAT pathway INK-p38-MAPK pathway; TLR pathway |
| USP2, USP4, USP11, USP15, USP17, USP18, USP25, A20 and MCPIP1 |
| NFκβ Signalling pathway | USP2, USP4, USP6, USP7, USP11, USP15, USP21, A20, CYLD, MCPIP1, OTUD5, OTUD7B and Cezanne |
| p53- and Cyclin dependent kinase Inhibitor (CDK) related pathways | USP2, USP4, USP5, USP7, USP10, USP11, USP22, USP29, SP37, UCHL1 and OTUB1 |
| PI3K-AKT related pathways-RTK dependent pathways, MTOR pathway, GSK3β pathway | USP1, USP8, USP 9X, USP22 and UCHL1 |
| TGF-β pathway | USP4, USP9X, USP11, STAMBPL1and UCHL5 |
| Wnt pathway | USP4, USP15, USP34, CYLD, UCHL1 and TRABID |
| ROR (Reactive oxygen species related) pathway | USP1, USP7, USP10 and A20 |

| DUBs altering the Cell Cycle progression | USP2, USP3, USP7, USP13, USP17L2, USP19, USP23, USP37, USP39, USP44, USP50, CSNS, BAP1, CYLD and OTUB-6B |

| Angiogenesis and metastasis related DUBs | USP2, USP2a, USP8, USP18, USP19, USP20, USP28, USP33, USP47, Cezanne, ATXN3YL, UCHL1 and MCPIP1 |

| DUBs involved in Apoptosis | USP2, USP7, USP8, USP9X, USP15, USP16, USP17, USP18, USP19, USP52, A20, ATXN3 CYLD, UCHL1 and MCPIP1 |

| DUBs induced upon cytokine secretion | USP17, USP17L2 and TUD-6B |
Table 2. Classification and characteristics of DUBs.

| DUB Family | No. of members | Features | Examples | References |
|------------|----------------|----------|----------|------------|
| Ubiquitin specific proteases (USPs) | > 50 | • Include three subdomains – finger, thumb and palm. Finger domain interacts with ubiquitin.  
• Carry cysteine and histidine boxes embedded in a region spanning approximately 300 to 800 a.a. with a regulatory aspartate box.  
• May have other extra domains namely, UIM, UAD, B-Box, DUSP, Zn finger, ULD, Exonuclease III domains.  
• Interaction with ubiquitin triggers a conformational change leading to their activation | CYLD, C19 family of papain protease | [9] |
| Ubiquitin C-terminal hydrolase (UCH) | 4 | • Can process only small peptides (20 to 30 aa) from the C-terminus of ubiquitin.  
• Involved in ubiquitin recycling by targeting inappropriately conjugated ubiquitin on nucleophiles.  
• Also generate monoubiquitins by processing polyubiquitin chains and ubiquitin conjugated to ribosomal protein precursor. | UCHL1, UCHL3, UCHL5/UCH37 and BAP1 | [9] |
| Ovarian Tumor domain proteases (OTUs) | 15 | Include 3 sub- families Otubains, A20 like OTUs and OTUDs | • Have an active cysteine protease domain. The core domain has five β-strands, situated between the helical domains.  
• The catalytic triad is incomplete and is stabilized by hydrogen bonding complex.  
• May carry auxiliary domains like-Zn finger domain, UIMs and UAD. | Otubains (OTUB1 and OTUB2) A20-like OTUs (A20/ TNFAIP3; Cezanne, Cezanne 2, TRABID and VCPPI1) OTUDs(OTUD1, OTUD2/ YOD1,OTUD3, OTUD4, OTUD5, OTUD6A, OTUD6B and ALG13) | [9] |
| Josephin family of DUBs | 4 | • The family is named due to a pivotal role played by ATXN-3 in spinocerebellar ataxia and Machado-Joseph disease.  
• In addition to the catalytic triad of one cysteine and two histidine boxes, the members may have UIMs.  
• ATXN-3 has a polyubiquitin chain editing activity and ubiquitin hydrolase activity while ATXN3L, JOSD1 and JOSD2 show DB activity. | ATXN3, ATXN3L, JOSD1 and JOSD2 | [9] |
| JAMM proteases | 12 | • Are zinc-metalloproteases that target lys-63 linked polyubiquitin. Also show isopeptidase activity for ubiquitin or ubiquitin like proteins.  
• Carry a well conserved JAMM domain (Jab1/Csn5 and MPN domain).  
• Involved in receptor recycling and vesicle trafficking. | AMSH/STAMBP, STAMBPL, BRCC36, POH1/ PSMD14, MYSM1, MPND and CSN5/ JAB1 | [9] |
| MCPIP family | ~7 | • Anomalous cysteine protease with only cysteine and aspartate boxes within the conserved N-terminal catalytic region.  
• Carry an N-terminal UAD, a conserved middle zinc-finger domain and a proline-rich domain at its carboxy terminus. | MCPIP1 | [13] |

