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Can genomic evolution be predicted in plasma cell malignancies?

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Earlier studies utilizing a high-resolution analysis of recurrent copy number alterations, coupled with expression analysis in primary Multiple Myeloma (MM) cells, have identified MM as a complex disease, driven by numerous molecular processes that alter genetic and epigenetic landscape of the disease, along with the presence of many highly recurrent and focal copy number alterations have in the MM genome. Massively parallel sequencing have described the mutational changes in myeloma. Our large exome sequencing study with deep coverage (240x) in 84 myeloma samples have identified new candidate genes, including truncations of SP140, LTB, ROBO1, and clustered missense mutations in EGR1. Importantly the most frequent mutations were observed in N-RAS, K-RAS and B-RAF genes, indicated involvement of MEK/ERK pathway activation on disease process as well as mutations involving FAM46C, TP53 genes. An important observation from this study has been significant genomic heterogeneity in myeloma. Mutations were often present in subclonal populations, and multiple mutations within the same pathway (e.g., KRAS, NRAS, and BRAF) were observed in the same patient. In vitro modeling predicts only partial treatment efficacy of targeting subclonal mutations, and even growth promotion of nonmutated subclones in some cases. These results emphasize the importance of heterogeneity analysis for treatment decisions. A study utilizing high-resolution single-nucleotide polymorphism arrays (N = 24), has suggested selection and growth of genetically distinct subclones, which were not initially competitive against the dominant population but survived following therapy, with new acquired anomalies and subsequent outgrowth. Our further analysis of the exome sequencing data, in serial sampling performed in 15 patients, revealed diverse patterns of clonal evolution: linear evolution, differential clonal response, and branching evolution. Diverse processes contributing to the mutational repertoire including kataegis and somatic hypermutation have been identified, and their relative contribution changed over time. This study demonstrates that the myeloma genome is heterogeneous, with clonal diversity at diagnosis and further evolution over time. We have further evaluated the expression of mutated genes in MM using RNA-seq and identified a pattern of differential and limited expression of mutant alleles. We observe that only quarter of the mutations are expressed and among mutated genes that are expressed, there are often allele-specific patterns of expression. These results highlight the important contribution of RNA-sequencing to identify clinically significant mutations and for their therapeutic applications. In

summary, the early mutational analyses of clinical annotated samples provided insight into molecular mechanism of disease behavior, and help identify novel therapeutic targets for the development of molecularly-based therapies to improve outcome in myeloma.

We have now extended our study to evaluate the genomic evolution in the early stages of plasam cell malignancy - smoldering multiple myeloma (SMM). We performed WGS on paired samples from SMM patients progressing to MM. We observed a very similar genomic landscape, at the smoldering stage is very similar to MM. We also report 2 different patterns of progression: one pattern where the subclonal architecture was retained as the disease progressed to MM. We call it the “static progression model” which suggest that progression solely reflected the time needed to accumulate a sufficient disease burden; the 2nd group labelled by us as “spontaneous evolution model” where we did not observe any major change in the subclonal composition between SMM to MM. We also observe that the AID plays a major role in shaping the early mutational changes while APOBEC plays role in later changes. These results provide an important insight into myelomagenesis and clonal evolution in the plasma cell disorders.