Molecular pathology: the future of diagnosis and treatment

Defined by the Association of Clinical Pathologists as simply “the study of molecules in a disease state” (1), molecular pathology (MP) uses the tools of molecular biology to better understand the aetiology, pathogenesis, diagnosis and prognosis of diseases (2). These tools include fluorescent *in situ* hybridisation (FISH), mass spectrometry and expressional proteomics amongst others (3,4), using analytes including DNA, mRNA, lipids and proteins (2). Via these methods, MP is involved in the discovery and clinical validation of biomarkers (5,6).

The goal of MP is to use these biomarkers to specify preventative or therapeutic regimens for a patient (7). MP lies in the interface between diagnosis and treatment, and has growing importance in characterising not only a disease, but also the patient (2). When coupled with the recent advances in genomics, MP has the potential to revolutionise diagnosis and treatment of genetic, infectious and neoplastic diseases. In particular, its utility within personalised medicine cannot be underestimated (2). In this short essay the potential applications of MP and some unresolved challenges will be briefly outlined.

Currently, MP is mainly involved with molecular diagnostics. Serum viral RNAs can be used to diagnose viral infections for example; or a mutation in tumour cell genes can be used to diagnose specific neoplasms (1). There are also several ways that MP can be used specifically in the prevention and/or treatment of disease: genetics can be used to screen individuals for preventable inheritable conditions (e.g. APC testing in colorectal cancer patients); treatment and response can be monitored using biomarkers (e.g. Bcr-Abl testing for relapse in leukaemia); personalised medicine can be applied to cancer patients by tailoring drugs to certain specific cancers (1,8). Using biomarkers, MP allows for extremely specific diagnoses and, thus, guides personalised treatment regimens (8).

Personalised therapies would be useless in patients without their required genotype, and so MP is vital in indicating their appropriateness (2,8) – an important consideration in an environment of shrinking healthcare budgets. Two major examples include: copy number variation of Her2, which is used to decide whether treatment with trastuzumab is indicated; and KRAS sequencing, a standard test in colorectal cancer patients used to determine whether to prescribe antibodies to epidermal growth factor (2).

The integration of molecular diagnostics throughout pathological fields is variable however: some fields are now almost entirely molecular (e.g. clinical genetics), while others are less so (e.g. anatomic/surgical pathologists). To achieve the potential it promises, a more comprehensive adoption of MP must be implemented in pathological laboratories (8,9).

That is not to say MP should replace the traditional morphological analysis, immunohistochemistry (IHC) and chemical techniques used in conventional pathology laboratories; both are complementary to each other (2,10). Microscopic assessment in particular is required to provide understanding and context to the molecular profiles that are subsequently provided via MP (8).

Despite molecular biology having existed for over 50 years, translating biomarker status into clinical information is only now becoming a reality. Many reasons have been suggested for this: most significantly poor study design, particularly regarding insufficient statistical power (11). This calls for specific training amongst upcoming pathologists in the discovery and validation of biomarkers (8).

It is becoming accepted that there is a need to integrate biomarker research and diagnostics laboratories more effectively using biobanks of material as repositories for future study. The key issue here is quality control: the samples must be collected and appropriately stabilised in such a way as to prevent degradation, which will require changes in laboratory practice (2,8,12). In addition, processing must downscale to decreased tissue sample sizes as specimens become ever smaller (e.g. from interventional radiology)

(2). There is also a balance between the right of individuals to their genomic anonymity, and the greater good for society that this research brings – a debate that has still not been settled to satisfaction (8,13).

Further ethical issues are found in the application of biomarkers themselves. To use in a clinical context confidence in the biomarker must be sufficiently high. Conversely, the potentials of novel biomarkers can be highly attractive. Unfortunately, there is a high level of biomarker marketing which often contains unverified (not peer-reviewed) and invalidated methods, both in laboratory and clinical contexts (2). Another issue is the use of patented genes as biomarkers in clinical trials, which is currently being debated by the US Supreme Court (2).

Novel computerised technologies are likely going to be part of future diagnosis. Digital pathology, a photographic technique which digitalises a histological image, can be automatically set to analyse IHC preparations and count FISH hybridisations for example (8,14). Objectivity and quantification are thus added to these previously subjective techniques. These are already receiving the validation and regulatory approval required (8).

The main issue with MP is the vast quantity of data it produces and its translation into clinically useful information. In an era of next-generation sequencing and the realisation that multiplex testing will be required as the number of available biomarkers continues to rise, the volume of data is only going to increase exponentially. The more information available, the less easily interpretable it is. Thus to be of any real benefit, bioinformatics will have to adapt accordingly. Indeed the pace of advancement in this field is likely to be the limiting factor in ongoing MP development. It is also being recognised that validation of bioinformatical approaches requires the same calibre as other aspects of MP (2,8).

Conclusion

MP has the potential to revolutionise diagnostics and therapeutics for a whole raft of diseases, moving us closer toward the goal of true personalised medicine. To become a reality several hurdles must be overcome. The fusion of diagnostic and research laboratory approaches will require an extensive revision of pathology practice, including preparation for ever-smaller sample sizes. Molecular techniques need comprehensive adoption across pathological fields, and bioinformatics must adapt rapidly to the influx of information. Training will be required to ensure studies into biomarkers are of sufficient statistical power. Finally, ethical issues surrounding gene patents, biobanking and unscrupulous marketing must all be resolved.

Word count: 1,000 words.

Reference List

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