[15]. Now it is well known that DUBs can function as both, an oncoprotein or a tumor suppressor and can also interact with a viral oncoprotein to drive oncogenesis [12,14]. Interestingly, viral DUBs have also been implicated as mediators of oncogenesis [11,16]. This review highlights the role of the interaction between viral oncoproteins and cellular DUBs (Table 3) and that of viral DUBs in virus mediated oncogenictransformations (Table 4).

**Review**

**Rendezvous of cellular DUBs with viral oncoproteins**

Oncogenic viruses build a strong line of communication within the host cell to support their survival and propagation. Viral oncoproteins act as pawns for hijacking cellular machinery (Figure 2). The examples of viral manipulation of cellular DUBs are elaborated below:

**Human papilloma Virus (HPV) and CYLD**

HPV is the causative agent of cervix, head and neck cancers. The E6 oncoprotein of HPV promotes nuclear factor-κB(NFκB) signaling by antagonizing the functions of the cellular DUB, CYLD. Stimulation of NFκB signaling leads to increased cellular proliferation and survival in most cancers. The NFκB signaling is negatively regulated by IκB protein that in turn is regulated by the IκB kinase (Iκκ) complex which is composed of Iκκ-γ (the regulatory unit), Iκκ-α and Iκκ-β (the catalytic units). CYLD deubiquitinates the K-63 ubiquitinated Iκκ-γ and other upstream regulators of NFκB such as TNF receptor associated...
### Table 3. Interaction between Cellular DUBs and viral oncoproteins.

| Cellular DUB                                      | Virus                          | Viral protein | Function                                                                                          | References |
|--------------------------------------------------|-------------------------------|---------------|---------------------------------------------------------------------------------------------------|------------|
| Cylindroma-tosis tumor suppressor (CYLD)         | Human papilloma virus- 16/18 (HPV) | E6            | • Inhibits CYLD-mediated deubiquitination of Iκκ-γ, TRAF2 and TRAF-6  
• Activates NFκB signaling cascade.  
• Ubiquitates CYLD and targets it for proteasomal degradation under hypoxia. | [17]       |
|                                                  | Human T-cell leukemia virus type-1 (HTLV-1) | Tax           | • Constitutively phosphorylates and inactivates CYLD  
• Deubiquitinates and inactivates Tax for Iκκ's activation. | [25]       |
| USP 7/ HAUSP                                     | Herpes simplex virus type-1 (HSV-1) | ICP0          | • Tethers USP7 to the cytoplasm. and promotes TRAF6 and Iκκ-γ deubiquitination.  
• Inhibits TLR-induced NFκB and JNK signaling cascade for cytokine secretion. | [20]       |
|                                                  | Epstein Barr Virus (EBV)       | EBNA1         | • Recruits USP7 to the Ori P of episomal viral DNA.  
• USP7 in association with GMP5 deubiquitinates the monoubiquitinated H2B on the FR-controlled promoters and stimulates transcription. | [21]       |
|                                                  | Kaposi's sarcoma associated Herpes virus (KSHV) | vIRF4        | • Interferes with the p53-MDM-USP7 axis.  
• Inhibits USP7 by acting as a pseudosubstrate and inhibiting its catalytic activity. | [22]       |
| USP11                                            | HPV-16                        | E7            | • USP11 stabilizes and modulates the activity of E7 involved in cell transformation. | [19]       |
| USP15                                            | HPV-16, HPV-18                | E6            | • USP15 deubiquitanizes and stabilizes E6 to promote cellular transformation. | [18]       |
| USP20                                            | HTLV-1                        | Tax           | • USP20 deubiquitnates K-63 ubiquitinated Tax.  
• Inhibit Tax-mediated activation of Iκκ-γ.  
• USP20 also inactivate TRAF-6 (activated by Tax) to attenuate NFκB signaling pathway. | [20]       |
| A20                                              | EBV                           | LMP1          | • LMP1 stimulates A20 activity.  
• A20 inhibits the LMP1 triggered NFκB signaling pathway.  
• A20 also reverses the LMP1-mediated K-63 ubiquitination and activation of IRF7. | [23]       |
| STAMBPL1                                         | HTLV-1                        | Tax           | • STAMBPL1 protects Tax by translocating it to the cytoplasm from the nucleus.  
• The cytoplasmic Tax interacts with Iκκ-γ to activate Iκκ and consequently the NFκB pathway. | [24]       |

