



SDI FINAL EVALUATION FORM 1.1

PART 1:

Journal Name:	International Journal of Biochemistry Research & Review
Manuscript Number:	2014_IJBcRR_15864
Title of the Manuscript:	Comprehensive Roles ofTP53 in Cell Signaling, Apoptosis, and Carcinogenesis – A Review
Type of Article:	Review Article

PART 2:

FINAL EVALUATOR'S comments on revised paper (if any)	Authors' response to final evaluator's comments
The authors reply to my extensive criticisms is “all possible changes are made” but they do not highlight what changes (if any) they have made. Ref 2 is on “New insight into p53 signaling...” and hence key to this review. The reference by the first author’s name does not exist. The paper is by Mirzayans R et al and not Razmik M et al. Since no changes are made, the “revised” version remains too outdated and too biased in terms of targeting p53 in cancer therapy. As I had stressed in my original comments (see last paragraph below), this speculation turned out to be an empty promise. Please read new articles such Curr Issue Mol Biol 12: 143-146, 2010. There is no way to figure out what revisions (if any) they have made. They have highlighted three references in yellow. Is this the only “revision” that they have made? Apparently the authors have simply ignored all of my comments. I will paste all of them here (in red font) because all are also applicable to the “revised” version. The current manuscript on the “comprehensive roles of p53 in cell signaling...” needs to be extensively revised to provide the current understanding on: (i) p53-mediated cell fate in different cell types (Int J Mol Sci 14: 22409-22435); (ii) DNA damage-induced p53 dynamics in regulating cell fate and the critical role of WIP1 (and not MDM2) in this regulation (Science 2012, 336, 1440–1444); Critical role of p21 in inducing senescence and suppressing apoptosis independent of its influence on the cell cycle (Cell Cycle 7: 106, 2008; Int J Mol Sci 14: 22409-22435); the properties of mutant p53 (Ref. 2); and pros and cons of modulating p53 for cancer therapy (Curr Issues Mol Biol 12: 143-146, 2010; Apoptosis 19: 1055-1068, 2014). At the very least, the	• Reference 2 is quite right, as I have re-checked it. • Other details, which you mentioned, were considered as well and possible additions have been made in the manuscript. • Article ‘empty promise’ was considered and added in my manuscript, along with its reference • Other articles as mentioned were not added in the text because they are not relevant with the theme of the manuscript



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authors should cite such recent papers of paramount importance to the p53 field and direct the reader to the new understanding of the tumor suppressing function of p53.

Most of the sections of this review paper, particularly the abstract, Introduction, Figure 3 and Figure 6, could all have been prepared in the 1990's soon after the discovery of the role of p53-p21 signaling the DNA damage surveillance network (see, e.g., Science 266 (5192): 1821-1828, 1994; Cancer Res 55: 5991-6001, 1995). Now we know that such generalized hypothesis (p53 either activates G1 arrest or apoptosis) do not apply to all cell types, as some cell types such as lymphocytes are programmed to die through apoptosis, whereas others are not and instead exhibit p53-dependent senescence which is an anti-apoptotic event. These important aspect of the p53 signaling was extensively reviewed in the late 1990's (e.g., Cancer Res 59: 1391-1399, 1999) and recently (e.g., Int J Mol Sci 14: 22409-22435; ref 2 cited in the current paper).

This manuscript covers, in a lay language format, a large number of topics on the basic and outdated concepts on p53 with ignoring the tremendous developments in the p53 field over the past two decades. The authors mention right upfront the word "senescence" as p53-regulated events which is now globally accepted to be one of the most important anti-apoptotic effects induced by stress in solid cancer and many cell types, but this important topic is not covered in the current review paper which is entitled "Comprehensive roles of TP53 in cell signaling, apoptosis, and carcinogenesis..." The authors cite recent comprehensive review articles such as ref 2 (New insight in p53 signaling...) which addresses the role of p53-p21 signaling in blocking apoptosis and inducing senescence, the current knowledge on DNA damage-induced p53 dynamics and cell fate (being senescence and not apoptosis in p53-proficient cancer cells), the properties of cancer-associated mutant p53, and pros and cons of targeting p53 for cancer therapy. Unfortunately, all of these new developments in the p53 field are completely overlooked in the current review paper.