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# Introduction: The Changing Directions of p53 Research

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The p53 protein was first uncovered as a tumor antigen. Animals bearing tumors initiated by some viruses or transformed cells produced antibodies directed against a cellular protein of 53,000 Daltons.[1,2] The p53 protein was also shown to form a complex with the viral oncogenic products from SV40,[1,2] the adenoviruses,[3] and subsequently the human papilloma viruses.[4] The early c-DNA clones of the mouse or human p53 gene cooperated with other oncogenes to transform cells in culture,[5,6] but these c-DNAs proved to encode a mutant p53 protein that acted as a dominant negative mutation and that had properties of a gain-of-function mutation.[7] Later the wild-type p53 gene was shown to function as a tumor suppressor gene in cell culture[8] and in human tumors.[9] From attempts to understand the functions of the p53 protein it became apparent that it responded to a wide variety of cellular stresses, such as DNA damage, resulting in the modification of the p53 protein and increased concentrations of the p53 protein in a cell. This activated the p53 protein so it functioned as a transcription factor. The genes regulated by the p53 protein form the p53 pathway[10] and can result in cell cycle arrest, apoptosis, and cell senescence. These observations helped to explain how the p53 protein functioned as a tumor suppressor by eliminating cells that make errors or mutations at a high rate in attempting to duplicate themselves under conditions of stress. In this way, p53 functions act to prevent cancers over a lifetime of exposures to stress. Just how important this process is to understanding cancer origins comes from the growing awareness that p53 gene mutations are the most common type of mutations observed in a wide variety of cancers. More than half of all cancers harbor p53 mutations, and in some cancers a p53 mutation can be found in 95% of the tumors produced in humans. In addition, a number of other mutations inactivate or dampen p53 functions in a cell. Gene amplifications in the MDM-2 and MDM-4 genes (the ubiquitin ligase complex that helps to degrade p53) and WIP-1 (a protein phosphatase) in cancers lower or eliminate p53 activities.[11] Inherited mutations in the p53 gene increase the frequency of cancers in a family and lower the age of onset of those cancers.[12]

Based upon these observations and many others, an entire field has grown up around cellular stresses, genome surveillance, and responses to cell cycle errors that can all lead to an enhanced mutation frequency, and p53 plays a central role in each of these processes. This has resulted in more than 50,000 publications in this broad area of research. Some of these concepts are well-summarized in the book *The p53 Family* (2010, Cold Spring Harbor Laboratory Press).[13] The research groups that populate this field organize and run 4 different meetings throughout the world on a 2-year cycle: The p53 Meeting, The p63 and p73 Meeting (the sisters of the p53 transcription factor), The MDM-2 Meeting (the negative regulator of p53) and The Mutant p53 Meeting. The p53 protein is now 32 years old, and things are beginning to change. The field has taken a surprisingly new set of directions which was totally unanticipated and which has invigorated research efforts.

The reviews presented in this issue of *Genes & Cancer* were chosen to accomplish two things; first to introduce the reader to these new topics and areas of p53 research, and second to permit the young investigators in the second and third generations of the p53 research field to summarize these new fields of endeavor that they have opened and led into totally new directions. These new areas of research include the role of the p53 protein in regulating the production of induced pluripotent stem cells (iPS cells) and their associated epigenetic changes as well as the role of the p53 protein in regulating the production of cancer stem cells (Spike and Wahl[14]), the role of the p53 protein in regulating cellular metabolic changes observed in cancerous cells (Puzio-Kuter[15]), and the role of p53-regulated ribosomal biogenesis in the surveillance of metabolic control (Deisenroth and Zhang[16]). The roles of the p53 protein (Hu, Zheng, and Wang[17]) and the p63 and 73 proteins (Rufini *et al*.[18]) in regulating fertility in females have been surprising new developments over the past few years. The roles of p63 in skin development and p73 in the development of the nervous system and the immune system in organisms have recently come to be understood (Rufini *et al*.[18]). There is a new understanding in how the p73 gene product can act as a tumor suppressor (Rufini *et al*.[18]). The functions of the p53 protein in surveillance of the formation of the cerebellum and its interactions with the sonic hedgehog pathway have only recently been uncovered (Mendrysa, Ghassemifar, and Malek[19]).

