p53 Protein Isoforms: Key Regulators in the Front Line of Pathogen Infections?

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In response to extra- or intracellular stresses, the cellular gatekeeper p53 is able to integrate multiple diverse signals to determine the outcome of cell fate, by regulating the expression of numerous responsive genes [1,2]. The tumor suppressor p53 has been extensively investigated in the field of cancer research [3], however there are reports it has a broader role in several other biological processes, such as metabolism, reproduction, or the immune response [1–4].

Bacterial and viral infections represent a major type of cellular stress, triggering different biological countermeasures, notably mediated by the p53 pathway. In the process of evolutionary adaptation to the host environment, pathogenes have developed diverse strategies to hijack and exploit such host machinery. This is particularly well-illustrated for viruses, with many examples of virally induced deregulation of the p53 pathway (e.g., E1B of Adenoviruses; EBNA3C of Epstein-Barr virus, NS1 of influenza viruses) [5–7]. Similar interplays have also been reported for bacteria models, such as Salmonella or Helicobacter infections [8,9]. The mechanisms and biological significance underlying regulation of p53 in the context of infection are not fully understood and often appear contradictory.

In addition to full-length p53, the TP53 gene physiologically expresses several protein isoforms, due to the use of alternative promoters, splicing sites, and translational initiation sites (Figure 1A) [10–12]. This constitutes an additional layer of p53 regulation concomitant to transcriptional, translational, and post-translational regulatory mechanisms [10–12]. Two of the most characterized isoforms are Δ133p53γ, which lacks the entire transactivation domain and part of the DNA-binding domain, and p33B, within which the oligomerization domain is replaced by 10 new amino acids (Figure 1B) [10,11]. p33B has been shown to modulate p53 transcriptional activity in a promoter-dependent manner [13]. In contrast, Δ133p53γ acts as a modulator of full-length p53 in response to stress, inhibiting p53-mediated apoptosis and G1 cell cycle arrest without inhibiting p53-mediated G2 cell cycle arrest. This suggests that Δ133p53γ promotes p53-dependent cell survival in response to stress [14,15]. Moreover, in normal human fibroblasts, Δ133p53γ inhibits whereas p33B promotes p33-mediated replicative senescence [16]. An additional isoform has been described, Δp33, which lacks part of the DNA-binding domain and the nuclear localization signal (Figure 1B) [12,17]. Δp33 was reported to be transcriptionally active toward specific p53 target genes and involved in the intra-S phase checkpoint in UV-damaged cells. However, the biological activity and relevance of this isoform remain controversial [13,18]. Figure 1C shows a schematic overview of the reported biological functions of the p53 isoforms.

Although several studies report on the suppressive function of p53 isoforms and related deregulation of their expression in human cancers [18], investigations into the putative role of p53 isoforms and their regulation in pathogen infections have only recently begun. Three pioneer reports, including ours, have recently highlighted the role of p53 isoforms in epithelial cells infected by different pathogens: a gram-negative bacterium (Helicobacter pylor), a RNA, and a DNA virus (influenza and Simian virus 40, respectively) [19–21]. Despite major differences in terms of models and experimental strategies, these studies share some interesting preliminary conclusions regarding a new facet of p53 isoform biology.

Within SV40 lytic infection, p53 is targeted and inactivated by T-Ag, and Δp33 has been identified as a new player in SV40 replication by Rohaly and colleagues. They revealed that an ATR–DNA damage response pathway mediates the phosphorylation and stabilization of Δp33, enhancing its transcriptional activity in a promoter-dependent manner [19]. The activation of such an ATR–Δp33–p21 pathway results in down-regulation of cyclin A-Cdk2/1 (AK), maintaining the host cell in S-phase, which consequently favors viral amplification (Figure 2). Additionally, the same authors reported that the ATR–Δp33–p21 pathway also increases the subpopulation of host DNA polymerase α interacting with T-Ag, whose initiation is a prerequisite of origin-dependent viral replication [19].

