How can we use genomic sequencing to understand therapy related clonal evolution in multiple Myeloma?

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Currently the greatest problem in successfully treating cancer is the genomic adaptability of the tumor cells leading to their continued growth and survival. Our recent results have defined the mutational spectrum in multiple myeloma (MM) at the time of initial diagnosis and found heterogeneity across samples, with largely distinct sets of chromosomal rearrangements and gene mutations present in individual patients. We have described a complex subclonal structure, including subclonal driver mutations. Using Bayesian Dirichlet analysis of sequencing data, we showed that most patients had 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. Serial sampling of patient MM cells has revealed diverse patterns of clonal evolution, including: linear evolution in which a new subclone emerged in the late sample that was not evident despite the deep sequencing in the earlier sample; differential clonal response in which each subclone was identified at the two time points, but their relative proportions changed over time, reflecting random drift of subclones over time; differential response among subclones to chemotherapy or clonal expansion, due to selective advantage of one subclone over the others; and branching evolution in which one or more new clones have emerged, while others have declined in frequency or disappeared altogether in the time between the early and late time-points, as was observed in 2 cases with extramedullary relapse. Surprisingly, the pattern of genomic evolution could not be predicted by response to treatment, time interval between sampling, or by treatment type. Utilizing 96 possible mutated trinucleotides, we have also identified biologically distinct mutational signatures responsible for the majority of observed mutations. These data suggest a pattern of parallel, divergent, or even convergent evolution. The evolution and subclonal progression is consider a cumulative effect of inherent genomic characteristics of tumor cells besides, impact of BM microenvironment as well as therapy. We have observed a significant complex mutational spectrum in samples at relapse after initial successful therapy. Multiple mutational signatures are considered to be involved including homologous recombination, APOBEC and AID. Some of the chemotherapetic agents may induce specific pathway, such as homologous recombination or Deaminase that induce mutations. An ongoing study to evaluate the impact of treatment on genomic instability and its underlying mechanisms, identify new genes and pathways involved in genomic instability, and evaluate inhibitors of genomic instability, alone and in combination with existing treatments in MM is ongoing and will provide important future therapeutics.