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The role of p53 (and p73) in the central and peripheral nervous system is a new concept that deserves attention and which may link p53 functions to neurodegenerative processes. The functions of p53 in response to inflammation and in chemoprevention (Gukov, Gurova, and Komarova[20]) extends p53 research into immunology, where many more functions of p53 will be uncovered in the years to come. The role of p53 in longevity and aging has opened a new chapter in the relationships between p53 functions that control the insulin like growth factor pathway, metabolic activity, cancer, and longevity (Feng, Lin, and Wu[21]). The impact of allele specific mutant p53 proteins upon the nature of the gain of function phenotypes of cancers and its prognostic value has a great potential to become an important biomarker for many cancers (Rivlin, Brosh, Oren, and Rotter[22]). The presence of inherited mutant p53 alleles in a population may be more common than previously thought and can cause specific subsets of cancers in pediatric populations (Pinto, Ribeiro, Figueiredo, and Zambetti[23]). The inherited Li-Fraumeni Syndrome mediated in large part by p53 mutations has a number of genomic consequences just beginning to be appreciated (Malkin[24]). Finally we have come to realize that there is not just one p53 protein (and not one p63 or p73 protein) but many that come from an active program of cell- and tissue-specific splicing of the m-RNAs of p53 (Khoury and Bourdon[25]). The differential functions of these p53 proteins will need to be understood, and that will surely take efforts in both biochemistry and genetics to sort out.

While these topics surely form a large part of the future of p53 research, they are by no means the only topics that will fill the pages of this journal and others. It has become clear that some of the p53, p63, and p73 functions are sexually dimorphic. Part of this derives from the roles of these transcription factors in organs found only in females (uterus and ovary), but several p53-regulated genes (MDM-2, WIP-1, LIF) are also estrogen regulated. Are the p53 signal-transduction pathways regulated differently in males and females, and is this responsible for the sexual dimorphism observed in the frequency and age dependence of different cancers? The role of p53, p63, and p73 in the stability of the genome in the female germ line is just becoming clear (see the review by Rufini *et al*.[18]). This suggests that polymorphisms or mutations in these genes could introduce genomic instability leading to further germ-line mutations that increase the probability of all types of genetic disorders. Does the germ-line mutation rate differ in individuals with different p53, p63, or p73 alleles? Could the connection between p53 and p73 in the development and functions of the central nervous system result in a connection between psychological stress and cancer? Is it possible that p53 and or p73 could play a role in neurodegenerative diseases? The roles of p53 in the central nervous system and the immune system could even mediate the connection between the functions and activities of these two physiological processes. The reciprocal relationship between p53 and NFκB functions[26] suggests why chronic inflammatory responses can lead to cancers and, interestingly, what to do about this (see the review by Gukov *et al*.[20]). There is certainly a role for p73 in inflammatory pathways (see the review by Rufini *et al*.[18]), as p73-knockout mice have abnormal inflammatory disorders. The role of p53 regulation of both stem cell formation and stem cell longevity could lead to a clearer understanding of organismal longevity and the metabolic impacts upon longevity. Just how all of this is mediated and controlled will depend upon our understanding of the many protein modifications of p53, p63, and p73 as well as the many isoforms of these proteins. Thus it becomes clear that all of the novel functions of the p53 family of transcription factors reviewed in this issue of *Genes & Cancer* should be examined for functional interactions and overlapping activities. While it has been clear for a long time that the p53 protein integrates the diversity of cellular stress responses and leads to a suitable outcome (death or cell cycle arrest), the chapters in this review issue suggest a new set of p53 functions: the integration of the central nervous system, immune system, metabolic functions, fertility, longevity, stem cell production, and viability and disease processes such as cancers and diabetes. The p53 protein could be an integrator or communicator between these physiological systems and processes. So when p53 mutations occur and have specific gain-of-function phenotypes, be they germ-line mutations or somatic mutations that lead to cancers, the nature of the p53 mutation may become a valuable biomarker that, along with the spectrum of other gene mutations, encodes prognostic information and indicates just which drugs are best to employ for the eradication of a cancer. The future of the p53 field of research as summarized in these reviews will be filled with surprises. Just possibly, some of the speculations provided here in this introduction will even turn out to be correct.

— Arnold J. Levine
Invited Editor

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