### Table 4. Viral DUBs and their functions.

| Viral DUB                                      | Virus                          | DUB Activity | Function                                                                                          | References |
|------------------------------------------------|-------------------------------|--------------|---------------------------------------------------------------------------------------------------|------------|
| UL48 capsid-associated tegument protein        | HCMV                          | Ubiquitin-specific C-terminal hydrolase (UCH) and Isopeptidase activity for Lys -63 residue | Efficient viral growth at low MOI in cultured cells. Specific mechanism is unknown. | [30]       |
| ORF64 tegument protein                         | KSHV                          | Ubiquitin specific cysteine protease (USP) which deubiquitinylates Lys-63                     | Deubiquitinates RIG-I to inhibit the host's anti-viral IFN signaling cascade. | [38]       |
| UL36 –inner tegument protein                   | HSV-1                         | USP with a lys-48 preferential activity.                                                      | Maintains the contact between capsid and tegument. Role as a DUB is unknown. | [29]       |
| BPLF1– viral tegument protein                  | EBV                           | USP as well as DUB                           | Deubiquitinates and inactivates the viral ribonucleotide reductase subunit RR1.  
Inhibits host translesion synthesis by deubiquitinating PCNA. | [34]       |
| BSLF1 - component of viral helicase-primase complex | --                            | DUB                                      | Function as DUB unknown | [35]       |
| BXLF1– viral thymidine kinase                  | --                            | DUB                                      | Function as DUB unknown | [33]       |
| EBNA3C- Latent viral antigen                   | --                            | DUB                                      | Stabilizes itself to promote B-cell transformation.  
Stabilizes Mdm2 to promote p53 degradation.  
Stabilizes Cyclin D1to promote pRb degradation. | [36]       |

Factors-2 (TRAF2) and TRAF6 leading to the activation of NFκB signaling cascade. Under hypoxic conditions, the E6
Figure 2. Cell signaling pathways and the regulatory networks of cellular DUBs and viral oncoproteins. (A) (i) The E6 oncoprotein of HPV promotes NFκB signaling by promoting K-48 ubiquitination of cellular DUB- CYLD (a negative regulator of NFκB signaling- mediates TRAF-2, TRAF-6, Rip1 and Iκκ-γ via K-63 ubiquitination). Besides, E6 is also stabilized by USP15 to activate E6-mediated NFκB signaling. (ii) Tax protein of HTLV-1 is protected from K-48 ubiquitination and subsequent degradation by its translocation from nucleus to cytoplasm by STAMBPL1. The cytoplasmic Tax is kept in an active state by phosphorylation and inactivation of CYLD (as CYLD is responsible for deubiquitination of Tax at K-63 residue and its inactivation inside the HTLV-1 infected cells). Tax is able to activate the NFκB signaling pathway by promoting K-63 ubiquitination of Iκκ-γ. Besides, HTLV-infected cells also suppress the levels of USP20 which prevents the inhibition of Tax activity and Tax-mediated activation of TRAF-6. (iii) ICP0 oncoprotein of HSV chaperones USP7 from cytoplasm to nucleus where it inactivates NFκB, p38 and JNK signaling pathways (by promoting deubiquitination of K-63 linked ubiquitin on Iκκ-γ and TRAF-6) triggered by TLRs to immunoprotect the virus. (iv) The EBV transforming oncoprotein- LMP1, stimulates the expression of A20 cellular DUB to cause the inactivation of TLR-mediated signaling by promoting A20 interaction with TRAF-2. Activated A20 further prevents the LMP1-mediated NFκB signaling by promoting K-48 ubiquitination of TRAF-6 and Rip1. A20 also prevents LMP1 mediated K-63 ubiquitination and activation of interferon regulatory factor IRF7. (B) (i) The EBNA1 oncoprotein of EBV translocates USP7 to the cytoplasm in order to recruit it to the viral episomal DNA at OriP along with guanosine 5’ monophosphate synthetase (GMPS). This causes deubiquitination of monoubiquitylated H2B and its transcriptional activation. (ii) The peptides vif1 and vif2 derived from the vIRF4 of KSHV act as pseudosubstrate and catalytic inhibitor of USP7 to interfere with the K-48 ubiquitination of Mdm2 and the subsequent activation of p53. vIRF4 can also abrogate the inactivation of NFκB signaling by USP7. CagA, the oncoprotein of Helicobacter pylori also targets USP7.
oncoprotein exhibits increased interaction with CYLD and stimulates CYLD's ubiquitination and proteasomal degradation. Thus, the E6 oncoprotein tinkers with CYLD to create an ambience that may lead to cellular transformation [17].

