The treatment implication of spatiotemporal genetic variation in plasma cell malignancies

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The biologic basis for cancer initiation and progression has important implications for the way we use both cytotoxic and targeted therapies. In plasma cell malignancies sequence analysis has detected the presence of sub-clonal heterogeneity at the genetic level. Thus within the same Ig sequences there are subclones defined by acquired sequence variants and biological behavior. This subclonal variation has also been shown at the cellular level and the biological differences associated with these initiating cells combined with the process of natural selection are the essential features for Darwinian type evolution. It has been shown that this evolutionary behavior underlies the progression of MGUS, to SMM, MM and finally to plasma cell leukaemia. Early during the process of progression clonal sweeps leads to the eradication of prior clones but as the disease progresses access to the myeloma niche becomes restricted and spatial genetic variation develops driven by regional evolution.

Evolutionary development patterns underlie the initiation and progression of all cancers as well as governing the response to therapy. In this context treatment can be considered as an evolutionary selective pressure and the knowledge gained by understanding these interactions can help in the design of therapeutic strategies. Different genetic sequences can be seen at different tumor sites and this spatial genetic variation can explain differential responses. Different patterns of mutation can be seen at different time points and this temporal variation can explain the development of treatment resistance and clonal tides. Chemotherapy treatments are based on combinations to ensure treatment resistant clones are eradicated by initial therapy. It is not surprising then that single agent targeted therapies against specific mutations while associated with initial responses are associated with rapid relapse as the non-mutated clones come to dominate the marrow. Sub-clonal genetic variation also has implications for the assessment of disease response. Importantly response to mutationally targeted treatment may not impact the size of the whole clone but only of the mutated subclones being targeted. Thus the effectiveness of such agents may be missed if assessment doesn't take account of mutational variation

The acquired features of the clonal cells modify the tumor microenvironment (TME) to facilitate disease progression and so could be therapeutically targeted. These acquired TME occur within

both the immune microenvironment and within the tumor niche of the bone marrow. The acquired variability within these two components of the TME can explain resistance to immune and other therapies and so understanding the system further is of crucial importance.

In conclusion the effective us of both novel agents and immunotherapy will require us to understand in detail the co-evolution of the tumor in the context of its microenvironment. The understanding of this system will not only improve the use of current therapies but will provide targets for future therapies based on tumor acquired genetic variants and the changes they induce in the TME.