

Molecular Medicine: The Way Forward

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The past two decades have witnessed a tremendous leap in advances and new knowledge in molecular and cell biology. This field has no doubt provided us with powerful tools and cutting edge technology that has enabled scientists and researchers to study disease at the molecular and cellular level, a depth and breadth never envisioned before. Almost all diseases are now discussed in the context of genetic and environmental factors. The study of genes, or genomics, now cuts across many scientific disciplines and the impact can be seen in many facets of medicine today. In fact, molecular medicine has now become a highly recognisable term to describe a vast expanding field of studying diseases at the most fundamental level.

As we marvel at these advances in genomics and molecular medicine we ask whether in the local setting we are indeed learning, adapting and utilising the relevant technologies in our medical practice. Arguably, we are still trailing behind in many areas but perhaps, not too far. We now have many scientists and clinicians trained or exposed to this field. Reassuringly, a significant majority of research proposals under the Intensification of Research in Priority Areas (IRPA) grant scheme involves studies in molecular medicine. Clinicians and scientists now interface and collaborate in many related research projects. Although we have yet to reach a critical mass of researchers in this field, at least the infrastructure and the core group of experts are available at all the major research institutions. Molecular diagnostic services are now being offered routinely for a number of diseases in some centers albeit not extensively advertised.

Are the advances in molecular medicine changing our local practice? In many ways the answer is a 'yes', although the impact is mainly felt in institutions which have the facilities and those with access to the services. There is still a lot to be done to facilitate the transfer of technology and services across all major tertiary hospitals. To this end, perhaps the relevant institutions should first

come together and establish a molecular diagnostics network to facilitate the availability of such services nationwide.

There are also clinicians who are skeptical about how this new biology affects clinical care. Certainly, the full value of molecular medicine is yet to be seen and many of us wonder about its impact on the cost of health care. It may be worthwhile then to highlight some of the applications of genomics in medicine in our local practice quoting some relevant examples.

Diagnosics

Molecular biology techniques in diagnostics have been widely utilized albeit the numbers of tests offered vary from one institution to another. In clinical practice, molecular analysis of the hepatitis C virus is now available, both qualitatively as well as quantitatively. The HCV-RNA testing is the gold standard for diagnosis as compared to serological techniques. Quantisation of the numbers of the viral genome per milliliters of serum even helps the clinician monitor response to therapy and relapse of disease. A locally developed DNA-based diagnostic kit for typhoid is also now available. The capability and expertise of our local laboratories in the field of infectious diseases were evident during the recent SARS outbreak, when a group of scientists in UKM successfully cloned and sequenced the viral genome within 6 days. A remarkable achievement indeed! In the field of haematology, the molecular diagnosis of thalassaemia is now currently a routine in many centres. This is particularly crucial in identification of alpha thalassaemia carriers and in the diagnosis of beta thalassaemia with normal or equivocal HbA₂ on the Hb electrophoresis. The identification of the mutations also aids in pre-natal and pre-implantation diagnosis should these be sought for by parents. Certainly the use of genomics has increased the diagnostic precision in many diseases.

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Prognosis

Molecular techniques are also being used to prognosticate disease in the local setting, especially when correlation exists between phenotype and genotype. For example, genotyping of the hepatitis C virus is crucial to determine the duration of treatment and predicts poor and good responders to therapy. In thalassaemia, different mutations in the beta globin gene result in variability of globin chain production by the red blood cells, which in turn determine whether the condition will manifest as the transfusion-dependent thalassaemia major or the less severe thalassaemia intermedia. In G6PD deficiency, a common cause of neonatal jaundice in Malaysia, we are beginning to discover the correlation with the different genetic variants and the severity of neonatal jaundice.

Prognostication of disease using molecular methods is also being applied in the management of cancers. The presence of the translocation t(9;22) and rearrangements involving the *MLL* gene predicts poorer prognosis in childhood acute lymphoblastic leukaemias. Patients with presence of these molecular signatures are now given intensive therapy including early bone marrow transplantation.

Screening

The knowledge that certain gene mutations are associated with specific cancers also allows for early screening. Perhaps the best example would be screening for *BRCA1* and *BRCA2* genes in those with familial breast cancer. Siblings identified to carry the same mutation as the index patient with breast cancer have >80% chance of developing the same cancer. This would allow the siblings to be monitored closely and be treated early should a cancer evolve. Similarly, those with mutations in the *APC* gene have a high risk of developing colon cancer. The penetrance of such a mutation, if present in a family member is >90%, which translates to a near-certainty of developing cancer, so much so that a prophylactic colectomy is one of the options given to predisposed individuals. Currently, screening for *BRCA1*, *BRCA2* and the *APC* genes are very much done on a research basis but soon these tests will be readily available as a service.

The screening for cancer predisposition genes does not involve just the technical aspects alone. There are ethical dilemmas and controversies, which can complicate decisions especially when counseling patients with respect to the other family members. One may argue that identification of the presence of cancer predisposition

genes could marginalize individuals and would prejudice them against obtaining employment and health insurance. However the advantage for the particular individual is a chance to prevent, through modification of lifestyle amongst others, or obtain treatment for the cancer early. With 40,000 cancer cases being diagnosed annually in Malaysia, early screening for cancer using molecular markers will soon be a necessity rather than a privilege.

Basic Science

The biggest contribution that molecular biology has given to medicine would be in the greater understanding of diseases. In cancers, we know now that mutations in the oncogenes and tumour suppressor genes disrupt the normal regulatory mechanisms controlling cell signaling and the cell cycle machinery. We now know that the *bcr-abl* translocation in chronic myeloid leukaemia results in a chimeric protein, which has excessive tyrosine kinase activity that drives cells to proliferate uncontrollably. Knowledge about this fusion protein inevitably led to the discovery of the wonder drug Imatinib which is a tyrosine kinase inhibitor. We also know that the cancer cells become resistant to chemotherapy drugs by the efflux of the drugs extracellularly, a process mediated by the multidrug resistant proteins including the P-glycoprotein. These are just a few examples on how science has helped us understand disease better. It is also comforting to know that many local institutions are now involved in fundamental research to study diseases at the molecular and cellular level.

Conclusion

In summary, the field of genomics is open for all of us to learn, adapt and utilise in our practice. Currently, the microarray approach allows one to study the expression of thousands of genes at one time consolidating further the already vast armamentarium of analysing the diseased tissue. Now the field of proteomics (the study of proteins which the genes code for) would even open the scope wider. Certainly, the field of genomics has changed the face of medicine, and its impact is significantly making its mark in our local medical and scientific fraternity. Many of the tests are relatively expensive, but the results they give improve diagnostic precision, allow disease prevention, make possible early treatment in individuals at risk, ensure better prognostication and widen the targets for development of new therapies. Already the projection for the immediate future is personalised medicine based on genomic and proteomic profiling of the patient as well as the disease. The best is certainly yet to come.