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p53: Recent advances in our understanding of this key tumour suppressor

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p53: *TP53* & p53 based regulatory networks

The p53 tumour suppressor protein and the gene that encodes it (*TP53*) is perhaps the most studied and researched area in modern biology. Discovered just over 30 years ago as a cellular protein of 53,000 Daltons that could bind to the large T antigen of SV40 virus, for a time p53 languished as a relatively poorly studied nuclear 'oncogene'. However work from several groups in the late 1980s led to its' recognition as a tumour suppressor. It is now recognised to be mutated, deleted or inactivated by some other mechanism in most human cancers. Recent issues of *The Journal of Pathology* have carried a number of pertinent review articles that summarise our understanding of how p53 exerts its tumour suppressive activities in particular by regulating apoptosis and cellular senescence [1]. In addition *TP53* is an example of one of the most heavily regulated genes in the human genome, and this array of regulatory mechanisms has been reviewed by Hollstein and Hainault [2].

Why is *TP53* and its protein product so carefully regulated? Presumably, because the consequences of inappropriate expression of this 'killer' protein can be so devastating. Understanding why it is so important to carefully regulate the levels of proteins in biological systems, particularly when they function in protein complexes (as most do) has been reviewed by Veitia and Birchler [3]. This provides a framework for understanding the ideas of dominant negative mechanisms in disease [4], a concept that is central to understanding how mutant p53 protein exerts many of its effects.

1. **Tumour suppression by p53: the importance of apoptosis and cellular senescence**
   Valentina Zuckerman, Kamil Wolyniec, Ronit V Sionov, Sue Haupt, Ygal Haupt
   The Journal of Pathology 2009; 219: 3-15. (Invited Review)

2. **Massively regulated genes: the example of *TP53***
   Monica Hollstein, Pierre Hainaut
   The Journal of Pathology 2010; 220: 164-173. (Invited Review)

3. **Dominance and gene dosage balance in health and disease: why levels matter!**
   Reiner A. Veitia, James A. Birchler
   The Journal of Pathology 2010; 220: 174-185. (Invited Review)

4. **Dominant negative factors in health and disease**
   Reiner A Veitia
   The Journal of Pathology 2009; 218: 409-418. (Invited Review)

The complexity of p53 regulatory systems (as highlighted by Hollstein and Hainault) is also being emphasized by studies that link p53 to the regulation of microRNAs [5]. Subramanian *et al.* have shown that in MPNST p53 inactivation is associated with loss of expression of one miRNA with important biological functions in the regulation of cell proliferation and apoptosis. This study reveals additional mechanisms through which p53 acts as a tumour suppressor gene and suggests that miR34a-inhibitory pathways might act as alternative mechanisms to reduce p53 activity in human cancers.

5. **Genome-wide transcriptome analyses reveal p53 inactivation mediated loss of miR-34a expression in malignant peripheral nerve sheath tumours**
   Subbaya Subramanian, Venugopal Thayanithy, Robert B West, Cheng-Han Lee, Andrew H Beck, Shirley Zhu, Erinn Downs-Kelly, Kelli Montgomery, John R Goldblum, Pancras CW Hogendoorn, Christopher L Corless, Andre M Oliveira, Sarah M Dry, Torsten O Nielsen, Brian P Rubin, Jonathan A Fletcher, Christopher DM Fletcher, Matt van de Rijn
   The Journal of Pathology 2010; 220: 58-70. (Original Paper)

Animal models, p53 and cancer

There is no question that animal models have taught us a great deal about the role of p53 in cancer and in biology in general [6]: since it should be recognized that p53 has roles outside 'mere' tumour suppression. A recent study in the *Journal* has teased out the role for transcriptional regulation by p53 as a central component of the tumour suppressive effects in skin [7]. The data distinguish between the effects of growth-inhibitory signals on the p53 pathway and highlight the importance of p63-mediated suppression of cell senescence in *ras*-induced skin cancer.

6. **What have animal models taught us about the p53 pathway?**
   Guillermina Lozano, Gerard P Zambetti
   The Journal of Pathology 2005; 205: 206-220. (Invited Review)

7. **The transcriptional regulatory function of p53 is essential for suppression of mouse skin carcinogenesis and can be dissociated from effects on TG-β-mediated growth regulation**
   Roshini M Ponnamperuma, Kathryn E King, Tamador Elsir, Adam B Gli.k, Geoffrey M Wahl, Monica Nister, Wendy C Weinberg
   The Journal of Pathology 2009; 219: 263-274. (Original Paper)

Can human studies inform our understanding of p53?

While *in vitro* and model animal systems are of great importance, there remains an important place for translational studies in clinical settings. As is the case with the work of Subramanian *et al.* [5] a number of recent papers in the *Journal* have made use of patient cohorts to pose biologically *and* clinically important questions: questions that mouse and other model systems could not usefully be used to address.

