



## p53 in cancer: preface

The prominent role of p53 in tumor suppression has unequivocal supporting evidence, as demonstrated by the fact that it is either mutated or functionally inactivated in all human cancers, and further evidenced by the high susceptibility to cancer of patient suffering Li-Fraumeni syndrome.

During tumor development, a TP53 mutation is typically followed by loss of heterozygosity and consequent complete loss of p53, which can enhance the initiation and progression of cancer by various processes, including enhancing genetic instability and increasing invasiveness and metastatic potential. Besides leading to functional loss of p53, some mutations of the *TP53* gene can result in gain-of-function properties that facilitate tumor progression and increase its aggressiveness. In wild-type p53-harboring cancers, other mechanisms are in place to render p53 functionally inactive. Some of these mechanisms, such as up regulation/amplification of p53 main negative essential regulators, MDM2 and MDMX, lead to decrease turnover of p53 protein, whilst others, such as post-translational regulation by RNA-binding proteins, aim at suppressing its activity, although there is a high level of inter-dependency in these mechanisms of p53 suppression.

Given its central role in tumor suppression, p53 has been the subject of a decade-long history of intensive investigation, aimed at understanding the mechanisms underlying its ability to restrain tumor initiation and progression. However, what is known about p53 is probably only the tip of the iceberg, especially in light of the more recently discovered non-canonical roles of p53 in cellular homeostasis. While numerous studies have demonstrated the tumor suppressive function of p53 through pro-death processes like cell cycle arrest, senescence and apoptosis, p53 has recently been found to regulate additional diverse processes, including cellular metabolism, stem cell function, invasion and metastasis, which all can contribute to tumor suppression. Another branch of p53 field that is probably still in its infancy regards the investigation of non-cancer related roles of p53 in guarding homeostasis. For instance, p53 has been implicated in various disease processes, including fibrosis, metabolic diseases and age-related diseases such as Alzheimer and Parkinson's disease. Better understanding of the mechanisms of p53 control and its non-canonical roles both in cancer and non-cancer contexts is likely to further our knowledge not only of p53 pathways, but more broadly of the mechanisms that cells have evolved to preserve their homeostasis and increase their fitness.

In this volume, the reader can find papers describing mechanisms of post-transcriptional and post-translational control of p53 and its regulators MDM2 and MDMX, its interaction with other pathways, like the mTORC1 pathway, and its role not only in cancer but also in aging and inflammation.

We start off with a review by Chen, discussing the function of disordered regions and describing their dynamic intra molecular interactions with the structured domains regulating p53 DNA binding and MDM2 ubiquitin E3 ligase activity. The author provides new insight on how p53 is controlled by stress signals, and suggests potential targets for the search of allosteric regulators of the p53 pathway.

The second paper by Zhang *et al.* reviews the most recent progress in understanding the role of TP53 mutations in development, progression and metastasis of epithelial ovarian cancer and discusses the potential of TP53 mutations as diagnostic biomarkers and therapeutic targets in epithelial ovarian cancer.

The third paper by Duan and Maki reviews the crosstalk between p53 and the IGF-1R/AKT/mTORC1 signalling pathway and discusses how this crosstalk can determine the choice of p53 response (apoptosis *vs.* arrest).

Lucchesi *et al.* describe a new level of p53 modulation, by RNA-binding proteins, which post-transcriptionally control p53 expression and activity.

The fifth paper explores the role of p53 in organismal aging processes. The authors discuss evidence supporting both an aging-accelerating and aging-suppressing function of p53, and highlight the complexity of p53 influence over organismal aging.

The Editorial by Duffy *et al.* makes a very precise summary about the current state of targeting p53 as a cancer therapy. Both promise and challenge of therapeutically targeting p53 as a viable cancer treatment option are briefly discussed.

Mitchell and Iwakuma summarize p53 regulation of the cell-mediated adaptive immune response, focusing on p53 communication with cytotoxic T-lymphocytes in cancer cells, with perspective on the role of p53 mutation in immunotherapy.

Kogan and Carpizio explore the therapeutic potential of pharmacologically targeting mutant p53, reviewing the new compounds and approaches aimed at reactivating mutant p53.

Kunst *et al.* present another Editorial describing the contribution of the p53 family including p53, p63 and p73 to liver biology and the tumorigenesis of hepatocellular carcinoma (HCC). A brief description of the therapeutic potential to target p53 for treatment of HCC is also included.

Acedo and Zawacka-Pankau provide a brief commentary on an interesting feedback loop between Nrf2 and mutant p53 with a

focus on the work by Walerych *et al.* published in the August issue of Nature Cell Biology, which demonstrated Nrf2-dependent upregulation of the expression of 26S proteasome genes as a major feature shared by a number of gain of function mutant of p53.

The 11th paper reviews the role of the MDM2-p53 signalling axis in the DNA damage response, and discusses how post-translational modification of Mdm2 regulates the Mdm2-p53 signalling axis to govern p53 activities in the cell.

The last paper by de Polo *et al.* discusses the role of the MDMX-MDM2 complex in the modulation of p53, with particular focus on MDMX and its post-translational modifications in response to stress.

In summary, this volume reviews some of the most canonical functions of p53 in cancer progression and offers new insight into new mechanisms of p53 regulation and function. New cross talks between p53 pathway and other key cellular pathways, like mTORC1 and immune response, are also described, and novel perspective on the therapeutic potential of mutant p53 are presented.

## Acknowledgments

Here I would like to thank Dr. Anna de Polo for her great assistance in preparation of the preface.

*Funding:* None.

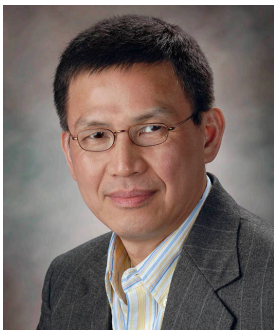
## Footnote

*Provenance and Peer Review:* This article was commissioned by the editorial office, *Translational Cancer Research* for the series “p53 Biology and Cancer”. The article did not undergo external peer review.

*Conflicts of Interest:* The author has completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2016.12.16>). The series “p53 Biology and Cancer” was commissioned by the editorial office without any funding or sponsorship. ZMY served as the unpaid Guest Editor of the series and serves as an unpaid editorial board member of *Translational Cancer Research*. The author has no other conflicts of interest to declare.

*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Submitted Nov 06, 2016. Accepted for publication Nov 16, 2016.

doi: 10.21037/tcr.2016.12.16

**View this article at:** <http://dx.doi.org/10.21037/tcr.2016.12.16>

**Cite this article as:** Yuan ZM. p53 in cancer: preface. *Transl Cancer Res* 2016;5(6):625-626. doi: 10.21037/tcr.2016.12.16