A single ngs assay for the simultaneous detection of igh translocations, copy number alterations and sequence mutations in circulating multiple myeloma cells (cmmcs)

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Abstract

Background

Multiple myeloma (MM) is a genetically complex disease characterized by the clonal proliferation of plasma cells in the bone marrow. At present, risk stratification and management of MM patients rely on invasive bone marrow (BM) biopsies for identifying cytogenetic abnormalities using karyotyping and fluorescence in situ hybridization.

Objective

Here, we present a liquid biopsy-based NGS assay for the simultaneous detection of immunoglobulin heavy-chain translocations, copy number alterations, single nucleotide variants (SNV) and indels from Circulating Multiple Myeloma Cells (CMMCs).

Methods

Pools of cells from a MM cell line (NCI-H929) and pools of CMMCs from 4 MM patients were sorted by the DEPArray™ PLUS System after enrichment by CD138 and staining using the CELLSEARCH® System. After lysis, samples underwent whole-genome DNA library preparation using the DEPArray LibPrep kit and targeted enrichment using a custom panel (Twist Bioscience). hgDNAs from 5 reference normal cell lines were also analyzed.

Results

All known alterations of the NCI-H929 cell line were detected from pools of 50 cells. The performance in terms of SNV calling was estimated from well-characterized normal cell lines, obtaining a mean true positive rate of 98.8% and a mean positive predictive value of 99.3%. Targeted NGS analysis of as few as 50 CMMCs isolated from four MM patients enabled the identification of cytogenetic abnormalities, such as t(14;16), gain (1q), 16q copy neutral loss of heterozygosity (CN-LOH), which are associated with poor prognosis. Variants of strong clinical significance in the KRAS gene were also detected. A hyperdiploid MM pattern, known to be associated with a favorable outcome, was identified in two out of the four patients analyzed.

Conclusion

Here we present a new liquid biopsy-based workflow to simultaneously detect different types of genomic alterations in circulating multiple myeloma cells that has the potential to become an effective non-invasive disease monitoring tool.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.