Crum and colleagues have invested considerable energy in marshalling our knowledge of ovarian carcinogenesis. Recently they employed an unusual 'experiment of nature' to investigate the role of p53 in pelvic serous carcinogenesis [8]. Patients with germ line p53 mutation form part of the Li-Fraumeni Syndrome, and Xian *et al.* followed the development of neoplasia in the Fallopian tubes of such patients. Their work, reviewed in a Commentary by Herrington and McCluggage [9], indicates that p53 mutation and LOH occurs as an early event in the neoplastic cascade, but is not sufficient for carcinogenesis. Their data are also suggestive of a model in which the distal fallopian tube is a commoner origin of ovarian cancers than the ovary itself. Such studies illustrate that carefully conducted clinical observations can provide profound biological insights that help our *understanding of disease*.

8. **The Li-Fraumeni syndrome (LFS): a model for the initiation of p53 signatures in the distal Fallopian tube**
   Wa Xian, Alexander Miron, Michael Roh, Dana R Semmel, Yosuf Yassin, Judy Garber, Esther Oliva, Annekathryn Goodman, Karishma Mehra, Ross S Berkowitz, Christopher P Crum, Bradley J Quade
   The Journal of Pathology 2010; 220: 17-23. (Original Paper)

9. **The emerging role of the distal Fallopian tube and p53 in pelvic serous carcinogenesis**
   C Simon Herrington, W Glenn McCluggage
   The Journal of Pathology 2010; 220: 5-6. (Invited Commentary)

Immunohistochemical studies of p53 protein expression in cancers are numerous, although their clinical value is highly uncertain due to the relative inability of staining to accurately identify p53 mutation status. Another strategy for illuminating the function of p53 in tumours is to correlate p53 expression patterns with p53-target gene expression and link these data with carefully defined clinical parameters. When such studies are performed with sufficient statistical power and with carefully directed questions they can provide clinical and biological insights. This is especially so in the context of a clinical trial setting. The Nottingham Breast Group have a long history of such studies and their recent report [10] describing the analysis of the p53 pathway in breast cancer is of great interest. A crucial element of their work is that the validity of the data generated in one large cohort was then tested in a second patient population: the conclusions drawn can thus be seen to be robust. A key idea that stems from the work of Abdel-Fateh *et al.* is that the careful analysis of several elements of the p53 pathway (p53, mdm4, mdm2, bcl-2, p21) identifies biologically and clinically distinct tumour subgroups. In an accompanying Commentary [11], Thompson and Lane point to the importance of these studies and how they illuminate the complexities of p53 pathway protein expression, the interactions with tumour biology and the response to therapy. This work opens up a whole host of similar studies applied to other cancer types and it may be that p53 status using the 5-protein signature (or an improved version of p53-network proteins) will yet prove to have clinical value.

10. **The biological, clinical and prognostic implications of p53 transcriptional pathways in breast cancers**
Tarek M Abdel-Fatah, Desmond G Powe, Johnson Agboola, Martyna Adamowicz-Brice, Roger W Blamey, Maria A Lopez-Garcia, Andrew R Green, Jorge S Reis-Filho, Ian O Ellis
The Journal of Pathology 2010; 220: 419-434. (Original Paper)

11. **p53 transcriptional pathways in breast cancer: the good, the bad and the complex**
Alastair M Thompson, David P Lane
The Journal of Pathology 2010; 220: 401-403. (Invited Commentary)

The notion that monitoring p53 and other elements of the p53 pathway can have clinical relevance has been a topic of investigation for nearly 20 years. But of course nature is rarely simple and Derenzini *et al.* [**12**] have developed the idea that activity of the p53 pathway can be influenced by the status of the retinoblastoma protein. It will be intriguing to see if the clinical algorithm being developed as a consequence of the work of Abdel-Fateh *et al.* [**10**,**11**] may be modified in the future by the addition of analysis of Rb?

12. **The p53-mediated sensitivity of cancer cells to chemotherapeutic agents is conditioned by the status of the retinoblastoma protein**
Massimo Derenzini, Elisa Brighenti, Giulio Donati, Manuela Vici, Claudio Ceccarelli, Donatella Santini, Mario Taffurelli, Lorenzo Montanaro, Davide Treré
The Journal of Pathology 2009; 219: 373-382. (Original Paper)

Questions

The following questions can be answered by reading and reflecting upon the above annotation and the papers that are cited within it. Within the Royal College of Pathologists **Continuing Professional Development (CPD) scheme**, CPD points may be earned by writing reflective notes on the papers in this Virtual Issue and the questions are designed to act as a focus for this activity. To do this, you may wish to use the Royal College of Pathologists' **reflective notes form**.

Question 1 What does the term *dominant negative* mean and why is it relevant to the understanding of p53 in human disease?

Question 2 What is *cellular senescence* and how does p53 contribute to it?

Question 3 How does p53 contribute to the mechanisms of apoptotic cell death?

Question 4 What are the mechanisms that regulate the level of p53 protein in cells?

Question 5 What is the Li-Fraumeni Syndrome and how can its study inform our understanding of other diseases in which p53 is altered?

Question 6 How can p53 contribute to drug resistance in tumours?

Question 7 Assessing the expression of p53 protein and some of its downstream targets may correlate with clinical behaviour of breast tumours. What are the caveats to this view?

Question 8 How can animal models inform our understanding of p53?