Neuropathology: Advances in technology and biology

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Central and peripheral nervous system tumours and their underlying molecular pathways

CNS and PNS tumours are highly heterogeneous and complex neoplasms, which require tailored treatment. However, to date, therapeutic decisions for these patients are predominantly made on risk group assignment based on clinical parameters and histological assessment of end stage disease. Perhaps not surprisingly therefore, these tumours are still associated with high mortality and morbidity. It is encouraging however, that our understanding of the molecular pathways involved in the pathogenesis of the majority of these neoplasms is rapidly increasing. Bottillo et al. and Subramanian et al. report on the significance of NF1 mutations in sporadic malignant peripheral nerve sheath tumours (MPNSTs) [1] and on the role of down-regulation of p53 and subsequent loss of miR-34a in the progression from neurofibroma to MPNSTs [2] respectively. Among CNS tumours, not only the pathogenesis of high grade glial tumour is rapidly being elucidated but progresses are made also in understanding more rare entities such as pilocytic astrocytomas, where genetic aberrations that activate the ERK/MAP kinase pathway have been reported [3]. A mechanism-specific and therefore more efficient therapy for these neoplasms seems to be a step closer.

1. Germline and somatic NF1 mutations in sporadic and NF1-associated malignant peripheral nerve sheath tumours
   Irene Bottillo, Terje Ahlquist, Helge Brekke, Stine A Danielsen, Eva van den Berg, Fredrik Mertens, Ragnhild A Lothe, Bruno Dallapiccola

2. Genome-wide transcriptome analyses reveal p53 inactivation mediated loss of miR-34a expression in malignant peripheral nerve sheath tumours
   *The Journal of Pathology* 2010; 220: 58-70. (Original paper)
3. Activation of the ERK/MAPK pathway: a signature genetic defect in posterior fossa pilocytic astrocytomas
   Tim Forshew, Ruth G Tatevossian, Andrew RJ Lawson, Jing Ma, Geoff Neale, Babatunji W Ogunkolade, Tania A Jones, Johan Aarum, James Dalton, Simon Bailey, Tracy Chaplin, Rowena L Carter, Amar Gajjar, Alberto Broniscer, Bryan D Young, David W Ellison, Denise Sheer

Impact of gene technology on neuropathology

The availability of molecular markers of specific diseases has progressively influenced decision making in neuropathology over the last decade. In neuro-oncology for example, demonstration of 1p;19q LOH is essential to support the morphological diagnosis of oligodendroglioma and analysis of IDH1 status has been shown to effectively discriminate between primary and secondary glioblastoma.

More recently, techniques such as next-generation DNA sequencing [4] and ‘single-molecule genomics’ [5] have revolutionized cancer genomics and have the potential to make a huge impact on personalized medicine in the future.

Molecular profiling of individual cancer reflects the individuality of each tumour, reveals the presence or absence of distinct disease-associated molecular signatures and as such represents a crucial component for the translation of molecular advances in oncology to tailored clinical practice.

It is an exciting time ahead for disciplines such as neuropathology and neuroscience, which face the challenge to try and integrate the massive amount of information gathered through these techniques into a morphological and functional interpretation frame.

4. Does massively parallel DNA resequencing signify the end of histopathology as we know it?
   Samuel AJR Aparicio, David G Huntsman

5. Single-molecule genomics
   Frank McCaughan, Paul H Dear

Genes and proteins: The importance of a well kept balance

The increasing awareness of the interactions between genes in the control of gene expression is a burgeoning field of research. The advances in understanding and the way that these recently uncovered mechanisms of protein expression control can cause neurological disease are making the field an exciting and fast paced area. The relationship between gene dosage and phenotype is becoming clearer with important concepts in co-ordinated gene expression, and the subsequent effects of haploinsufficiency being explained [6]. Many puzzles still remain, even where genetic influences are known to be at work, for example in neural tube defects [7].
However, the uncovering of the sensitivity of the central nervous system to disorders of protein regulation, such as seen in vanishing white matter disease, where loss of translational control occurs, Charcot Marie Tooth disease with abnormalities of aminoacyl-tRNA synthetases (ARSs), and other abnormalities of CNS specific microRNA, all point to key pathways in understanding the molecular basis of many CNS diseases [8].

6. **Dominance and gene dosage balance in health and disease: why levels matter!**
   Reiner A. Veitia, James A. Birchler

7. **Genetics and development of neural tube defects**
   Andrew J Copp, Nicholas DE Greene

8. **Dysregulation of protein synthesis and disease**
   John PC Le Quesne, Keith A Spriggs, Martin Bushell, Anne E Willis
   *The Journal of Pathology* 2010; 220: 140-151. (Invited review)

**Post hoc; post translational change and inflammation**

The post-translational modification of proteins is epitomised and exemplified by the glycation of proteins, with compelling data for the involvement of advanced glycated endproducts (AGEs) in a range of neurodegenerative diseases [9]. The interaction of AGEs with the receptor RAGE, and the role of glycation in altering protein conformation, promoting fibril formation and stimulating oxidative stress and inflammation is a hot topic in this area. Similarly the neuroprotection afforded by anti-inflammatory drugs has stimulated interest in the role of inflammation in the pathogenesis of these diseases. The finding of elevated progranulin [10] in an Alzheimer’s disease model, following on from demonstration of loss of progranulin in fronto-temporal dementia, may lead to better understanding of the relationship between dementia and inflammation.

