variety of immunostimulatory or cytotoxic molecules, for example, GM-CSF or IL-12, or toxins or radiation, for example, I\(^{131}\) or Y\(^{90}\), selectively to tumor sites for greater antitumor activity and less toxicity. This study represents one such exciting approach.

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Defining the genetic chaos in myeloma

Progress in understanding the malignant transformations that occur in multiple myeloma (MM) plasma cells has been slow, largely due to the significant heterogeneity of genetic and signaling abnormalities, which include extensive chromosomal abnormalities, gene mutations, and deregulated proliferative and apoptotic pathways—indeed, a genetic chaos. Moreover, it remains a major controversy to identify the clonal precursor(s) of the malignant plasma cell. Current prognostic markers have been inadequate to accurately define disease progression, therapeutic response, and clinical outcome. Dr John Shaughnessy and colleagues (page 1745) are first off the block to assemble a high-density microarray of MM plasma cells and to demonstrate that the MM plasma cells are distinctly different than normal plasma cells. In the work presented by Zhan and colleagues, purified plasma cells from 74 newly diagnosed patients and 31 healthy donors were examined for expression of 5,483 genes contained on the Affymetrix HuGeneFL GeneChip. Although the HuGeneFL GeneChip is an early chip design that has been replaced by more extensive and refined gene probe sets, the data presented provide a compelling new definition of MM subgroups and identify a number of new genes as potential therapeutic targets. Hierarchical clustering of plasma cell gene expression demonstrated 4 distinct genetic subgroups. Using links to clinical databases for the patients, the genetic profiles were correlated with clinical outcomes. Many of the genes that distinguish the malignant plasma cell from normal plasma cells were not surprising, though these expectations solidify the validity of the results. The most significant gene expression changes differentiating the MM1 (which included the benign PC dyscrasia, MGUS) and MM4 subgroups code for activities that implicate MM4 as having a more proliferative phenotype and show close similarities with a variety of MM cell lines (validating use of cell line models, at least for the MM4 subgroup). Beyond the clustering of gene expression, Zhan and colleagues identified gene expression spikes in subsets, which reflect the genetic heterogeneity, some of which correlate with genes known to be deregulated by chromosomal translocations. This first written report provides a snapshot of genetic abnormalities that may contribute to the malignant MM phenotype, and additional data presented at the recent ASH meeting have been extended to nearly 150 patients. We certainly anticipate that ongoing efforts to use gene profiling to identify classes of genes may provide a new framework for studying the biology of the disease, mechanisms for its progression, and potential therapeutic targets. And not withstanding the power of gene profiling, protein and signaling profiles will add important components to fully understand and treat this malignancy.

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