**HPV and USP15**
The E6 oncoprotein of HPV is also known to interact with USP15 to stabilize itself within the host cell. USP15 deubiquitinates E6 and enhances its intracellular stability. A high level of E6 ensures unfettered proliferation and transformation of the host cells [18].

**HPV and USP11**
The E7 oncoprotein of HPV is known to transform host cells by interfering with the Rb-E2F axis through some undefined mechanisms. The HPV-infected cells program cellular DUB-USP11 to deubiquitinate E7 and protect it from proteasomal degradation. This increases the interaction of E7 with pRb and increases transforming potential of E7 by compromising pRb tumor suppressor activity. Thus, USP11 indirectly contributes toward malignancy in host cells by conferring intracellular stability to the E7 viral oncoprotein [19].

**Herpes Simplex Virus (HSV) and USP7**
Infection of the immuno-suppressed patients by HSV is responsible for development of oral or genital tumors. Upon infection, HSV triggers the cytokine innate immune response via Toll-like receptors (TLRs) which entail NFkB and MAPK signaling. The immediate early viral protein, infected cell protein 0 (ICP0), circumvents the signaling events by engaging a deubiquitinating enzyme, USP7 also known as herpesvirus-associated ubiquitin-specific protease (HAUSP). ICP0 interacts with USP7 present inside the promyelocytic leukemia bodies (PML) within the nuclear compartment and tethers it to the cytoplasm. In cytoplasm, USP7 interacts with TRAF6 and Iκκ-γ and removes their K-63 ubiquitin residues. The deubiquitination curbs the release of NFkB from the Iκκ inhibitory complex and suppresses the cytokine secretion. Thus, HSV evades the host cytokine tsunami by engaging USP7 [20].

**Epstein Barr Virus (EBV) and USP7**
The EBV infected host cells in various phases of latency or after transformation are vulnerable to a plethora of malignancies like the Burkitt's lymphoma, Hodgkin's lymphoma, nasopharyngeal lymphoma, etc. Binding of the Epstein Barr nuclear antigen 1 or EBNA1 oncoprotein to the family of repeats (FR) on 'Ori P' drives the replication of episomal viral DNA in the latently infected cells. EBNA1 disrupts the PML congregations inside the nucleus, interacts with USP7 and sequester it to Ori P in the cytoplasm. At Ori P, USP7 deubiquitinates the monoubiquitinated H2B leading to the transcriptional activation of FR-controlled LMP1 and Cp promoter sessential for the virus life cycle. In parallel, EBNA1 binding to the N-terminal TRAF-like domain of USP7 also jeopardizes the stability of p53 leading to unbridled proliferation of EBV infected cells [21].

