Cell Death and Differentiation (2011) 18, 563–564

www.nature.com/cdd

Meeting Report

First International p53 Isoforms Meeting: 'p53 isoforms through evolution: from identification to biological function'

V Marcel[1], M Olivier[2], B Mollereau[3], P Hainaut*[,2] and J-C Bourdon[1]

Cell Death and Differentiation (2011) **18,** 563–564; doi:10.1038/cdd.2010.156; published online 10 December 2010

International p53 Isoforms Meeting, Lyon, France, 13–15 September 2010

After three decades of research, it has been shown that the tumor suppressor *TP53* gene expresses diverse p53 protein forms: the mutant p53 proteins (ex: p53R175H); the polymorphic p53 proteins (ex: p53R72P); the post-translationally modified p53 proteins (ex: p53 phosphorylated on Ser15); and finally the p53 protein isoforms. The p53 isoforms, physiologically expressed in normal tissues, are generated by the usage of alternative promoters, splicing sites and translational initiation sites, thus containing different N- and C-terminal domains compared with the canonical p53 protein. p53 isoforms are not newcomers in the field: alternative splicing of mouse and human p53 was first described in the mid-eighties. However, the field took off only after the discovery in 1997–98 of two additional members of the *TP53* gene family, *TP63* and *TP73*. Both genes express several p63 or p73 protein isoforms with distinct N- and/or C-termini termini because of presence of internal promoters and alternative splicing sites.

The First International p53 Isoforms Meeting (http://www.iarc.fr/p53isoforms/) was held at the International Agency for Research on Cancer (IARC) in Lyon, France on 13–15 September 2010. The aims were to provide a forum to scientists to exchange their latest and unpublished results on p53 isoforms in human, mouse, zebrafish and *Drosophila* biological models, and to establish a clear nomenclature to designate the p53 isoforms. About 110 scientists from 26 countries attended the meeting, which included 25 invited lectures, 12 communications selected from abstracts and 21 posters. The presentations were mainly focused on animal models expressing various p53 isoform patterns, on the identification of novel p53 isoforms, on the characterization of biological functions and regulation of p53 isoforms, as well as their relevance to human cancer using clinical studies.

In the opening lecture, Professor Varda Rotter (Weizmann Institute of Science, Israel) presented her discovery in 1985 of the first p53 isoform, p53AS, expressed in mouse L12 cells. In the mouse p53AS isoform, the negative C-terminal regulatory domain of the classical p53 protein is replaced by additional residues because of alternative splicing of the intron 10. The p53AS isoform behaves as an activated p53 protein, binding DNA, inducing apoptosis and transactivating *Bax*, *p21* and *cyclin G* promoters. However, as p53AS did not seem to have a human counterpart, it was thought to represent a mouse-specific variant and it was not studied further. Similarly for the human *TP53* gene, the alternative splicing of intron 2-producing p53EII mRNA, described in 1987 by Professor Greg Matlashewski (McGill University, Canada), was not studied for several years because it was thought to be a low-abundant human-specific splice variant with no biological relevance. It is only with the discovery in 1997–1998 of two genes homologous to *TP53*, *TP63* and *TP73*, that interest in the p53 protein isoform arose. In their keynote lectures, Dr Alea Mills (Cold Spring Harbor Laboratory, USA) and Professor Gerry Melino (University Tor Vergata, Italy and Medical Research Council, UK) reported, using mice models devoid of a subset of p63 or p73 isoforms, respectively, that p63 and p73 isoforms have differential and important roles in development, cancer formation, aging and neurodegeneration, despite their low-protein expression level. The discovery of p63 and p73 isoforms led Dr Pierre Hainaut (IARC, France) to characterize in 2002 the biochemical and biological activities of the human Δ40p53 isoform, lacking the first transactivation domain and encoded by the p53EII mRNA. The completion of the human genome sequencing project in 2003, showing that 90% of the human genes express multiple mRNA variants because of alternative splicing and alternative promoter usage, convinced Dr Jean-Christophe Bourdon (University of Dundee, UK) to perform a systematic mapping of p53 mRNAs and to describe, for example, Δ133p53 isoform lacking the first 132 residues. This isoform is produced by an internal promoter within the *TP53* gene that is conserved in *TP63* and *TP73* genes across species (*Drosophila*, zebrafish and human), suggesting it plays an important role. To date, at

[1]Centre for Oncology and Molecular Medicine, INSERM-European associated Laboratory, University of Dundee, Ninewells Hospital, Dundee, Scotland, UK; [2]Molecular Carcinogenesis Group, International Agency for Research on Cancer, Lyon Cedex 08, France and [3]Apoptosis and Neurogenetics Group, Ecole Normale Supérieure de Lyon, Laboratory of Molecular Biology of the Cell, CNRS UMR5239, Lyon, France
*Corresponding author: P Hainaut, Molecular Carcinogenesis Group, International Agency for Research on Cancer, 150 cours Albert-Thomas, Lyon Cedex 08 69372, France. Tel: (33) 472738532; Fax: (33) 472738322; E-mail: hainaut@iarc.fr

least 12 human p53 protein isoforms have been detected in human cells (see figure at http://www-p53.iarc.fr/Download/Book_p53Isoforms2010_Final.pdf).

