Supplementary Figure 1. A schematic diagram showing the role of c-Abl in the protection of p53 by phosphorylation of HPV-E6/E6AP (HPV-infected cells) and Mdm proteins (Non HPV-infected cells).

Supplementary Figure 2. The structural basis for the importance of Y636: Effect of Y636 modifications on the interaction of neighbouring E6AP molecules. (A) The crystal structure of trimeric E6AP HECT domain bound to one UbcH7 E2 enzyme shows the crucial role of Y636 in mediating interactions between the monomers in the trimer, as well as its vicinity to the UbcH7 binding site. E6AP molecules are coloured green, pink and cyan, while UbcH7 is coloured in yellow. The side chains of Y636 and E544 are represented in yellow and white spheres, respectively, and oxygen atoms are colored red. For clarity, only residues until position 720 are shown. (B) Atomic details of the interaction between Y636 and E544 on neighbouring E6AP proteins. We note that the hydrogen bond distance (between the hydroxyl of Y636 and the carboxyl of E544) is too short in the crystal structure (2.4Å), but can easily be relieved by short minimization. (C) Phosphorylation of Y636 leads to electrostatic repulsion between the negative charges of E544 and pY636, as well as to steric clashes which can only be relieved by significant change of the orientation of the two monomers, thereby abolishing the trimeric interaction. (D) Possible compensatory interaction of Y636D-E544R mutant, creating a salt bridge with optimal 3.5A distance between the negative charge in D636 and R544 in adjacent molecules.

Supplementary Figure 3. Phosphorylation of E6AP by c-Abl in vivo. An extended presentation of the experiment in Figure 2. Wt and c-Abl null MEFs were treated with
cisplatin (20µM) as indicated. Cell extracts from wt and c-Abl null MEFs were subjected to immunoprecipitation using anti-E6AP antibody (I) followed by western blotting using anti-phosphotyrosine (II).

**Supplementary Figure 4. Interaction between E6AP and c-Abl.**

Interaction between E6AP and c-Abl in HEK293 cells. HEK293 cells were transfected with the indicated expression plasmids (7µg each). Twenty-four hours post-transfection, cell extracts were subjected to immunoprecipitation using anti-E6AP antibody followed by western blotting using anti-GFP (I). The expression levels of E6AP in the transfected cells were monitored with anti-E6AP antibody (II). Important to note that the GFP fusion wt c-Abl construct is cleaved in the lysate, whereas the c-AblΔSH3 mutant is not.

**Supplementary Figure 5. Interaction between E6AP and c-Abl.**

(A) A schematic representation of the c-Abl protein and the mutants used in this study. Wt c-Abl contains a SH3 domain, SH2 domain, tyrosine kinase (Y kinase), polyproline region (PPR), DNA binding domain (DBD) and an actin-binding domain (Actin). The c-Abl kinase defective (c-Abl KD) mutant contains a mutation at lysine 290 while c-AblΔproline lacks the proline rich region. (B) HEK293 cells were transfected with the indicated expression plasmids (10µg each). Twenty-four hours post-transfection, cell extracts were subjected to a binding assay using E6AP. Following the incubation, the reaction were subjected to immunoprecipitation using anti-E6AP antibody, followed by western blotting using anti-c-Abl antibody (I). The amount of pulled down E6AP was monitored using anti-E6AP antibody (II).
Supplementary Figure 1

- DNA damage
- HPV-infected
  - HPV-E6
  - E6AP
  - p53 degradation
- c-Abl
- Non HPV-infected
  - Mdm2
  - Mdmx
  - Active p53
- p53 degradation
Supplementary Figure 2

A

E6AP 1

UbcH7

E6AP 2

E6AP 3

B

E544

Y636

C

E544

Y636F

D

E544R

Y636D
Supplementary Figure 3

Figure 2 (adapted from blot below)

C-Abl        +        -
I
IP: α-E6AP
IB: α-phosphotyrosine
E6AP

II
IP: α-E6AP
IB: α-E6AP
E6AP

C-Abl        +        +        +        +        -        -        -        -
Cisplatin    -        1hr       2hr       3hr       -        1hr       2hr       3hr

I
IP: α-E6AP
IB: α-phosphotyrosine
E6AP

II
IP: α-E6AP
IB: α-E6AP
E6AP
**Supplementary Figure 4**

**A**

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**B**

- GFP
- GFP c-Abl wt
- GFP c-Abl ΔSH3
- Myc-E6AP

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**I**

- 150kDa
- 98kDa
- 64kDa
- 50kDa
- 36kDa

**II**

- E6AP

**Notes:**
- IP : Anti – E6AP
- IB : Anti - GFP
- GFP c-Abl ΔSH3
- Cleaved GFP c-Abl wt
- GFP
Supplementary Figure 5

A

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K290

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I

IB: α-c-Abl
IP: α-E6AP
IB: α-c-Abl

II

IB: α-E6AP