Spatial Genomic Heterogeneity in Multiple Myeloma: Surrogate Markers and Its Significance for Understanding the Evolutionary Processes Leading to Relapse

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Introduction

Multiple Myeloma frequently presents with genomic variation between individual cancer foci, also termed spatial heterogeneity (SH). The extent of SH differs considerably between patients with some having extensive heterogeneity while others show homogeneous mutational profiles within the bone marrow (Fig. 1). Since SH poses a significant challenge to personalized therapy, surrogate markers would be useful clinically. In this respect an understanding of the spatial evolutionary patterns taking place during treatment and the clonal architecture they give rise to at relapse would also be of fundamental importance. To address these points we have analyzed paired samples from multiple sites which were either collected at baseline or longitudinally during treatment.

Aims

- Identify features associated with spatial heterogeneity
- Understand spatial evolutionary patterns during treatment

Surrogate markers for spatial heterogeneity

Anatomical distance and molecular markers are not associated with SH

FL size and age at diagnosis are associated with unshared mutations

Evolutionary pattern during treatment

Selection for clones with similar features

Clonal sweep despite “stable” disease

Figure 1. For the paired analysis samples were collected from multiple sites. An example for a patient with site-specific (unshared) mutations is shown in the upper panel. In the lower panel examples for similar mutational profiles (left) and distinct clones (right) at different sites are depicted.

Figure 2. The anatomical distance between investigated sites, adverse molecular markers, the ISS, and the number of FLs did not correlate with spatial heterogeneity (upper panel). In contrast, FL size (Ps) and age at diagnosis were highly associated with the proportion of unshared mutations. A linear model including both features explained 49% of the variation in SH (lower panel).

Figure 3. In the upper panel a patient with distinct KRAS mutations affecting the exact same amino acid at relapse is shown, highlighting that treatment could select for clones with similar or even identical features. The patient shown in the lower panel experienced a clonal sweep. Notably, this clonal replacement occurred without major M-protein changes (stable disease).

Conclusion

- The strong association of unshared mutations with age at diagnosis and size of focal lesions allows for the identification of patients with increased levels of spatial heterogeneity for whom treatment approaches can be modified.
- The existence of clonal sweeps, which replace previously dominant clones even in poorly responding patients, highlights the need for regular molecular testing.

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