**Kaposi’s Sarcoma-Associated Herpes Virus (KSHV) and USP7**
Persistent infection of the immuno-compromised host with KSHV is associated with the development of Kaposi’s sarcoma, primary effusion lymphoma and certain types of multi centric Castleman’s disease. The yeast-two hybrid analysis has revealed that the viral interferon regulatory factor 4 (vIRF4) of KSHV physically interacts with USP7 to inhibit its functioning. The inhibitory functions of vIRF4 (912 amino acids in length) are attributed to two peptides regions, Vif1 and Vif2 of vIRF4. Both Vif1 (residue 202-216) and Vif2 (residue 220-236) can bind to USP37 and curb its function as a p53 deubiquitinase. Thus, upon viral infection, vIRF4 is able to interfere with p53-HAUSP-Mdm2 axis to overcome the cell cycle pause and apoptosis induced by p53. These events promote uncontrolled cell proliferation and eventual transformation of host cells [22].

**EBV and A20 deubiquitinase**
The latent membrane protein-1 (LMP1) of EBV acts like an oncoprotein as it can transform both B and non B-cells. LMP1 induces the expression as well as activity of A20 - a dual E3 ubiquitin ligase and deubiquitinase, to inhibit TLR signaling and activation of. Briefly, this is achieved when the N-terminal OTU domain of A20 (with DUB activity) cleaves the K-63 linked ubiquitin from TRAF6 and receptor interacting protein 1 (Rip1). The C-terminal Zn finger domain of A20 subsequently catalyzes K-48 linked ubiquitination of TRAF6 and Rip1 leading to their proteasomal degradation. LMP1 also engages A20 which exercises its control over LMP1 at two levels. Firstly, A20 interacts TRAF2 to inhibit the LMP1 mediated NFkB and JNK signaling. Secondly, A20 counteracts the LMP1-mediated ubiquitination and activation of interferon regulatory factor 7 (IRF7). Thus, LMP1 effectively stimulates A20 to annihilate the inflammatory response of host cell [23].

**Human T-cell leukemia virus type 1 (HTLV-1) and STAMBPL1**
HTLV-1 is a viral carcinogen responsible for adult T-cell leukaemia (ATL). The Tax oncoprotein of HTLV-1 is known to activate the host NFkB pathway and engage the host transcriptional machinery to drive viral gene expression. Tax is known to shuttle across nuclear-cytoplasmic compartments of a cell to ensure its multiple functions. The K-63 ubiquitinated Tax (by UbC13) interacts with Iκκα to permanently activate the Iκκ complex. Signal-transducing adaptor molecule binding protein-like 1 (STAMBPL1) is a DUB from the JAMM metalloprotease deubiquitinase family which acts as an accomplice to Tax. STAMBPL1 usually acts on the K-63 linked ubiquitin and plays a role in cell surface receptor recycling. In case of ATL, STAMBPL1 cooperates with Tax and promote its translocation from nucleus to the cytoplasm. This shuttling protects Tax from its K-48 linked ubiquitination and proteasomal degradation inside the nucleus. Thus, STAMBPL1-mediated protection of Tax and its subsequent movement to
Viral DUBs

The viral DUB UL48 (253 kDa) of HCMV was discovered as a characteristic Cys-His-Asp catalytic triad. The HCMV mutants of cysteine or histidine in the catalytic triad are replication competent but severely compromised for viral infection at very low multiplicity of infection. Therefore, the DUB activity of UL48 may be crucial in establishing infection in the host [30].

HTLV-1 and CYLD

The catalytically active CYLD is capable of deubiquitinating Tax oncoprotein at K-63 in the nucleus. This deubiquitinated Tax protein is incapable of activating IkBα but not Tak1 (an activator of IkB-β). As a result, IkBα—a NFκB inhibitor, is stabilized. To circumvent these events, the HTLV-1 transformed T-cells constitutively phosphorylate CYLD to make it catalytically compromised. Thus, the virus overcomes the CYLD-mediated NFκB in activation which is conducive for the proliferation of virus infected host cell [25].

HTLV-1 and USP20

The cellular USP20 is also capable of subverting the activity of Tax oncoprotein of HTLV. USP20 can either deubiquitinate TRAF-6 and inactivate it or can deubiquitinate the K-63 polyubiquitinated Tax to prevent its association with IkB-γ for its activation. Since such undesirable activity of USP20 can be detrimental for the NFκB signaling stimulated propagation of HTLV infected cells, its expression is automatically suppressed. This strategy favors unchecked proliferation and eventual transformation of the HTLV-infected cells [26].

