Editorial

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Genome Research and Molecular Pathology

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Editorial

Until a decade ago, detection genome abnormalities relied on laborious chain termination DNA sequencing. With the advent of parallel sequencing technologies, we are in the era of rapid genomic sequencing with relatively low cost. As a result, many pathological specimens, particularly cancer samples of variety of origins, have been analysed for genome integrity. Large numbers of genome abnormalities, including amplifications, deletions, mutations and genome rearrangements that underlie human cancers have been uncovered. The abnormalities of somatic or germline mutations for human cancers or other diseases are distributed almost in all chromosomes. Based on some recent studies, some of these abnormalities have also been found in the benign tissues adjacent to cancers, suggesting that the morphological alterations in the cancer cells occur possibly in the late stage of cancer evolution. The emergence of large amount of high quality genome data of human cancers in the next several years and the availability of these data in the public domain will facilitate to revise some of the concept in pathology and to better guide diagnosis and therapy of human diseases.

The large amount of information of molecular biology for human diseases generates significant challenge to pathologists for applying this valuable knowledge to the diagnosis today. In the early days, a pathology diagnosis was largely built on the promises of altered morphology caused by the diseases, though evaluating specimens, such as blood samples, body fluids, body excretions, or tissues removed from surgical resection. The morphological details including chemistry of the specimens provide information or feature of variety of diseases. For human cancer, tissue differentiation level such as atypia, dysplasia, anaplasia based on the resemblance of malignant cells to its original tissue has been very useful in predicting the potential tumour aggressiveness and sensitivity to the therapy. However, morphology evaluation by individual pathologist inevitably is limited by its inherent subjectivity. It also provides less accurate guidance for treatment of cancers. With increasing number of markers emerged in recent years, new pathological concepts have been sprung up to interpret the human diseases and been applied to the diagnoses and new treatments. Molecular pathology, more specifically, cancer molecular pathology has been the most rapidly expanding and dynamic area in the field of pathology. The development of molecular pathology was dated as early as the days when Philadelphia chr (Ph chr) was identified for the diagnosis of chronic myelogenous leukemia (CML), and the subsequent treatment targeting at oncogenic fusion BCR-ABL1. Since then, hundreds of genomic and molecular features of human disease have been characterized, and applied to the clinical setting for diagnosis of human diseases and guidance of therapy. Current applications of mutations of BRCA1 and BRAC2 in the diagnosis of breast and ovarian cancers are some of many other examples. Molecular pathology has become an indispensable discipline of pathology in recent years.

Genome alterations are fundamental in the development of human cancers. Although strong associations of human malignancies with the genomic alterations identified in genome sequencing suggest the significant roles of some of these alterations in tumorigenesis, the roles of these genome abnormalities are yet to be confirmed experimentally. Many alterations remain to be characterized. Nevertheless, some of these abnormalities, including deletion or mutation of previously known tumour suppressor genes, like *Pten*, *CDKN2* and *TP53* or mutation and copy number gaining of proto-oncogene, such as RAS, EGFR, c-MET and RAF, are characterized as the critical drivers for human cancer development. Therapeutic interventions targeting at these driver gene events have shown significant impacts on the improvement of cancer survival. Specific mutations of genomes only occur in a fraction of patients with the similar types of cancers. Most recent drugs have been targeting at specific genes. Thus, to achieve desirable effect, patients will be matched with appropriate targeted therapy based on genotype status. This forms the foundation of precision medicine in the treatment of human cancers. Even though numerous genome abnormalities may be found in cancers, only small numbers of these abnormalities are the driving force for cancer development. Most other changes are classified as 'passenger' alterations, playing little role in producing cancer. The 'driver' alteration is defined as change that would lead to malignant phenotype of human tissues. To qualify for 'driver' alteration, the changes of the genome should fulfil the following 4 criteria: 1) the genome alteration occurs in both primary tumour and the matched metastatic cancer loci. 2) The product of this alteration is able to transform benign cells to malignant cells in vitro. 3) The genome alteration produces the similar cancer phenotype in animals. 4) Targeting at this genome

alteration yields significant effects on cancer that contains the alteration.

Probably most point mutations in cancer genome represent passenger alterations for the functions of proteins, and constitute the tolerable alterations. Only a small fraction of the mutations or genome rearrangements lead to the catastrophic consequence of the affected cells, and produced morphologically recognizable cancers. These genome structural abnormalities, unlike epigenomic alterations in cancer genomes, contribute to the phenotype of human cancers that is not reversible. Some of the gene mutations and fusion genes resulted from chromosome rearrangements are known to alter epigenome and thus change gene transcription, RNA splicing and protein translation, for many critical proteins of growth factor receptors, oncogenes and tumour suppressor genes. The causes of genome mutations and chromosome rearrangements are still unclear. Nonetheless, the failure of DNA repairing stands out as one of possible causes of genome abnormalities. Investigation into the regulation of DNA repairing in both physiological and pathological conditions may yield critical information for the understanding cancer genome development.

The last 10 years represent an exciting period for molecular pathology. We expect that molecular pathology as a discipline will play increasingly dominant role in the coming years in making diagnosis of human diseases and providing guidance for therapy. For new pathologists in the training, this is the indispensable field for the career of pathology. Likely, most pathologists in the future will be familiar with molecular pathology of human diseases, making molecular pathology as one of the fundamental bases of the discipline.