

Systemic modeling of multiple myeloma and osteoclast interactions in the bone marrow microenvironment

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Abstract

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in bone marrow. Interaction of myeloma cells with bone marrow microenvironments is crucial for MM pathogenesis and drug resistance. Binding myeloma cells to bone marrow stromal cells activates pleiotropic proliferative and anti-apoptotic cascades, triggers NF- κ B activation, and induces secretion of growth factors and cytokines. Osteoclasts are derived from bone marrow stem cells and play a very important role in bone degeneration. Previous studies found that osteoclasts enhanced myeloma cell growth and survival. Bone marrow is considered as a hypoxic environment with heterogeneous oxygen diffusion. However, the interactions between osteoclasts and myeloma cells under hypoxic condition have been poorly understood. In this study, we proposed a computational approach for systemic modeling of myeloma and osteoclast interactions, based on our experimental data. We developed an Integer Linear Programming (ILP) model to infer the osteoclast-mediated MM-specific signaling pathways in myeloma cells under hypoxia and normoxia condition, respectively. Analyzing the inferred specific pathways in myeloma cells provides insight into the molecular mechanisms of myeloma cell survival and growth. Furthermore, we also applied our model to predict the treatment effects when the inferred signaling pathways in myeloma cells were perturbed with drugs. In summary, our computational model can be used to elucidate potential mechanisms of myeloma cells and provides clues for new therapies.