Predictive Genomics and the Treatment of Multiple Myeloma

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Genetic instability, a central feature of malignant cells, plays an important role in oncogenesis by perturbing critical cell signaling pathways, including activation of oncogene and/or deletion of tumor suppressor genes; moreover, ongoing genomic changes are associated with tumor progression, invasiveness, and drug resistance. We hypothesized that the inherent genomic instability in tumors would lead to a heterogeneous tumor cell population at diagnosis, thereby providing a substantial substrate for ongoing selection during progression of the disease. We have here investigated serial samples from patients with multiple myeloma (MM) using a variety of methodologies to study the genomic evolution. Purified MM cells, as well as matching normal samples from the same patients, were collected at 2 time points at least 4 months apart and subjected to genomic analyses. To compare the changes between matching normal and MM cells collected at two time points (range 5-18 months apart), we utilized SNP 6.0 array to identify copy number alterations (CAN); identified genome-wide rearrangements utilizing a low-coverage whole genome shotgun approach generated via next-generation sequencing; and, importantly, for the first time in 13 patients performed whole exome sequencing based on a solution phase capture and next generation sequencing. Variants identified in both the rearrangement and exome screens were validated on orthogonal platform. Our analysis demonstrates: 1) a significant intratumoural heterogeneity at the initial time of evaluation, suggesting that even at diagnosis multiple sub-clones may be co-existing; 2) discernable shifts in the clonal structure of disease at the time of progression (2^{nd} sample) that indicates appearance of previously undetected sub-clones. We have observed frequent mutational changes (3 or more samples) involving CCND1, DTX1, KRAS genes. The changes are irrespective of intervention and disease status. We have also observed appearance of new copy number alterations and heterozygosity between 2 serial samples, ranging from 0.021 - 2.674 % (i.e. per 100 informative loci investigated), as well as insertion/deletion changes. These data therefore confirm evolution of genomic changes in MM patients over time and identify molecular alterations associated with progression of disease and development of drug resistance. This study begins to define the clonal architecture of MM and will provide insights into the impact of this structure and heterogeneity on pathogenesis and progression of disease. A comparison of these findings to those from whole genome sequencing in Waldenstrom's Macroglobulinemia patients will be presented at the workshop.