Focus on the p53 Gene and Cancer: Advances in TP53 Mutation Research

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For the p53 Special Issue

The year 1989 was critical for the p53 gene (TP53), with the publication of the first mutations and its entry into the world of tumor suppressor genes [Baker et al., 1989; Takahashi et al., 1989]. The p53 gene went from being a gene which everyone strongly recommended to avoid studying because it was considered to be uninteresting and non-innovative to a star gene. It reached a highpoint in 1993 when it was called “molecule of the year” by the journal Science [Harris, 1993; Lane and Benchimol, 1990]. From a more personal point of view, I decided to work on p53 in 1984, following my appointment as Assistant Professor. With a teaching workload of 190 hours per year, I had to select a research topic which was not going to be a subject of frantic international competition. I still ask myself whether I made the right choice!

This 1989 transition which, retrospectively, could have been anticipated, opened up a new era in which thousands of people became involved and in which tens of millions of dollars were invested. Was it worth all this effort? Have the thousands of published studies devoted to definition of p53 gene status—in order to more clearly define clinical aspects such as response to treatment or prognosis—actually improved patient management?

The objective of this special issue of Human Mutation is not to provide a definitive answer to these questions. If only one lesson can be drawn from the history of studies of the p53 gene, as well as other genes, it is that all conclusions are only contextual and circumstantial, and never definitive and absolute. Nevertheless, almost 15 years after identification of the first p53 mutations, it is now possible to present a review of various aspects of these studies. An unexpected, but very informative, aspect is the discovery of the relationship between the nature of mutational events leading to alteration of the p53 gene and the deliberate or accidental exposure of patients to carcinogens. In 1991–1992, the first compilations of p53 gene mutations demonstrated the specificity of G→T transversions that were specifically detected in smoking-related cancers [Caron de Fromentel and Soussi, 1992; Hollstein et al., 1991]. Since this observation, many studies have analyzed this molecular archaeology and have demonstrated significant correlations between gene p53 mutations and exposure to various types of carcinogens. These studies have also led to the creation of gene p53 mutation databases which are accessible to the entire scientific community [Soussi et al., 2000; Hainaut and Hollstein, 2000; Olivier et al., 2002].

The clinical significance of p53 gene mutations has been the subject of a number of controversies, a fairly common situation for this type of study. The situation concerning p53 has been exacerbated by the marked diversity of methodological approaches. One of the major difficulties concerns comparison of immunohistochemical analyses that are used to evaluate accumulation of stable p53 mutations in tumor cells and molecular analyses that demonstrate the nature of the mutational events that inactivated the p53 gene. It has now been clearly established that the concordance between these two approaches is only 70%, with a marked heterogeneity between the various types of cancers [Soussi and Béroud, 2001]. The frequency of nonsense or frameshift mutations not leading to the synthesis of mutant p53 protein is heterogeneous from one type of cancer to another and may also present geographical variations related to exposure to different carcinogens. TP53 mutations now also appear to be heterogeneous not only in terms of loss of function, but also in terms of a possible gain

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of function which could result in an oncogenic role for certain p53 mutations.

In this special issue of Human Mutation, each author has tried to review the abundant literature on a particular type of cancer as exhaustively as possible. First, Béroud and Soussi (2003) present an update of the UMD software for p53 mutation analysis and show that mutations reported with a low frequency in the database should be interpreted very cautiously. In the section devoted to molecular epidemiology, the authors emphasize the important connections between exposure to various types of carcinogens and the particular spectrum of p53 mutations in the liver [Staib et al., 2003], lung [Toyooka et al., 2003], and skin cancer [Giglia-Mari and Sarasin, 2003]. In the same section, Vähäkangas [2003] summarizes recent information concerning workers exposed to occupational carcinogens. An analysis of mutations at CpG sites in p53 and their relation to human cancer is presented by Soussi and Béroud [2003].

The review by Blons and Laurent-Puig [2003] on head and neck cancer is a nice transition between molecular epidemiology, as the pattern of mutations in these tumors is closely linked to tobacco exposure, and the clinical section, showing that these mutations are associated with a poor response to therapy. In cervical cancer associated with human papillomavirus infection, the frequency of p53 mutation is as low as the viral oncoprotein E6 has the ability to associate with and neutralize the function of p53 protein [Tommasino et al., 2003]. The situation is fairly complex in breast cancer, as the frequency and spectrum of p53 mutations differ between sporadic and hereditary breast tumors [Gasco et al., 2003]. Furthermore, in sporadic breast tumors, only a subset of p53 mutations are linked to poor response to treatment [Børresen-Dale, 2003]. In ovarian, gastric, and colon cancer, the significance of p53 mutation is not sufficiently clear to guide clinical decisions [Schuijer and Berns, 2003; Fenoglio-Preiser et al., 2003; Iacopetta, 2003]. Hematological malignancies present a rather low incidence of genetic alterations in the p53 protein (10–20%), but the prognosis of patients with a mutation in the p53 gene is worse than those expressing the wild-type p53 protein [Peller and Rotter, 2003]. Germline mutations of the p53 gene are associated with a high predisposition to develop tumors from various organs (Li-Fraumeni syndrome). Varley [2003] reviews not only the clinical significance of these germline mutations but also the ethical problems associated with their analysis.

We have also included a review of murine models which, in the case of p53, have provided a wealth of information on the relationships between p53 and cell transformation [Parant and Lozano, 2003]. The growth of transgenesis methods, allowing the possibility of temporally and spatially modulating the expression of a particular gene or expressing p53 mutations via a knock-in approach, is promising to provide a better understanding of the function of the various p53 gene mutations. The recent publication of a humanized mouse with a human p53 [Luo et al., 2001] gene is an original approach to this type of analysis. This approach could also be used for molecular epidemiology.

We can no longer discuss p53 without mentioning the other members of the family: p63 and p73 [Bénard et al., 2003]. Although mutations of these two genes are very uncommon in human cancers, these two proteins nevertheless participate (in collaboration with p53), in the cellular response to genotoxic agents used in cancer chemotherapy [Yang and McKeon, 2000]. The recent discovery that some p53 mutations could interfere with wild-type p63 and p73 proteins and inhibit their apoptotic activity indicates that this signalling pathway could be central to the mechanisms of resistance to treatment, thereby explaining certain contradictions reported in the literature [DiComo et al., 1999; Strano et al., 2000].

I sincerely hope that this special issue of Human Mutation will remain a reference work as, for the first time in the field of p53, it presents the views of organ specialists who do not often have the opportunity to publish their work together. I would like to express my gratitude to all of the authors who agreed to participate and who contributed within a relatively short deadline to this special issue by providing high-quality original reviews. I thank Christophe Béroud for his collaboration as Guest Editor. I would also like to thank the Human Mutation editorial team–R.G.H. Cotton, H.H. Kazazian Jr., and M.H. Paalman—for inviting me to prepare this special issue. Thanks also to Wiley-Liss colleagues Sarah Merriman, for untiring work in the managing of the manuscripts; to John Dufour, for skilled preparation of the manuscripts; and to Patrick Snajder, the journal’s talented Production Editor. The articles are presented by the publishers online for free access and are available from the journal website: www.interscience.wiley.com/human-mutation.

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