Supplementary Table S1| **Established and Proposed E3s for p53**

E3	Comments	Refs
MDM2-MDMX	Genetically established as critical E3 for p53 (detailed in Review). Other substrates include β-arrestin and IGF-1 Receptor	1, 2, See Review for references related to p53
PIRH2	Initial report indicated binding to central region of p53 (aa 82-292). Structural data shows binding to C-terminal p53 tetramerization domain. Levels correlate with poor survival in hepatocellular carcinoma. There is evidence for targeting of p27 for degradation (see also Table 1 of Review)	3-6
COP1 (constitutive photomorphogenesis protein 1 homologue)	Originally identified in plant as suppressor of morphogenesis. Protein is overexpressed in adenocarcinomas of breast and ovary. Was recently reported to regulate JUN and ETS families of transcription factors and loss of function towards these transcription factors associated with prostate cancer (see also Table 1 of Review)	7,8
Synoviolin (HRD1)	Transmembrane protein of the endoplasmic reticulum. Synoviolin overexpression causal in rheumatoid arthritis. *Syvn*$^{-/-}$ mice are embryonic lethal, however connection of lethality to p53 is not established	9,10
CARP 1 and 2	Can target phospho-Ser20 p53 – unlike Mdm2 and other E3s. Includes N-terminal FYVE domain. CID (caspase interacting domain) and RING finger implicated in p53 binding. CARPs implicated in degradation of procaspase forms of caspases 8 and 10. Targets RIP for degradation in endosomes downregulating NF-κB signaling	11-13
TOPORS	First dual function ubiquitin and SUMO ligase, targets p53 for both modifications. RING finger required for ubiquitination but not sumoylation. Activity increased by phosphorylation N-terminal to RING finger, likely due to enhanced E2 binding. Targeted for degradation by Plk1-mediated phosphorylation. This degradation results in decreased sumoylation but increased ubiquitination of p53. Thus, overall role of Topors-mediated ubiquitination is unclear. Also binds Topoisomerase, loss implicated in retinitis pimentosa and retinal dystrophy	14-22
SCF$^{\beta\text{-TrCP}}$	Activation of IκB kinase 2, which is essential to the NF-κB signaling pathway, results in phosphorylation of p53 (Ser362 and Ser366) creating a binding site for β-TrCP leading to p53 ubiquitination and degradation (see Review for additional information on β-TrCP)	23
SCF^{JFK}	Binds p53 between aa113-236. JFK is Kelch-containing F-box protein. Some increase in cancer cells, although causality not established	16, 19, 21,24

Supplementary Table S1 (cont.)| **Established and Proposed E3s for p53**

E3	Comments	Refs
TRIM24	Loss of expression of *D. Melanogastor* ortholog (Bonus) results in embryonic lethality rescued by $p53^{-/-}$ background. RING B-box coiled-coil E3	25
CUL7	Binds tetramerization domain of p53 and inhibits p53 activity. E3 function towards p53 not clear CUL7 and the related protein PARC (RING-IBR-RING) bind p53 directly through their CPH (Cul7, PARC, and HERC2) domains and are known to dimerize (see Table 1 of Review)	26-30
MKRN1	Ubiquitinates Lys291 and 292 of human p53 (288, 289 of mouse) near C-terminal region of DNA binding core. Also E3 for hTERT and co-regulator of androgen receptor and retinoic acid receptor. Targets p21 for ubiquitination and degradation. Has complex biology in decreasing p53 – keeping cells alive but preventing cell cycle arrest in response to apoptosis thereby increasing genotoxic stress	31, 32
ICP0	HSV-1 RING finger protein. Associates with and ubiquitinates p53 *in vitro* and in cells. Not evident whether or not ICP0 results in degradation of p53 or what type of chains are formed	33
ARF-BP1	Large HECT domain E3 also known as HECTH9, MULE and HUWE1 (HECT, UBA, and WWE domain-containing protein 1). Binds to and targets p53 for ubiquitination and degradation. Similar to MDM2, its activity is inhibited by its binding to ARF (see Review). Other substrates include both pro- and anti-apoptotic molecules including MCL-1 and N-MYC	34-36
E6-AP	Founding member of the HECT domain family. Targets p53 for degradation specifically in cells infected with oncogenic isotypes of HPV. HPV E6 from these strains serves as an adaptor between E6-AP and p53. Other substrates include, among others, RING1B component of PRC. Reported to function as a co-activator of nuclear hormone receptors and implicated as pathogenic factor in Angelman Syndrome	37-40

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