In human lung epithelial cells, we have investigated the roles of both Δ133p53γ and p33B isoforms in the context of influenza virus infection [20]. Our results have shown that infection differentially modulates the expression of Δ133p53γ and p33B at both transcriptional and posttranscriptional levels. Reciprocally, we have revealed that the modulation of Δ133p53γ and p33B isoforms play distinct roles in the viral cycle by acting as regulators of the p53-dependent antiviral activity (Figure 2). However, the upstream signaling cascade(s) and different downstream biological processes, both affected by cross-talk between full-length p53 and p33 isoforms, still require full character-
Figure 1. p53 protein isoforms and their biological functions. (A) Schematic representation of the human TP53 gene. The human TP53 gene contains 11 exons encoding several p53 products. The usage of the distal promoter (P1) leads to the production of p53 and Δ40p53 isoforms, while the internal promoter regulates the expression of Δ133p53 and Δ160p53 isoforms. (B) Schematic representation of some human p53 isoforms. The canonical p53 protein (p53α) contains a transactivation domain (TAD), a proline-rich domain (PXXP), a DNA binding domain (DBD), and a C-terminal domain—with a nuclear localization signal (NLS) and an oligomerization domain (OD). The C-terminal p53 isoform p53β is produced by an alternative splicing in intron 9, leading to the replacement of the OD by 10 new residues. The N-terminal p53 isoform Δ133p53 is encoded by a transcript initiated in intron 4 and lacks the TAD, PXXP, and part of the DBD. The Δp53 protein isoform is generated by a noncanonical alternative splicing between exons 7 and 9 and lacks part of the DBD and the NLS (Panels A and B adapted from Marcel et al. 2011 [10]). (C) Overview of known biological functions of p53 protein isoforms. The green and red boxes indicate biological processes that are known to be either negatively or positively regulated by full-length p53, respectively. The different arrows indicate the type of regulation by the p53 isoforms.

doi:10.1371/journal.ppat.1003246.g001
Recently, *Helicobacter pylori* has been shown to interfere with p53 function via up-regulation of the Δ133p53 isoform both in vitro (gastric epithelial cells) and in vivo (Mongolian gerbil) [21]. Moreover, Wei and colleagues have identified the AP-1 transcription factor (cFos/cJun) as the upstream positive regulator of Δ133p53 transcriptional activity (Figure 2), leading to the suppression of both p53 and p73 functions and consecutively increasing cell survival. They also revealed that Δ133p53 is involved in the up-regulation of NF-κB in a p53-dependent manner, in the context of *H. pylori* infection (Figure 2). This study highlighted new and interesting ideas not only to decipher specific aspects of functional p53/NFκB antagonism but to better understand *H. pylori* pathogenesis and associated tumorigenesis.

In conclusion, these three studies, based on different pathogen models, have highlighted for the first time the functional role of different p53 isoforms in the context of infection. A preliminary model emerges in which the isoforms act as regulators of the p53-mediated cellular response against pathogens. As an illustration, both influenza viruses and *H. pylori* have an impact on Δ133p53 to interfere with full-length p53 activity via mechanisms remarkably similar to those previously described in the field of cancer [10]. However, the relative contribution of each p53 isoform in the hijacking of the p53 pathway by pathogens and/or the cellular antimicrobial response needs to be further explored. Based on these observations, we recommend that any future investigations focusing on the interplay between p53 and pathogens need to consider specific p53 isoforms, taking into account their different parameters such as relative ratios, chemical modifications, subcellular localizations, and tissue-specific expression. This new approach will certainly help to provide new insights into the multiple roles that p53 plays in pathogenesis, particularly by exploring the different biological processes involved, such as apoptosis, cell cycle, and immune responses.

**Acknowledgments**

The authors would like to thank Dr. Virginie Marcel (CRCL, Lyon, France) for her critical reading of this Opinion.
1. Lane D, Levine A (2010) p53 research: the past thirty years and the next thirty years. Cold Spring Harb Perspect Biol 2: a000893. doi:10.1101/cshperspect.a000893.

2. Levine AJ (1997) p53, the cellular gatekeeper for growth and division. Cell 88: 323–331.

3. Vousden KH, Lane DP (2007) p53 in health and disease. Nat Rev Mol Cell Biol 8: 275–283. doi:10.1038/nrm2147.

4. Lee H-R, Kim MH, Lee J-S, Liang C, Jung JU (2009) Viral interferon regulatory factors. J Interferon Cytokine Res 29: 621–627. doi:10.1089/jir.2009.0067.

5. Muñoz-Fontela C, Pazos M, Delgado I, Murk W, Mungamuri SK, et al. (2011) p53 serves as a host antiviral factor that enhances innate and adaptive immune responses to influenza A virus. J Immunol 187: 6428–6436. doi:10.4049/jimmunol.1101459.

6. Rivas C, Aaronson SA, Muñoz-Fontela C (2010) Dual role of p53 in innate antiviral immunity. Viruses 2: 298–313. doi:10.3390/v2010298.

