J Clin Exp Pathol 2017, 7:2 (Suppl)
DOI: 10.4172/2161-0681-C1-035

Chromosome microarray analysis - Changing the landscape of clinical cytogenetics

M Anwar Iqbal
University of Rochester Medical Center, USA

The conventional technique of G-banded chromosome analysis reliably detects large chromosomal abnormalities and rearrangements at a minimum size of about 3-10 Mb, and requires dividing cells. Its main limitation is that smaller chromosomal deletions or duplications may be overlooked. Fluorescence in situ hybridization (FISH) was developed to rapidly detect smaller chromosomal abnormalities with locus-specific probes, but one must clinically suspect a specific diagnosis associated with a particular chromosome or chromosomal region to request the appropriate probe. Array-based comparative genomic hybridization (aCGH) developed as a method to examine the entire genome for copy number changes caused by deletions, duplications, or whole chromosome aneuploidy. It improved resolution over conventional G-banded karyotype in detecting much smaller chromosomal abnormalities, as small as 50 to 100 kb, and does not require dividing cells. It has become a first-line diagnostic tool for the detection of chromosome abnormalities at both macro and micro level in postnatal, high-risk pregnancies and in products of conception samples. Application of these technologies in cancer research has produced a wealth of useful information about copy number alterations (CNAs), Loss of heterozygosity (LOH) and mutations of specific genes and their implications in cancer classification, disease progression, therapy response, and patient outcome. There is an increasing interest in the genetic diagnostic community in applying this new technology for cancer diagnosis. Our experience on more than 4000 cases performed using the aCGH, and aCGH and SNP arrays in postnatal, prenatal and cancer will be presented.

anwar_iqbal@urmc.rochester.edu

Drug-responsive chromatin structures and the underlying genetic alterations in leukemia

Jason X Cheng
University of Chicago Medical Center, USA

Chemical modifications of DNA/histone play an important role in organization of human chromatin into distinct structural domains that control gene expression, stem cell differentiation and tumorigenesis. Drugs that target various chromatin modifiers have become one of the promising treatments for many types of cancer including solid tumors and hematologic malignancies such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). However, most, if not all of the cancers treated with epigenetic drugs eventually develop drug resistance and render epigenetic drugs ineffective in cancer patients. The mechanisms underlying the selectivity and efficacy of epigenetic-modifying drugs are still unknown. Therefore, a major challenge in today's cancer treatment is to unravel the mechanisms of drug resistance and to develop strategies to prevent or reverse drug resistance in various types of cancer. In this study, we developed a new method to simultaneously measure 5-methylcytosine (5-mC) and hydroxymethylcytosine (5-hmC). CDMIAs revealed significantly drug-responsive changes in 5-mC/5-hmC at the promoters of differentiation/lineage-controlling genes such as PU.1/SPI1. Immunoprecipitation experiments demonstrated lineage-specific, drug-sensitive interactions between the PU.1/SPI1 and GATA1 transcription factors and the DNA/histone modifying complexes. ChIP-seq and chromatin conformation capture (3C) showed that distinct chromatin structures at the gene locus in a lineage-specific manner. Importantly, novel mutations in TET2, TET3, DNMT3L and PU.1/SP1 were revealed by genome-wide sequencing and confirmed by Sanger sequencing. These mutations correlated with the altered interactions between PU.1/SPI1 and the DNA/histone modifying complexes and predicted the responses to epigenetic modifying drugs. Examination of clinical specimens from patients with MDS confirmed the presence of distinct lineage/differentiation-specific chromatin structures. These results demonstrate the importance of functional genomics in the pathogenesis of MDS and leukemia and may identify novel therapeutic targets.

Jason.Cheng@uchospitals.edu