The first meeting sessions were devoted to the establishment and the analyses of animal models expressing specific p53 isoforms. Developmental or physiopathological disorders associated with disturbances in the expression of p53 isoforms have been studied in zebrafish, *Drosophila* and mouse. In zebrafish and mouse, overexpression of the counterparts of the human Δ40p53 or Δ133p53 isoforms led to phenotypes characterized by hypoplasia, dysplasia, altered development and/or early senescence. *Drosophila* appeared as a simpler and helpful model for the understanding of the functions of p53 isoforms as shown by Professor Bertrand Mollereau (Ecole Normale Supérieure de Lyon, France). Indeed, only two *Drosophila* p53 isoforms have been detected, a full-length p53 isoform (Dp53) and a truncated isoform (DΔ110p53). However, the tissue-specific expression of *Drosophila* p53 isoforms lead to complex morphogenetic and developmental disorders, supporting roles of p53 isoforms in essential biological functions, such as apoptosis, autophagy, aging and stem cell maintenance. These animal models appear extremely promising for unraveling the biological significance of the p53 isoforms. They should soon be complemented by sophisticated mouse models, in which each p53 isoforms are specifically knocked out.

Communications dedicated to human cellular models provided proof of principles for molecular and biochemical functions of p53 isoforms. Among the significant findings, the human Δ133p53 isoform has been reported to be transcriptionally controlled by p53 itself and to have dual functions in biological processes, such as cell cycle arrest, apoptosis, cell migration, angiogenesis and metabolism. The emerging picture is that p53 isoforms exert their biological effects through regulation of gene expression *via* modulation of p53 transcriptional properties or independently of p53.

As the *TP53* gene expresses several p53 isoforms because of the usage of alternative promoters, splicing sites and translational initiation sites, an entire session addressed the regulation of p53 isoforms. This session was opened by Professor Jamal Tazi (IGMM, France) who provided an overview of recent advances on splicing and showed how mutation in *cis*-regulator elements may lead to alteration of splicing with dramatic pathological consequences such as progeria. He also showed how novel non-cytotoxic small drugs can be used to specifically target splicing factors and modulate gene expression, thus opening perspectives for therapy. Splicing appears to be a major mechanism in the regulation of p53 isoform for the definition of both the N- and C-termini. For example, it was reported that Δ40p53 production was dependent upon the presence of G-quadruplex structures modulating the alternative splicing, leading to p53EII mRNA expression. The availability of small drugs specifically targeting splicing processes may provide pharmacological tools to manipulate isoform production as well as to correct their possible deregulation in cancer.

The final part of the meeting was dedicated to the clinical impact of p53 isoforms. It was reported that p53 transcriptional and splicing processes may be affected by common *TP53* polymorphisms, some of them being strong modifiers in Li–Fraumeni Syndrome, which predisposes to multiple cancers because of inheritance of *TP53* mutation. In breast cancers, Professor Alastair Thompson (University of Dundee, UK) reported that p53 isoforms had a strong and significant effect on prognosis. For example, p53γ isoform expression seems to abrogate the poor prognosis effect commonly associated with *TP53* mutation.

At the end of the meeting, an open discussion took place on issues that may have an important influence on future developments: (1) What is the strict definition of an 'isoform', in regard to the fact that p53 is known to be highly polymorphic, mutant and post-translationally modified?; (2) What is the best nomenclature for making sense of the current diversity of p53 isoforms in humans as in animal models?; (3) How can the emerging 'isoform community' work together to address the roles of isoforms in a concerted manner and to integrate this information within the broad body of p53 knowledge? These points, as well as a detailed review of the state-of-the-art on isoforms, will be topics for a forthcoming review. Overall, the First International p53 Isoforms Meeting was a highly interactive meeting that opened new perspectives and collaborations.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements. We thank all the speakers for their participation at the First International p53 Isoforms Meeting and their stimulating scientific contributions. The meeting was funded by IARC, the College of Medicine of the University of Dundee and the Laboratory of Molecular Biology of the Cell (UMR5239, CNRS at ENS de Lyon). We thank Michelle Wrisez and all members of the Molecular Carcinogenesis Group at IARC for their help with logistics and organization. Links: IARC TP53 database: http://www-p53.iarc.fr/; abstracts of the International p53 Isoforms meeting: http://www-p53.iarc.fr/Download/Book_p53Isoforms2010_Final.pdf).