Viral DUBs

Many viral proteins are being dubbed for having deubiquitinating activity. Such DUBs play key roles in the viral infection, survival and persistence. Of late, the human adenovirus, bunyavirus, coronavirus and herpesvirus have been reported to encode viral DUBs [27]. Examples of viral DUBs from oncogenic viruses are given in Table 4.

Herpes simplex virus-1 (HSV-1) and UL36USP

The cleavage product UL36USP of the HSV-1 tegument protein UL36 (3266 amino acids), formed during the late stage of viral replication, act as a ubiquitin-specific cysteine protease [28]. UL36 belongs to a unique class of viral DUB which bears no similarity to the eukaryotic DUBs. UL36 has a K-48 biased DUB activity. UL36USP DUB activity is confined to the N-terminal 500 amino acids. The relevance of the DUB activity of UL36 in viral life cycle remains to be unraveled [29].

Human cytomegalovirus (HCMV) UL48 protein

The viral DUB UL48 (253 kDa) of HCMV was discovered as a homolog of UL36 of HSV-1. UL48 has a ubiquitin C-terminal hydrolase/isopeptidase dual activity and is capable of cleaving both K-48 and K-63 linked ubiquitin moiety albeit the K-63 linked ubiquitin is preferred. UL48 is a cysteine peptidase with a characteristic Cys-His-Asp catalytic triad. The HCMV mutants of cysteine or histidine in the catalytic triad are replication competent but severely compromised for viral infection at very low multiplicity of infection. Therefore, the DUB activity of UL48 may be crucial in establishing infection in the host [30].

DUBs of EBV

Multiple sequence alignment, pattern search for conserved catalytic domain, Hidden-Makov model and search for conserved cysteine and histidine boxes with functional validation have revealed the presence of at least three ubiquitin-specific proteases encoded by EBV, viz., BPLF1, BSLF1, and BXLF1 [31]. Of the three proteins, BSLF1 protein along with BBLF4 and BBLF2/3 forms a helicase-primease complex for the viral DNA replication during the lytic phase of replication [32]. Its role as a DUB is unclear. BXLF1, on the other hand, functions as a viral thymidine kinase and its role as a DUB needs investigation [33].

BPLF1 is 3,149 amino acids long tegument protein with its N-terminus 205 residues carrying the deubiquitinate activity. The association of large (RR1) and small (RR2) subunits of viral ribonucleotide reductase (RR) is essential for an active holoenzyme. During the late stage of infection, the N-terminal 246 amino acids of BPLF1 associate with RR2 to juxtapose and deubiquitinate RR1 leading to the inactivation of viral RR. Thus, virus utilizes BPLF1 to switch off the RR activity dispensable during the later stages, which is otherwise essential for dNTP synthesis during the early phase of infection [34].

Unlike RR2 (viral partner of BPLF1), the proliferating cell nuclear antigen (PCNA) is an important host interacting partner of BPLF1. PCNA is an active participant in the post replication repair pathway in host cells. Lesions in DNA cause stalling of replication forks. The damaged DNA can still replicate by translesion synthesis or avoid doing so by template switching. During translesion synthesis, the host replication protein A coats single stranded damaged DNA and recruits Rad18. Rad18, in turn, monoubiquitinates PCNA at K-164 to augment its interaction with polymerase η for translesion synthesis. The interaction between BPLF1 and PCNA leads to deubiquitination of PCNA to prevent its participation in translesion synthesis. Interestingly, BPLF1 not only disengages PCNA and derails the post-replication repair in the host but also engages free PCNA at viral episomal DNA to promote its own replication [35].

EBV nuclear antigen 3C (EBNA3C) which is responsible for B-cell transformation in the latent stage of EBV infection, also acts like a viral DUB. The N-terminal domain of EBNA3C encompasses the consensus cysteine box motif which works with the C-terminal consensus histidine box to carry out the DUB activity. The N-terminal domain of EBNA3C binds to the central acidic domain of Mdm2 inside the nucleus to stabilize Mdm2. EBNA3C also augments the E3 ligase activity of Mdm2 and brings p53 in close proximity to form a ternary complex to mediate p53 degradation [36]. EBNA3C via its N-terminal domain also binds to pRb and Cyclin D1. Through its association with Cyclin D1, EBNA3C promotes the nuclear localization of Cyclin D1 which prevents former’s phosphorylation by GSK3β. As a result there is a decrease in the polyubiquitination and degradation of Cyclin D1. The resultant enhancement of the Cyclin D1/cdk6 kinase activity
promotes the degradation of tumor-suppressor pRb and unchecked progression of cell cycle from G1 to S phase. This leads to accumulation of genomic aberrations which causes cellular transformation [37].

