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2

The malignant clone and the bone-marrow environment

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Multiple myeloma (MM) is characterized by the clonal expansion of monoclonal immunoglobulin-secreting plasma cells within the bone marrow (BM). It has become clear that the intimate reciprocal relationship between the tumor cell clone and the niches of the BM microenvironment plays a pivotal pathophysiologic role in MM. We and others have identified several new molecular targets and derived novel therapies which induce cytotoxicity against MM cells in the BM milieu, including thalidomide, bortezomib, and lenalidomide. Importantly, these agents induce tumor-cell death, as well as inhibit MM-cell–BM-stromal-cell (BMSC) adhesion and related tumor-cell growth, survival, and migration. Moreover, they block both constitutive and MM-cell binding-induced growth factor and cytokine secretion in BMSCs. Further, they also block tumor angiogenesis and can augment anti-MM immunity. Although all three of these agents are now FDA-approved to treat MM, patients inevitably relapse, and further improvements remain urgently needed. Here we review our current knowledge of the MM cell clone, as well as the impact of the BM microenvironment on tumor-cell growth, survival, migration and drug resistance. Delineating the mechanisms and sequelae of the

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reciprocal relationship between the MM cell clone, distinct BM extracellular matrix proteins, and accessory cell compartments may provide the basis for new effective therapeutic strategies to re-establish BM homeostasis and thereby improve MM patient outcome.

Key words: multiple myeloma; translocations; mutations; epigenesist; telomeres; extracellular matrix; bone-marrow microenvironment; bone-marrow niches; angiogenesis.

Multiple myeloma (MM) is a malignant disorder of post-germinal center B cells, characterized by the clonal proliferation of malignant plasma cells within the bone marrow (BM) compartment. Tumor cells derived from MM patients are extremely heterogeneous: either hypodiploid with immunoglobulin H (IgH) translocations or hyperdiploid with multiple trisomies. Recent correlation of these IgH translocations with cyclin D (cyclin D1, D2, and D3) gene expression profiles, specific trisomies, and clinical features have provided the basis for a new classification system with prognostic and therapeutic implications.[1]

The pivotal role of the BM microenvironment in MM pathogenesis is now well established. Specifically, the balanced homeostasis between the cellular, the extracellular, and the liquid compartments within the BM is disrupted, resulting in multiple effects including immune suppression, cytopenias and lytic bone lesions. Importantly, these effects are caused not only by expanding MM cells which impact the BM, but also by the impact of tumor cells on the functions of other cells within the BM milieu. Specifically, direct cell–cell/cell–extracellular matrix (ECM) interaction or cytokines/growth factors modulate functions of BM cells, including endothelial cells, osteoclasts, osteoblasts, fibroblasts, and immune effector cells, which in turn promote tumor-cell growth, survival, migration, and drug resistance. For example, BM angiogenesis is normally tightly regulated by pro- and anti-angiogenic molecules. In MM, BM microvascular density (MVD) is increased and correlates with disease progression and poor prognosis. Importantly, the therapeutic success of thalidomide, bortezomib and lenalidomide in relapsed/refractory disease is associated with targeting MM-cell–host-BM interactions, including tumor angiogenesis, and/or cytokines/growth factors in the BM milieu. Combinations of targeted therapies can increase cytotoxicity, decrease drug resistance, and improve the favorable side-effect profile as in acute lymphocytic leukemia or Hodgkin's disease, with the promise of converting MM to a chronic disease with the prospect of cure.

THE GENETIC BACKGROUND OF THE MALIGNANT MM-CELL CLONE: TRANSLOCATIONS, MUTATIONS, EPIGENESIS, AND TELOMERES

As in other tumors such as colon cancer, a model of multi-step MM development has been proposed based upon clinical data as well as data from cytogenetics, analysis of Ig gene mutations, and recurrent chromosomal abnormalities. This model suggests that: (1) in at least 30% of cases MM arises from the benign plasma-cell neoplasm monoclonal gammopathy of undetermined significance (MGUS), with an incidence of approximately 1% per year; (2) it then progresses to (non-symptomatic) smoldering MM; and (3) it finally evolves to symptomatic intramedullary MM, with extramedullary spread/plasma-cell leukemia (PCL) seen as the disease advances.[2–5]

Studies on the chromosome content suggest a model of two molecular pathways of MM pathogenesis: a non-hyperdiploid (or hypodiploid) pathway with high incidence of five recurrent IgH translocations and loss of chromosome 13/13q14; and a hyperdiploid pathway with multiple trisomies but a low incidence of both the five recurrent IgH