Why is subclonal evolution important to the study of WM?

Zachary Hunter, Mehmet Kemal Samur, Steven Treon, Nikhil C. Munshi

Dana Farber Cancer Institute, VA Boston Healthcare System Harvard Medical School, Boston MA

Cancer is a multistep process wherein a normal cell acquires, by mutation, a variety of characteristics to progress from benign to malignant transformation. Once the malignant transformation has occurred, the cancer cells continue to acquire new genomic changes which enable them to evolve into a more aggressive phenotype, survive effects of host microenvironment including anti-tumor immunity, and develop resistance to therapy. Such a genomic evolution requires the acquisition of a “hypermutator” phenotype. Consistent with this view, the majority of cancers display a complex spectra of diverse genetic alterations apparent at diagnosis and acquire additional changes with progression of the disease, indicating a striking genomic instability. Previously, we have demonstrated that MM patients display a complex dynamic of clonal evolution. Interestingly, the number of mutations was the only factor correlating with overall as well as relapse free survival, thus highlighting the importance of understanding the mechanisms of genomic instability in MM. Moreover, in spite of several novel agents becoming available for treatment in recent years, MM remains incurable. Our analysis also showed that most cases had a complex subclonal structure and showed clusters of subclonal variants, including subclonal driver mutations. The most represented point mutation consisted in C>T transitions at CpG trinucleotides, reflecting spontaneous deamination of methylated cytosine to thymine. Kataegis, a process of hypermutation resulting in regions with clusters of C>T transitions, was also detected. Copy number analysis also revealed the presence of chromothripsis, a mechanism of genomic instability defined by tens to hundreds of chromosomal rearrangements involving localized genomic regions, in a minority of samples. Chromothripsis has been shown to be associated with poor outcome in MM. Using Bayesian Dirichlet analysis of sequencing data, we showed that all patients carry a cluster of variants present in all cells. Rarely, patients had only few subclonal variants and no significant clustering at the subclonal level, while most patients showed a major cluster of clonal mutations, and

one or more clusters of subclonal variants. Interestingly, few patients had a dominant subclone, indicating a complex dynamic of subclonal evolution. The central problem is that a fraction of cells survives the treatment (as MRD) and eventually lead to disease relapse. Since genomic instability serves as a tool for acquisition of genomic and functional changes required for development of drug resistance, it is necessary that we elucidate mechanisms underlying genomic instability to delineate pathogenesis, overcome drug resistance, and develop better strategies for treatment. A similar complex clonal dynamic is observed in Waldenstrom's macroglobulinemia and is considered associated with progressive disease. With the approval of targeted therapy such changes associated with evolution provides survival capabilities and are important component of WM and study of associated mutational changes with clonal evolution will provide an important avenue for therapeutic intervention.