9. **The sour side of neurodegenerative disorders: the effects of protein glycation**
   Hugo Vicente Miranda, Tiago Fleming Outeiro
   *The Journal of Pathology* 2010; 221: 13-25. (Invited review)

10. **Progranulin expression correlates with dense-core amyloid plaque burden in Alzheimer disease mouse models**
    Sandra Pereson, Hans Wils, Gernot Kleinberger, Eileen McGowan, Mado Vandewoestyne, Bianca Van Broeck, Geert Joris, Ivy Cuijt, Dieter Deforce, Michael Hutton, Christine Van Broeckhoven, Professor Samir Kumar-Singh MD, PhD, VIB
Protein aggregates and lessons from the heart

The aggregation of proteins into amyloid fibrils has been the subject of a vast amount of literature, especially in the area of familial amyloidotic polyneuropathy (FAP) where transthyretin (TTR) mutations lead to amyloid deposits. *In vivo* TTR amyloid fibril formation mechanism has been noted to be closely related to the microenvironment, and clues as to the initiation of the formation of fibrils and their propagation are studied in the study by Misumi *et al.*, [11], where the chain reaction of protein fibril formation appears to be intimately involved with the basement membrane.

11. **Chain reaction of amyloid fibril formation with induction of basement membrane in familial amyloidotic polyneuropathy**
   Yohei Misumi, Yukio Ando, Mitsuharu Ueda, Konen Obayashi, Hirofumi Jono, Yu Su, Taro Yamashita, Makoto Uchino

The role of aggregation of proteins in prion disease has been a key question in neuropathology, and the process described by Sasaki and colleagues [12] explores the molecular basis of this as it relates to the diagnosis of prion disease using proteinase resistance of PrPSC. The early stage findings of proteinase sensitive oligomers of abnormal PrP, suggests that further exploration of the diagnostic sensitivity and definitions of disease are needed. The finding of the uptake and processing of prion material by human embryonic stem cells [13] raises key questions for the transmission of disease, but also for the use of such cells in a therapeutic context.

12. **Development of oligomeric prion-protein aggregates in a mouse model of prion disease**
   Kensuke Sasaki, Haruhiko Minaki, Toru Iwaki

13. **Human embryonic stem cells rapidly take up and then clear exogenous human and animal prions *in vitro***
   Zuzana Krejciova, Steve Pells, Enrico Cancellotti, Paz Freile, Matthew Bishop, Kay Samuel, G Robin Barclay, James W. Ironside, Jean C. Manson, Marc L. Turner, Paul De Sousa, Mark W. Head

**Autophagy, the ultimate in self-absorption**

Intracellular components are degraded via two principle pathways, autophagy and the ubiquitin-proteasome pathways. Autophagy delivers cytoplasmic proteins and effete organelles to the autophagosome, a double-membraned vesicle, whose contents fuse with lysosomes for degradation of the contents. Autophagy is thought not only to supply nutrients for survival during states of cellular stress, but also to play a role in normal cell function by removing suboptimal components. Once material is taken into autophagosomes or primary phagosomes, a range of processes occur to break down the material, including lysosomal and proteasomal processing [14] Neurons have similar digestion mechanisms in place, but neurons are also crucially dependent on autophagy during periods of stress. Key papers have shown that when nerve cells have defective autophagy
they can degenerate. Autophagy may also directly trigger cell death. Many subsequent studies have linked autophagy directly to the pathology seen in many neurodegenerative conditions, for example granulovacuolar bodies seen in Alzheimer’s disease, but also there has been enormous expansion in the interest in mitochondrial autophagy [14]. These current papers bring the field up to date, and show some of the issues in the study of this field with respect to the technical aspects of studying autophagy [15].

14. **Autophagy: cellular and molecular mechanisms**
   Danielle Glick, Sandra Barth, Kay F. Macleod
   *The Journal of Pathology* 2010; 221: 3-12. (Invited review)

15. **Autophagy: assays and artifacts**
   Sandra Barth, Danielle Glick, Kay F Macleod

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](http://www.thejournalofpathology.com).

**Question 1**  How does p53 inactivation relate to the molecular pathology of malignant nerve sheath tumours?

**Question 2**  What cellular processes are mediated by the ERK/MAPK pathway?

**Question 3**  What is massively parallel DNA resequencing?

**Question 4**  How does genetic dominance operate?

**Question 5**  What is the evidence for genetic factors in the aetiology of neural tube defects?

**Question 6**  How can dysregulation of protein synthesis cause disease?

**Question 7**  Why does it matter that human embryonic stem cells can take up prions?

**Question 8**  What is autophagy and how is it regulated?