ORF64 of KSHV
KSHV uses many viral genes to overcome the host innate immune response triggered via TLRs. The tegument protein ORF64 of KSHV is a viral cysteine protease with DUB activity that targets IFN signaling. KSHV replication is found to be especially sensitive to interferon alpha (IFNα). ORF 64 acts on retinoic acid inducible gene–I (RIG-I)- the pattern recognizing receptor in host cells, to attenuate IFN signaling. The(RIG-I) senses the viral nucleic acid and gets ubiquitinated on its N-terminal CARD domain by TRIM25 tripartite motif protein 25 (TRIM25). This leads to the activation of IFN cascade. ORF64 deubiquitinates the K-63 ubiquitin present on the CARD domain of RIG-I and prevents RIG-I interaction with MAVS-CARD - its downstream signaling partner. These events lead to a down regulation of IFN-β expression and enhanced viral resistance [38].

Conclusion
Ubiquitination is a reversible post-translational modification which might influence proteins stability, cellular localization and activity. Whereas, ubiquitination is mediated by E3 ubiquitin ligases, it can reversed by a family of protease known as deubiquitinases or DUBs. Close to 100 different DUBs are known in human cells that can be divided into 6 sub families. Many viral proteins have also evolved to play DUB like roles. Though the viral DUBs exhibit cysteine protease activity, they appear to be unrelated to their eukaryotic counter parts. Many oncogenic viruses hijack the host deubiquitinase machinery or exploit their own DUBs to drive cellular transformation.

The relevance of viral and cellular DUBs in cancer biology is continuously being highlighted through various research efforts being made in this field. So far, seven cellular DUBs- CYLD, USP7, USP11, USP15, USP20, A20 and STAMBPL1 (AMSH-LP) out of>100 known DUBs have been associated with viral oncoproteins. Out of these, five DUBs, CYLD, USP7, USP11, USP15 and USP20 belong to the USP family of cysteine protease; A20 belongs to the OTU family of cysteine proteases and STAMBPL1 belongs to the Zinc-metalloprotease family of DUBs.

Based on available literature, DUBs may be classified into two groups –(1) Cancer associated DUBs (CADs)-DUBs with altered expression or inherent mutation and (2) Cancer related redundant pathway associated DUBs (CRRPADs) (Table 2).

In stark contrast to the 52 DUBs implicated in cancer (an assimilation of all the CADs and CRRPADs) only 7 have been reported as interacting partners for viral oncoproteins. Thus, concerted efforts need to be made to overcome the lacunae in understanding the role of remaining cancer related DUBs in virus-induced carcinogenesis.

Since DUBs seem to play a significant role in cancer biology, many strategies are being adopted to manipulate them by chemotherapy (i.e., by using DUB inhibitors like ubiquitin aldehyde (Ubal), ubiquitin vinylsulfone (UbVS), pS091, P022077,UI11, etc.) [12,39]. Efforts are also under way to find inhibitors that can abrogate the interaction of cellular DUBs with viral oncoproteins. Considering the importance of neo-viral DUBs in cellular transformation, an intensive search for specific inhibitors for viral DUBs is of paramount importance. Simultaneously, finding crucial roles for DUBs in cancer-related pathways would establish them as the next generation cancer chemotherapeutic target akin to the UPS which have been successfully targeted by drug Borteozomb.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions

| Authors’ contributions | NS | VK |
|------------------------|----|----|
| Research concept and design | -- | ✓ |
| Collection and/or assembly of data | ✓ | -- |
| Data analysis and interpretation | -- | ✓ |
| Writing the article | ✓ | -- |
| Critical revision of the article | -- | ✓ |
| Final approval of article | -- | ✓ |
| Statistical analysis | -- | -- |

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