Roles of bone marrow microenvironment in clonal evolution and drug resistance of multiple myeloma

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Recent studies with next generation sequencing have revealed the complex genomic architecture of multiple myeloma. A model combining “Big Bang” dynamics and Darwinian type of branching evolution has been put forward to explain the development and progression of the disease. As a result of branching evolution, multiple clones emerge with distinct characteristics in terms of growth advantage and drug sensitivity. It is widely believed that the interaction with bone marrow microenvironment accelerates clonal heterogeneity of myeloma cells. The bone marrow microenvironment also confers drug resistance to myeloma cells via at least two overlapping mechanisms. First, bone marrow stromal cells (BMSCs) produce soluble factors, such as interleukin-6 and insulin-like growth factor-1, to activate signal transduction pathways leading to drug resistance (soluble factor-mediated drug resistance). Second, BMSCs up-regulate the expression of cell cycle inhibitors, anti-apoptotic members of the Bcl-2 family, and ABC drug transporters in myeloma cells upon direct contact (cell adhesion-mediated drug resistance). Elucidation of the mechanisms underlying drug resistance may greatly contribute to the advancement of multiple myeloma therapies. We have demonstrated that epigenetic alterations play important roles in drug resistance of myeloma cells, especially cell adhesion-mediated drug resistance (CAM-DR). We found that class I histone deacetylases (HDACs) are up-regulated in myeloma cells via VLA-4-mediated adhesion to BMSCs and determine the sensitivity of myeloma cells to proteasome inhibitors (Oncogene 28: 231, 2009; Blood 116: 406, 2010). The histone H3-K27 methyltransferase EZH2 regulates the transcription of several anti-apoptotic genes and drug transporters in an Ikaros-dependent manner, rendering the acquisition of CAM-DR and stemness by immature myeloma cells, including myeloma stem cells (J. Clin. Invest. 125: 4375, 2015; Cancer Res. 78: 1766, 2018). In addition, another histone methyltransferase, MMSET, was shown to confer drug resistance to myeloma cells by facilitating DNA repair (Leukemia, submitted for publication). These findings provide a rationale for the inclusion of epigenetic drugs, such as HDAC inhibitors and histone methylation modifiers, in combination chemotherapy for myeloma patients to increase the therapeutic index.