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EDITORIAL

Exploring the future of research in the Tp53 field

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These nine reviews uncover and probe the questions that remain to be answered in the quest to understand the single most common mutated gene in human cancers. They create a dialog to elucidate 1. The nature of Tp53 tumor suppression [1]; 2 and 3. cell cycle regulation [2, 3]; 4. the nature of cell death [4]; 5. the need for excellent Tp53 datasets of information [5]; 6. and how these datasets are used to explore that information [6]; 7. The interpretations, present and future, of " Tp53 gain of function missense mutations" [7]; 8. The targets for future clinical research [8], and 9. The functions of splice variants of the Tp63 and 73 gene, as a guide to understanding the regulation of the Tp53 gene [9]. Eight of these nine reviews are largely written by first authors who are students, postdoctoral fellows or young faculty, giving a much-needed youthful fresh interpretation to each of these topics by the next generation to tackle these questions.

The role of the Tp53 gene in tumor suppression is not due to one or even a few genes or nodes in the p53 pathway but rather the cooperation and interaction of several genes in that pathway [1, 10] that remain to be elucidated. There is a great deal of redundancy and feedback loops in the Tp53 pathway [11]. It is the loss of the functions of the Tp53 gene itself that is the vulnerable node and that is why it is such a common target for mutation in many types of cancers. The very large number of stressful inputs to the MDM-2-p53 node and the redundancy of G-1, S, G2, and M phase checkpoints is a model for the efficiency of information transfer [2, 3, 11]. The epigenetic modifications that both activate the p53 protein for transcription and help to choose the transcriptional programs that mediate p53 responses, needs to be explored so as to understand that efficiency of information transfer from one node to another [11, 12]. There are at least five p53 regulated paths to cell death; apoptosis, ferroptosis [4], necroptosis mediated by Fas or TNF, and senescence mediated immune killing. Why is this so? Is it possible that the way a cell dies can determine how efficiently it presents antigens to the immune system [13]? and, therefore, the nature of the immune response. P53 appears to regulate some aspects of both the innate and adaptive responses [14, 15]. Datasets of information about the p53 gene, its' mutations and its' pathway are often collected or interpreted with an unintended bias. That is why we need many diverse datasets [5] with defined methods of collection and lots of information. Based upon the use of multiple datasets the missense mutations in the proline domain were uncovered and shown to be enriched for mutant p53 skin cancers and a set of p53 protein–protein interactions [6]. Polymorphisms in the proline domain define a region of human chromosome 17 that includes the Tp53 gene under linkage disequilibrium and as their haplotypes are uncovered they should add interesting p53 protein interactions between different inbred groups. At present the literature is confused at best, as to the existence of p53 missense mutation "gain of functions". Different mutant alleles and even different cancer types seem to give rise to large numbers of different mechanisms and phenotypes that mediate this set of observations. Even the existence of "gain of function" has been questioned [7]. An interesting and new interpretation of this phenomenon as a "separation of functions" rather than a "gain of function" deserves to be tested as this conversation moves forward [7]. One of the slower progressing areas of research has been the development of clinical treatments in humans using our hard won knowledge of the Tp53 pathway. There are drugs and approaches in the clinic for the treatment of Tp53 mutations and genes in the p53 pathway [13] and there is a detailed discussion of this issue here [8]. Another area that has moved too slowly has been our understanding of the Tp53 splice variants and their functions. The review of Tp63 and Tp73 splice variants [9] herein is a great map to guide us to important new Tp53 functions that now need to be explored in more detail.

There are of course additional questions for the Tp53 field. How does the wild-type and mutant p53 protein impact the innate and adaptive immune system [14]? Can it impact tumor responses for checkpoint therapy or CAR-therapy [13]? How is the decision made to initiate the different transcriptional programs for activated p53 to stop the cell cycle and repair the damage or alternatively to kill the cell and how does it make the choice which pathway is to kill the cell [12]? How does the p53 protein recognize epigenetic changes that occur at the DNA level (methylated CpG dinucleotides) and/or the protein modifications of histones and transcription factors? Why does decitabine and azacytidine have differential killing effects upon Tp53 wild-type and mutant cancer cells in humans with cancers [10, 13]? What is the frequency of inherited Tp53 mutations in the human population [5]? Why is it that not everyone who has an inherited Tp53 mutation appears to develop cancers over their lifetime and if not what is the mechanism that prevents the loss of a Tp53 mutant allele from leading to cancer? Why do 90% of women with inherited Tp53 mutations develop breast cancer, the most common cancer in these patients? These and other questions will be reviewed in future issues of *Cell Death and Differentiation*.

Arnold J. Levine [1]✉

[1]*Institute for Advanced Study, Princeton, NJ 08450, USA.*

✉*email: alevine@ias.edu*

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

AJL is a founder, shareholder, receives fees from, and is a member of the board of directors of PMV pharmaceutical company, which produces small molecules that reactivate mutant p53 proteins. He also chairs the SAB of Janssen Pharmaceutical company and is a member of the board of Meira GTX, a gene therapy company for restoring eyesight. He is also a member of the board of directors of GeneCentric, a RNA seq diagnostic company for cancer treatments. He also receives funding from a grant from the NCI, P01CA087497-20, and is a member of the SAB of Rome, a company that explores the role of repetitive DNA sequences in cancers.

ETHICS STATEMENT

This editorial did not require ethics approval.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Arnold J. Levine.