A phenotype-structured approach to study intra-clonal heterogeneity and drug resistance in multiple myeloma

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Abstract

Multiple myeloma (MM) is a blood cancer with a complex genetic landscape, resulting from the infiltration of abnormal and highly proliferating plasma cells to the bone marrow. This cancer evolves from an earlier stage called monoclonal gammopathy of unknown significance (MGUS) due to successive genetic modifications in different genes. These mutations lead to the emergence and competition of various tumor clones, which causes resistance to treatment. In our research, we introduce a model describing intraclonal heterogeneity and drug resistance in MM. This model accurately describes the diverse growth patterns seen in MM, in consistency with a previously established multiscale model. Our simulations show that increasing the mutation rate upregulates tumor diversity, while elevating access to growth factors speeds up tumor evolution and expands it. In particular, the model suggests that the abundance of growth factors mainly increases tumor size without changing clonal dynamics. The model also shows that elevated mutation rates and growth factor levels increase the risk of drug resistance and relapses. The study suggests that treatment timing can influence tumor growth patterns and the appearance order of distinct clones in branching evolution. Due to its low computational cost, our model is ideal for the analysis of MM clone intraclonal evolution scenarios and its interplay with chemotherapy.