OVERVIEW

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The *TP53* Gene Network in a Postgenomic Era

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For the TP53 Special Issue

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ABSTRACT: Inactivation of TP53 pathways are the most common defects observed in human cancer. Although missense mutations remain the most frequent genetic event, it is now evident that dysfunction of several members of this network such as MDM2, MDM4 (mdmX), or miR-125b can substitute for *TP53* mutations. This special issue on *TP53* brings the *TP53* gene into the post-genomic era. Several fundamental features of wild type and mutant proteins and their modifications are reviewed, as well as animal models and clinical aspects such as recommendations for patient care. The complex structure of this gene warrants innovative strategies to infer a more accurate status of human tumors. Recommendations and guidelines for reporting and annotating *TP53* variants are also provided, to help researchers generate standardized data that are easy to understand, analyze, and exchange across various cancer variant databases.

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KEY WORDS: TP53; p53; cancer; tumor; clinical; patient care; oncology; LSDB; mutation nomenclature

In 2003, *Human Mutation* published its first special issue on TP53 (Soussi, 2003; http://onlinelibrary.wiley.com/doi/10.1002/humu.v21:3/issuetoc). That issue included the most exhaustive series of reviews devoted to the analysis of *TP53* mutations in various types of cancer ever published. Furthermore, thanks to the expertise of the various authors, the quality of the data makes those reviews still highly accurate and up to date.

Since 2003, the field of molecular genetics has undergone several revolutions, both conceptual and methodological, that have radically changed the landscape of cancer biology. TP53 has not been excluded from this process, with the identification of a complex network that includes several paralogs sharing multiple functionalities (Kaghad et al., 1997; Yang et al., 1998). The identification of at least 12 TP53 protein isoforms adds several layers of complexity to this intricate and enigmatic network (Bourdon et al., 2005).

This second special issue provides an up-to-date review of the most important novelties linking basic and clinical research, using the *TP53* gene as a paradigm. It will be a perfect complementary companion to the previous issue published in 2003 covering all aspects related to TP53 alteration in human cancer.

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The patient is the central element in the circle of basic and clinical research, as illustrated in the TP53 wheel shown in Figure 1, as clinical and genetic data collected by clinicians raise multiple issues that are then investigated through basic research to provide meaningful information, which in turn helps clinicians to improve patient care or can be used for direct appraisals in clinical analyses.

TP53 mutations can occur in a germline context, leading to hereditary disorders such as Li–Fraumeni syndrome, as discussed by Kamihara et al. (2014) in this issue. Recent evidence has broadened this view, with the identification of *TP53* germline mutations in patients with early-onset breast cancer or pediatric adrenocortical carcinoma. De novo mutations are fairly frequent and analysis of family history is therefore often insufficient to infer mutation causality. For this reason, *TP53* mutation databases and other references play a very important role in clinical genetics to ensure correct diagnosis. As reviewed by these authors, the management of individuals with germline *TP53* mutations is now well organized and improvements in both genetic screening and imaging procedures will improve the follow-up of these patients.

Somatic mutations in the *TP53* gene are the most common somatic alterations in human cancer. As reported by Leroy et al. (2014a), the 45,000 *TP53* mutations included in the latest issue of the *TP53* Mutation Database and their analysis are still invaluable for pinpointing the various domains associated with the elusive tumor suppressor function of the TP53 protein.

The recent revolution in molecular diagnostics brought about by high-throughput sequencing will change cancer gene mutation management and, as discussed by Soussi (2014), will have important impacts in the management of locus specific databases.

The complex architecture of the *TP53* gene, involving at least eight mRNAs translated in up to 12 different protein isoforms, will lead to profound changes in the strategy used for screening *TP53* mutations. It will also deeply modify mutation nomenclature. Soussi et al. (2014) provide specific recommendations for the detection and reporting of *TP53* variants that are equally valid for other cancer genes.