7. Lazo PA, Santos CR (2011) Interference with p53 functions in human viral infections, a target for novel antiviral strategies? Rev Med Virol. doi:10.1002/rmv.696.

8. Wu S, Ye Z, Liu X, Zhao Y, Xia Y, et al. (2010) Salmonella typhimurium infection increases p53 acetylation in intestinal epithelial cells. Am J Physiol Gastrointest Liver Physiol 298: G784–G794. doi:10.1152/ajpgi.00526.2009.

9. Wei J, Nagy TA, Vilgehn A, Zaika E, Ogden SR, et al. (2010) Regulation of p53 tumor suppressor by Helicobacter pylori in gastric epithelial cells. Gastroenterology 139: 1333–1343. doi:10.1053/j.gastro.2010.06.018.

10. Marcel V, Dichtel-Daniy M-L, Sagne C, Hafsi H, Ma D, et al. (2011) Biological functions of p53 isoforms through evolution: lessons from animal and cellular models. Cell Death Differ 18: 1815–1824. doi:10.1038/cdd.2011.120.

11. Khoury MP, Bourdon J-C (2010) The isoforms of the p53 protein. Cold Spring Harb Perspect Biol 2: a000927. doi:10.1101/cshperspect.a000927.

12. Marcel V, Hainaut P (2007) p53 isoforms - a conspiracy to kidnap p53 tumor suppressor activity? Cell Mol Life Sci 66: 391–406. doi:10.1007/s00018-006-8336-3.

13. Bourdon J-C, Fernandez K, Murray-Zmijewski F, Liu G, Diot A, et al. (2005) p53 isoforms can regulate p53 transcriptional activity. Genes Dev 19: 2122–2137. doi:10.1101/gad.139905.

14. Aoubala M, Murray-Zmijewski F, Khoury MP, Fernandez K, Perrier S, et al. (2011) p53 directly transactivates At33p53a, regulating cell fate outcome in response to DNA damage. Cell Death Differ 18: 248–258. doi:10.1038/cdd.2010.91.

15. Chen J, Ng SM, Chang C, Zhang Z, Bourdon J-C, et al. (2009) p53 isoform del133p53 is a p53 target gene that antagonizes p53 apoptotic activity via BclXL activation in zebrafish. Genes Dev 23: 278–290. doi:10.1101/gad.1761609.

16. Fujita K, Mondal AM, Horioka I, Nguyen GH, Kumamoto K, et al. (2009) p53 isoforms Delta133p53 and p53beta are endogenous regulators of replicative cellular senescence. Nat Cell Biol 11: 1135–1142. doi:10.1038/ncb1928.

17. Rohaly G, Chemnitz J, Dehde S, Nunex AM, Heukeshoven J, et al. (2005) A novel human p53 isoform is an essential element of the ATR-intrax-8 phase checkpoint. Cell 122: 21–32. doi:10.1016/j.cell.2005.04.032.

18. Bourdon J-C (2007) p53 and its isoforms in cancer. Br J Cancer 97: 277–282. doi:10.1038/sj.bjc.6603886.

19. Rohaly G, Korf K, Dehde S, Dornreiter I (2010) Simian virus 40 activates ATR-Delta p53 signaling to override cell cycle and DNA replication control. J Virol 84: 10727–10747. doi:10.1128/JVI.00122-10.

20. Terrier O, Marcel V, Cartet G, Lane DP, Lina B, et al. (2012) Influenza A viruses control expression of prostatic human p53 isoforms p53b and Delta133p53. J Virol 86: 8452–8460. doi:10.1128/JVI.07143-11.

21. Wei J, Noto J, Zaika E, Romero-Gallo J, Correa P, et al. (2012) Pathogenic bacterium Helicobacter pylori alters the expression profile of p53 protein isoforms and p53 response to cellular stresses. Proc Natl Acad Sci USA 109: E2543–E2550. doi:10.1073/pnas.1205664109.

22. Campbell HG, Slatter TL, Jeffs A, Mehta R, Rubio C, et al. (2012) Does At33p53 isoform trigger inflammation and autoimmunity? Cell Cycle 11: 446–450. doi:10.4161/cc.11.3.19054.

23. Bernard H, Gamzy-Sussini B, Ainaoui N, Van Den Breghe L, Pourichard A, et al. (2012) The p53 isoform, At33p53a, stimulates angiogenesis and tumour progression. Oncogene. doi:10.1038/onc.2012.242.