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Molecular diagnostics and the training of future tissue- and cell-based pathologists

For many years, the discovery of the DNA helix in 1953[1] and the subsequent discoveries in the area of molecular biology had relatively little impact in the practice of histo- and cytopathology. However, the sequencing of the human genome[2] and the advent of so-called personalized medicine[3] has begun to revolutionize the practice of tissue and cellular pathology, creating a layer of molecular complexity between the traditional morphological assessment and the therapeutic decision. This calls for a morpho-molecular approach to our routine pathology daily practice,[4] which, in the context of cytopathology, could represent a totally new approach to its practice.[5] This diagnostic need is already having a dramatic effect on how we practice pathology. No longer can we rely on morphological classification and the routine incorporation of protein-based tests such as immunohistochemistry: pathologists need to expand their diagnostic armamentarium, as for many of the commonest cancers, the value of traditional pathology has not diminished, but it is simply no longer sufficient.

The diagnostic molecular characterization of cancer cells has two main values, namely:

1 Predominantly diagnostic and taxonomical value

Classic examples are (1) the incorporation of clonality analysis (immunoglobulin/T-cell receptor gene rearrangements), which provides an important tool in the diagnosis of suspect lymphoproliferative disorders; or (2) the presence of chromosomal aberrations in sarcomas, leukaemias and lymphomas, allowing a subclassification of these tumours, in many cases with clear prognostic and therapeutic implications.

2 Predominantly therapeutic value

The presence of certain biomarkers will indicate the likelihood of patients responding to specific therapies. Fine needle aspiration cytology offers a suitable alternative in a variety of clinical settings in which it may be useful to obtain material to study prognostic and predictive markers. This is particularly relevant to obtaining material from metastatic sites. The study of KRAS in colon cancer, CKIT in gastrointestinal stromal tumours and EGFR mutational status in lung cancer are good examples of the value of molecular cytopathology.[6] For instance, the presence of a mutation in the *EGFR* gene makes lung cancer more likely to respond to small molecular inhibitors. As lung cancer is frequently diagnosed and treated on the basis of a cytological diagnosis, this is a relevant area for the application of molecular studies on cytology samples.

In an ever-expanding area of knowledge, the article in this issue of *Cytopathology* by Boyd and Boyle[7] is an account of what was arguably the first dedicated meeting of tissue and cellular pathologists in the UK with an interest in molecular diagnosis. Their article provides a useful snapshot/overview of where we are in this field both practically and conceptually: a field that is leading the key future scientific and diagnostic developments in cancer. Indeed, the number of new therapeutic antibodies and small molecular inhibitors available represents a challenge for personalized cancer medicine. The European Medicines Agency has approved a number of compounds for therapeutics with specific molecular targets. While this is happening, the current mode of a single biomarker for an individual drug has become outdated and newer, more sophisticated technologies are required. Next-generation sequencing (NGS) has the potential to provide a global view of the cancer genome, or large segments of the genome in its more adaptable technology platform types see figure 1.[8] As the price of whole genome sequencing continues to fall this will undoubtedly replace the single biomarker approach. NGS could hand a golden opportunity to cytopathologists, to provide clinicians huge and solid data

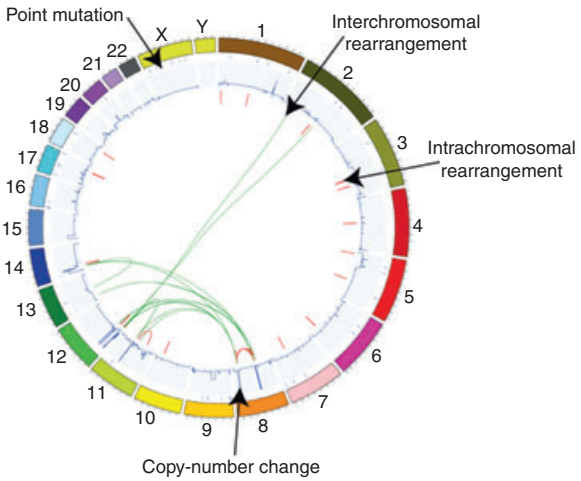

Figure 1. Landscape of somatic mutations present in a single cancer genome. Used with permission from MR Stratton *et al*.[8]

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derived from material obtained by minimally invasive methods.[9] Our understanding of molecular pathology must evolve in the course of our training programmes to bring into play all that high-throughput technologies have to offer. Now is the time to re-engineer cytopathology training.

While other subspecialties in laboratory medicine seem to have embraced the 'molecular diagnostic challenge' readily (such as molecular virology, molecular haematology or genetics) there is a sense that tissue and cellular pathologists have been more reticent to do so. The need to overcome this situation has been clearly highlighted from within the pathology community,[10,11] as it has severe implications for both the diagnostic and academic/research dimensions of pathology as a whole. These opinions point to a clear conclusion: the number of pathologists with expertise in genomic medicine and genome-based research is low and we need to overcome this by embedding the training of molecular diagnostics and genome-based applied research into our traditional pathology training.

Although in its early stages, there are very encouraging steps towards the integration of modern, genome-based practical training in the national and the European context. In the UK, an Interdisciplinary Committee at the Royal College of Pathologists is working on new modular systems for the inclusion of molecular diagnostic training in all areas of pathology, tissue and cellular pathology included, for both medical pathology trainees and clinical scientists alike. This, together with the recent relevance of molecular pathology activities in the Royal College of Pathologists and in other pathology fraternities such as the Association for Clinical Pathology, is announcing a very much needed repositioning of histo- and cytopathology to embrace molecular diagnostics.

In the European context, the forthcoming publication of the *Requirements for Recognition of Post-Graduate Training in Pathology* by the Board of Pathology of the European Union of Medical Specialists (UEMS), which is also published in this issue of *Cytopathology*,[12] recognizes the need for incorporation of molecular pathology during training. This document, which provides 'guidance and quality standards for recognition of training programs in Pathology of EU/EFTA [European Union/European Free Trade Association] member states', makes it clear in its preamble that the scope of pathology extends from 'the gross examination to the molecular lab, including conventional and advanced microscopy and supporting techniques of molecular pathology to demonstrate expression of genes and gene products'. 'Obligatory professional activities' within the mandatory training programmes in pathology include acquiring skills 'to evaluate additional investigational methods, such as histochemical and immunohistochemical stains and molecular methods, to support the pathological diagnosis' as well as gaining the ability 'to integrate molecular data with morphological findings to achieve a conclusive diagnosis'. The emphasis of this editorial and the leading topic in this issue of *Cytopathology* is molecular biology, but it should be noted here that the 'Obligatory professional activities' include the requirement to 'undertake the microscopical examination of sufficient cytopathology samples, including gynaecological and non-gynaecological (fine-needle and other) samples so as to acquire the appropriate competencies necessary for independent specialist practice.' Cytopathology is no longer a 'subspeciality' and is included in the 'common trunk' of 3–4 years of training.

Although this publication is highly significant in its official recognition of the importance of embracing molecular pathology, its implementation on the ground as a European standard of quality will need substantial efforts from all academic pathology training centres. It is difficult to overemphasize the importance of pathology trainees now and in the future acquiring an understanding of the various molecular biological techniques and their relevance in the practice of modern diagnostic medicine. The resulting pathologists will then be experts in the combination of morphology, immunohistochemistry and molecular testing towards the provision of diagnostic opinions and, by doing so, will ensure the central relevance of tissue- and cell-based pathology in modern diagnostic and academic medicine.

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