Although wild-type *TP53* is considered to be a "tumor suppressor gene," it must be noted that specific selection is required to express oncogenic mutant *TP53* in tumor cells. As discussed by Bisio et al. (2014), the tremendous diversity of mutant *TP53* leads to considerable complexity in the various gains of function observed in various types of cancer. An important question for clinical evaluation is whether or not each hot spot *TP53* mutant should be considered to be a unique oncogene. As reviewed by Donehower (2014), mutant *TP53* gain of function is an important issue in tumor development, as clearly confirmed by the generation of murine models that express endogenous *TP53* genes with mutations similar to those observed in human cancer. These models have also revealed that each *TP53* variant is associated with specific oncogenic activities that shape the profile of tumors in mice.

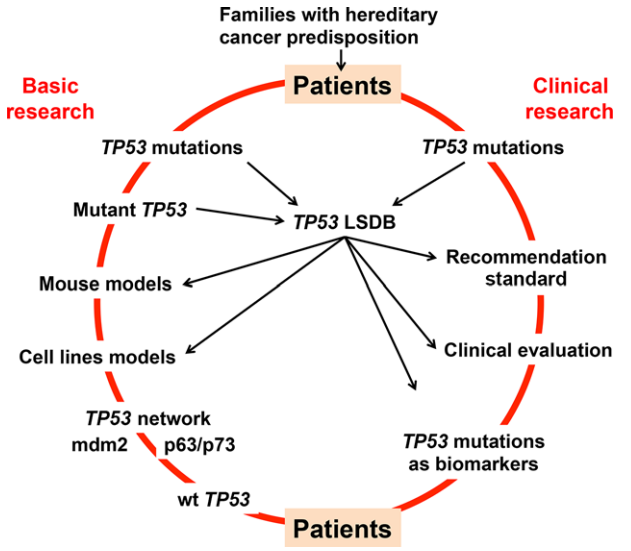

Figure 1. The TP53 wheel illustrates the various aspects covered in this special issue, emphasizing the need for multidisciplinary teams to move data collected from patients to the laboratory and then back to the clinic to improve patient care.

For more than 40 years, cell lines have been derived from human tumors. They have become essential tools, used on a day-to-day basis in laboratories all over the world. However, cell line misidentification is a common problem, and, as discussed by Leroy et al. (2014b), the *TP53* status of several cell lines remains controversial. Novel tools designed to infer the status of the most common cell lines are discussed here and made available to the scientific community.

In addition to *TP53* gene mutations, other mechanisms such as viral infection or deregulation of key factors regulating *TP53* activity can also lead to *TP53* inactivation. Eischen and Lozano (2014) provide an overview of *MDM2* and *MDMX*, two negative regulators of *TP53* that are amplified in a specific subset of cancers. In vitro analyses as well as murine models developed by these authors and discussed in their review provide important clues concerning cross-regulation of *TP53* via *MDM2* and *MDMX*.

The *TP53* gene is part of a three-member family that also includes *TP63* and *TP73*. As reviewed by Candi et al. (2014), these other two genes share several properties with *TP53* but have several specific tissue restrictions. Nevertheless, the cross-talk between the three pathways is undeniable, as illustrated by the observation that some mutant TP53 can directly or indirectly impair the proapoptotic activities of the other two gene products.

Posttranslational modifications are an essential factor in TP53 function. Nguyen et al. (2014) discuss multiple pathways that integrate various stress signals to modulate TP53 response via modifications such as phosphorylation, methylation, acetylation, or ubiquitination, to name just a few. The observation that these regions are very rarely mutated in human cancer raises some interesting questions that are discussed in the review.

The enormous volume of available clinical data concerning *TP53* mutations has modified the management of patients with chronic lymphocytic and other forms of leukemia. Malcikova et al. (2014) discuss the body of evidence showing that *TP53* gene mutations are associated with very poor prognosis, and how *TP53* status can be used in clinical practice.

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