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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 the Article	Review Article

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments	This manuscript covers, in a lay language format, a large number of topics on the basic and outdated concepts on p53 with ignoring the tremendous developments in the p53 filed over the past two decades.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. 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,	Due to some technical problems the manuscript contained combined words. As far as recent literature is concerned so this manuscript is drafted to keep in view the basics of p53 and its associated processes, which can help a researcher to have a general overview of this gene and its expression. All the possible changes have been made



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	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). Thus, 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 authors should cite such recent papers of paramount importance to the p53 filed and direct the reader to the new understanding of the tumor suppressing function of p53.	
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<u>Minor</u> REVISION comments		
<u>Optional/General</u> comments	Aside from tremendous amount of errors both in English and the use of awkward/outdated/incorrect scientific statements, this review paper on "comprehensive review of p53 signaling" simply overlooks the tremendous advances that has been made in the past two decades in this filed. I have made detailed comments to help the authors to be educated with these advancements and rewrite the paper accordingly.	